# Radical Hysterectomy in Patients with Locally Advanced Cervical Cancer: Would it be an Option in Centers Lacking Brachytherapy Technique?

Saadeldin I[1], Zawam H[1], IbrahimA[1], Hashem W[1]

[1] Department of Clinical Oncology, Kasr Al-Ainy School of Medicine, Cairo University, Egypt

## Abstract:

**Background:** Locally advanced cervical cancer patients' treatment depends optimally on multimodality options, which could be very challenging, due to the lack of intracavitary brachytherapy in many centers. Although non-surgical option is very appealing, yet it is not always available. An alternative non-standard approach is neo-adjuvant concurrent chemo-radiotherapy (CCRT) followed by radical hysterectomy.

**Patients and methods:** A retrospective study involving patients with pathologically proven cervical cancer, FIGO stages IB2 till IVA who presented to Clinical Oncology Department, Cairo University, during the period from January 2015 till December 2020. Data was retrieved from our medical records. Patients were divided into 2 arms; (Arm A: 40 patients) included patients treated with neoadjuvant CCRT, followed by radical hysterectomy and (Arm B: 41 patients) included those who received the standard of care; CCRT followed by intracavitary brachytherapy.

**Results**: The loco-regional control rate was 75% in arm A, compared to 85.3%in arm B, with non-significant P-value (p=0.24). However, relapse rates were significantly higher in arm A (47.5%) than in arm B (14.5%) (p= 0.007). Moreover, distant metastases were higher in arm A (22.5%) than in arm B (4.9%) with a statistically significant P-value = 0.025.

There was no significant difference between the two groups as regards survival data (PFS and OS). However, concerning the toxicity profile, both arms experienced comparable toxicity profile pattern after CCRT; Yet dysuria was the most common early and late toxicity after intracavitary brachytherapy (arm B) presenting 39% and 29.7% respectively.

**Conclusion**: Offering surgery as an alternative approach to intracavitary brachytherapy is an acceptable option, in centers lacking brachytherapy technique, without compromising survival outcome.

**Received:** 20 November 2023
**Accepted:** 31 December 2023

**Authors Information:**
*Ibtessam Mohamed Saadeldin*
Department of Clinical Oncology, Kasr Al-Ainy School of Medicine, Cairo University, Egypt
email: ibtessamsaad@yahoo.com

*Hossam Hamdy Zawam*
Department of Clinical Oncology, Kasr Al-Ainy School of Medicine, Cairo University, Egypt
email: Dr.hus83@gmail.com

*Amal Tarek Hussein*
Department of Clinical Oncology, Kasr Al-Ainy School of Medicine, Cairo University, Egypt
email: Dr.Amal.tarek@gmail.com

*Wedad M. Bassam Hashem*
Department of Clinical Oncology, Kasr Al-Ainy School of Medicine, Cairo University, Egypt
email: weedo_82@hotmail.com

**Corresponding Author:**
*Wedad M. Bassam Hashem*
Department of Clinical Oncology, Kasr Al-Ainy School of Medicine, Cairo University, Egypt
email: weedo_82@hotmail.com

## Background:

Cervical cancer ranks fourth in terms of incidence among cancers in women worldwide, after lung, colorectal, and breast cancer. According to GLOBOCAN 2020 estimates, there were about 604 000 new cases of cervical cancer worldwide each year, along with 342 000 fatalities. Low- and middle-income countries (LMICs) account for the majority of new cases and deaths (about 85% and 90%, respectively) [1].

The two main methods of managing cervical cancer are radiation therapy or surgery combined with concurrent chemotherapy (CCRT). Surgery is the cornerstone in the early stages of cervical cancer, depending on the stage. Pelvic exenteration has a role in stage IVA disease [2].

The recommended course of treatment for patients with locally advanced cervical cancer is definitive concurrent chemo-radiation. By combining EBRT with brachytherapy, also known as intracavitary radiotherapy (ICRT), the risk of treatment complications is reduced and loco-regional control is maximized [2].

Thus, our aim of work was to investigate the loco-regional control rate & survival data in patients with locally advanced cervical cancer treated with neo-adjuvant chemotherapy, radiotherapy or both, followed by radical hysterectomy, versus those who received CCRT followed by intracavitary brachytherapy.

## Patients and Methods:

*Study design:*

- This is a retrospective study involving patients with pathologically proven cervical cancer, locally advanced disease including FIGO stage IB2 till stage IVA who presented to Kasr Al-Ainy, Clinical oncology and radiotherapy department, Cairo University during the period from January 2015 to December 2020.
- Data was retrieved from patients' medical records including patients' age, residency, initial symptoms, pathological subtype, histopathological grade, FIGO stage, date of diagnosis, details of management including surgery, chemotherapy and radiation therapy, follow-up details, patterns of failure and patient survival status at last follow up.
- Cervical carcinoma constituted 203 cases cancer patients presented at NEMROCK during the study period from January 2015 till December 2020.

*Patient population:*

Female patients with pathologically proven locally advanced cervical cancer including FIGO stage IB2 till stage IVA.

According to the retrospective study' arms, we included the patients with these criteria:

- Pathologically proven cervical cancer patients
- Stage IB2-Stage IVA according to FIGO classification 2009
- No other primary malignancies
- Patient had Eastern Cooperative Oncology Group performance status of 0 to 2
- No evidence of distant metastasis

There were some patients who were not in our study arms that were excluded from our study as:

- Metastatic disease
- Incomplete patient data
- Presence of other primary malignancy

The patients were divided into two arms:

Arm A: Female patients with locally advanced cervical cancer who received concurrent chemo-radiotherapy, followed by radical surgery.

Arm B: Female patients with locally advanced cervical cancer who received the standard of care; concurrent chemo-radiotherapy followed by intra-cavitary brachytherapy.

*Data Collection:*

A data collection excel sheet was designed to register all eligible patients' epidemiological, clinic-pathological, treatment, and survival data.

The main data categories extracted from each evaluable record were:

- Epidemiological data including age, geographical area, HPV status
- Clinico-pathological data including clinical presentation, clinical examination, TNM staging, Pathology results, tumor grade, parametrial invasion, lymph node invasion.
- All Treatment Modalities received by the patient including, neoadjuvant treatment with assessment of response
- Neoadjuvant chemotherapy (date, dose, type, number of cycles, toxicity profile and interruptions)
- Radiotherapy details (dose, number of sessions, duration, toxicity)
- Surgical details (date, pathology, grade, parametrium invasion, lymph node invasion)
- Brachytherapy details (dose, number of sessions, duration, toxicity).
- Relapse/metastatic data including site of relapse, date of relapse, loco-regional recurrence or distant metastasis.
- Survival outcome including progression free survival (PFS) and overall survival (OS).
- Toxicity Profile,

Toxicity pattern was reviewed / graded based on Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.0) published May 28, 2009 (Cancer Institute, 2009):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

*Study Outcome:*

- Primary outcomes:

- To identify the loco-regional recurrence control rate; it was evaluated by calculating time from starting treatment till any recurrence in pelvis as cervical recurrence or urinary bladder.

- Secondary outcome parameters:

- To identify the progression free survival; from the date of starting the chemo-radiotherapy to the date of progression or relapse or death from any cause.

- To detect the toxicity profile and morbidity.

- To detect overall survival rate; It was defined as calculation evaluating time from date of diagnosis till date of death or last date of follow up.

*Statistical Analysis:*

The information collected was processed, digitized and managed in databases in Excel files (Microsoft Office) and final formal statistical analysis was performed in which descriptive results for categorical variables was presented by rate and odds ratio and for numerical variables by measures of central tendency and dispersion. Finally, comparative analysis between

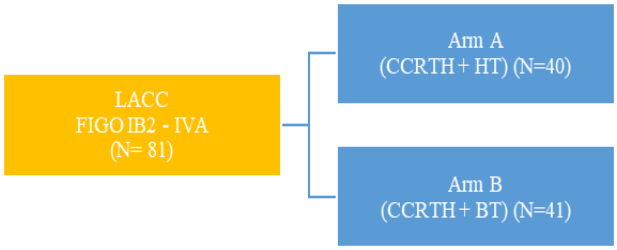
categorical variables was performed by Chi-square test and for numerical variables by student t-test. Survival analysis was performed by Kaplan-Meier method [3].

*Ethical consideration:*

The study has been approved by the research ethics committee of Cairo university school of medicine and the scientific research committee of Cairo university department of oncology and nuclear medicine in August 18, 2021.

## Results:

The patients' data was retrieved from archiving medical records of Kasr Al-Ainy clinical oncology department, from January 2015 to December 2020. Patients should have locally advanced pathologically proven cervical cancer, with FIGO stage IB2- IVA. The total number of patients was 203 patients and after exclusion of patients who are not eligible for our comparative study, as those who are metastatic, or those with a very early stage (IA1, IA2, IB1), the total number included was 81 eligible patients.




The Patients were divided into two arms.

Arm A (CCRTH+ HT) included patients who received external beam concurrent chemo-radiotherapy, followed by surgery (N=40),

and Arm B (CCRTH+ BT) which included patients who received concurrent chemo-radiotherapy followed by intracavitary brachytherapy (N=41).

*Descriptive data analysis:*

Patients' characteristics:

The age of patients included in the study ranged between from 33 years to 76 years with median value 56 year. The most common initial presentation of our cohort of patients was vaginal bleeding 77% of patients, followed by postcoital bleeding in 12%, whereas vaginal discharge accounted for 11% of patients.

Sixty-nine patients (85.2%) had squamous carcinoma, followed by adenocarcinoma in 11 patients (13.5%), and only one case with leiomyosarcoma representing 1.2%. Pathological grade was assessed according to cells differentiation into well (Grade 1), moderate (Grade 2) and poorly differentiated (Grade 3) tumor cells. Grade 2 represented 62.9%, and Grade 3 was in 37% of cases.

The patients included in our study were locally advanced cervical tumors staged by FIGO staging system from stage IB2 till stage IVA, the most common stage among the patients was stage IIB in 26 patients (32.1%) and the second most common was stage IIIC1 in 16 patients (19.8%), followed by stage IB2 and IIA representing 16%. It was noticed that stage IVA accounted for 3.7%.

Management Data:

a) Lines of Treatment:

There were two lines of treatment received; arm A included patients who received CCRTH followed by surgery (40 patients), while arm B included patients who received CCRTH then intracavitary brachytherapy (41 patients).

Radiation Treatment:

Radiation treatment data analysis included external beam radiation therapy (EBRT) and intracavitary radiation therapy (ICRT).

EBRT: This includes patients who received full course of radiation therapy with chemotherapy (n= 81). The most common dose regimen used in those patients was 45 Gy over 25 fractions in 5 weeks of treatment in 84% of cases; the second most common dose regimen used was 50 Gy over 25 fractions in 5 weeks of treatment representing 14% of patients. (Table 1)

ICBT: Patients who received ICRT were 41 patients (50.6%) and were included in arm B, with different dosage regimens, the most common dose used was 700cGy/fraction over 3 fractions in two weeks period in 34% of cases, then followed by 800cGy/fraction over 3 fractions in 2 weeks period in 27% of cases. (Table 1).

Table 1: Treatment received data.

| **EBRT dose** | **Total** |
|---|---|
| 45 Gy/25 Fr | 68 (84%) |
| 50 Gy/25 Fr | 11 (13.6%) |
| 50.4 Gy/28 Fr | 2 (2.47%) |
| **Brachytherapy dose** | **Total** |
| 7 Gy/2 Fr | 5 (12.2%) |
| 8 Gy/2 Fr | 4 (9.8%) |
| 6 Gy/3 Fr | 7 (17.1%) |
| 7 Gy/3 Fr | 14 (34.1%) |
| 8 Gy/3 Fr | 11 (26.8%) |
| **NACT regimens** | **Total** |
| Carboplatin/ Paclitaxel | 10 (52.6%) |
| Cisplatin / Paclitaxel | 6 (31.6%) |
| Carboplatin / Gemcitabine | 3 (15.8%) |

**Note:** (Total number of EBRT=81, total number of Brachytherapy=41, total number of NACT regimens=19)

Chemotherapy:

Nineteen patients received neo-adjuvant chemotherapy (23.5%). Several regimens were received; the most common regimen was 3 cycles Paclitaxel-Carboplatin in 52.6% of the cases and 6 patients (31.5%) received 3 cycles Paclitaxel-Cisplatin (Table 1).

All of the 81 patients (100%) received CCRTH. The used regimen was weekly Platinum-based chemotherapy only. Weekly Cisplatin was used in most of the cases (97%) in a dose of 40mg/m2. The remaining 3% received weekly Carboplatin (AUC2). Chemotherapy cycles were given weekly with total number of cycles from five to six weeks. The chemotherapy received without interruptions.

Surgery:

Arm A included patients who received CCRTH followed by surgery (CCRTH + HT).

Types of Surgery: Most of the patients (38 patients [95%]) underwent total abdominal hysterectomy with bilateral pelvic lymphadenectomy. One patient underwent total abdominal hysterectomy without lymphadenectomy, and another one patient underwent subtotal hysterectomy.

Parametrial invasion: Patients who had parametrial invasion were 10 patients representing 25% of cases.

Lymph Node Invasion: Right and/or left pelvic lymph node metastases were detected in 5 patients presenting only 12.5% of patients.

Follow up data analysis:

Follow up of patients was in form of regular clinical examination every 2 months after end of treatment, radiological examination in case of suspicious local recurrence or distant metastasis and pathological examination for any suspicious lesion locally. The median follow-up period was 18 months.

Treatment response assessment:

Patients were assessed clinically (general examination as well as vaginal examination (PV)) after ending their CCRTH. Patients in arm A did pelvic MRI 1 month after surgery, then every 3 months in the first year post operatively, then biannually for 2 more years. Patients in arm B had their MRI pelvis 1 month after BT, then every 3 months during the first year of their follow up period, then biannually for 2 more years.

Arm A (CCRTH + HT): During their follow up, 34 patients (85%) maintained complete remission after surgery. Six (15%) patients had recurrent disease. (Figure 1)

Arm B (CCRTH + BT): assessment of response showed that 35 patients achieved complete remission (85.4%), 4 (9.8%) patients had stationary disease and 2 (4.9%) patients achieved progressive disease (Figure 1).

Loco-regional Control:

Local control was achieved by 80% of patients who had no progressive disease on regular follow up. The loco-regional control rate in arm A was 75%, while in arm B was 85.4%, P-value was 0.24, which is not statistically significant. (Figure 2)

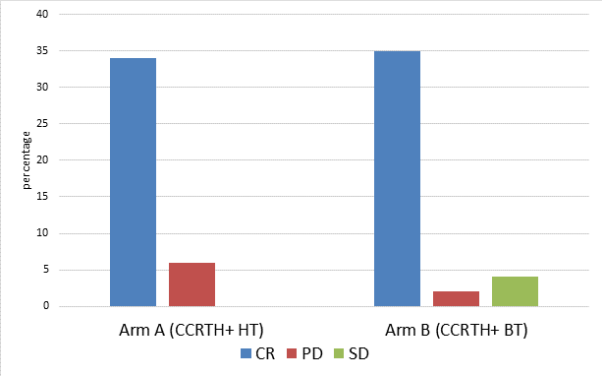



Figure 1: Bar chart showing treatment response between the two arms

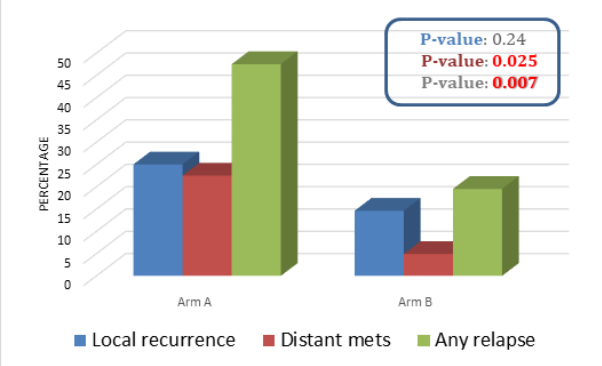



Figure 2: Bar chart of local recurrence, distant metastasis and any relapse between the two arms

Distant metastasis:

Distant failure was assessed and data showed that 86.4% of patients had no metastatic disease on follow up.

In arm A, 77.5% of patients didn't develop distant metastasis. In arm B, 95.1% didn't develop distant metastasis, with a statistically significant P-value= 0.025. (Figure 2)

Any local or distant relapse:

Local and distant failure were assessed on follow up data analysis. From the whole group; 66.7% of patients were disease free on their last follow up with no local or distant failure.

In arm A, 52.5% of patients were disease free, while in arm B was 85.5% with a statistically significant P-value = 0.007. (Figure 2)

*Survival data analysis:*

Overall Survival (OS):

The median OS of the whole cohort of patients was 39 months.

The median OS of arm A was 39 months, and arm B was 39.8 months, (95% CI: 28.133 to 39.933), with P-value equals 0.5 (Figure 3).

The median OS didn't statistically differ in patients aged ≥ 60 years (39.06 months), and in those less than 60 years (39.83 months), P-value equals to 0.9.

The median OS in patients with stage I disease was not reached, while in stage II, the median OS was 39 months and in patients with stage III or IV, the median OS was 39.8 months, with P-value equals to 0.8, it is not statistically significant. (Figure 4)

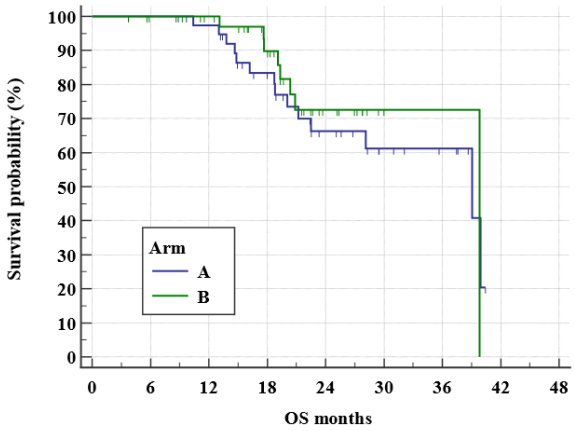



Figure 3: Kaplan-Meier survival curve showing the Overall survival between the 2 arms

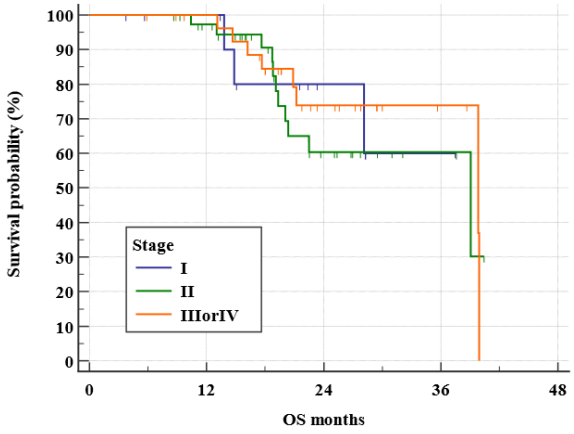



Figure 4: FIGO staging correlation to OS

Progression free survival:

Our study had shown that the median PFS of all patients was 38.5 months. (95% CI: 24.6 to 34.4). The median PFS in arm A was 29.1 months, while in arm B was not reached, (95% CI: 14.7 to 34.3) with P-value of 0.24. (Figure 5)

The median PFS in 60 years or more was 33 months, while the median PFS was 29.1 in patients less than 60 years, with P-value=0.35.

The median PFS in stage I was not reached, in stage II was 34.4 months, while in stages III and IV; The median PFS was 32.8 months, with P-value equals 0.7, with no statistical significance.

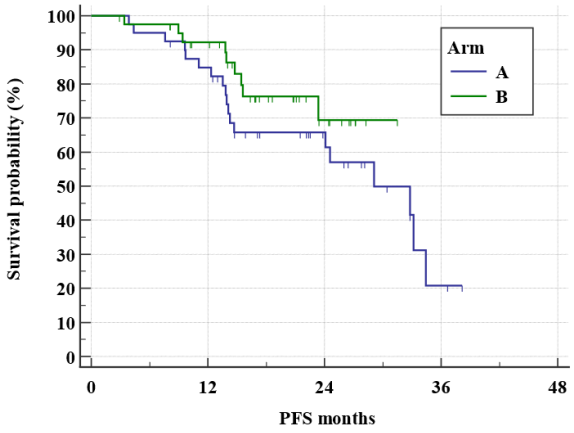



Figure 5: PFS analysis between the 2 arms

*Toxicity analysis:*

We calculated the toxicity profile for each arm, to know the extent of morbidity the patients were exposed to. Toxicity after concurrent chemotherapy, after external beam radiotherapy and after intracavitary radiotherapy is demonstrated in tables 2, 3 and 4 respectively.

Table 2: Toxicity pattern after neoadjuvant chemotherapy (including concurrent chemotherapy)

| | **Toxicity post neoadjuvant chemotherapy (N=81)** | | | | | |
|---|---|---|---|---|---|---|
| | **Hematological** | | | **Non- Hematological** | | |
| Grade | **Anemia** | **Neutropenia** | **Elevated KFTs** | **Fatigue** | **Vomiting** | **Neuropathy** |
| G1 | 4 (4.9%) | 2 (2.5%) | 2 (2.5%) | 2 (2.5%) | 5 (6.2%) | 3 (3.7%) |
| G2 | 13 (16%) | 7 (8.6%) | 6 (7.4%) | 11 (13.6%) | 13 (16%) | 2 (2.5%) |
| G3 | 2 (2.5%) | 1 (1.2%) | 3 (3.7%) | 5 (6.2%) | 5 (6.2%) | 1 (1.2%) |
| G4 | 1 (1.2%) | 1 (1.2%) | 2 (2.5%) | 1 (1.2%) | 2 (2.5%) | 0 |

Table 3: Toxicity pattern after EBRT received by both arms

| | Toxicity post CCRTH (N=81) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Early toxicity** | | | | **Late toxicity** | | |
| Grade | **Dysuria** | **Vomiting** | **Fatigue** | **Wet desquamation** | **Dysuria** | **vomiting** | **Incontinence** |
| G1 | 2 (2.5%) | 3 (3.7%) | 2 (2.5%) | 2 (2.5%) | 3 (3.7%) | 1 (1.2%) | 2 (2.5%) |
| G2 | 7 (8.6%) | 5 (6.2%) | 8 (9.9%) | 3 (3.7%) | 15 (18.5%) | 4 (4.9%) | 3 (3.7%) |
| G3 | 13 (16%) | 3 (3.7%) | 1 (1.2%) | 1 (1.2%) | 5 (6.2%) | 3 (3.7%) | 1 (1.2%) |
| G4 | 1 (1.2%) | 1 (1.2%) | 1 (1.2%) | 1 (1.2%) | 1 (1.2%) | 0 | 0 |

Table 4: Toxicity pattern after intracavitary brachytherapy (arm B)

| | **Toxicity post brachytherapy (N=41)** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Early toxicity** | | **Late toxicity** | | | | |
| Grade | **Dysuria** | **Incontinence** | **Dysuria** | **Proctitis** | **Dyspareunia** | **Bleeding** | **Fatigue** |
| G1 | 3 (7.3%) | 1 (2.4%) | 2 (4.9%) | 2 (4.9%) | 1 (2.4%) | 1 (2.4%) | 2 (4.9%) |
| G2 | 9 (22%) | 4 (9.7%) | 8 (19.5%) | 8 (19.5%) | 2 (4.9%) | 2 (4.9%) | 4 (9.7%) |
| G3 | 2 (4.9%) | 1 (2.4%) | 2 (4.9%) | 2 (4.9%) | 2 (4.9%) | 0 | 2 (4.9%) |
| G4 | 2 (4.9%) | 0 | 1 (2.4%) | 0 | 1 (2.4%) | 0 | 1 (2.4%) |

## Discussion:

Cervical cancer is the fourth most common cancer to affect females and the fourth leading cause of death globally, accounting for 85% of cases in developing nations where the majority of cases are diagnosed with locally advanced disease. In these countries, cervical cancer is also one of the leading causes of death [4,5].

According to National Cancer Institute Cairo University registry data from 2000 to 2011, invasive lesions accounted for 59.58% of all female genital tract malignancies, and cervical cancer represents the most common cancer of the female genital system with an incidence of 32.7%. These findings highlight the significance of evaluating the management outcomes for patients with locally advanced cervical cancer and developing alternative strategies given the dearth of available treatment options [6].

This retrospective study included 81 patients with locally advanced cervical cancer FIGO stage IB2 till IVA who presented to Kasr Al-Ainy Clinical Oncology department, Cairo University from January 2015 to December 2020. Several epidemiological & clinical factors were studied as well as toxicity profile & treatment strategies potentially influencing Progression-free survival (PFS) in addition to overall survival (OS).

The patients included in this study ranged in age from 33 to 76, with a mean age of 56. The average age at diagnosis for cervical cancer was 53 years in 2018, with a range of 44 to 68 years, according to a global analysis [7].

Vaginal bleeding was the most frequent initial symptom, occurring in 77% of patients. Studies showed that this was also the most common way that cervical cancer presented itself [8, 9]. According to a different study, the first symptom for 88.9% of patients with cervical cancer was unprovoked vaginal bleeding [10]. Pelvic pain and vaginal discharge accounted for 9% of the other initial presentations. None of the cases had signs of acute renal failure or fistula (rectovaginal or vesicovaginal), which are known to be uncommon presentations of cervical cancer [11, 12]. These symptoms are indicative of complications in locally advanced cervical cancer.

Squamous cell carcinoma, which accounted for 85% of the patients included in the analysis, was the most common pathological subtype. Studies and reports from the World Health Organization have shown that squamous cell carcinoma is the most common pathological variant in cervical cancer, accounting for 70–80% of cases. Adenocarcinoma was the second most common type and accounted for 13.5% of the included patients [13, 14]. This was comparable to the incidence of adenocarcinoma in a prior study that cited WHO reports indicating that adenocarcinoma affected 10 to 25% of patients with cervical cancer [15]. Adenocarcinoma was found in 5.8% of the patients in a retrospective study, which involved 1011 patients with cervical cancer [10]. In our patients, Grades 2 and 3 were the most prevalent grades accounting for 62.9% and 37% of the total. But as of right now, no one grading system has gained widespread acceptance and is still deemed to have dubious therapeutic value. Tumor grade was not considered in the management of patients with cervical cancer according to the most recent recommendations of the European Society of Gynecological Oncology (ESGO), the European

Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) [14, 16].

FIGO stages IB2 through IVA corresponded to the cervical cancer staging of the involved patients. With a percentage of 32.1%, stage IIB was the most common among the patients. Stage IIIC1, at 19.8%, was the second most common, followed by IB2 and IIA at 16%. Only 3.7% of the patients were in stage IVA. Similar findings to our study were found in a previous European review article on the management of cervical cancer involving 11775 patients, which indicated that stage II cervical cancer represented 30% of cases, stage III represented 19% of patients, and stage IVA only represented 4% of patients [17].

For appropriate staging and metastatic work-up, the patients were evaluated clinically, including a radiological examination under anesthesia and an MRI of the pelvis and a CT scan of the chest, abdomen, and pelvis. The staging system used by FIGO was primarily based on clinical examination, with the addition of specific procedures that FIGO permitted to alter the staging. The FIGO Gynecologic Oncology Committee revised this in 2018 to allow imaging and pathological findings, when available, to determine the stage and to support the clinical findings regarding the size and clinical extent of the tumor [2].

Concurrent chemotherapy and radiation therapy was administered to all patients, as opposed to radiotherapy alone. This indicates the significance of concurrent chemotherapy treatment, which has been used in multiple studies. At four years, the combined-therapy group in GOG 123 had significantly higher rates of both overall survival (P=0.008) and progression-free survival (P<0.001) [18]. With an average weekly dose of 40 mg/m2 for an average of five weeks, cisplatin was the most often used regimen. This was consistent with a 1999 study by Rose PG et al. that demonstrated the advantages of concurrent chemoradiotherapy and cisplatin in enhancing the rates of survival and progression-free survival in patients with locally advanced cervical cancer [19].

In our study, patients were divided into two arms, in arm A; patients received CCRTH followed by radical surgery, while in arm B; patients received CCRTH followed by brachytherapy.

The Local control in arm A was 75%, while in arm B was 85.4%, the median OS in arm A was 39 months, and in arm B was 39.8 months, which is not statistically significant. The median PFS in arm A was 29.1 months, while in arm B it was not reached.

In our study, the relapse rates, whether local or distant, were higher in arm A (47.5%) than arm B (14.5%) with a statistically significant (P-value= 0.007). Moreover, distant metastases were higher in arm A (22.5%) than arm B (4.9%) with a statistically significant (P-value = 0.025).

Similar to our findings, the Ferrandina study's median overall survival (OS) was 28 months for patients who underwent hysterectomy following CCRTH. Of the 152 patients, 111 (73%) had absent or microscopic residual disease at pathological examination; the 5-year OS was 90% and the 5-year disease free-survival (DFS) was 83% [19]. In the Takekuma trial, the group that underwent a hysterectomy after CCRTH had a median overall survival of 3.8 years. The discrepancy between the median overall survival in our study and this study might have resulted from the small number of patients who had surgery, from situations in which brachytherapy delivery was impeded, or from the requirement for an extended period of follow-up [21].

Zheng D et al. conducted another study that demonstrated the significant benefit of local control rate in LACC with 3 year OS (87.1%) and 5 year OS (72.8%) following radical surgery following CCRTH in terms of OS and PFS [22]. In bulky Stage IB cervical carcinoma in GOG 71, the cumulative incidence of local relapse was lower in the RT + Hystrecetomy group (at 5 years, 27% vs. 14%) [23]. However, a meta-analysis evaluating the role of adjuvant hysterectomy following CCRT in cases of locally advanced cervical cancer found that while it was linked to a lower recurrence rate, adjuvant hysterectomy following CCRT did not improve survival [24]. According to Shi D et al.'s second meta-analysis, surgery performed after CCRTH did not affect overall survival, and further research is required to determine whether concurrent chemoradiation is preferred by DFS, PFS, and LC [25].

In patients who received definitive concurrent chemoradiotherapy in the form of EBRT of whole pelvis concurrently with weekly Platinum based chemotherapy, then received intracavitary brachytherapy, the most common dose regimen used in patients was 7Gy/3Fr.

The literature demonstrated that brachytherapy provides the maximum local control of cervical cancer by delivering a high central dose to the primary tumor reaching from 80 to 90 Gy with reduced dose to adjacent organs. The total cumulative dose received to the tumor by EBRT and ICRT was biologically equivalent to 83.2 to 93.3 Gy [2]. Since the brachytherapy modality was only recently made available in our center a few years ago, there was no prolonged follow-up, which may have contributed to the lack of statistical significance when compared to arm A. The local control of this arm was 85.3%, and the median OS was 39.8 months. The 5-year disease survival rate was 60% and the clinical locoregional control rate was 85% in a systemic review. Comparable to our study, 13% of patients who received CCRTH followed by brachytherapy experienced late grade 3 toxicities [26]. Pelvic control rates were 82% in patients who received radiation and chemotherapy-RT with HDR BT in the prospective studies with a follow-up of more than 24 months, according to a pooled analysis of the American Brachytherapy Task Group [27]. According to the French prospective multicentric study, 3D BT had a 91.9% local relapse-free survival rate at 24 months. With half the toxicity seen with 2D dosimetry, it had better local control. Compared to definitive radiotherapy, the combination of radiation and surgery was more toxic. It was important to increase target volume coverage for patients with advanced tumors without increasing toxicity [28].

## Conclusion:

Management of locally advanced cervical cancer is a challenging matter especially in developing countries. Our aim is to determine whether these cases could be managed without compromise in centers that don't have brachytherapy machines.

We investigated the loco-regional control rate, toxicity and survival data in patients with locally advanced cervical cancer FIGO Stage IB2 till IVA), treated with neoadjuvant chemo- radiotherapy, followed by radical hysterectomy (Arm A), compared to those who received the standard of care; chemo-radiotherapy followed by brachytherapy (Arm B) regarding OS, DFS and toxicity profile.

The Loco-regional control rate in arm A was 75% while in arm B was 85.3%, with no significant P-value (P-value=0.24). However, relapse rates were higher in arm A (22.5%) than in arm B (14.5%) with a statistically significant P-value= 0.007. Moreover, distant metastases were higher in arm A (22.5%) than in arm B (4.9%) with a statistically significant P- value (P-value=0.025).

There was no significant difference between the two groups in the survival data (PFS and OS). However, regarding the toxicity profile, both arms had received CCRTH, with similar toxicity profile pattern. The surgical morbidity could not be assessed as those patients were referred to another institution for surgery. In brachytherapy arm, the most common early and late toxicity was dysuria which represented 39% and 29.7%, respectively.

**Acknowledgements:**

The Authors would like to thank Ms. Aya B for manuscript editing.

**Funding:**

None.

**Availability of data and materials:**

The datasets used during the present study available from the corresponding author on reasonable request.

**Authors' contributions:**

WH drafted the manuscript. HZ & AT performed clinical data acquisition and analysis. All authors participated in clinical data acquisition. IS critically revised the manuscript. All authors read and approved the final manuscript.

**Ethics approval and consent to participate:**

An acceptance from Kasr Al-Ainy Institutional scientific and ethical committees was taken on our study design. A written informed consent was a pre-requisite to enroll the patients into the study.

**Consent for publication**

Not applicable.

**Competing interests**

All authors declare that they have no competing interests.

## References:

1. Bhatla N, Aoki D, Sharma DN, et al. Cancer of the cervix uteri: 2021 update. Int J Gynaecol Obstet. 2021 Oct;155 Suppl 1(Suppl 1):28-44.
2. Bhatla N, Aoki D, Sharma DN, et al. Cancer of the cervix uteri staging. Int J Gynaecol Obstet. 2018 Oct;143 Suppl 2:22-36.
3. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association 1958; 53(282): 457-481.
4. Freddie B, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, a cancer journal for clinicians, 2018;68(6):394-424.
5. Manirakiza A, Sinha S, Rubagumya F, et al. Locally Advanced Cervical Carcinoma Management. Cervical Cancer: Screening, Treatment and Prevention-Universal Protocols for Ultimate Control. 2018 May 16:77.
6. Howayda S Abd El All,Amany Refaat, Khadiga Dandash, et al. Prevalence of cervical neoplastic lesions and Human Papilloma Virus infection in Egypt: National Cervical Cancer Screening Project, Infectious Agents and Cancer volume 2, Article number: 12 (2007)
7. Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. The Lancet Global Health. 2020 Feb 1;8(2):e191-203.
8. Canavan TP, Doshi NR, et al. Cervical cancer. American family physician. 2000 Mar 1; 61(5):1369-76.
9. Kumar V, Abbas AK, Fausto N, et al. Cervical cancer. Robbins Basic Pathology (8th ed.), Saunders Elsevier. 2007:718-21.
10. Derks K, Steenhuijsen JL, van den Berg HA, et al. Impact of brachytherapy technique (2D versus 3D) on outcome following radiotherapy of cervical cancer. J Contemp Brachytherapy. 2018 Feb;10(1):17-25.
11. Narayanan P, Nobbenhuis M, Reynolds KM, et al. Fistulas in malignant gynecologic disease: etiology, imaging, and management. Radiographics. 2009 Jul; 29(4):1073-83.
12. Hsu L, Li H, Pucheril D, et al. Use of percutaneous nephrostomy and ureteral stenting in management of ureteral obstruction. World journal of nephrology. 2016 Mar 6; 5(2):172.
13. Kurman RJ, Carcangiu ML, Herrington CS, et al. WHO Classification of Tumours of Female Reproductive Organs. International Agency for Research on Cancer: Lyon, 2014.
14. McCluggage WG. Towards developing a meaningful grading system for cervical squamous cell carcinoma. J Pathol Clin Res. 2018

Apr;4(2):81-85.
15. Lax SF, Horn LC, Löning T, et al. Kategorisierung der Tumoren der Cervix uteri. Der Pathologe. 2016 Nov 1;37(6):573-84.
16. Cibula D, Pötter R, Planchamp F, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. Int J Gynecol Cancer. 2018 May;28(4):641-655.
17. Yan DD, Tang Q, Chen JH, et al. Prognostic value of the 2018 FIGO staging system for cervical cancer patients with surgical risk factors. Cancer management and research. 2019; 11:5473.
18. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med. 1999 Apr 15;340(15):1154-61.
19. Rose PG, Ali S, Watkins E, et al. Gynecologic Oncology Group. Long- term follow- up of a randomized trial comparing concurrent single agent cisplatin, cisplatin- based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: A Gynecologic Oncology Group Study. J Clin Oncol. 2007;25:2804–2810
20. Ferrandina G, Legge F, Fagotti A, et al. Preoperative concomitant chemoradiotherapy in locally advanced cervical cancer: Safety, outcome, and prognostic measures. Gynecol Oncol. 2007 Oct;107(1 Suppl 1):S127-32.
21. Takekuma M, Takahashi F, Mabuchi S, et al. Propensity score-matched analysis of systemic chemotherapy versus salvage hysterectomy for persistent cervical cancer after definitive radiotherapy/concurrent chemoradiotherapy. BMC Cancer. 2020 Nov 30;20(1):1169.
22. Zheng D, Mou HP, Diao P, et al. Chemoradiotherapy in combination with radical surgery is associated with better outcome in cervical cancer patients. Oncotarget. 2018 Jan 5;9(2):2866.
23. Keys HM, Bundy BN, Stehman FB, et al. Gynecologic Oncology Group. Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. Gynecol Oncol. 2003 Jun;89(3):343-53.
24. Shim SH, Kim SN, Chae SH, et al. Impact of adjuvant hysterectomy on prognosis in patients with locally advanced cervical cancer treated with concurrent chemoradiotherapy: a meta-analysis. Journal of gynecologic oncology. 2017 Dec 11;29(2).
25. Shi D, Liang Z, Zhang C, et al. The effect of surgery on the survival status of patients with locally advanced cervical cancer after radiotherapy/chemoradiotherapy: a meta-analysis. BMC cancer. 2018 Dec 1;18(1):308.
26. Banerjee R, Mitchell K. Brachytherapy in the treatment of cervical cancer: a review. Int J Womens Health. 2014 May 28;6:555-64.
27. Mayadev J, Viswanathan A, Liu Y, et al. American Brachytherapy Task Group Report: A pooled analysis of clinical outcomes for high-dose-rate brachytherapy for cervical cancer. Brachytherapy. 2017 Jan-Feb;16(1):22-43.
28. Charra-Brunaud C, Harter V, Delannes M, Haie-Meder C, Quetin P, Kerr C, Castelain B, Thomas L, Peiffert D. Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: results of the French STIC prospective study. Radiother Oncol. 2012 Jun;103(3):305-13.