ANTICANCER RESEARCH *41*: 3037-3043 (2021)
doi:10.21873/anticanres.15086

Pelvic Exenteration in Advanced Gynecologic Malignancies – Who Will Benefit?

EVA KATHARINA EGGER[1], HANNA LIESENFELD[1], MATTHIAS B. STOPE[1], FLORIAN RECKER[1], ANNA DÖSER[1], DOMINIQUE KÖNSGEN[1], MILKA MARINOVA[2], TOBIAS HILBERT[3], DANIEL EXNER[4], JÖRG ELLINGER[5] and ALEXANDER MUSTEA[1]

[1]*Department of Gynecology and Gynecological Oncology, University Hospital Bonn, Bonn, Germany;*
[2]*Department of Radiology, University Hospital Bonn, Bonn, Germany;*
[3]*Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany;*
[4]*Department of Surgery, University Hospital Bonn, Bonn, Germany;*
[5]*Department of Urology, University Hospital Bonn, Bonn, Germany*

Abstract. *Background/Aim: In selected patients, pelvic exenteration (PE) is curative, but morbidity and mortality are feared. Unfortunately, prerequisites for indicating PE are not generally defined. The aim of the study was to identify prognostic factors for survival after PE in advanced pelvic gynecological malignancies for finding possible prerequisites for the indication of PE. Patients and Methods: Between 2002 and 2016, 49 patients underwent pelvic exenteration for advanced pelvic malignancies apart from ovarian cancer. Progression-free survival (PFS) and overall survival (OS) were calculated based on the Kaplan-Meier method. Factors significantly affecting 5-year overall survival were identified using multivariate regression analysis. Survival distributions between the best and the worst group were compared by the log rank test. Results: Forty-nine patients with recurrent or primary pelvic gynecological malignancy (20 recurrent disease, 29 primary disease) were included. Seventeen patients had oligometastatic disease at surgical intervention. Resection margin, age, primary versus secondary exenteration and metastatic disease were independent prognostic factors in multivariate regression analysis. A significant difference was observed in 5-year overall survival regarding the best group (57.14%) and the worst group (10%) (p=0.009). Cervical cancer was the only identified risk factor for increased morbidity. Conclusion: Pelvic exenteration is a valuable therapeutic option with most long-term survivors in the group of patients below 63 years, as primary treatment, with clear microscopic margins and no distant metastases. These four factors may serve as valuable prerequisites for the indication of pelvic exenteration as survival and morbidity in this group of patients compares favorably to alternative therapeutic options.*

Correspondence to: Eva Egger, Department of Gynecology and Gynecological Oncology, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany. Tel: +49 22828715447, Fax: +49 22828716091, e-mail: eva-katharina.egger@ukbonn.de

Key Words: Pelvic exenteration, survival benefit, pelvic gynecologic malignancies.

Pelvic exenteration was introduced in 1948 for advanced pelvic malignancies with palliative intent to relieve symptoms as no other therapy remained available (1). Currently, evidence for pelvic exenteration compared to non-surgical therapies, such as chemoradiation, radiation and systemic therapies, allows no conclusions concerning equivalence or superiority of pelvic exenteration regarding overall survival and progression-free survival (2-5). Unfortunately, pelvic exenteration may be associated with significant postoperative morbidity. However, in some patients it may also be the only curative treatment (6-9). Moore *et al*. identified prognostic factors for the survival effect of systemic therapy in cervical cancer patients (2). Similar factors to justify pelvic exenteration have not yet been identified. Herein, we aimed to identify prognostic factors for survival after pelvic exenteration. Furthermore, risk factors for unfavorable postoperative courses were evaluated.

Patients and Methods

Data collection. This study was conducted in accordance with the standards of the ethics committee of the Faculty of Medicine at the University of Bonn, Germany (Nr: 454/20). Data of all 49 patients with pelvic exenteration apart from ovarian cancer at the University of Bonn between 2002 and 2016 were retrospectively reviewed. Age, prior therapies, date of surgery, preoperative staging, type of surgery, type of reconstructive surgery, tumor entity, tumor stage, resection margins, distant metastasis, lymphovascular invasion, number and type of transfused blood products, duration of surgery,

duration of mechanical postoperative ventilation, duration of intensive care, length of in-hospital stay, the time interval between first diagnosis and relapsed disease in case of pelvic exenteration in relapsed disease, overall survival and progression-free survival were analyzed. All postoperative complications were graded according to the Memorial Sloan Kettering cancer center secondary surgical event score in grade 1 to 5 (10).

Statistical analysis. The survival analyses for progression-free survival (PFS) and overall survival (OS) are based on the Kaplan–Meier method. The time-to-event intervals were described in months from the date of surgery until the date of the event. The data were censored at the date of the last follow up if there wasn't an event. Using multivariate regression analyses, four factors significantly influencing the 5-year overall survival were identified. Based on these four factors, the best group of patients and the worst group of patients were identified. Using log-rank test, 5-year-survival-curves were compared on a 95% confidence level. Possible risk factors for an unfavorable postoperative course were evaluated by hypothesis testing on a 95% confidence level. All statistical tests were two-sided. All statistical analyses were performed using Minitab Version 18, Minitab LLC., State College, Pennsylvania, USA.

Results

Patient characteristics. Pelvic exenteration was performed in 49 patients with a median age of 65 years (range=33-86 years) between 2002 and 2016. Two patients had synchronous cancers (vulvar and anal cancer; vulvar and cervical cancer). There were 29 primary exenterations and 20 secondary exenterations. Pelvic exenteration was performed in 17 (34.7%) patients with oligometastatic disease for local symptom control. Metastatic sites were not regional lymph nodes (n=7), bone (n=2), spleen (n=1), small intestines (n=2), liver (n=3) and lung (n=2). Microscopic peritoneal involvement was seen in 5 (29.4%) out of 17 metastasized patients. Nine patients had received radiation therapy in previous treatment lines (adjuvant chemoradiation, adjuvant radiation, chemoradiation only, radiation only). Two patients had received neoadjuvant chemotherapy before pelvic exenteration. In recurrent disease, the median time interval from the first diagnosis to recurrent disease was 16.5 months (range=5-468 month). Table I shows the different tumor entities and characteristics of patients.

Staging. The pelvic and abdominal preoperative work-up included a cystoscopy in 42 patients, a rectoscopy in 34 patients, an abdominal CT scan in 40 patients, magnetic resonance imaging in 9 patients and an abdominal CT scan and pelvic magnetic resonance imaging in 14 patients. Two patients received a positron emission tomography-computed tomography scanning (PET-CT). All patients had a preoperative CT scan of the thorax.

Surgery details. Table II shows the surgical details. Two small intestine resections were necessary due to fistulas between the uterus and the small intestines after prior radiation therapy. Lymph node resection was omitted in 9 patients. There were 28 anterior, 7 posterior and 14 complete exenterations. Nineteen additional perineal resections and only 1 lateral extended endopelvic resection (LEER).

Table I. *Tumor entities and characteristics of patients*.

Parameter	Patients (n=49)	Percentage
Diagnosis		
Cervical cancer	17	34.7%
Vulvar cancer	18	36.7%
Endometrial cancer	4	8.2%
Anal cancer	1	2%
Vulvovaginal melanoma	2	4.1%
Vaginal cancer	8	16.3%
Rhabdomysarcoma of the vagina	1	2.0%
Primary diagnosis *versus* relapse		
Primary diagnosis	29	59.2%
Relapse	20	40.8%
Relapse		
First relapse	16	32.7%
Second relapse	3	6.1%
Third relapse	1	2.0%
Distant metastasis present		
Yes	17	34.7%
No	32	65.3%
Cardiovascular risk factors		
Yes	27	55.1%
No	22	44.9%
Smoking		
Yes	13	26.5%
No	36	73.5%
ASA-Score		
ASA 1	9	18.4%
ASA 2	26	53.1%
ASA 3	14	28.6%

ASA-Score: American Society of Anesthesiologists-Score.

Final pathology report. Table III shows the details of the final pathology report. There were three patients with pT1 stages in final pathology. One patient had a large vaginal carcinoma, one patient had a rhabdomyosarcoma after neoadjuvant chemotherapy, and one patient had a synchronous pT3 anal cancer. The 19 final pT2 stages were cervical and vaginal cancers infiltrating in the bladder without mucosal infiltration.

Postoperative complications. Postoperative complications were graded according to the Memorial Sloan Kettering Cancer center – secondary surgical event score (MSKCC-SSE Score) (11). Severe complications (grade 3-5) occurred in 16 patients (32.7%). Table IV shows all postoperative complications by grade. Cervical cancer was the only significant risk factor for severe complications (p=0.006).

Table II. *Details of performed surgery.*

Duration of surgery in minutes	
Median	436
Range	290-780
Number of erythrocyte concentrates	
Median	0
Range	0-16
Number of fresh frozen plasmas	
Median	0
Range	0-16
Days in intensive care unit	
Median	1
Range	0-12
Mechanical ventilation in days	
Median	0
Range	0-4
Hospital stay in days	
Median	24
Range	13-87
Type of surgery	
Anterior PE	28
Posterior PE	7
Complete PE	14
Additional perineal resection	19
LEER procedure	1
Type of reconstruction	
Ileum conduit	28
Sigma conduit	6
Transversum conduit	2
Mainz Pouch I	6
Colostomy	19
End-to-end anastomosis	2
Additional surgery steps	
Omental flap	26
Local peritonectomy	1
Small intestine resection	2
Omentectomy	3
Inguinal lymph node resection	6
Pelvic lymph node resection	24
Paraaortic lymph node resection	15

PE: Pelvic exenteration, LEER: lateral extended endopelvic resection.

Table III. *Pathological details.*

T-Status		
T1	3	6.1%
T2	19	38.7%
T3	20	40.8%
T4	9	18.4%
Nodal status		
N0	19	38.8%
N1	21	42.9%
Nx	9	18.4%
R-Status		
R1	14	28.6%
R0	35	71.4%
Grading		
G1	2	4%
G2	18	36.7%
G3	28	57.1%
Lymphangiosis		
L1	19	38.7%
L0	30	61.2%
Hemangiosis		
V1	11	22.4%
V0	23	46.9%

Table IV. *Postoperative complications graded according to the MSKCC-SSE –Score (11).*

No SSE	15
G1 SSE	5
G2 SSE	13
G3 SSE	13
G4 SSE	2
G5 SSE	1

SSE: Secondary surgical event in grade 1 (G1) to 5 (G5).

Age (p=0.478), a higher risk classification according to the American Society of Anesthesiologists (ASA) (p=0.335), duration of mechanical ventilation (p= 0.774), duration of surgery (p=0.463), transfusion of blood products (p=0.509), suspected pelvic wall infiltration (p=0.593), neoadjuvant chemotherapy (p=0.245), and type of surgery (p=0.335) were not significant concerning the incidence of severe complications.

The following parameters were not suitable for evaluation as they were less common in patients affected by postoperative complications: smoking, relapsed disease, radiation therapy, M1, L1, higher T-Stage, cardiovascular risk factors, duration of intensive care. Severe postoperative complications in detail were 4 fistulations followed by abdominal abscesses in two cases. One out of those four patients died in the postoperative course. Further severe complications were 1 necrosis of the sigma conduit, 1 sepsis, 1 ureteral stenosis, 4 wound infections with secondary dehiscence, 1 lung embolism, 1 deep vein thrombosis, and 1 ileus.

Survival analysis. The 5-year overall survival was 31.5% and the 5-year over all progression-free survival was 28.7%. All parameters considered for the analysis regarding median overall and median progression-free survival are shown in Table V. Multivariate regression analysis, using a 95% confidence interval, identified 4 factors significantly affecting the 5-year overall survival: Resection margins, age, primary versus relapsed disease, and distant versus no distant metastatic disease. The group of patients with histologically

Table V. *Survival analysis with respect to risk factors.*

Factor	Median OS in month	Median PFS in month
M0	48	24
M1	16	11
All	30	17
L0	31	13
L1	24	22
First diagnosis	36	17
Relapsed disease	24	13
R0	38	22
R1	16	10
Cervical cancer	>22	17
Vulvar cancer	30	16
No SSE, SSE grade 1 and 2	30	16
SSE grade 3,4 and 5	24	16

M0: No distant metastasis, M1: distant metastatic disease, L0: no lymphangiosis, L1: lymphangiosis, R0: tumorfree margins, R1: margins affected by tumor, SSE: secondary surgical event, OS: overall survival, PFS: progression free survival.

Table VI. *Multivariate 5-year overall survival analysis.*

Group	5-year overall survival
Best (primary disease, R0, <63 years, M0)	57.1%
Worst (relapsed disease, R1, >63 years, M1)	10.0%

R0: Histologically confirmed tumor-free margins, R1: histologically confirmed tumor affected margins, M0: no distant metastasis, M1: distant metastatic disease.

confirmed tumor-free margins (R0), aged under 63 years without metastatic disease (M0), whenever PE was the primary treatment had a 5-year overall survival of 57.1%. This group showed the best 5-year overall survival and was therefore considered as the best group. The group of patients with histologically affected margins (R1), aged above 63 years with metastatic disease (M1), whenever PE was the secondary treatment had a 5-year overall survival of only 10%. This group showed the worst 5-year overall survival and was therefore considered as the worst group. The analysis of both survival curves by the log-rank test identified this difference to be significant (p=0.009). Table VI shows this survival analysis in groups. Figure 1 shows the survival curves of the best and the worst group.

Discussion

In selected cases, pelvic exenteration will be the only curative treatment. As randomized trials are missing there is no evidence to favor pelvic exenteration over nonsurgical treatments such as chemoradiation, radiation and systemic therapy in advanced gynecologic pelvic malignancies (12). Furthermore, the curative potential of pelvic exenteration is often weighted against mortality, morbidity, and mutilation. While mortality has declined in recent years from 23% to 2%, severe morbidity will still occur in 21% to 34% of all patients undergoing pelvic exenteration (1, 4, 6, 7, 9, 13, 14). However, early postoperative morbidity is not necessarily a permanent condition. Surgical intervention, antibiotics and anticoagulation as well as physical therapy substantially improved the long-term outcome in our cohort. Our data on morbidity of 32% and mortality of 2% are in accordance with the literature. The only identified significant risk factor for morbidity was cervical cancer. We identified four positive prognostic factors for PE in our cohort: primary exenteration, clear microscopic margins, no distant metastases and an age below 63 years.

Primary pelvic exenteration. There is a lack of data regarding the rationale for the choice of therapy in advanced pelvic malignancies. Therefore, primary exenteration in cervical, vulvar and vaginal cancer remains a matter of debate despite its proven curative effect (4, 6, 7, 13, 15). Nevertheless, the indication for any therapy in advanced pelvic malignancies has to be carefully assessed and patients thoroughly counseled as morbidity and therapeutic failures are possible in nonsurgical alternatives as well. Definite chemoradiation in patients diagnosed with FIGO stage VIA cervical cancer harbors the risk of fistulation in 22% to 47.8% (16, 17). Predictive factors for locoregional failure of definite chemoradiation in cervical cancer are: tumor size exceeding 5 cm, young age, non-squamous histology, positive lymph nodes, and being diagnosed with FIGO stage III or IV cervical cancer (16-22). Regarding chemotherapy and antiangiogenic therapy, the Moore criteria (pelvic disease, prior radiotherapy, age, race and ECOG above 1) are prospectively validated prognostic factors for survival in cervical cancer patients receiving chemotherapy and bevacizumab. It is important to consider that survival will decrease substantially the more of these factors accumulate (2, 3).

Neoadjuvant chemotherapy in vulvar cancer has shown favorable response rates of 80%. Unfortunately, optimal resection margins in order to omit mutilation are not defined yet as quick recurrences are possible (23, 24). Definite chemoradiation only shows low clinical response rates in vulvar cancer patients eligible for pelvic exenteration and a high morbidity (10, 25-29).

In FIGO stage III and IVA vaginal cancers, radiation therapy may lead to a 5-year disease-specific survival of 58%. Major morbidities will be seen in 21%, including bladder dysfunction, urethral stricture, and severe proctitis. However, the therapeutic success decreases significantly at tumor sizes above 4 cm (30).

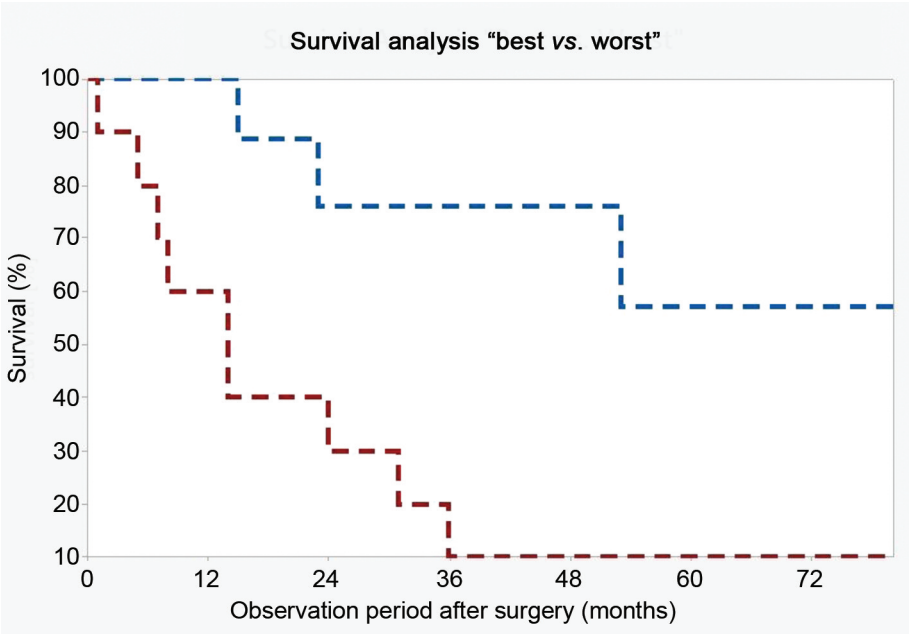

Figure 1. *Survival analysis of the best group and the worst group. Survival rate of the best group in blue: histologically confirmed tumor free margins (R0), aged under 63 years without metastatic disease (M0) with primary PE. Survival rate of the worst group in red: histologically affected margins (R1), aged above 63 years with metastatic disease (M1), whenever PE was the secondary treatment.*

In endometrial cancer distant disease will be seen more frequently than central recurrences only or a primary adjunct organ infiltrating tumor. Therefore, primary exenteration is rarely indicated in endometrial cancer patients. In selected patients, recurrent endometrial cancer treated with pelvic exenteration shows 5-year survival rates of 60% to 72% and a morbidity of 30% (7, 14).

Taken together, our median survival data of 36 months in the group of patients with primary pelvic exenteration is confirmed by others (4, 14, 15). Primary pelvic exenteration seems a reasonable consideration especially in cervical and vaginal cancer whenever the pelvic tumor size exceeds 4 to 5 cm (22, 30).

Clear microscopic margins and no distant metastases. The rate of tumor-free microscopic margins after pelvic exenteration ranges between 45% and 83% (4, 6, 7, 13, 14, 31). In lateral pelvic wall involvement this rate drops below 43% (13, 31). Whenever resection margins are affected by tumor the two-year survival rate decreases to 10% and less (4, 6, 15). In our cohort the median overall survival for patients with tumor affected resection margins was as low as 16 months. Unfortunately, the preoperative prediction of negative margins may fail in the clinical workup especially in cases of prior radiation therapy and lateral pelvic wall involvement (6, 13, 31-33). Many studies agree that tumor involved resection margins of the surgical specimen and distant metastases are negative prognostic factors for survival after pelvic exenteration (4, 6, 13, 31, 34, 35). Nevertheless, the ethical discussion about the value of pelvic exenteration in these situations is still ongoing as pelvic exenteration may relieve symptoms in the palliative setting (4, 6, 13, 31, 35). Next to clear microscopic margins, two studies proposed no lymphovascular space invasion as a significant prognostic factor for survival in pelvic exenteration for cervical cancer (6, 15). Further factors mentioned in these studies were no nodal involvement concerning an age of more than 43 years (15), and a curative intent (6).

Age. In general, age above 75 years is a risk factor for morbidity and mortality in extensive surgery (36). However, in advanced cervical cancer patients, young age is a risk factor for decreased survival. This may reflect an aggressive tumor biology in younger advanced cervical cancer patients (6). An age above 60 years may be considered as a risk factor for an increased perioperative morbidity but seems to have no influence on survival rates after pelvic exenteration (4, 15, 37, 38). In our cohort an age below 63 years was a significant factor with positive influence on survival.

Despite several limitations of our study such as its retrospective nature and the inclusion of several tumor entities, we were able to identify four prognostic factors favoring pelvic

exenteration in advanced pelvic gynecologic malignancies with long-term survivorship. These factors may serve as prerequisites for a safe indication for pelvic exenteration.

Conclusion

The therapeutic potential of pelvic exenteration in advanced pelvic gynecologic malignancies is seen especially in patients under 63 years, whenever it is the primary treatment, in the absence of metastatic disease and whenever clear microscopic margins are accomplished. These four factors may serve as valuable prerequisites for the indication of pelvic exenteration as survival and morbidity in this group of patients compares favorably to alternative therapeutic options.

Conflicts of Interest

The Authors declare that no conflicts of interest exist with regard to the present study.

Authors' Contributions

Study conception: Egger EK, Alexander Mustea. Study design: Egger EK, Alexander Mustea. Data acquisition: Hanna Liesenfeld, Florian Recker, Anna Döser. Quality control of data and algorithms: Dominique Könsgen. Data analysis and interpretation: Dominique Könsgen, Milka Marinova. Statistical analysis: Egger EK, T Hilpert. Manuscript preparation: Egger EK. Manuscript editing: Matthias Stope. Manuscript review: Jörg Ellinger, Milka Marinova, Alexander Mustea.

References

1 Brunschwig A: Complete excision of pelvic viscera for advanced carcinoma; a one-stage abdominoperineal operation with end colostomy and bilateral ureteral implantation into the colon above the colostomy. Cancer *1(2)*: 177-183, 1948. PMID: 18875031. DOI: 10.1002/1097-0142(194807)1:2<177::aid-cncr2820010203>3.0.co;2-a

2 Tewari KS, Sill MW, Monk BJ, Penson RT, Long HJ 3rd, Poveda A, Landrum LM, Leitao MM, Brown J, Reid TJ, Michael HE and Moore DH: Prospective validation of pooled prognostic factors in women with advanced cervical cancer treated with chemotherapy with/without bevacizumab: NRG oncology/GOG study. Clin Cancer Res *21(24)*: 5480-5487, 2015. PMID: 26672085. DOI: 10.1158/1078-0432.CCR-15-1346

3 Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, Leitao MM, Michael HE, DiSaia PJ, Copeland LJ, Creasman WT, Stehman FB, Brady MF, Burger RA, Thigpen JT, Birrer MJ, Waggoner SE, Moore DH, Look KY, Koh WJ and Monk BJ: Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet *390(10103)*: 1654-1663, 2017. PMID: 28756902. DOI: 10.1016/S0140-6736(17)31607-0

4 Marnitz S, Köhler C, Müller M, Behrens K, Hasenbein K and Schneider A: Indications for primary and secondary exenterations in patients with cervical cancer. Gynecol Oncol *103(3)*: 1023-1030, 2006. PMID: 16890276. DOI: 10.1016/j.ygyno.2006.06.027

5 Lin AJ, Dehdashti F, Massad LS, Thaker PH, Powell MA, Mutch DG, Schwarz JK, Markovina S, Siegel BA and Grigsby PW: Long-term outcomes of cervical cancer patients treated with definitive chemoradiation following a complete metabolic response. Clin Oncol (R Coll Radiol) *33(5)*: 300-306, 2021. PMID: 33581976. DOI: 10.1016/j.clon.2021.01.010

6 Schmidt AM, Imesch P, Fink D and Egger H: Indications and long-term clinical outcomes in 282 patients with pelvic exenteration for advanced or recurrent cervical cancer. Gynecol Oncol *125(3)*: 604-609, 2012. PMID: 22406639. DOI: 10.1016/j.ygyno.2012.03.001

7 Chiantera V, Rossi M, De Iaco P, Koehler C, Marnitz S, Gallotta V, Margariti AP, Parazzini F, Scambia G, Schneider A and Vercellino GF: Pelvic exenteration for recurrent endometrial adenocarcinoma: a retrospective multi-institutional study about 21 patients. Int J Gynecol Cancer *24(5)*: 880-884, 2014. PMID: 24685828. DOI: 10.1097/IGC.0000000000000002

8 Jalloul RJ, Nick AM, Munsell MF, Westin SN, Ramirez PT, Frumovitz M and Soliman PT: The influence of surgeon volume on outcomes after pelvic exenteration for a gynecologic cancer. J Gynecol Oncol *29(5)*: e68, 2018. PMID: 30022632. DOI: 10.3802/jgo.2018.29.e68

9 PelvExCollaborative: Pelvic exenteration for advanced nonrectal pelvic malignancy. Ann Surg *270(5)*: 899-905, 2019. PMID: 31634184. DOI: 10.1097/SLA.0000000000003533

10 Moore DH, Ali S, Koh WJ, Michael H, Barnes MN, McCourt CK, Homesley HD and Walker JL: A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. Gynecol Oncol *124(3)*: 529-533, 2012. PMID: 22079361. DOI: 10.1016/j.ygyno.2011.11.003

11 Strong VE, Selby LV, Sovel M, Disa JJ, Hoskins W, Dematteo R, Scardino P and Jaques DP: Development and assessment of Memorial Sloan Kettering Cancer Center's Surgical Secondary Events grading system. Ann Surg Oncol *22(4)*: 1061-1067, 2015. PMID: 25319579. DOI: 10.1245/s10434-014-4141-4

12 Ang C, Bryant A, Barton DP, Pomel C and Naik R: Exenterative surgery for recurrent gynaecological malignancies. Cochrane Database Syst Rev *(2)*: CD010449, 2014. PMID: 24497188. DOI: 10.1002/14651858.CD010449.pub2

13 Chiantera V, Rossi M, De Iaco P, Koehler C, Marnitz S, Fagotti A, Fanfani F, Parazzini F, Schiavina R, Scambia G, Schneider A and Vercellino GF: Morbidity after pelvic exenteration for gynecological malignancies: a retrospective multicentric study of 230 patients. Int J Gynecol Cancer *24(1)*: 156-164, 2014. PMID: 24362721. DOI: 10.1097/IGC.0000000000000011

14 Schmidt AM, Imesch P, Fink D and Egger H: Pelvic exenterations for advanced and recurrent endometrial cancer: clinical outcomes of 40 patients. Int J Gynecol Cancer *26(4)*: 716-721, 2016. PMID: 26937752. DOI: 10.1097/IGC.0000000000000678

15 Chiantera V, Rossi M, De Iaco P, Koehler C, Marnitz S, Ferrandina G, Legge F, Parazzini F, Scambia G, Schneider A and Vercellino GF: Survival after curative pelvic exenteration for primary or recurrent cervical cancer: a retrospective multicentric study of 167 patients. Int J Gynecol Cancer *24(5)*: 916-922, 2014. PMID: 24442006. DOI: 10.1097/IGC.0b013e3182a80aec

16 Moore KN, Gold MA, McMeekin DS and Zorn KK: Vesicovaginal fistula formation in patients with Stage IVA

cervical carcinoma. Gynecol Oncol *106(3)*: 498-501, 2007. PMID: 17561235. DOI: 10.1016/j.ygyno.2007.04.030

17 Kramer C, Peschel RE, Goldberg N, Kohorn EI, Chambers JT, Chambers SK and Schwartz PE: Radiation treatment of FIGO stage IVA carcinoma of the cervix. Gynecol Oncol *32(3)*: 323-326, 1989. PMID: 2920952. DOI: 10.1016/0090-8258(89)90633-1

18 Rose PG, Ali S, Whitney CW, Lanciano R and Stehman FB: Outcome of stage IVA cervical cancer patients with disease limited to the pelvis in the era of chemoradiation: a Gynecologic Oncology Group study. Gynecol Oncol *121(3)*: 542-545, 2011. PMID: 21420157. DOI: 10.1016/j.ygyno.2011.02.024

19 Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC Jr, Clarke-Pearson DL and Liao SY: Randomized comparison of fluorouracil plus cisplatin *versus* hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol *17(5)*: 1339-1348, 1999. PMID: 10334517. DOI: 10.1200/JCO.1999.17.5.1339

20 Green J, Kirwan J, Tierney J, Vale C, Symonds P, Fresco L, Williams C and Collingwood M: Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. Cochrane Database Syst Rev *(3)*: CD002225, 2005. PMID: 16034873. DOI: 10.1002/14651858.CD002225.pub2

21 Biewenga P, Mutsaerts MA, Stalpers LJ, Buist MR, Schilthuis MS and van der Velden J: Can we predict vesicovaginal or rectovaginal fistula formation in patients with stage IVA cervical cancer? Int J Gynecol Cancer *20(3)*: 471-475, 2010. PMID: 20375815. DOI: 10.1111/IGC.0b013e3181d224c8

22 Bae HS, Kim YJ, Lim MC, Seo SS, Park SY, Kang S, Kim SH and Kim JY: Predictors of radiation field failure after definitive chemoradiation in patients with locally advanced cervical cancer. Int J Gynecol Cancer *26(4)*: 737-742, 2016. PMID: 26937749. DOI: 10.1097/IGC.0000000000000662

23 Domingues AP, Mota F, Durão M, Frutuoso C, Amaral N and de Oliveira CF: Neoadjuvant chemotherapy in advanced vulvar cancer. Int J Gynecol Cancer *20(2)*: 294-298, 2010. PMID: 20169671. DOI: 10.1111/igc.0b013e3181c93adc

24 Raspagliesi F, Zanaboni F, Martinelli F, Scasso S, Laufer J and Ditto A: Role of paclitaxel and cisplatin as the neoadjuvant treatment for locally advanced squamous cell carcinoma of the vulva. J Gynecol Oncol *25(1)*: 22-29, 2014. PMID: 24459577. DOI: 10.3802/jgo.2014.25.1.22

25 Lupi G, Raspagliesi F, Zucali R, Fontanelli R, Paladini D, Kenda R and di Re F: Combined preoperative chemoradiotherapy followed by radical surgery in locally advanced vulvar carcinoma. A pilot study. Cancer *77(8)*: 1472-1478, 1996. PMID: 8608531. DOI: 10.1002/(SICI)1097-0142(19960415)77:8<1472::AID-CNCR8>3.0.CO;2-E

26 Landoni F, Maneo A, Zanetta G, Colombo A, Nava S, Placa F, Tancini G and Mangioni C: Concurrent preoperative chemotherapy with 5-fluorouracil and mitomycin C and radiotherapy (FUMIR) followed by limited surgery in locally advanced and recurrent vulvar carcinoma. Gynecol Oncol *61(3)*: 321-327, 1996. PMID: 8641609. DOI: 10.1006/gyno.1996.0150

27 Tans L, Ansink AC, van Rooij PH, Kleijnen C and Mens JW: The role of chemo-radiotherapy in the management of locally advanced carcinoma of the vulva: single institutional experience and review of literature. Am J Clin Oncol *34(1)*: 22-26, 2011. PMID: 20087157. DOI: 10.1097/COC.0b013e3181cae6a1

28 Montana GS, Thomas GM, Moore DH, Saxer A, Mangan CE, Lentz SS and Averette HE: Preoperative chemo-radiation for carcinoma of the vulva with N2/N3 nodes: a gynecologic oncology group study. Int J Radiat Oncol Biol Phys *48(4)*: 1007-1013, 2000. PMID: 11072157. DOI: 10.1016/s0360-3016(00)00762-8

29 Forner DM and Mallmann P: Neoadjuvant and definitive chemotherapy or chemoradiation for stage III and IV vulvar cancer: A pooled Reanalysis. Eur J Obstet Gynecol Reprod Biol *212*: 115-118, 2017. PMID: 28351815. DOI: 10.1016/j.ejogrb.2017.03.030

30 Frank SJ, Jhingran A, Levenback C and Eifel PJ: Definitive radiation therapy for squamous cell carcinoma of the vagina. Int J Radiat Oncol Biol Phys *62(1)*: 138-147, 2005. PMID: 15850914. DOI: 10.1016/j.ijrobp.2004.09.032

31 Höckel M and Dornhöfer N: Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. Lancet Oncol *7(10)*: 837-847, 2006. PMID: 17012046. DOI: 10.1016/S1470-2045(06)70903-2

32 Kaur M, Joniau S, D'Hoore A, Van Calster B, Van Limbergen E, Leunen K, Penninckx F, Van Poppel H, Amant F and Vergote I: Pelvic exenterations for gynecological malignancies: a study of 36 cases. Int J Gynecol Cancer *22(5)*: 889-896, 2012. PMID: 22617477. DOI: 10.1097/IGC.0b013e31824eb8cd

33 Seagle BL, Dayno M, Strohl AE, Graves S, Nieves-Neira W and Shahabi S: Survival after pelvic exenteration for uterine malignancy: A National Cancer Data Base study. Gynecol Oncol *143(3)*: 472-478, 2016. PMID: 27760707. DOI: 10.1016/j.ygyno.2016.10.018

34 Soeda S, Furukawa S, Sato T, Ueda M, Kamo N, Endo Y, Kojima M, Nomura S, Kataoka M, Fujita S, Endo H, Takahashi T, Watanabe T, Yamada H and Fujimori K: Pelvic exenteration as potential cure and symptom relief in advanced and recurrent gynaecological cancer. Anticancer Res *39(10)*: 5631-5637, 2019. PMID: 31570460. DOI: 10.21873/anticanres.13759

35 Evers BM, Townsend CM Jr and Thompson JC: Organ physiology of aging. Surg Clin North Am *74(1)*: 23-39, 1994. PMID: 8108769. DOI: 10.1016/s0039-6109(16)46226-2

36 Saunders N: Pelvic exenteration: by whom and for whom? Lancet *345(8941)*: 5-6, 1995. PMID: 7799711. DOI: 10.1016/s0140-6736(95)91146-4

37 Sharma S, Odunsi K, Driscoll D and Lele S: Pelvic exenterations for gynecological malignancies: twenty-year experience at Roswell Park Cancer Institute. Int J Gynecol Cancer *15(3)*: 475-482, 2005. PMID: 15882172. DOI: 10.1111/j.1525-1438.2005.15311.x

Received March 26, 2021
Revised April 11, 2021
Accepted April 30, 2021