

An analysis of outcomes of patients with locally advanced cervical cancer treated by emergency hysterectomy due to vaginal hemorrhage followed by chemoradiation and surgery in cases of locally advanced cervical cancer

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Objectives: The standard treatment for patients with locally advanced cervical cancer (LACC) consists of chemoradiation followed by vaginal brachytherapy. However, many patients with LACC undergo hysterectomy while receiving comprehensive cancer treatment. The aim of the present study was to analyze the survival data of those patients who underwent hysterectomy due to vaginal bleeding or hemorrhage prior to definitive chemoradiation. **Materials and methods:** The study group included 35 patients with stage IIB (according to the FIGO classification) cervical cancer who received chemoradiation following emergency hysterectomy performed due to severe bleeding. The control group consisted of 44 patients with stage IIB cervical cancer treated with primary chemoradiation without completion hysterectomy. We compared the rates of treatment toxicity and overall survival. **Results:** We did not observe an inferior survival probability among patients treated with hysterectomy prior to receiving chemoradiation compared to those treated with chemoradiation alone ($P = 0.77$). The 5-year survival probability of patients treated with initial surgery was 62%, compared to 61% for those treated with primary chemoradiation. Six (17%) patients from the group treated with hysterectomy experienced severe adverse events. The application of radiation therapy after hysterectomy was associated with a higher rate of early gastrointestinal toxicity compared to the rate found in patients treated with chemoradiation alone. **Conclusion:** Hysterectomy performed due to vaginal hemorrhage prior to chemoradiation in patients with stage IIB cervical cancer is not associated with an inferior probability of survival. However, this treatment approach is associated with a higher rate of toxicity when compared to patients with stage IIB cervical cancer treated only with chemoradiation.

Keywords

Cervical carcinoma; Locally advanced cervical cancer; Radical hysterectomy; Chemoradiation

1. Introduction

Locally advanced cervical cancer (LACC) is usually defined as stage IB3-IVA disease according to the International Federation of Gynecology and Obstetrics (FIGO) classification from 2018 [1, 2]. During the 1990s, chemoradiation therapy (CRT) was widely accepted as the standard treatment for women with LACC. Among the patients in this group, treatment consisting of surgery followed by CRT resulted in higher rates of severe adverse events with no improvement in survival compared to the rates of patients treated with CRT alone. Consequently, this type of surgical treatment is no longer recommended [1] for patients with LACC.

However, although international guidelines and studies have shown that the surgery has limited benefit for LACC patients, many of these women still require hysterectomy. Wu *et al.* [3] studied a large group consisting of 2473 patients with stages IIB-III cervical cancer, 542 (21.9%) of whom underwent an additional hysterectomy. Of these patients, some required hysterectomy before CRT and others after CRT. Hysterectomy performed after CRT is referred to as completion hysterectomy. In 2012, a randomized study entitled GYNECO 02 was conducted to determine whether additional hysterectomies prolonged survival in LACC patients treated with primary CRT and thereby to resolve the controversy. However, since the total number of patients enrolled in the

study proved insufficient, it was prematurely shut down [4]. Nevertheless, by analyzing the 3-year survival rate in the 61 patients who were enrolled, Morice *et al.* [4] demonstrated that completion hysterectomy had no impact on either overall survival (OS) or disease-free survival (DFS) in patients with a complete response after radiotherapy. Other authors presented similar results, even when they included an analysis of minimally invasive surgery [5–7]. Moreover, if a patient has an incomplete response to CRT, the preferred treatment is still completion hysterectomy to remove radioresistant tumors.

Hysterectomy may also be performed on LACC patients after neoadjuvant chemotherapy. In fact, the National Comprehensive Cancer Network guidelines for the treatment of women with cervical cancer recommend neoadjuvant chemotherapy followed by hysterectomy for patients with stages IIB–IVA disease when beam radiation and/or brachytherapy are unavailable [8].

Other groups of LACC patients who may require hysterectomy include those who cannot receive radical CRT as well as those who present with severe hemorrhage, have large fibroids or an additional ovarian tumor, or have contraindications for radiotherapy. In the study of 2473 LACC patients conducted by Wu *et al.* [3], 420 patients underwent hysterectomy before receiving radiotherapy. However, in clinical practice it is rare for a patient to undergo hysterectomy prior to radiation. Furthermore, in most cases, the surgical intervention is unplanned and performed only when there are acute indications, such as hemorrhage. Consequently, few studies have focused on long-term outcomes in a LACC patient group treated with hysterectomy before the start of chemoradiation due to palliative indications. Thus in our study we aimed to analyze the survival rates of a selected group of patients who underwent hysterectomy due to vaginal bleeding prior to chemoradiation.

2. Methods

A retrospective and comparative longitudinal observational study was conducted on a group consisting of 35 patients with LACC (stage IIB, according to the International Federation of Gynecology and Obstetrics (FIGO) classification from 2009) who received chemoradiation following salvage hysterectomy between February 2008 and September 2014 in the Clinical Department of Gynecological Oncology of the Franciszek Łukaszczyk Oncological Center in Bydgoszcz, Poland. The group included patients who were initially diagnosed with LACC and referred for primary chemoradiation with brachytherapy (CRT and BT) but later required primary surgical treatment due to hemorrhage. Generally, we qualified patients to surgical management when severe bleeding hampered the application of radical CRT and BT. Such an assessment was based on the personal clinical experience of well-established gynecological and radiation oncologists. We did not use any objective criteria, and the only inclusion criteria for undergoing hys-

terectomy was severe bleeding that prevented the application of radical CRT or BT. Prior to surgery, we routinely applied pharmacological management (tranexamic acid and etamsylate) and/or vaginal packing, and if hemorrhage was still present, the patient was qualified for hysterectomy. In all cases, the operation was performed due to emergency indications. Furthermore, in our institution physicians cannot perform uterine artery embolization, so surgery was the only option for stopping the bleeding.

We performed both bilateral adnexectomy and radical abdominal hysterectomy on this group of LACC patients with the intention of removing the tumor with clear margins. Generally, we performed C2 radical hysterectomy according to the Querleu-Morrow classification [9]. This group was compared with a stage-, age-, and performance-matched control group of 45 cervical cancer patients treated with CRT and BT alone during that same time period. Of those patients who received only CRT and BT, 12 were treated in the Clinical Department of Gynecological Oncology of the Franciszek Łukaszczyk Oncological Center in Bydgoszcz, Poland, and 32 in the Department of Radiotherapy and Gynecological Oncology of the Greater Poland Cancer Center in Poznan, Poland.

Prior to treatment, patients from both groups were staged based on clinical examination and magnetic resonance imaging results and in accordance with the classification of the International Federation of Gynecology and Obstetrics. Patients from both the study and the control groups also received radical CRT and BT. Initially, therapy consisted of pelvic conformal external beam radiotherapy (EBRT), delivering 45–50.4 in 25–28 fractions of 1.8 Gy over 5 weeks. Concurrently, we administered intravenous cisplatin (40 mg/m²) once a week for 5 cycles. For patients in the study group, CRT was begun 4 to 6 weeks after the surgery. Chemoradiation was followed by high-dose rate (HDR) BT consisting of 25 to 35 Gy in 2 or 3 fractions. In cases where patients were treated with primary CRT, the CRT was followed by vaginal BT consisting of HDR (30 to 40 Gy in 3 or 4 fractions) or low-dose rate (LDR; with median dose of 55 Gy in 1 or 2 fractions). BT was administered in the 2nd or 3rd week after chemoradiation. In both groups we evaluated early radiation-related toxicity from the lower gastrointestinal and genitourinary tracts. The radiation-related toxicity was assessed using the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for the Research and Treatment of Cancer (EORTC).

Information on any patients who died was retrieved from the database of the regional office of the National Health System of Poland. Survival analyses were conducted using Kaplan-Meier survival curves. Patient survival was tracked with respect to both 5-year overall survival and median overall survival (mOS), as well as inter-quartile range (IQR), and was shown to correspond to the 25th–75th percentile. A statistical analysis was conducted using MedCalc 11.4.2.0 software.

Table 1. Clinical and demographic characteristics of patients with stage IIB cervical cancer treated with primary hysterectomy following by chemoradiation (CRT) and brachytherapy (BT) and of patients treated with primary CRT and BT.

	Stage IIB cervical cancer patient treated with radical hysterectomy before CRT and BT	Stage IIB cervical cancer patients treated with primary CRT and BT	P-value
	N = 35	N = 44	
Age, years			
Median (range)	54 (33–72)	52 (31–70)	0.22
Histopathological type of cervical cancer			
Squamous cell carcinoma	34 (97%)	44 (98%)	1.00
Cervical adenocarcinomas	1 (3%)	1 (2%)	
Tumor grade			
G1	0 (0%)	4 (9%)	0.08
G2	22 (63%)	31 (70%)	
G3	13 (37%)	9 (21%)	
Performance status according to the World Health Organization (WHO) classification			
Grade 0	32 (91%)	40 (91%)	1.00
Grade 1	3 (9%)	4 (9%)	

CRT, chemoradiation; BT, brachytherapy.

This retrospective chart review study involving human participants was carried out in accordance with the ethical standards of the institutional and national research committee, as well as with the 1975 Helsinki Declaration and its later amendments, or with comparable ethical standards. The study also received the approval of the Centre of Postgraduate Medical Education Ethical Committee (7/PB/2020).

3. Results

We found no differences between the study and the control groups when it came to patient age, the histopathological type of cervical cancer, tumor grade, and performance status. Table 1 presents the clinical and demographic characteristics of the patients in both groups.

The median patient follow-up period was 100 months (IQR: 89–108 months). We observed no significant differences in overall survival rates when we compared the LACC patients treated initially with surgery and followed by CRT and BT to the patients treated with primary CRT and BT ($P = 0.77$) without completion hysterectomy. The indication for initial surgery was related to clinical LACC symptoms, such as vaginal bleeding or hemorrhage. The 5-year survival rate of the patients treated with initial surgery was 62% compared to 61% for those treated with primary chemoradiation. Among those patients treated with primary surgery, the mOS was not achieved (IQR: 22.42–94.06 months). Similarly, the mOS was not reached (IQR: 22.03–110.10 months) in the group of patients treated with CRT and BT alone (Fig. 1).

Among the 35 patients who were treated surgically, 6 (17%) experienced severe adverse events, the most common type (4 patients or 11%) being severe wound infection. However, one patient was diagnosed with ureter damage, including uretero-vaginal fistula, and required repeat surgery with a uretero-cysto-neostomy (3%). Another patient required postoperative exenteration (3%). Six (13%) patients needed

blood transfusions, but there were no surgery-related deaths (defined as death occurring before the 30th postoperative day). A significantly higher rate of early gastrointestinal toxicity was observed in the group of patients treated with hysterectomy and adjuvant CRT compared to the group treated with CRT alone. However, the early genitourinary toxicity rates were similar in the two groups (Table 2). There were no treatment-related deaths in either group.

4. Discussion

In Europe and the United States, most LACC cases are managed with CRT followed by BT. In cases where the patient's cancer extends beyond the cervix, surgery should be avoided as it offers no clear survival benefit and carries a high risk of adverse events. Nevertheless, for patients suffering from LACC, surgery can play an important role in selected clinical situations. For example, Wu *et al.* [3] showed that more than one fifth of women with LACC underwent hysterectomy during cancer management. In a recent prospective trial, about 3% of patients with LACC designated for primary chemoradiation required additional surgical treatment [10]. In their analysis of the SEER database, Wu *et al.* [3] reported an improved survival rate for LACC patients who had a hysterectomy compared to those who did not receive such surgical treatment. The majority of the studies concern cases where hysterectomy is performed after either radiotherapy (as a completion surgery) or neoadjuvant chemotherapy. In our study, we evaluated those LACC patients who had salvage hysterectomy prior to radiotherapy. The hysterectomy was performed as an unplanned surgery due to severe bleeding. Finally, we observed no difference in survival rates for these patients compared to the stage-matched controls who were treated with CRT and BT alone. Moreover, in the literature we found only sparse data on salvage hysterectomy performed on LACC patients due to severe bleeding. Con-

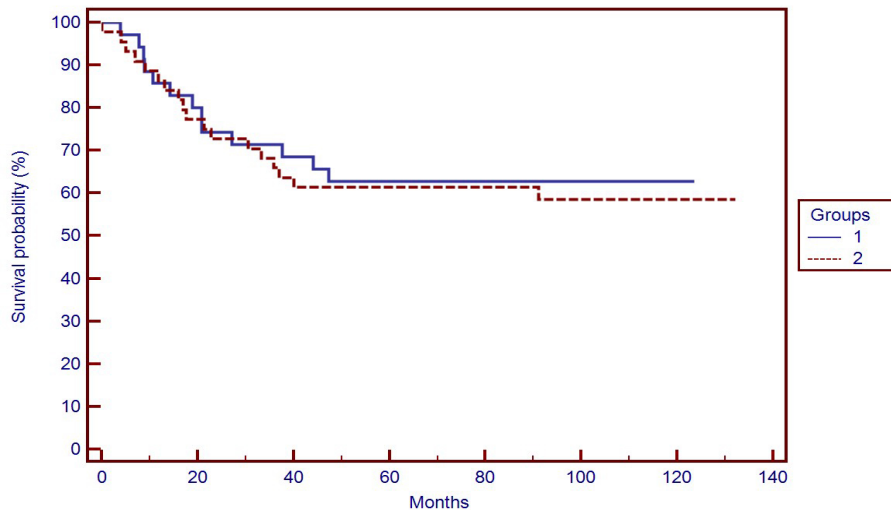


Fig. 1. Survival analyses of locally advanced cervical cancer patients treated with primary surgery and primary chemoradiation. Group 1: stage IIB cervical cancer patients (N = 35) treated with primary surgery followed by chemoradiation with brachytherapy (CRT and BT), median overall survival (mOS) not reached (IQR: 22.42 to 94.06 months, 5-year overall survival = 62%). Group 2: stage IIB cervical cancer patient (N = 45) treated with CRT and BT alone, mOS not reached (IQR: 22.03–110.10 months, 5-year overall survival = 61%). $P = 0.77$. IQR, inter quartile range (IQR), corresponds to 25th–75th percentiles.

sequently, our results can be compared only with the results of studies where patients had surgery combined with either radiotherapy or chemotherapy. For instance, in their study, Sakuragi *et al.* [11] presented data from 27 patients with stage IIB cervical cancer who underwent Okabayashi-Kobayashi radical hysterectomy. The authors included only patients with one-side parametrial invasion. Most of the patients who participated received adjuvant chemotherapy but only a few received radiotherapy [11]. The 5-year overall survival rate was 78%, and local recurrence was observed in 14.8% of patients. In our study, we observed a 5-year survival rate of 62% for LACC patients treated with initial surgery. However, all our patients received adjuvant CRT. Additionally, we included patients with both-side parametrial invasion, and any patients suffering severe hemorrhage were treated surgically. In their research, Hockel *et al.* [12] were credited with developing extended mesometrial resection (EMMR) for those patients with locally advanced cervical cancer FIGO stages IIB and IIIA without preoperative tumor involvement of the bladder or urethra. In a study conducted by Wolf *et al.* [12], the authors described 48 cervical cancer patients with LACC who underwent EMMR, including 41 who were stage IIB. The patients were treated with adjuvant chemotherapy when two or more lymph node metastases were present. No adjuvant radiotherapy was applied. The 5-year overall survival rate was 62.6%, and the 5-year recurrence-free survival rate was 54.1%. In their study, Ho *et al.* [13] reported a 58.5% 5-year recurrence-free survival rate for IIB LACC patients who were treated with surgery upfront. In a different study, Xia *et al.* observed similar survival rates for LACC patients treated with surgery prior to CRT. Finally, in one of the most recent trials, Martnitz *et al.* [14] demonstrated that stage IIB cervi-

cal cancer patients may benefit from the surgical staging of lymph nodes prior to chemoradiation. In summary, these results suggest that, for selected patients, hysterectomy as a first line of management for stage IIB cervical cancer is not associated with a poorer prognosis and some patients may even reap benefit from the surgery.

Sometimes vaginal bleeding or hemorrhage can interfere with the start of chemoradiation or exclusive radical radiotherapy, which means that such patients will receive lower doses of radiotherapy or brachytherapy as a palliative treatment. In these cases, performing a hysterectomy before beginning cancer treatment allows the patient to receive the full dose of radiation. Such surgery can also help to remove chemo- and radioresistant tumor lesions. However, the application of this type of surgery is associated not only with an increased risk of side effects, but with further impairment of patient quality of life as the radiation-induced tissue fibrosis [3]. Overall, the best rationale against treating a LACC patient with hysterectomy is that it precludes possible adverse events from a surgical intervention not associated with improved patient survival. In our study, 17% of patients who had hysterectomies experienced severe adverse events. In the study conducted by Wolf *et al.* [12], which included women treated with EMMR, 60% of patients experienced postoperative complications. Grade 2–3 complications were reported in 25% and 15% of patients, respectively. Duenas-Gonzales *et al.* [15] conducted a phase II study comparing the effects of neoadjuvant chemotherapy followed by radical hysterectomy with the effects of adjuvant chemoradiation alone in LACC patients. The authors did not observe a greater number of major surgical complications in the group of patients who underwent completion hysterectomy. By

Table 2. Early lower gastrointestinal and genitourinary radiation-related toxicity in stage IIB cervical cancer patients treated with salvage hysterectomy due to hemorrhage followed by chemoradiation (CRT) and brachytherapy (BT) and patients treated with primary CRT and BT.

Grade	Radical hysterectomy and adjuvant chemoradiation and brachytherapy	Chemoradiation with brachytherapy	P-value
	N = 35 (%)	N = 44 (%)	
Genitourinary tract			
No toxicity	20 (57%)	34 (77%)	P = 0.07
1	9 (26%)	4 (9%)	
2	5 (14%)	4 (9%)	
3	0 (0%)	2 (5%)	
4	1 (3%)	0 (0%)	
Lower gastrointestinal tract			
No toxicity	9 (26%)	27 (61%)	P < 0.01
1	20 (57%)	7 (16%)	
2	2 (6%)	2 (5%)	
3	3 (8%)	8 (18%)	
4	1 (3%)	0 (0%)	

The radiation related toxicity was assessed using the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for the Research and Treatment of Cancer (EORTC). The *P*-value was calculated using Fisher's exact test with Freeman-Halton extension for 3 × 2 table; for the statistical purposes, grades 1 and 2, as well as grades 3 and 4, were merged into one subgroup.

contrast, Mazon *et al.* [16] found that post-radiation hysterectomy is linked to a significant increase in the incidence of late, severe urinary and gastro-intestinal morbidity. Furthermore, in a group of 150 FIGO stage III cervical cancer patients (subdivided according to whether they received CRT alone or neo-adjuvant CRT followed by radical surgery), Fanfani *et al.* [17] noted that the number of early, treatment-related complications, such as urinary and gastrointestinal complications, was lower in the patients who had adjuvant surgery compared to those treated with CRT alone. In these patients, most of the reported complications were grade 1–2, whereas grade 3 urinary and gastrointestinal morbidity made up 3.9% of all treatment-related complications, and grade 4 with 14.3%. Overall, the authors observed no significant differences in grade 3–4 toxicity between the group that received adjuvant surgery and the group that did not [17]. In our study, we observed a moderate rate of severe adverse events in the group of patients treated with hysterectomy prior to CRT. Nevertheless, the overall incidence of adverse events reported in our study was high, with the most common type being wound infection. Furthermore, any patient with immediate indications for surgery due to severe bleeding was treated, and the cervical tumor was locally advanced. Consequently, our results cannot be compared to the results of other studies where patients were treated with hysterectomy only after neoadjuvant chemotherapy or primary CRT. We also observed that patients treated with hysterectomy were more prone to gastrointestinal toxicity associated with adjuvant radiation compared to patients treated with primary CRT alone. However, in most cases, we observed grade 1 toxicity which is easily managed through a conservative approach.

The main advantage of our study is that it focuses on the performance of emergency hysterectomy due to hemorrhage

in LACC patients. This situation is rare in clinical practice and the data on it in the literature is sparse. Our study also had limitations, mainly, the small number of subjects and being retrospective. These limitations are, in turn, related to the overall low incidence of uncontrolled bleeding among the LACC patients. Furthermore, the emergent nature of the situation hampered prospective trial planning. Due to the above stated limitations the results of our study should be interpreted cautiously.

5. Conclusions

The results of our study combined with a review of the literature suggest that hysterectomy due to vaginal bleeding or hemorrhage in LACC patients and performed prior to chemoradiation is not associated with inferior patient survival rates. However, this type of surgical treatment is associated with a higher rate of toxicity.

Author contributions

Study concept and design: LW, AL, SS; Data acquisition: AL, SS, KK, MC, GC, JT, ZWF; Data analysis and interpretation: LW, AR, JT, MC; Statistical analysis: SS, KK, GP; Manuscript preparation: LW, AL, AR, ZWF, GC; Correspondence: LW. All authors have read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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