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Review Article

Role of Pelvic Exenteration in the Treatment of Persistent or Recurrent Gynecological Cancers

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Abstract

Objective: To assess the oncological outcomes of Persistent/Recurrent Gynaecological Cancers who underwent Pelvic Exenteration (PE) in terms of DFS and OS in a 23 years-single center experience. Secondary outcome was to identify factors associated with recurrence.

Methods: From June 1996 to March 2019, data of all patients who underwent PE were retrospectively collected. The Kaplan-Meier method was used to estimate DFS and OS. Univariable and multivariable logistic regression analysis was performed to identify potential independently associated predictors of recurrence.

Results: 192 patients were considered for final analysis. After surgery 77 women (40.1%) received a post-operative oncologic treatment. Overall 106 patients (55.2%) experienced a relapse with a median follow-up of 58 months (range, 2 to 236 months).

Presence of LVI (adjusted HR 2.2, 95% CI 1-4.9, P=0.05) was the only factor that retained an independent association with relapse at multivariable analysis. Positive lymph nodes were associated with death at univariable analysis (HR 3.9, 95% CI 1.7-9.4, P=0.002).

When stratifying patients by cervical cancer, among 115 women, 67 (58.3%) relapsed. Presence of LVI (HR 2.7, 95% CI 1.1-6.6, P=0.02) and patients with pathologic risk factors such as tumor size, positive lymph nodes and LVI (HR 3.1, 95% CI 1.4-6.8, P=0.005) were associated with recurrence both at univariable and multivariable analysis.

Conclusion: Pelvic exenteration may have a therapeutic role in cervical and endometrial tumors that recur at least 6 months after primary treatment. Patients affected by vulvar cancer or either with tumor size >5 cm, positive lymph nodes, LVI have worse oncologic outcomes.

Keywords: Gynecological cancer; Oncologic outcomes; Cervical cancer; Pelvic exenteration

Background

Pelvic exenteration is an extremely aggressive and complex surgical procedure, which consists in the complete excision of the pelvic viscera, first described by Brunschwig in 1948 [1].

In the recent years, due to the improvement of surgical techniques, devices and perioperative management, indications to perform pelvic exenteration have expanded from the classic indication of centrally persistent or recurrent cervical cancer to locally advanced primary cancers or recurrent cancers of the endometrium, vulva, vagina and ovary in selected cases [2].

Considering that up to 30% to 45% of cervical cancer recurrences are central-pelvic in a previous irradiated field [3,4], it is easily understandable that an increasing number of patients will eventually need this type of surgery.

Moreover survival rates after pelvic exenteration have been reported as 32% to 47% highlighting the importance of this surgical procedure as potentially curative [5-12].

However, it is important to underline that pelvic exenteration is an extremely aggressive surgery that leads to major physical changes that may significantly impact on patient self-image with potential physical, sexual and psychological issues [13]. For this reason a careful selection of patients is mandatory. Unfortunately there is a lack of data as regarding oncologic outcomes and especially which are the criteria (margins status, lymph node status, and tumor size, histology) to identify patients who are more likely to benefit from this surgery.

The aim of our retrospective analysis was to evaluate the oncologic outcomes in patients affected by persistent or recurrent gynecological malignancies who were submitted to exenterative surgery (anterior, posterior or total exenteration). Secondary outcome was to identify factors associated with recurrence in order to guide us in a better selection of patients suitable for surgery.

Methods

This study was approved by the Institutional Review Board at European Institute of Oncology. We identified all patients with a

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diagnosis of persistent or recurrent gynecologic malignancy who underwent planned pelvic exenteration at the Gynecologic Oncology Service of European Institute of Oncology from June 1996 to March 2019.

Patients' characteristics (age, Body mass index or BMI, oncologic history, diagnosis, indication for surgery, type of procedure) were retrospectively identified from a review of medical records. Persistent disease was defined as presence of disease within 6 months from primary treatment.

Neoadjuvant treatments (defined as any treatment that was delivered within 4 weeks before surgery) such as chemotherapy, radiotherapy or chemoradiation were registered.

We included all identified patients regardless of type of pelvic exenteration (anterior, posterior or total exenteration) as originally defined by Alexander Brunschwig [1]. Removal of pelvic lymph nodes may also be part of the surgical procedure. All surgeries were performed by dedicated gynecologic oncologists.

Use of Intraoperative Radiation Therapy (IORT), which was introduced in 2001, was also recorded. IORT was used in case of positive lymph nodes or when minimal or microscopic disease persisted on the margins to the pelvic side-wall at frozen sections, at discretion of the radiotherapist based on the site and the technical possibility of dose delivery.

All histological characteristics including FIGO stage, tumor type, size, grade, lymph nodes and margins status were retrospectively identified through a review of patients' medical records. Tumor grading was not assigned in the case of serous, melanoma, clear cell, carcinosarcoma or mixed histotypes, since, by default; these are classified as poorly differentiated and are no longer graded by pathologists [14]. All pathologic evaluation was performed by dedicated gynecologic pathologists.

All patients' medical records were reviewed until the last recorded follow-up at our institution. We determined whether patients received any adjuvant treatment after surgery, including chemotherapy, radiotherapy, hormones, or a combination of those.

Adjuvant treatment was mainly indicated for medically fit patients with pathologic risk factors (positive or close resection margins, tumor diameter >5 cm, positive lymph-nodes or lymphatic spaces invasion, all variously associated) on the surgical specimen.

Pattern of first recurrence was recorded. Recurrences were classified as local (confined to the pelvis), distant or multisite. Disease-Free Survival (DFS) was calculated from the date of surgery to the first documented recurrence, or death from disease. Overall Survival (OS) was calculated from the date of surgery to date of death, or last follow-up. The Kaplan-Meier method was used to estimate DFS and OS, and estimates were compared with the Log-rank test.

Associations were analyzed using the Chi square test for categorical variables and the Mann-Whitney U Test for continuous variables. Univariable and multivariable logistic regression analyses were performed to identify factors associated with recurrence. Statistical significance was set at P>0.05. Statistical analysis was done using SPSS software.

Results

We retrospectively identified 208 women that were scheduled to undergo a planned pelvic exenteration for a persistent or recurrent gynecologic malignancy. Eight women were lost to follow-up, 5 were submitted to palliative pelvic exenteration and 3 underwent PE as primary treatment (1 melanoma, 1 sarcoma and 1 malignant amartoma), so 192 patients were considered for the final analysis. Patients' characteristics are depicted in Table 1. The overall median age was 56 years (range 23 to 81 years) and median Body Mass Index (BMI) was 24 kg/m^2 (range, 13 kg/m^2 to 64 kg/m^2). An ECOG

Table 1: Patients' Characteristics (N=192).

Variable	median	range
Age (years)	56	23-81
Body mass index (kg/m^2)	24	13-64
	N	**%**
Type of tumor		
Cervical	115	59.9
Vulvar	21	10.9
Vaginal	29	15.1
Endometrial	18	9.4
Other	9	4.7
Histotypes		
Squamous	130	67.7
Adenocarcinoma	40	20.8
Adenosquamous	7	3.6
Endometrioid	4	2.1
Serous	2	1
Clear cell	3	1.6
Sarcoma	3	1.6
Melanoma	3	1.6
GRADE		
1	25	13.1
2	54	28.1
3	58	30.2
Not graded	55	28.6
Lymphovascular space invasion (LVI)	50	26
Previous oncologic treatment	183	95.3
Chemotherapy	36	
Radiotherapy	50	
Chemoradiation	59	
Surgery	38	
Reason for surgery		
Persistent disease	82	42.7
Recurrent disease	110	57.3
Neoadjuvant treatment (within 4 weeks before surgery)	50	26
chemotherapy	39	-
Radiotherapy	9	-
Chemoradiation	2	-

Table 2: Perioperative characteristics (N=192).

Variable	N	%
Type of exenteration		
Total	102	53.1
Anterior	77	40.1
Posterior	13	6.8
Stoma	105	91.3
Temporary	27¥	
Permanent	78	
Urinary diversion	186	91.6
Continent (Indiana pouch)	75	41.9
Incontinent	104	58.1
Bricker	22	
Wallace I	4	
Wallace II	72	
Ureterocutaneostomy	2	
Colon conduit	4	
Intraoperative Radiotherapy (IORT)	55	28.6
Tumor size (mean ± DS)	38.9 ± 23.8	
Margins		
Positive	60	31.2
Negative	132	68.7
Pelvic lymph nodes (surgically assessed)	142	73.9
Positive	44	31
Negative	98	69
Adjuvant treatments	77	40.1
Chemotherapy	61	
Radiotherapy	13	
Chemoradiation	3	
Relapse	106	55.2
Local	42	39.7
Distant	33	31.1
Multisite	31	29.2

¥ In only 16 patients the stoma was actually closed.

performance score of 0 or 1 was documented in all patients. The most common oncologic diagnosis was cervical cancer (n=115, 59.9%), the most frequent histology was squamous (n=130, 67.7%). Mean tumor size was 38.9 ± 23.8 mm and Linphovascular Involvement (LVI) was found in 50 cases (26%).

One hundred and eighty-three patients (95.3%) had previously received an oncologic treatment (chemotherapy, surgery, radiation or a combination of those) as depicted in Table 1.

Overall 50 patients (26%) received a neoadjuvant treatment (within 4 weeks before surgery): thirty-nine patients underwent neoadjuvant chemotherapy, 11 had received preoperative radiotherapy, 2 of those with concomitant chemotherapy. All the remaining patients did not receive any neoadjuvant treatment within 4 weeks before surgery.

One hundred and ten (57.3%) patients underwent surgery for

Table 3: Univariable and multivariable analysis of factors related to relapse.

Variable	Univariable		Multivariable	
	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Diagnosis				
Cervical	Reference			
Vulvar	1.01 (0.4-2.7)	0.92		
Vaginal	1.3 (0.6-2.9)	0.53		
Endometrium	1.4 (0.5-3.8)	0.51		
Other	0.81 (0.3-4.4)	0.87		
Histology				
Squamous	Reference			
Adenocarcinoma	1.2 (0.3-4.7)	0.8		
Adenosquamous	0.5 (0.1-2.3)	0.4		
Serous	NA	0.5		
Endometrioid	0.5 (0.1-4.1)	0.9		
Other	1.2 (0.1-13.2)	0.8		
Grade	1.03 (0.8-1.4)	0.82		
Tumor size				
≤ 5 cm	Reference		Reference	
> 5 cm	1.4 (0.7-2.8)	0.3	1.4 (0.7-2.9)	0.4
Neoadjuvant chemotherapy				
No	Reference			
Yes	1.1 (0.6-2.4)	0.7		
Indications for surgery				
Persistent	Reference			
Relapse	0.8 (0.4-1.4)	0.4		
LVI				
No	Reference		Reference	
Yes	2.8 (1.4-5.8)	0.004	2.2 (1-4.9)	0.05
Type of pelvic exenteration				
Total	Reference			
Anterior	1.1 (0.6-1.9)	0.8		
Posterior	1.6 (0.5-5.1)	0.4		
Lymph nodes				
Negative	Reference			
Positive	1.9 (0.9-4)	0.09		
Margins				
Negative	Reference		Reference	
Positive	1.9 (1-3.6)	0.05	1.5 (0.7-3)	0.2
IORT	Reference		Reference	
	1.5 (0.8-2.8)	0.2	1.4 (0.7-2.8)	0.4
One or more risk factors				
No	Reference		Reference	
Yes	2.2 (1.2-4.1)	0.01	1.8 (0.9-3.5)	0.07

All variables were tested for multicollinearity. Clinically significant variables and variables with p <0.3 on univariable analysis were included in the multivariable analysis.

recurrent disease and 82 (42.7%) for persistent disease.

Perioperative characteristics are reported in Table 2. Intraoperative Radiation Therapy (IORT) was delivered in 55 (28.6%) women. Use of IORT was introduced in 2001.

Intraoperative characteristics, including type of surgical procedures, are depicted in Table 2.

One hundred and thirty-two patients (68.8%) had negative margins, 60 (31.2%) had a positive margin. Lymph nodes status was surgically assessed in 142 women and 44 of those had positive pelvic lymph nodes. Twelve patients who had positive lymph nodes underwent IORT.

After surgery 77 women (40.1%) received a post-operative oncologic treatment (chemotherapy, hormones, radiation or a combination of those) as showed in Table 2.

The most common adjuvant treatment was chemotherapy (n=61), mainly indicated for medically fit patients who had already undergone radiotherapy and with pathologic risk factors (positive resection margins, tumor diameter >5 cm, positive lymph-nodes or lymphatic spaces invasion, all variously associated) on the surgical specimen.

Overall 106 patients (55.2%) experienced a relapse. Pattern of first recurrence is showed in Table 2. Most women experienced a local relapse (n=42), 33 patients developed distant metastasis and 31 had a multisite relapse. Most of these patients (n=78, 73.6%) subsequently died of disease. Stratifying by gynecological cancer, among the 115 women affected by cervical cancer, 67 (58.3%) patients relapsed.

Table 3 summarizes the univariable and multivariable analysis of factors associated with relapse: positive margins (HR 1.9 95% CI 1-3.6, P=0.05), LVI (HR 2.8, 95% CI 1.4-5.8, P=0.004) and population with one or more pathologic risk factors such as positive resection margins, tumor diameter >5 cm, positive lymph-nodes or lymphatic spaces invasion, (HR 2.2, 95% CI 1.2-4.1, P=0.01) were associated with relapse at univariable analysis. However, presence of LVI (adjusted HR 2.2, 95% CI 1-4.9, P=0.05) was the only factor that retained an independent association also in multivariable analysis. We did not insert lymph node status in multivariable analysis because lymphadenectomy was performed only in 142 patients, therefore, had all the not surgically assessed lymph nodes cases been excluded from our multivariable analysis, it would have constituted a critical bias. Positive lymph nodes were also associated with death at univariable analysis (HR 3.9, 95% CI 1.7-9.4, P=0.002) also when patients were stratified by cervical cancer only (HR 5.4, 95% CI 1.7-17.8, P=0.005). No other factors were associated with risk of death at univariable analysis.

In cervical cancer, squamous histology was related to a decreased risk of recurrence (HR 0.1, 95% CI 0.01-0.7, P=0.02) both at univariable analysis and multivariable analysis (adjusted HR 0.06, 95% CI 0.01-0.5, P=0.01).

When stratifying patients by cervical cancer (Table 4) also presence of LVI (HR 2.7, 95% CI 1.1-6.6, P=0.02) and patients with pathologic risk factors who underwent adjuvant treatments (HR 3.1, 95% CI 1.4-6.8, P=0.005) were associated with recurrence at univariable analysis. They both retained statistical significance on multivariable analysis and persistence of disease almost reached statistical significance as showed in Table 4.

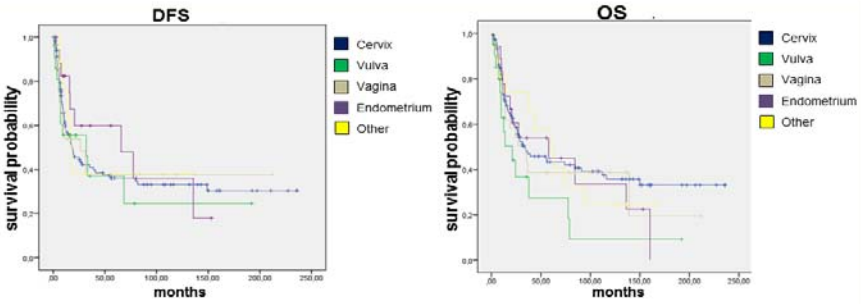
Table 4: Univariable and multivariable analysis of factors related to relapse in patients affected by cervical cancer (n=115).

Variable	Univariable		Multivariable	
	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Histology				
Squamous	0.1 (0.01-0.7)	0.02	0.06 (0.01-0.5)	0.01
Adenocarcinoma	0.4 (0.1-2.4)	0.3	0.7 (0.1-4.3)	0.7
Adenosquamous	Reference			--
Grade	Reference	--		
	0.9 (0.7-1.4)	0.9		
Tumor size				
≤ 5 cm	Reference			
> 5 cm	1.3 (0.5-3.4)	0.6		
Neaoadjuvant chemotherapy	Reference	--		
	1.4 (0.5-3.4)	0.5		
Indications for surgery				
Persistent	Reference		Reference	
Relapse	0.6 (0.3-1.2)	0.1	0.4 (0.2-1)	0.052
L VI				
No	Reference		Reference	
Yes	2.7 (1.1-6.6)	0.02	2.9 (1.1-7.9)	0.04
Type of pelvic exenteration				
Total	Reference			
Anterior	1.3 (0.6-2.9)	0.4		
Posterior	0.8 (0.1-9.2)	0.8		
Margins				
Negative	Reference		Reference	
Positive	1.6 (0.7-3.6)	0.2	0.9 (0.3-2.2)	0.8
Lymph nodes				
Negative	Reference			
Positive	1.7 (0.6-4.5)	0.3		
IORT	Reference		Reference	
	1.8 (0.8-4.1)	0.1	2.2 (0.9-5.9)	0.1
One or more risk factors				
No	Reference		Reference	
Yes	3.1 (1.4-6.8)	0.005	3.3 (1.3-8.1)	0.01

All variables were tested for multicollinearity. Clinically significant variables and variables with p <0.3 on univariable analysis were included in the multivariable analysis.

The median follow-up was 58 months (range, 2 to 236 months). At last follow-up, 25 (13%) patients were alive with recurrent disease, 53 (27.6%) were disease-free (some of these had a recurrence but treated with complete response), and 114 (59.4%) had died.

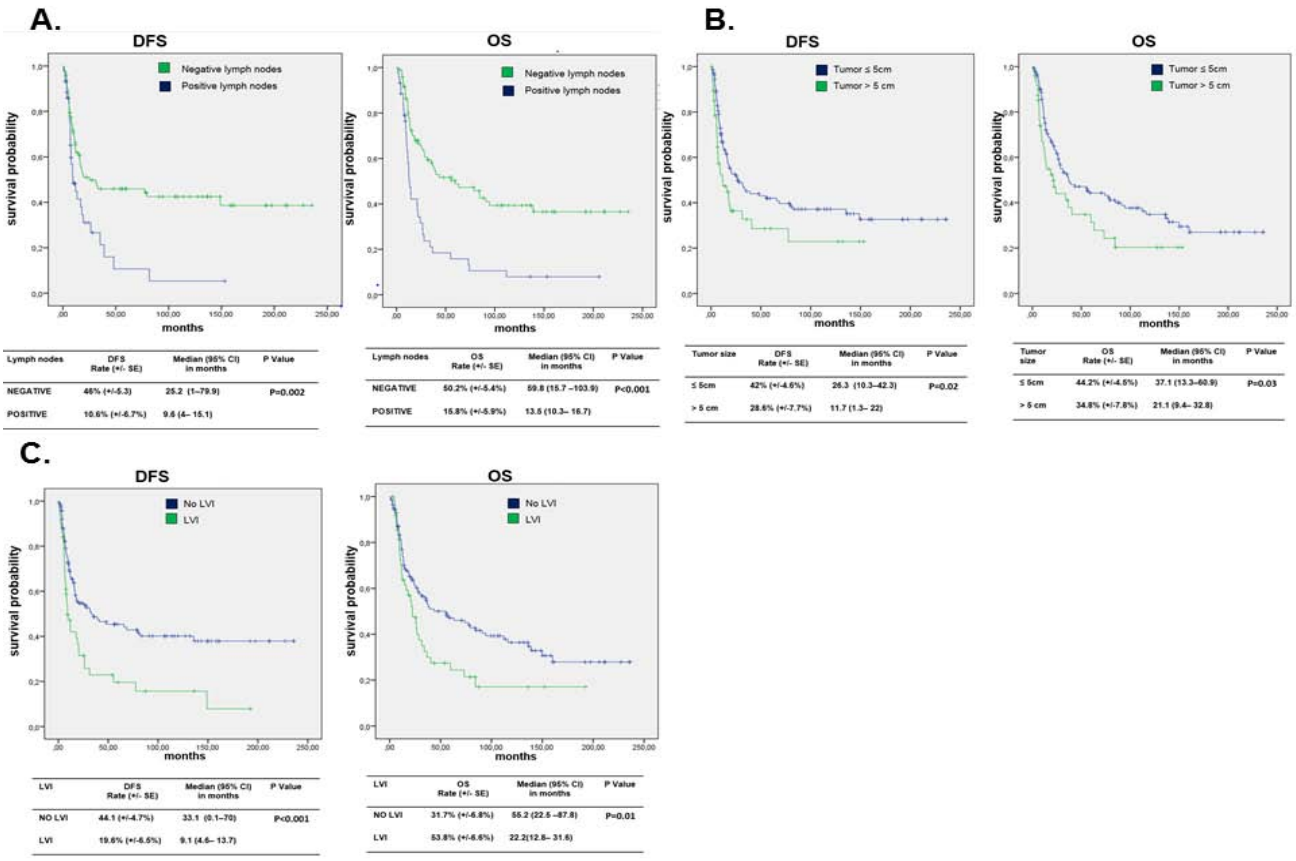
Five year Disease Free Survival (DFS) and 5-year Overall Survival (OS), stratified by type of tumor is showed in Figure 1. Vulvar and vaginal cancer are characterized by the shortest DFS (24.6% SE+/-13.3% and 37.7% SE+/-10.4% respectively) and OS (25.9% SE+/-12%



DIAGNOSIS	DFS Rate (+/- SE)	Median (95% CI) in months
CERVIX	36 % (+/-5%)	17.9 (8.7–27)
VULVA	24.6 % (+/-13.3%)	31.9 (0.1–63.8)
VAGINA	37.7 % (+/-10.4%)	26.3 (0.1–52.5)
ENDOMETRIUM	47.9 % (+/-14.9%)	65.8 (1–135.1)
OTHER	39.1 % (+/-17.2%)	17.9 (9.3–31.3)

DIAGNOSIS	OS Rate (+/- SE)	Median (95% CI) in months
CERVIX	41.5 % (+/-5.1%)	31.6 (19.7–43.5)
VULVA	25.9 % (+/-12%)	24.5 (5.6–43.3)
VAGINA	40.9 % (+/-9.9%)	26.7 (1–53.8)
ENDOMETRIUM	53.9 % (+/-12.1%)	57.9 (1–118.4)
OTHER	55.6% (+/-16.6%)	63.1 (53.5–72.6)

Figure 1: Five year Disease Free Survival (DFS) and 5-year Overall Survival (OS) stratified by tumor type.



Lymph nodes	DFS Rate (+/- SE)	Median (95% CI) in months	P Value
NEGATIVE	46% (+/-5.3)	25.2 (1–79.9)	P=0.002
POSITIVE	10.6% (+/-6.7%)	9.6 (4– 15.1)	

Lymph nodes	OS Rate (+/- SE)	Median (95% CI) in months	P Value
NEGATIVE	50.2% (+/-5.4%)	59.8 (15.7 –103.9)	P<0.001
POSITIVE	15.8% (+/-5.9%)	13.5 (10.3– 16.7)	

Tumor size	DFS Rate (+/- SE)	Median (95% CI) in months	P Value
≤ 5cm	42% (+/-4.6%)	26.3 (10.3–42.3)	P=0.02
> 5 cm	28.6% (+/-7.7%)	11.7 (1.3– 22)	

Tumor size	OS Rate (+/- SE)	Median (95% CI) in months	P Value
≤ 5cm	44.2% (+/-4.6%)	37.1 (13.3–60.9)	P=0.03
> 5 cm	34.8% (+/-7.8%)	21.1 (9.4– 32.8)	

LVI	DFS Rate (+/- SE)	Median (95% CI) in months	P Value
NO LVI	44.1 (+/-4.7%)	33.1 (0.1–70)	P<0.001
LVI	19.6% (+/-6.5%)	9.1 (4.6– 13.7)	

LVI	OS Rate (+/- SE)	Median (95% CI) in months	P Value
NO LVI	31.7% (+/-6.8%)	55.2 (22.5 –87.8)	P=0.01
LVI	53.8% (+/-6.6%)	22.2(12.8– 31.6)	

Figure 2: Five year Disease Free Survival (DFS) and 5-year Overall Survival (OS) stratified by: A) lymph nodes status B) tumor size C) LVI.

and 40.9% SE+/-9.9% respectively).

As showed in Figure 2, Patients with tumor size >5 cm, presence of LVI and positive lymph nodes presented a significant worse 5 year DFS and 5 year OS.

In cervical cancer population (Figure 3), patients with LVI had a significant worse 5-year DFS, and women with LVI, positive lymph nodes and tumor size >5 cm had a significant worse 5-year OS.

Discussion

In the current era of minimally invasive surgery, where less is more, pelvic exenteration, an extremely extensive surgery, remains the only potentially curative treatment for selected patients with advanced or persistent/recurrent gynecologic malignancies.

Survival rates after pelvic exenteration have been reported as 32% to 47% for overall survival and 40% to 52% for recurrence-free

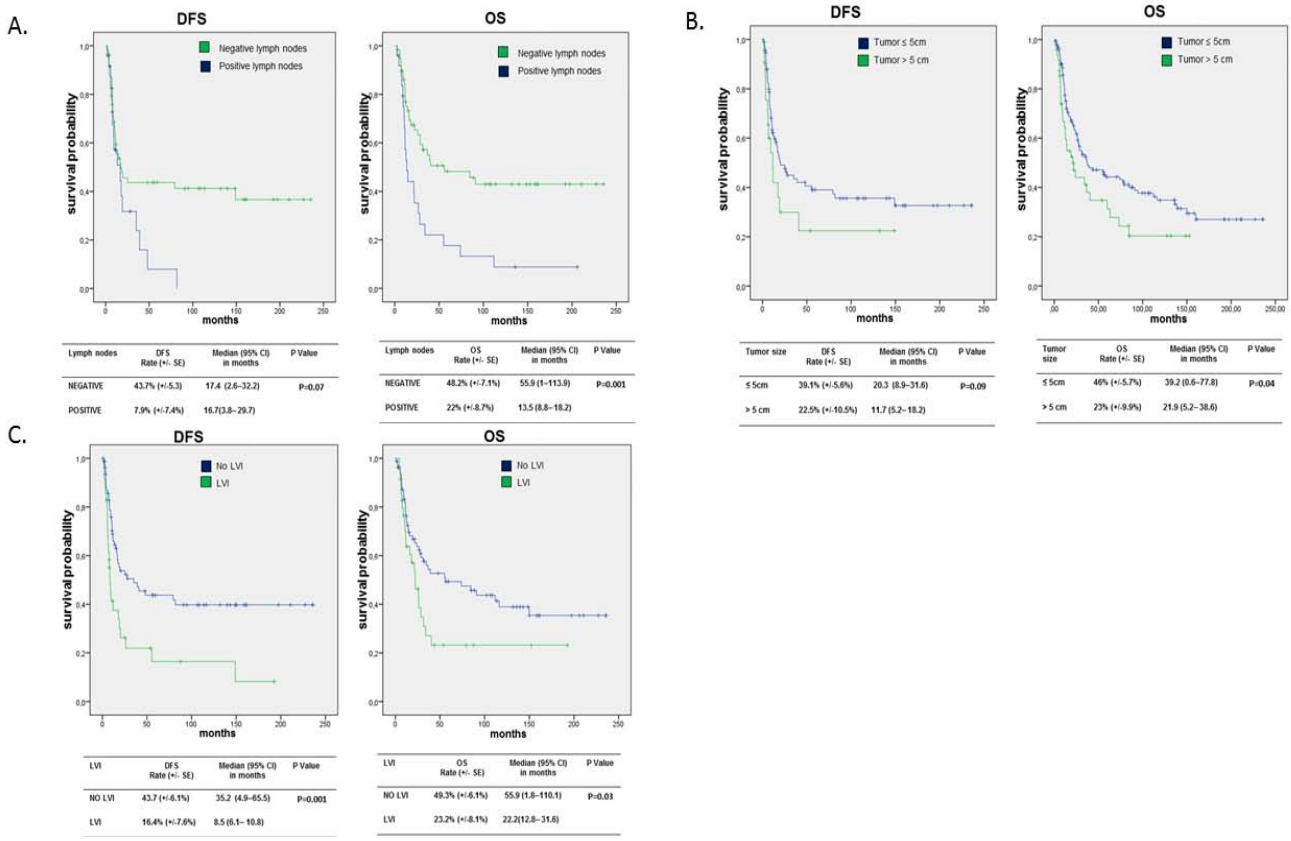


Figure 3: Five year Disease Free Survival (DFS) and 5-year Overall Survival (OS) in cervical cancer population stratified by: A) lymph nodes status B) tumor size C) LVI.

survival in gynecologic cancers [5-12], which are in line with our cumulative data. More in particular cervical and endometrial cancers were the malignancies with the longest OS (41.5% for cervical cancer and 53.9% for endometrial cancer) confirming that these patients are appropriate candidates for pelvic exenteration. Vaginal and vulvar tumors registered shorter OS (25.9% for vulvar cancer and 40.9% for vaginal cancer) suggesting that it is uncertain whether these patients are good candidates for such an aggressive procedure.

A couple of literature reviews tried to identify prognostic factors in patients affected by gynecological malignancies who have undergone pelvic exenteration however, not all reports consistently reported all of these factors [15-17].

Tumor size of lesions >5 cm diameter have been shown to have almost no chance of cure despite complete removal of the tumor [15,17]. In our analysis, tumor size was not statistically related to recurrence, even when we stratified our cohort by cervical cancer only, probably due to the small number of cases with tumor size >5cm. However it resulted in a significant worse 5year-DFS and 5year DFS.

According to some authors, time interval between the initial treatment and recurrence (less than 2 years, between 2 and 5 years and more than 5 years) is associated with a different 5-year OS of 16.8%, 28.0% and 83.2% respectively [18]. More in particular, a relapse occurring >2 years after initial treatment is associated with a better OS in patients affected by cervical cancer [19]. We did not observe a statistically significant difference between recurrent (after six months by the end of primary treatment) *versus* persistent (within six months by the end of primary treatment) tumors. However when we stratified by cervical cancer, we observed a trend that almost reached statistical significance in terms of association with relapse when PE was performed within 6 months after primary treatment.

Squamous cell carcinomas have been reported as associated with a significantly worse prognosis than adenocarcinomas [15,20], even if in these studies adenocarcinomas represented only a small portion of the population and lymphovascular space invasion was more frequently observed in the squamous carcinomas. In our cohort we observed a decreased association with recurrence for squamous carcinomas on our cumulative univariable analysis in cervical cancer population, most likely because these cases were compared to very unfavorable histotypes such as undifferentiated or adenosquamous carcinomas. Moreover, these findings are consistent with those reported in the Literature for primary cervical cancer, according to which adenosquamous histology is significantly associated with poorer DFS [21,22].

The presence of lymph node metastasis is still controversial in the Literature [15], however a poorer prognosis associated with lymph node metastasis has been reported by several authors [23-26]. In the present series lymph node status appeared an important prognostic factor, associated with both risk of death and relapse. Unfortunately in

our series pelvic lymphadenectomy was not systematically performed in all patients and for this reason we had to exclude lymph node status from our multivariable analysis in order to avoid selection bias.

Surgical resection margins status is reported as a major significant and independent prognostic factor associated with decreased survival [23,24,27]. Postoperative survival at two years drops from 55.2% with uninvolved margins to 10.2% with positive margins [18]. Some authors have found that the survival rate in patients with positive margins falls to 0% after three years [15]. We similarly observed a statistically significant association to relapse in patients with positive margins compared to negative margins at our univariable analysis; however we did not find any difference when we stratified our cohort for cervical cancer only.

Lymphovascular Space Invasion (LVSI) is considered in the scientific community as an independent prognostic factor which negatively impacted overall survival [6,15]. Our findings confirmed that presence of LVI is significantly associated with risk of recurrence, worse DFS and OS both in general and specifically in cervical cancer population.

The use of Intraoperative Radiation Therapy (IORT) combined with radical surgical resection in patients affected by recurrent gynecologic malignancies seems to provide some local control, especially in patients with positive or close margins [28-30]. According to our analysis IORT was not associated with reduced risk of recurrence, both on univariable and multivariable analysis. However we did not investigate, in case of a recurrence occurring after IORT, whether the recurrence was in the same site of the irradiation or elsewhere. Moreover in comparing patients who underwent IORT versus those who did not we may have occurred in several selection biases also related to the timing the procedure was implemented. For this reason, we feel that we were unable to assess the effective role of IORT, which will be further investigated in a future study.

Finally we observed that the presence of one or more pathologic risk factors (positive resection margins, tumor diameter >5 cm, positive lymph-nodes or lymphatic spaces invasion, all variously associated) may represent a selected high-risk population and it is associated with recurrence.

Points of weakness of the present study are represented by its retrospective nature and by the long time of observation (from 1996 to 2019), during which surgical performance (new devices), quality of perioperative care, treatments protocols and general life expectancy have improved over time. This long duration of time may indeed have reduced the quality of the analysis based on these points, as the population is not very homogenous.

One point of strength is represented by the number of cases. In fact, to our knowledge, this is one of the largest single centre studies of patients affected by recurrent/persistent gynecological malignancies who were submitted to pelvic exenteration. Another point of strength is our long follow up that reaches up to 236 months (median 58 months).

According to our analysis pelvic exenteration appears to have a therapeutic role in very well selected patients affected by persistent/recurrent gynecological cancers, especially in case of cervical and endometrial tumors that recur at least 6 months after primary treatment, as it leads to an acceptable survival rate that justify such an aggressive surgical procedure in a setting where there are no other therapeutic options.

Patients who present with vulvar cancer, persistence of disease (within 6 months after primary treatment) or pathologic risk factors such as tumor size >5 cm, positive lymph nodes, presence of LVI all variously associated, seem to have worse oncologic outcomes and surgery in this particular population, even though not always identified preoperatively, should be carefully discussed case by case. In such cases neoadjuvant chemotherapy should be considered even if we did not observe a statistical significance due to extreme heterogeneity of our cohort. In particular all the conditions that could potentially lead to an intraoperative risk factor such as positive margins (like in case of large tumor size, nearly lateral disease or suspicious lymph nodes) should be evaluated preoperatively in order to consider use of intraoperative treatments such as IORT.

Conducting a randomized controlled trial in this setting is extremely unlikely, as multiple factors need to be taken into consideration. Most of these factors, such as tumor spread, histology, previous oncologic treatments and patient morbidities may exclude one treatment from the other. Therefore, we believe there is a need for prospective non-randomized comparative trials, possibly multicentre, that compare exenterative surgery versus other treatment modalities in women with recurrent gynaecological malignancies with pathologic risk factors.

Synopsis

Pelvic exenteration may have a therapeutic role in cervical and endometrial tumors that recur at least 6 months after primary treatment. Patients affected by vulvar cancer or either with tumor size >5 cm, positive lymph nodes, LVI have worse oncologic outcomes.

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