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ORIGINAL ARTICLE

Survival After Pelvic Exenteration for Cervical Cancer

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Abstract

Background The purpose of this work was to identify the results of pelvic exenteration for recurrent, persistent or locally advanced cervical cancer in terms of survival performed for 41 patients in Salah Azaiez Institute.

Patients and Methods We conducted a retrospective unicentric study. The association between PE and OS was estimated using the method of Kaplan–Meier using SPSS ver 24.

Results Median age at the time of intervention was 53.9 years old. FIGO stage IIB was the most frequent (46.3%). Eighteen patients had pelvic exenteration after neoadjuvant treatment. Resection margins were free of tumor in 83.3% of cases. Twenty-three patients underwent pelvic exenteration for recurrence of cervical cancer treated. The median time of recurrence was 23.4 months. Free resection margins were obtained in 69.5% of cases. Postoperative complications were noted in 61% of patients. Two deaths were seen in the early postoperative period. After a median follow-up of 40.5 months, 24.4% of recurrences were noted. Overall survival at 5 years was 51% and recurrence-free survival at one year was 39%. Prognostic factors which impact overall and recurrence-free survival were the size of recurrence and resection margins after exenteration. The time between the end of initial treatment and recurrence was the only predictive factor of recurrence after pelvic exenteration.

Conclusion Pelvic exenteration remains a curative treatment of cervical cancer in certain indications despite high morbidity. A rigorous preoperative selection of candidate may reduce the morbidity and improve the survival of patients.

Keywords Cervical cancer · Locally advanced · Recurrence · Pelvic exenteration · Survival

Introduction

Cervical cancer still represents an important health problem worldwide. It is the fourth leading cause of cancer death in the world [1]. Squamous cell carcinoma is the most common histological type [2].

After positive diagnosis of cervical cancer, this latter must be staged according to the International Federation of Gynecology and Obstetrics (FIGO 2018) classification.

For locally advanced cervical cancer classification as FIGO stage IVA which involves the bladder and/or the rectum, the only therapeutic surgical procedure after neoadjuvant chemoradiation is pelvic exenteration [3].

Although radical surgery and radiotherapy represent effective treatment modalities, up to one-third of patients, all stages combined, will develop progressive or recurrent tumors, the pelvis being the most common site of recurrence [3]. The relapse rate of cervical cancer ranges between 11 and 22% in FIGO stages Ib-IIa and between 28 and 64% in FIGO stages IIb-Iva [3].

For recurrent cervical cancer, repeated radiotherapy for the same anatomical sites is contraindicated and chemotherapy is no longer effective due to a lack of vascularization [4]. The only lifesaving therapeutic weapon remains pelvic exenteration.

In 1948, Brunchwing published the first pelvic exenteration series with high morbidity and mortality [5].

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Pelvic exenteration (PE) is a radical surgical procedure in which pelvic organs are removed. It has made significant progress over the past 20 years with favorable survival outcomes although at cost of high-morbidity rates [6].

In this background, we decided to look into our own experience with pelvic exenteration for locally advanced, persistent or pelvic recurrent cervical cancer.

The aim of this study was to identify the expected results of pelvic exenteration in terms of overall survival and disease-free survival.

Materials and Methods

Type of Study

We carried out a unicentric retrospective and descriptive study of all women who underwent pelvic exenteration for cervical cancer during a period of 18 years between February 2000 and May 2017 in surgical department of Salah Azaiez Institute.

We divided our sample into two groups: pelvic exenteration after neoadjuvant treatment and pelvic exenteration after relapse.

Patient Selection

We included in this study all women who underwent pelvic exenteration with curative intention for locally advanced, persistent or recurrent cervical cancer, performed in our institute. Aborted exenteration due to intraoperative non-operability criteria were excluded. The non-inclusion criteria included: distant metastasis, latero-aortic lymphadenopathy, pelvic exenteration for another gynecologic cancer and palliative exenteration.

Ninety patients were identified through hospital databases and only 41 patients were included and analyzed.

Methods

Data were collected from medical records, histopathology reports, radiotherapy sheets and surgical reports. At the end of this clinical and radiological assessment, patients were classified according to FIGO 2018 staging.

For the group « pelvic exenteration after relapse», we also noted the following data: time between the end of neoadjuvant treatment and initial surgery, type of initial surgery, time between the end of initial treatment and recurrence and site of recurrence.

The treatment regimen was discussed and decided in all patients at the tumor board.

Types of surgeries done were:

- Radical hysterectomy.
- Anterior pelvic exenteration: removal of the entire bladder, uterus and vagina in patients for whom the bladder was invaded.
- Posterior pelvic exenteration: removal of uterus, vagina and the invaded part of the colorectum.
- Total pelvic exenteration: combined the two types of surgery mentioned.

As for the surgical extent relevant to the levator ani muscles, PE procedures were divided into Type I (above the levator ani muscles), type II (within the levator ani muscles) and Type III (below the levator ani muscles).

Recurrent cervical cancer was defined as a recurrence occurring after 6 months of clinical remission following initial treatment.

Persistent cervical cancer occurs within 6 months of the end of the initial treatment.

Overall survival (OS) time was calculated from the date of surgery until the last follow-up or until death.

Disease free survival (DFS) was calculated from the date of surgery to the date of recurrence.

Descriptive statistics are reported as frequencies and percentages or mean and standard deviations.

The association between PE and OS was estimated using the method of Kaplan–Meier and assessed using the log-rank test. Cox proportional hazards analysis was used for multivariate analysis of prognostic factors for overall survival and disease-free survival. The level of significance was defined as $p < 0.05$.

All statistical testing was conducted with SPSS ver.24.0.

Bibliographic research has been carried out from the PubMed and Google Scholar search engines using keywords: cervical cancer, locally advanced, recurrence, surgery, pelvic exenteration, survival.

Our work does not present any conflict of interest.

Results

We reviewed the cases of a total of 41 women who underwent PE between February 2000 and May 2017. Among them, twenty-three women (56.1%) underwent pelvic exenteration after persistent or recurrent cervical cancer. The remaining cases underwent pelvic exenteration after neoadjuvant treatment.

Their median age at diagnosis was 52 years (range, 33–70 years). At the time of pelvic exenteration, their median age was 55 years (range, 32–78 years).

Forty patients presented with symptoms at time of initial cancer diagnosis. The most common symptoms reported were vaginal bleeding (84.4%) followed by pelvic pain (14.6%).

Preoperative gynecological examination under general anesthesia was performed in 33 patients (80.48%).

Pretherapeutic pelvic MRI was practiced in only 12 patients (29.2%) as part of locoregional extension assessment. The mean radiological tumor size was 53 mm.

Cystoscopy was performed in 33 patients (80.48%). It was abnormal with positive biopsy in 4 cases.

Nine patients (21.9%) were evaluated with CT scan and no distant metastases were found.

First Group: Patients Who Underwent PE After Neoadjuvant Treatment

This group is composed of 18 patients diagnosed with cervical cancer for whom neoadjuvant treatment was been indicated. Their initial FIGO stage was IB1 (5.6%), IIA2 (11.1%), IIB (27.8%), IIIB (22.2%), IIIC1 (11.1%) and IVA (22.2%). Squamous cell carcinoma represented the most common histological type (83.3%).

The type of neoadjuvant treatment was radiotherapy (11.1%), radiochemotherapy (66.7%) or radiochemotherapy with brachytherapy (22.2%). Clinical response was absent in 66% of patients and there was a progressed disease in the remaining cases. At the end of neoadjuvant treatment, MRI was performed for only 7 patients (39%) and it showed progression in all cases.

Pelvic exenteration was performed after a median interval of 3.4 months after ending the neoadjuvant treatment. Anterior, total and posterior PE consisted of 77.8%, 16.6% and 5.6% of cases, respectively.

Total exenterations were supralevatorian and posterior exenteration was infralevatorian.

For fecal diversion, 16.6% of patients underwent low colorectal anastomosis with prophylactic colostomy while 5.6% of patients underwent definitive colostomy.

For urinary diversion, Bricker's ileal conduit was performed in 15 cases (88.2%) and ureterocutaneostomy in two cases (11.8%).

Procedures to reconstruct the pelvic floor were performed in one patient with epiplooplasty.

Total colpectomy was performed in 6 patients (33.3%) and pelvic lymphadectomy was performed in 40 cases (94.4%).

The median operation time was 363 (range, 240–420) minutes. The median blood loss was 1500 ml (range, 500–3500). The median postoperative hospital stay was 7.6 days (range, 5–12).

A complete tumor resection with negative margins was achieved in 83.3% of patients. The positivity of the margins was encountered on the circumferential cervical limit and on the anterior vaginal limit. The outcomes of histopathological analysis of the specimen are shown in Table 1.

Patients of this group did not receive any adjuvant treatment.

Second Group: Patient Who Underwent PE After Relapse

This group is composed of 23 patients who underwent initial treatment for cervical cancer and then they underwent pelvic exenteration for persistent or pelvic recurrent tumor.

Their initial FIGO stage was IIB in majority of cases (61%).

Squamous cell carcinoma was the most common histological type in 20 patients (87%).

Three initial treatment components have been described: Neoadjuvant treatment followed by radical hysterectomy was performed for 61% of patients. Non-surgical treatment made of radiotherapy, chemotherapy and/or brachytherapy was performed for 17% of cases while 22% of patients have had radical hysterectomy alone.

For patients with locally advanced cervical cancer, initial treatment was optimal in 6 cases (28.5%) made of radiochemotherapy with brachytherapy followed by radical hysterectomy. Resection margins were positive in two patients and no adjuvant treatment was established.

The remaining cases received non optimal initial treatment. Adjuvant treatment was indicated for three patients, made of brachytherapy and/or radiotherapy.

After primary treatment, 4 patients (17.4%) had persistent disease and 19 patients (82.6%) had locoregional recurrent disease. Median time to relapse was 12 (range, 2144) months.

During the recurrence, only 18 patients were symptomatic with vaginal bleeding as most frequent symptom. Physical examination was abnormal in 16 cases (88.8%).

The recurrence site was the vagina in 52.1% of patients and the pelvis in the remaining cases. The median recurrence size was 32 mm.

Neoadjuvant chemotherapy was performed for 3 patients and all patients of this group had undergone pelvic exenteration. This latter was anterior in 11 cases (47.8%) (Fig. 1) and total in 12 patients (52.2%). It was infralevatorian in 91.6%

Table 1 Outcomes of histopathological analysis of the specimen of the first group

Histopathological factors	Effective
Parameters invasion	44.4%
Lymphovascular space invasion	44.4%
Perineural invasion	55.6%
Bladder invasion	66.7%
Rectum invasion	16.6%
Iliac lymphnodes invasion	1/14

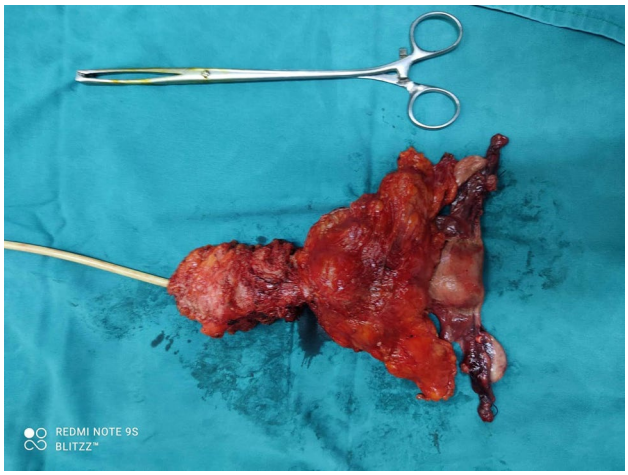

Fig. 1 Specimen of anterior pelvic exenteration with total colpectomy

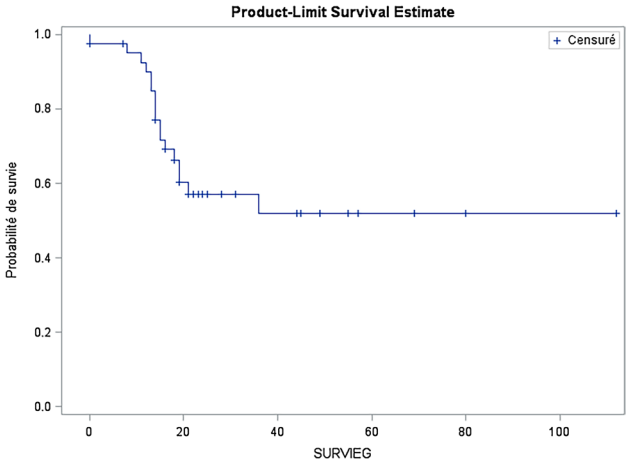

Fig. 2 Overall survival of patients who had pelvic exenteration

Table 2 Outcomes of histopathological analysis of the specimen of the second group

Histologic factors	Effective
Mean tumor size	50.6 mm
Lymphovascular space invasion	26%
Perineural invasion	30%
Bladder invasion	65.2%
Rectum invasion	26%

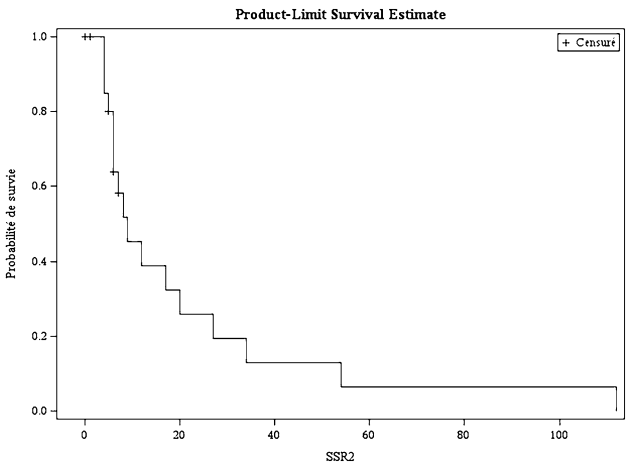

Fig. 3 Disease free survival of patients who had pelvic exenteration

of patients and supralevatorian in the remaining cases. For fecal diversion, definitive colostomy was performed in 11 patients and one patient had coloanal anastomosis protected by colostomy. For urinary diversion, Bricker's ileal conduit was performed in all cases.

Total colpectomy was done in 65.2% of patients and pelvic lymphadenectomy was performed in 21.7% of patients. The remaining cases had undergone pelvic lymphadenectomy during initial surgery.

The median surgery time was 384 (range, 300–540) minutes and the median blood loss was 1700 (range, 500–3000) ml. The median postoperative hospital stay was 11.6 (range, 5–67) days.

Surgical resection margins were free in 69.5% of cases. Outcomes of histopathological analysis are depicted in Table 2.

1. Postoperative morbidity

   The overall morbidity rate was 61% (25 patients among the 41) and reoperation was needed for 32% of patients.
2. Postoperative mortality

   No intraoperative deaths occurred. The overall perioperative mortality was 4.8%.

   The causes of death were pulmonary embolism and heart failure.
3. Survival

The median follow-up time was 40.5 months. Five-year OS was 51% (Fig. 2) and five-year DFS was 11% (Fig. 3).

OS and DFS were analyzed in terms of considerable clinical and histopathological factors and postoperative complications. Univariate analysis showed that recurrence size, resection margin status after initial surgery and resection margin status after PE were significantly associated with OS ($p = 0.03$, 0.001 and 0.03, respectively). In multivariate analysis, recurrence size and resection margin status after PE were the only independent predictive factors affecting OS.

Univariate analysis found that there were many factors impacting DFS (Table 3). Multivariate analysis did not found any factor significantly associated with DFS.

Discussion

In 1948, Alexander Brunschwig introduced pelvic exenteration as a palliative procedure for patients with advanced cervical cancer. At that time, the mortality rates were very high reaching 23% [5]. But now, 60 years after Brunschwig, pelvic exenteration has became the only optimal and curative treatment for selected patients with advanced or recurrent cervical cancer after non-surgical treatment. The mortality has decreased to rates less than 10% and 5-year overall survival was approximated at 60% with tolerable morbidity [3, 7]. After improvement in tools for preoperative assessments as pelvic MRI and PET scan, oncologic surgeons are better equipped to find the most eligible patients who are candidates to pelvic exenteration. In fact, PET scan has been shown to have a sensitivity of 100% and specificity of 73% in diagnosis of metastasis prior to exenteration in patients with recurrent cervical or vaginal cancers [8]. In this study, no patient had an evaluation with PET scan due to lack of means. In addition to the preoperative selection, laparotomy also can assess intraoperative resecability by looking for criteria that do not allow curative surgery with free margins. A discrepancy between the preoperative evaluation and surgical exploration was noted in 40% of cases of cervical cancer submitted to pelvic exenteration. In fact, Hockel et al. reported that 40–60% of exenterations decided were aborted exenterations [9, 10].

Pelvic exenteration remains a heavy intervention burdened with high morbidity. In the series by Marnitz et al., patients had a perioperative morbidity between 33 and 75% especially after total exenteration or exenteration type III or in case of radiotherapy anterior to exenteration [4].

Table 3 Univariate analysis of disease free survival after pelvic exenteration

Factors	«*p*» value
FIGO stage	0.02
LVSI after initial surgery	0.006
Perineural invasion after initial surgery	0.049
Resection margin status after initial surgery	0.03
Recurrence size	0.03
Tumor size after PE	0.04
LVSI after PE	0.004
Bladder invasion	0.0005
Type of drainage	0.01

At our Institute, only 61% of patients presented postoperative complications.

Mortality related to exenteration has fallen in recent years to reach 2.4% in the series of Golda et al. and 5% in the series of Schmidt et al. [11, 12]. These reduced mortality rates were comparable to the rate found in our study which was 4.8%.

In the year 1948, overall survival rates in the pelvic exenteration series did not exceed 20% at 5 years [5]. In recent years, there was a marked improvement in overall survival rates of up to 60% at 5 years [3]. In our study, the rate of 5-year overall survival was 51% with a median survival of 26 months which were within the range reported in the literature.

Prognostic factors impacting overall survival have been analyzed in different series. In fact, age of patients did not influence overall survival in several series of literature [4, 12]. In our study, since most of our patients were young, overall survival was not impacted.

Delay to recurrence after initial treatment impacted overall survival in some series in the literature. The longer the delay, the better the overall survival [4]. On the other hand, this delay to recurrence was not a prognostic factor for overall survival in our series.

Tumor recurrence size up to 5 cm was a poor prognostic factor in terms of overall survival in recent series [3]. In our study, patients with recurrent tumor size less than or equal to 5 cm had an overall survival of 70%. As soon as the size of recurrent tumor exceeds 5 cm, overall survival drops to 37%.

It has been shown that LVSI was an independent prognostic factor which negatively impact overall survival. This factor was not significantly associated to overall survival in our study.

Most authors in the literature have concluded that surgical resection margins were a significant and independent prognostic factor in terms of overall survival [3, 4, 13]. This was similar to our results where overall survival was 60% in the case of free margins while it was 25% in case of invaded margins.

Some series in the literature have studied prognostic factors associated with disease free survival like Sardain et al. who reported that a tumor recurrence size of more than 5 cm and LVSI after exenteration negatively impacted disease-free survival [3]. Westin et al. have shown that lymph node invasion and surgical margins invaded after exenteration were factors of poor prognosis in terms of disease-free survival [14]. These results were comparable to those in our series where tumor recurrence size, LVSI and surgical resection margins were significantly associated with disease-free survival. By the other hand, lymph node invasion did not impact disease-free survival.

In our study, we found also other factors impacting disease-free survival like FIGO stage, LVSI and perineural invasion after initial surgery.

Conclusion

The 5-year survival found in our study is concordant with international series. This study shows that the role of pelvic exenteration in locally advanced, persistent or recurrent cervical cancer is invaluable which is the only curative hope in selected patients. Prospective studies should be done to confirm our results.

Declaration

Conflict of interest The authors declare that they have no conflict of interest.

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About the Author

Imen Bouraoui The first author was a medical student that finish his general medical cursus and then she was specialized in oncologic surgery. She spent five years in the department of oncologic surgery, she assisted in several operations as an observator or operating assistant and she made many operations especially in breast cancer. She is preparing to pass her final exam this year.