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### ■■■ RESEARCH ARTICLE

# Acute gastrointestinal complications in the era of image guided high dose rate intracavitary brachytherapy following definitive chemoradiotherapy for cervical cancer

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### ■■■ ABSTRACT

**Background**: Cervical cancer ranks as the third most prevalent malignancy and leading cause of mortality among gynecologic malignancies. Concurrent chemo-radiotherapy (CHT-RT) is the definitive treatment for locally advanced cervical cancer. **Aim:** to assess the gastrointestinal toxic effects and grade the toxicity after definitive chemo radiation, followed by intracavitary brachytherapy, in the treatment of locally advanced cervical cancer. **Materials and Methods:** This prospective research was conducted on 30 individuals, aged above of 18 years old, females, with locally advanced disease (stages IB3 to IVA). **Results:** Regarding Kaplan-Meier survival curve, the mean time of progression free survival was 10.18 m and % at the end of study was 76.7. Acute GIT toxicity grade 0and 2 were the highest followed by grade 1 then grade 3. There was a significant difference with hypertension (HTN) regarding demographic data of the patients in relation to abdominal pain/ discomfort, until now there is no explanation for this, and further prospective studies are needed to reveal this result, treatment in relation to diarrhea and nausea in relation to sigmoid dose. **Conclusion:** There was significant relation between gastrointestinal toxicity and the dose and the site of brachytherapy, which nausea toxicities were related to dose of sigmoid. Also, diarrhea toxicities are related with median volume of rectum.

**Keywords:** Acute Gastrointestinal Complications, Brachytherapy, Chemoradiotherapy, Cervical Cancer, External beam radiation therapy

### ■■■ ARTICLE INFO

## INTRODUCTION

Cervical cancer ranks as the third most prevalent cancer and leading cause of death among gynecologic malignancies in the United States. However, its incidence and mortality rates are comparatively lower than those of uterine corpus or ovarian cancer. The incidence in Egypt is about 0.98% as there no effective and extensive screening with Pap smears, it is usually possible to identify and treat asymptomatic precursor lesions making it nearly preventable (Basoya and Anjankar 2022). HPV plays a crucial role in the formation of cervical neoplasia and is present in 99.7 percent of cervical malignancies (Walboomers, Jacobs et al. 1999, Adegoke, Kulasingam et al. 2012).

The histopathological classifications of cervical carcinoma the histologic types distribution in the United States in 2012 was as follow(Querleu and Morrow 2008): The distribution of squamous cell carcinoma is around 70 to 75 percent, whereas adenocarcinoma (including adenosquamous) accounts for about 25 percent. The standard treatment for cervical cancer often involves the use of either cisplatin alone or a combination of cisplatin and fluorouracil (FU) in chemotherapy. Among these options, we suggest the administration of cisplatin (40 mg/m$^2$) on a weekly basis throughout the course of radiation(Ang 2004, Kim, Shin et al. 2008).

External beam radiation therapy (EBRT) is administered once day over a course of 25

sessions, resulting in a total radiation dosage of 45 Gy. This treatment is often performed using 3D conformal therapy. If there is a significant presence of nodal illness, it is advisable to provide a boost to the nodes in conjunction with brachytherapy. Brachytherapy is started after achieving the most effective tumor shrinkage during EBRT. Cervical regression usually happens after a period of two to five weeks of treatment, depending on the initial stage and size of the tumor, as well as the response to therapy. The delivery may be performed using a low-dose rate (LDR), pulse-dose rate (PDR), or high-dose rate (HDR) device. LDR brachytherapy, as defined by the International Commission on Radiation Units, involves delivering doses of radiation at a rate of 0.4 to 2 Gy per hour. PDR brachytherapy, on the other hand, uses the HDR source but treats patients for just 10 to 30 minutes at a time. In contrast, HDR brachytherapy provides radiation at a rate more than 12 Gy per hour (Falkenberg, Kim et al. 2006, Liu, Wang et al. 2014).

The literature has documented side effects associated with brachytherapy treatment for gynecological malignancies, which may be attributed to the use of brachytherapy. Some of these known side effects include Common adverse effects include non-specific symptoms like weariness, sleeplessness, and hot flashes, as well as skin-related toxicities such radiation dermatitis and telangiectasia. Gastrointestinal toxicities, including symptoms such as nausea, diarrhea, constipation, intestinal fistula, proctitis, rectal ulcers, and rectovaginal fistula, may occur. Urinary toxicities include symptoms such as increased frequency or urgency of urination, involuntary leakage of urine, inflammation of the bladder, recurring infections of the urinary tract, and the formation of abnormal connections between the bladder and other organs. Common vaginal complications include vaginal dryness, vaginal narrowing, and mucositis. Additional hazards may include discomfort, hemorrhage, fibrosis, abscess formation, lower limb edema. (Kirchheiner, Nout et al. 2016, Mazeron, Fokdal et al. 2016, Colleoni, Luo et al. 2018, Salembier, Villeirs et al. 2018, Spampinato, Fokdal et al. 2021).

The objective of this study was to assess the gastrointestinal toxic effects and classify the severity of toxicity after definitive chemo radiation, followed by intracavitary brachytherapy, in the treatment of locally advanced cervical cancer.

## MATERIAL AND METHODS

This prospective study was carried out on 30 patients aged up to 18 years old, females, with locally advanced disease (stages IB3 to IVA), received definitive chemoradiotherapy, who were histopathologically proved to have cervical cancer, performance status (PS) 0-1 for avoiding further toxicity to worse PS patients with high radiotherapy dose and adequate organ function. The study was done from January 2022 to June 2023 after approval from the Ethical Committee Alexandria and Tanta University, Egypt. An informed written consent was obtained from the patients.

Exclusion criteria were patients with PS 2-4, patients who were diagnosed with early cervical cancer, patients pervious received pelvic radiotherapy, metastatic cervical carcinoma and patients have another primary cancer except non melanomatous skin cancer.

All patients were subjected to: history taking, clinical examination, pathological findings (pathologically proven to have cancer cervix), laboratory investigations [complete blood count (CBC), liver and renal function tests], radiological investigations [chest radiograph, computed Tomography (CT), magnetic resonance imaging (MRI), abdomen and pelvis and PET-CT if available to exclude any metastasis].

Ovarian preservation wasn't needed as median age of most patients was 58.5 years. All patients received concurrent chemoradiotherapy with used external beam radiotherapy (three dimension (3D) or intensity-modulated RT (IMRT)) followed by Brachytherapy as indicated.

### Concurrent Chemotherapy

All patients received concurrent (cisplatin 40 mg/m² weekly for 5-6 weeks) during radiotherapy, the maximum total does of cisplatin was 70 mg and patients received hydration protocol with attention to potassium

and magnesium levels and audiogram before starting.

## Chemotherapy modification dose

Chemotherapy holds for (ANC <500/mm$^3$. Platelets < 50,000/mm3, Febrile neutropenia or bleeding. Persistent (>24 hours) grade 3 or 4 nausea and vomiting. Renal Failure (creatinine > 2.0 mg or creatinine clearance <50 ml/min). Treatment of haematological toxicity according to grade with growth factor or other agent as clinically indicated with Cisplatin resumed at a dose of 40 mg/m$^2$ with the maximum total does of cisplatin was 70 mg. Cisplatin resumed at a dose of 30 mg/m$^2$ (60 mg max) after the resolution of nausea means grade < 3, resolution of renal failure means creatinine < 2.0 mg% or creatinine clearance > 50 ml/min. Cisplatin holds for neurotoxicity grade 2 or higher and resumed only if resolving to grade 1 or lower. Cisplatin holds for ototoxicity grade 2 or higher and resumed only if ototoxicity resolves grade 1 or lower. For persistent renal insufficiency, neurotoxicity, or ototoxicity, it was acceptable to replace cisplatin with carboplatin.

## External beam radiotherapy

**Dose and Fractionation:** In most patients, conventional total doses (45–50.4 Gy) were delivered in standard fraction sizes (1.8–2 Gy/day). IMRT used to deliver higher doses to reach to (55-60GY) to high-risk sites such as involved lymph nodes, residual and parametrial, using a sequential boost or SIB approach.

## Internal beam radiotherapy

**Pre-implant patient evaluation:** Before the first brachytherapy procedure, the patient underwent a gynaecologic examination to assess the anatomy, the remaining tumor, and medical factors, and decided which brachytherapy applicator is best suited to the patient's anatomy. Patients should have appropriate medical evaluations and a pre procedure anaesthesia assessment, which requires meeting with an anaesthesiologist to assure that adequate sedation could safely be provided to optimize patient comfort and safety. Depending on the type of procedure and anaesthesia used, instructions on fasting, bowel preparation, and preoperative testing, including

laboratory studies, electrocardiogram, and at least chest X-ray was ordered. Patients required anticoagulant medication for a medical condition had to be carefully evaluated. So, anticoagulation testing was done before the procedure. Epidural anaesthesia was the most common anaesthetic used for the procedure, rarely used general anaesthesia.

**Treatment planning:** It was done therapy using Varian Medical System as linear accelerator with concurrent weekly cisplatin (40 mg/m$^2$) during radiotherapy, then patient Underwent MRI to identify the response of cervix after that patient received 3-4 fractions of 7-8Gy of high dose rate CT guided cobalt Intracavitary brachytherapy technique.

## Statistical analysis

The statistical analysis was conducted using SPSS v26 software (IBM Inc., Chicago, IL, USA). The quantitative variables were expressed as the mean and standard deviation (SD) and compared across the three groups using an analysis of variance (ANOVA) test with a post hoc test (Tukey). The qualitative variables were expressed as frequency and percentage (%) and were evaluated using the Chi-square test. The study used Receiver Operating Characteristic curve (ROC) analysis to determine the overall predictive ability of the parameter and identify the optimal cut-off value. This analysis also assessed the sensitivity and specificity at the identified cut-off value. A two-tailed P value of less than 0.05 was deemed to be statistically significant.

## RESULTS

The mean age was 56.23 ± 13.45 years. Regarding PS, most of the patients (46.7%) had PS 0, while (53.3 %) of patients had PS of 1. Regarding marital status, 23 (76.7%) patients were married, while 4 (13.3%) patients were widows, and 3 (10%) patients were divorced. Regarding Co morbidity, 16 (53.3%) patients hadn't any Co morbidity, while 10 (33.3%) patients suffered from diabetes mellitus, 11 (36.7%) patients suffered from HTN, and 1 (3.3%) patient suffered from stroke/DVT. The mean of cardiac EF was 65.07 ± 5.28. Regarding tumor staging: 11(36.7 %) patients had stage II and 13 (43.3%) patients had stage III, only 1

(3.3%) patient had stage IB2, and 5 (16.7) patients had stage Iva.

Regarding pathology status, 29 (96.7%) patients had squamous cell carcinoma (SCC), while 1 (3.3%) patient had adenocarcinoma received same definitive Ch-Rth. Regarding grade of squamous malignancy: 22 (73.3%) patients were grade 2, while 8 (26.7%) patients were grade 3. The pathological data of 30 patients, almost patients were SCC (96.6%), most patients were grade 2 with percentage (73.3%), there weren't patients with metastatic disease. All patients treated with concurrent chemo-radio therapy using weekly platinum-based chemotherapy with a dose of 45 Gy in 1.8-2 Gy/fraction followed by brachytherapy with a dose of 7GY/4 Fr except two patients received 7GY/2Fr & 7GY/3Fr with prescription dose 7GY.(Table 1). The GIT symptoms, most common which occurred are nausea (63.3%) then diarrhea (50%) (grade1 (26.7%) grade2 (23.3%), sever symptoms occurred only in 2 patients such as GIT bleeding grade 3 and abdominal distention one was grade 2 and another one grade 3. Table 2

The volumes ($cm^3$) and doses (gy) for target volume and organs at risk as rectum, sigmoid colon, and bladder. In acute GIT toxicity, grades 2 and 0 were the highest being (33.3%) for each, followed by grade 1 (20%) then grade 3 (13.3%). The time when toxicity was occurred, most toxicity occurred during both EBRT& brachytherapy (46.7%). In acute urinary tract toxicity, grade 1 was the highest being (60%), followed by grade 0 (30%). In acute vaginal toxicity, grade 2 was the highest being 43.3%, followed by grade 1 33.3%. After 3 months of completing treatment, follow up by MRI pelvis with contrast complete response was 76.6% followed by progression was 13.3% then partial response was 10% as shown in Table 3.

Regarding age, MS, HTN, dose of brachytherapy, there was significant difference (P <0.05). Regarding PS, DM, pathology, grade of tumor and stage, there was no significant difference(p>0.05). All patients received 7GY/4Fx except 2 patients who received less than 4 fractions due to severe toxicity (grade 3), 10 patients had no toxicity, 10 patients had grade 2 toxicity, 6 patients had grade 1 toxicity

& only 2 patients showing grade 3 (Table 4). There was a significant difference concerning nausea and sigmoid dose (p value 0.001). Regarding demographic data of the patients in relation to vomiting. There was no significant difference with tumor size or stage. Regarding the relation of vomiting with the treatment parameters and vomiting in relation to dose histogram parameters, there was no significant difference (Table 5). Regarding Kaplan-Meier survival curve, the mean time of progression free survival was 10.18m and % at the end of study was 76.7 as shown in Figure 1.

**Case**

A female patient aged 37 years old, with International Federation of Gynaecology and Obstetrics (FIGO) stage IIIB cervical cancer for definitive CCRT with cisplatin dose of IMRT 45GY/1.8Gy. She received boost brachytherapy with dose 7Gy/4fr, prescription dose 7Gy, for one fraction; CTVHR D90 = 6 GY, Bladder $D2cm^2$ = 3Gy, Rectum $D2cm^2$ = 4.4Gy, Sigmoid $D2cm^2$ = 2.8Gy (Figure 2).

**DISCUSSION**

Cervical cancer represents the tenth most common cancer in Egypt, Gharbia population-based cancer registry (GPBCR), was the 1st and the only population-based cancer registry in Egypt. Breast and gynaecological malignancies together constitute 44.9% of female cancer in Egypt, Gharbia (Gharib, El-Shoeiby et al. 2018). The objective of this study was to assess the gastrointestinal toxic effects and classify the severity of toxicity after definitive chemo radiation, followed by intracavitary brachytherapy, in the treatment of locally advanced cervical cancer.

Our results show that 13 patients had stage III (43.3%) , 11 patients had stage II (36.7%), only 1 patients had stage I (3.3%) and 5 patients had stage IV, similar result from Mohammed El-Senoussi et al. (El-Senoussi, Bakri et al. 1998) and M. Mahmoud et al. (Mahmoud, Kilic et al. 2017). Regarding grade of squamous malignancy, 22 patients (73.3%) were grade 2, while 8 patients (26.7%) were grade 3, that was similar correlation with Mortazavis et al. (Mortazavi, Zali et al. 2002).

**Table 1.** Distribution of the studied cases according to demographic data, pathological data, treatment, and acute GIT toxicity parameters

| | | N=30 |
|---|---|---|
| **Age (years)** | | 56.23 ± 13.45 |
| **Marital status** | **Married** | 23(76.7%) |
| | **Divorced** | 3(10.0%) |
| | **Widow** | 4(13.3%) |
| **EF** | | 65.07 ± 5.28 |
| **PS** | **0** | 14(46.7%) |
| | **1** | 16(53.3%) |
| **Past history** | | 14(46.7%) |
| **DM** | | 10(33.3%) |
| **Stroke /DVT** | | 1(3.3%) |
| **HTN** | | 11(36.7%) |
| **HCV** | | 0(0.0%) |
| **Pathological data** | | |
| **Pathology** | **SCC** | 29(96.7%) |
| | **Adenocarcinoma** | 1(3.3%) |
| **Grade** | **Grade II** | 22(73.3%) |
| | **Grade III** | 8(26.7%) |
| **T** | **T1** | 1(3.3%) |
| | **T2** | 14(46.7%) |
| | **T3** | 10(33.3%) |
| | **T4** | 5(6.7%) |
| **N** | **N0** | 15(50.0%) |
| | **N1** | 15(50.0%) |
| **M0** | | 30(100.0%) |
| **Stage** | **Ib2** | 1(3.3%) |
| | **IIa/ IIb** | 11(36.7%) |
| | **IIIa/ IIIb** | 13(43.3%) |
| | **IVa** | 55(6.7%) |
| **Treatment parameters** | | |
| **CTh** | **No** | 2(6.7%) |
| | **Concurrent** | 28(93.3%) |
| **Type of chemotherapy** | **No** | 2(6.7%) |
| | **Cisplatin** | 24(80.0%) |
| | **Carboplatin** | 4(13.3%) |
| **Cycles** | **No** | 2(6.7%) |
| | **4 weeks** | 1(3.3%) |
| | **5 weeks** | 22(73.3%) |
| | **6 weeks** | 5(16.7%) |
| **Dose of EBRT** | | 45 GY/25Fx |
| **Dose brachytherapy** | **7GY/2Fx** | 1(3.3%) |
| | **7GY/3fx** | 1(3.3%) |
| | **7GY/4Fx** | 28(93.3%) |
| **Presication dose** | **7 gy** | 30(100%) |
| **Dewall time (min.)** | | 23.71 ± 4.41 |

Data are presented as mean ± SD or frequency (%). EF: ejection fraction, PS: Performance status, DM: diabetes mellitus, DVT: Deep vein thrombosis, HCV: hepatitis C virus, SCC: squamous cell carcinoma, GIT: gastrointestinal tract, HTN: hypertension.

**Table 2.** Distribution of the studied cases according to Acute GIT toxicity

|  | Grade 0 | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|---|
| Nausea | 11(36.7%) | 10(33.3%) | 9(30.0%) | 0(0.0%) |
| Vomiting | 18(60.0%) | 9(30.0%) | 3(10.0%) | 0(0.0%) |
| Anorexia | 24(80.0%) | 3(10.0%) | 2(6.7%) | 1(3.3%) |
| Diarrhea | 15(50.0%) | 8(26.7%) | 7(23.3%) | 0(0.0%) |
| Abdomen alain/discofort | 0(0.0%) | 15(50.0%) | 15(50.0%) | 0(0.0%) |
| Abdominal distension | 28(93.3%) | 0(0.0%) | 1(3.3%) | 1(3.3%) |
| Perforation | 30(100.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) |
| GIT bleeding | 28(93.3%) | 0(0.0%) | 0(0.0%) | 2(6.7%) |
| Fistula | 30(100.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) |
| Obstruction | 30(100.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) |

Data are presented as frequency (%). GIT: gastrointestinal tract.

**Table 3.** Descriptive analysis of the studied cases according to CTV, rectum, sigmoid, bladder, acute GIT toxicity, timing of toxicity, acute urinary tract toxicity, acute vaginal toxicity and follow up by MRI after 3 months.

|  |  | N=30 |
|---|---|---|
| **CTV** | **Volume (cm³)** | 28.66 ± 7.28 |
|  | **Dose (gy)** | 7.47 ± 1.0 |
| **Rectum** | **Volume (cm³)** | 45.51 ± 19.32 |
|  | **Dose (gy)** | 3.58 ± 0.38 |
| **Sigmoid** | **Volume (cm³)** | 26.79 ± 8.94 |
|  | **Dose (gy)** | 2.87 ± 0.72 |
| **Bladder** | **Volume (cm³)** | 54.35 ± 16.14 |
|  | **Dose (gy)** | 4.06 ± 0.79 |
| **acute GIT toxicity** |  | 20(66.7%) |
| **Acute GIT toxicity grade** | **Grade 0** | 10(33.3%) |
|  | **Grade 1** | 6(20.0%) |
|  | **Grade 2** | 10(33.3%) |
|  | **Grade 3** | 4(13.3%) |
|  | **Grade 4** | 0(0.0%) |
| **Timing of Toxicity** | **No** | 9(30.0%) |
|  | **During EBRT** | 5(16.6%) |
|  | **During brachy** | 2(6.7%) |
|  | **During both** | 14(46.7%) |
| **Acute urinary toxicity** |  | 21(70.0%) |
| **Acute urinary toxicity grade** | **Grade 0** | 9(30.0%) |
|  | **Grade 1** | 18(60.0%) |
|  | **Grade 2** | 2(6.7%) |
|  | **Grade 3** | 1(3.3%) |
|  | **Grade 4** | 0(0.0%) |
| **Acute vaginal toxicity** |  | 28(93.3%) |
| **Acute vaginal toxicity grade** | **Grade 0** | 2(6.7%) |
|  | **Grade 1** | 10(33.3%) |
|  | **Grade 2** | 13(43.3%) |
|  | **Grade 3** | 4(13.3%) |
|  | **Grade 4** | 1(3.3%) |
| **Follow up by MRI after 3 months** | **Complete response** | 23(76.7%) |
|  | **Partial response** | 3(10.0%) |
|  | **Progression** | 4(13.3%) |

Data are presented as mean ± SD or frequency (%), CTV: CT-scan venography,
GIT: gastrointestinal tract, EBRT: External Beam Radiation Therapy.

**Table 4.** Relation between Acute GIT toxicity grades with demographic, clinic pathological, treatment parameters

| | | N=30 | | | | | |
|---|---|---|---|---|---|---|---|
| | | Grade 0 (n = 10) | Grade 1 (n = 6) | Grade 2 (n = 10) | Grade 3 (n = 4) | Test of Sig. | p |
| **Acute GIT toxicity grade** | | | | | | | |
| **MS** | | | | | | | |
| Married | | 10(100.0%) | 3(50.0%) | 8(80.0%) | 2(50.0%) | **10.736***  | **0.015*** |
| Divorced | | 0(0.0%) | 1(16.7%) | 0(0.0%) | 2(50.0%) | | |
| Widow | | 0(0.0%) | 2(33.3%) | 2(20.0%) | 0(0.0%) | | |
| Age (years) | | 56.40 ± 9.14 | 65.17 ± 6.31 | 60.40 ± 11.19 | 32.0 ± 7.53 | **11.574*** | **<0.001*** |
| **PS** | | | | | | | |
| 0 | | 5(50.0%) | 1(16.7%) | 5(50.0%) | 3(75.0%) | 3.393 | 0.410 |
| 1 | | 5(50.0%) | 5(83.3%) | 5(50.0%) | 1(25.0%) | | |
| DM | | 5(50.0%) | 1(16.7%) | 4(40.0%) | 0(0.0%) | 3.716 | 0.305 |
| Stroke /DVT | | 0(0.0%) | 0(0.0%) | 1(10.0%) | 0(0.0%) | 2.607 | 1.000 |
| HTN | | 2(20.0%) | 1(16.7%) | 8(80.0%) | 0(0.0%) | **11.306*** | **0.007*** |
| **Pathology** | | | | | | | |
| SCC | | 10(100.0%) | 5(83.3%) | 10(100.0%) | 4(100.0%) | 3.629 | 0.335 |
| Adenocarcinoma | | 0(0.0%) | 1(16.7%) | 0(0.0%) | 0(0.0%) | | |
| **Grade** | | | | | | | |
| Grade II | | 8(80.0%) | 4(66.7%) | 6(60.0%) | 4(100.0%) | 2.441 | 0.531 |
| Grade III | | 2(20.0%) | 2(33.3%) | 4(40.0%) | 0(0.0%) | | |
| **T** | | | | | | | |
| T1 | | 1(10.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 10.970 | 0.207 |
| T2 | | 7(70.0%) | 3(50.0%) | 2(20.0%) | 2(50.0%) | | |
| T3 | | 2(20.0%) | 2(33.3%) | 4(40.0%) | 2(50.0%) | | |
| T4 | | 0(0.0%) | 1(16.7%) | 4(40.0%) | 0(0.0%) | | |
| **N** | | | | | | | |
| N0 | | 5(50.0%) | 3(50.0%) | 5(50.0%) | 2(50.0%) | | |
| N1 | | 5(50.0%) | 3(50.0%) | 5(50.0%) | 2(50.0%) | 0.290 | 1.000 |
| **Stage** | | | | | | | |
| Ib2 | | 1(10.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 10.715 | 0.238 |
| IIa/ IIb | | 5(50.0%) | 3(50.0%) | 19(10.0%) | 2(50.0%) | | |
| IIIa/ IIIb | | 4(40.0%) | 2(33.3%) | 5(50.0%) | 2(50.0%) | | |
| IVa | | 0(0.0%) | 1(16.7%) | 4(40.0%) | 0(0.0%) | | |
| **Treatment** | | | | | | | |
| CTh | No | 0(0.0%) | 0(0.0%) | 2(20.0%) | 0(0.0%) | 2.973 | 0.491 |
| | Concurrent | 10(100.0%) | 6(100.0%) | 8(80.0%) | 6(100.0%) | | |
| Type of chemotherapy | No | 0(0.0%) | 0(0.0%) | 2(20.0%) | 0(0.0%) | 4.318 | 0.714 |
| | Cisplatin | 9(90.0%) | 5(83.3%) | 7(70.0%) | 3(75.0%) | | |
| | Carboplatin | 1(10.0%) | 1(16.7%) | 1(10.0%) | 1(25.0%) | | |
| Cycles | 4 weeks | 1(10.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 2.607 | 1.000 |
| | 5 weeks | 7(70.0%) | 5(83.3% | 7(70.0%) | 3(75.0%) | 0.659 | 1.000 |
| | 6 weeks | 2(20.0%) | 1(16.7%) | 1(10.0%) | 1(25.0%) | 1.186 | 0.917 |
| Dose brahtherapy | 7GY/2Fx | 0(0.0%) | 0(0.0%) | 0(0.0%) | 1(25.0%) | 9.390* | 0.016* |
| | 7GY/3Fx | 0(0.0%) | 0(0.0%) | 0(0.0%) | 1(25.0%) | | |
| | 7GY/4Fx | 1(100.0%) | 6(100.0%) | 1(100.0%) | 2(50.0%) | | |
| Dewall time (min.) | | 25.13 ± 5.28 | 21.65 ± 3.29 | 22.53 ± 4.26 | 26.19 ± 2.04 | 1.517 | 0.234 |

Data are presented as mean ± SD or frequency (%), * significant*P* value <0.05, MS: Marital status, HTN: hypertension, PS: Performance status, DM: diabetes mellitus, DVT: Deep vein thrombosis, SCC: squamous cell carcinoma

**Table 5.** Relationship between nausea, vomiting with different parameters.

| | | | Grade 0 (n = 11) | Grade 1 (n = 10) | Grade 2 (n = 9) | Test of Sig. | p |
|---|---|---|---|---|---|---|---|
| **Nausea** | | | | | | | |
| CTV | Volume | | 29.94 ± 6.88 | 27.16 ± 9.91 | 28.74 ± 4.16 | 0.366 | 0.697 |
| | Dose (gy) | | 7.81 ± 0.85 | 6.95 ± 1.31 | 7.61 ± 0.49 | 3.554 | 0.169 |
| Rectum | Volume | | 45.83 ± 14.27 | 48.48 ± 30.25 | 41.81 ± 6.57 | 0.282 | 0.869 |
| | Dose (gy) | | 3.40 ± 0.36 | 3.67 ± 0.21 | 3.71 ± 0.49 | 2.234 | 0.127 |
| Sigmoid | Volume | | 25.20 ± 7.55 | 27.92 ± 10.84 | 27.48 ± 8.96 | 0.170 | 0.919 |
| | Dose (gy) | | 3.14 ± 0.55 | 2.25 ± 0.63 | 3.24 ± 0.55 | **8.882*** | **0.001*** |
| Bladder | Volume | | 48.45 ± 16.07 | 51.52 ± 14.97 | 64.71 ± 13.83 | 3.149 | 0.059 |
| | Dose (gy) | | 3.83 ± 0.89 | 4.12 ± 0.76 | 4.28 ± 0.71 | 1.145 | 0.564 |
| **Vomiting** | | | | | | | |
| MS | Married | | 17(94.4%) | 3(33.3%) | 3(100.0%) | **11.775*** | **11.775*** |
| | Divorced | | 0 (0.0%) | 3(33.3%) | 0 (0.0%) | | |
| | Widow | | 1(5.6%) | 3(33.3%) | 0 (0.0%) | | |
| Age (Years) | | | 57.44 ± 12.45 | 58.22 ± 14.71 | 43.0 ± 12.17 | 1.701 | 1.701 |
| PS | 0 | | 8(44.4%) | 5(55.6%) | 1(33.3%) | 0.668 | 0.880 |
| | 1 | | 10(55.6%) | 4(44.4%) | 2(66.7%) | | |
| DM | | | 8(44.4%) | 1(11.1%) | 1(33.3%) | 3.019 | 0.265 |
| Stroke /DVT | | | 1(5.6%) | 0 (0.0%) | 0 (0.0%) | 1.431 | 1.000 |
| HTN | | | 7(38.9%) | 1(33.3%) | 1(33.3%) | 1.431 | 1.000 |
| Pathology | SCC | | 18(100.0%) | 6(66.7%) | 2(66.7%) | 0.297 | 1.000 |
| | Adenocarcinoma | | 0 (0.0%) | 1(11.1%) | 0 (0.0%) | | |
| Grade | Grade II | | 11(61.1%) | 8(88.9%) | 3(100.0%) | 2.817 | 0.212 |
| | Grade III | | 7(38.9%) | 1(11.1%) | 0(0.0%) | | |
| T | T1 | | 1(5.6%) | 0 (0.0%) | 0 (0.0%) | 7.166 | 0.286 |
| | T2 | | 10(55.6%) | 4(44.4%) | 0 (0.0%) | | |
| | T3 | | 5(27.8%) | 4(44.4%) | 1(33.3%) | | |
| | T4 | | 2(11.1%) | 1(11.1%) | 2(66.7%) | | |
| N | N0 | | 10(55.6%) | 4(44.4%) | 1(33.3%) | 0.789 | 0.767 |
| | N1 | | 8(44.4%) | 5(55.6%) | 2(66.7%) | | |
| Stage | Ib2 | | 1(5.6%) | 0 (0.0%) | 0 (0.0%) | 6.082 | 0.464 |
| | IIa/ IIb | | 7(38.9%) | 4(44.4%) | 0 (0.0%) | | |
| | IIIa/ IIIb | | 8(44.4%) | 4(44.4%) | 1(33.3%) | | |
| | IVa | | 2(11.1%) | 1(11.1%) | 2(66.7%) | | |
| CTh | No | | 2(11.1%) | 0 (0.0%) | 0 (0.0%) | 1.183 | 0.631 |
| | Concurrent | | 16(88.9%) | 9(100.0%) | 3(100.0%) | | |
| Type of chemotherapy | No | | 2(11.1%) | 0 (0.0%) | 0 (0.0%) | 4.508 | 0.298 |
| | Cisplatin | | 15(83.3%) | 6(66.7%) | 3(100.0%) | | |
| | Carboplatin | | 1(5.6%) | 3(33.3%) | 0 (0.0%) | | |
| Cycles | No | | 2(11.1%) | 0 (0.0%) | 0 (0.0%) | 4.175 | 0.777 |
| | 4 weeks | | 1(5.6%) | 0 (0.0%) | 0 (0.0%) | | |
| | 5 weeks | | 13(72.2%) | 7(77.8%) | 2(66.7%) | | |
| | 6 weeks | | 2(11.1%) | 2(22.2%) | 1(33.3%) | | |
| Dose brahtherapy | 7GY/2Fx | | 0 (0.0%) | 0 (0.0%) | 1(33.3%) | 7.767 | 0.069 |
| | 7GY/3Fx | | 0 (0.0%) | 1(11.1%) | 0 (0.0%) | | |
| | 7GY/4Fx | | 18(100.0%) | 8(88.9%) | 2(66.7%) | | |
| Dewall time (min.) | | | 24.19 ± 4.99 | 23.33 ± 3.53 | 21.93 ± 3.66 | 0.366 | 0.697 |
| CTV | Volume | | 30.34 ± 7.55 | 25.45 ± 6.66 | 28.18 ± 5.84 | 1.399 | 0.264 |
| | Dose (gy) | | 7.64 ± 0.86 | 6.98 ± 1.27 | 7.89 ± 0.12 | 3.495 | 0.174 |
| Rectum | Volume | | 43.74 ± 11.85 | 51.48 ± 31.06 | 38.15 ± 9.59 | 0.837 | 0.658 |
| | Dose (gy) | | 3.48 ± 0.31 | 3.81 ± 0.43 | 3.53 ± 0.42 | 2.628 | 0.091 |
| Sigmoid | Volume | | 24.27 ± 6.07 | 33.41 ± 11.50 | 22.04 ± 5.33 | 5.611 | 0.060 |
| | Dose (gy) | | 2.94 ± 0.60 | 2.80 ± 1.02 | 2.69 ± 0.45 | 0.201 | 0.819 |
| Bladder | Volume | | 50.70 ± 15.81 | 55.10 ± 12.64 | 74.02 ± 17.68 | 3.082 | 0.062 |
| | Dose (gy) | | 3.96 ± 0.79 | 4.12 ± 0.92 | 4.50 ± 0.10 | 0.952 | 0.621 |

Data are presented as mean ± SD or frequency (%), *significant p value <0.05, CTV: CT-scan venography, MS: Marital status, HTN: hypertension, PS: Performance status, DM: diabetes mellitus, DVT: Deep vein thrombosis, SCC: squamous cell carcinoma.
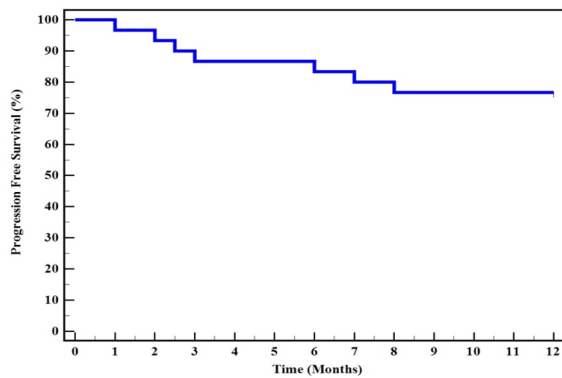
**Figure 1.** Kaplan-Meier survival curve for progression free survival

In comparable with Koji Matsuo et al. (Matsuo, Klar et al. 2021) as reported that cervical cancer was (48.1%) with grade 3 tumors, (44.7%) with grade 2 neoplasms and associated with older age, higher stage disease, larger tumor size, and lymph node metastasis. Regarding treatment of 30 patients, received concurrent chemoradiotherapy using weekly platinum based chemotherapy with a dose of 45 Gy in 1.8-2 Gy/fraction followed by brachytherapy years with significant difference <0.001 and patients with HTN, 80% of them had grade 2 toxicity with significant difference 0.007, no significant difference for PS, pathology, grade of tumor and stage with a dose of 7GY/4 Fr except two patient received 7GY/2Fr and 7GY/3Fr due to sever toxcity with prescription dose 7GY, that was similar to Sadia Sadiq, Abubaker Shahid et al. (Sadiq, Shahid et al. 2020) and EMBRACE-I (Pötter, Tanderup et al. 2021).

Our result showed median high risk clinical target volume (CTV) was 28.66 cm³ (IQR 25.57 – 33.25) with median dose to 90% of CTV (D90%) was 7.6 Gy that was almost similar to EMBRACE-I (Pötter, Tanderup et al. 2021) median high-risk clinical target volume was 28 cm³ (IQR 20–40) and median minimal dose to 90% of the clinical target volume ($D_{90\%}$) was 90 Gy (IQR 85–94) equi-effective dose in 2 Gy per fraction. And same as at this result of ABS (American Brachytherapy Society) (Viswanathan, Beriwal et al. 2012). The doses to OARs D2cc to rectum, sigmoid and bladder are respectively by median 3.6 Gy , 3.04 Gy,4.36 Gy ,while at Lombe, Dorothy Phiri et al (Lombe, Phiri et al. 2020) limiting the D2cc rectum to <70–75 Gy, D2cc sigmoid to <75 Gy, and D2cc bladder to <90 Gy.
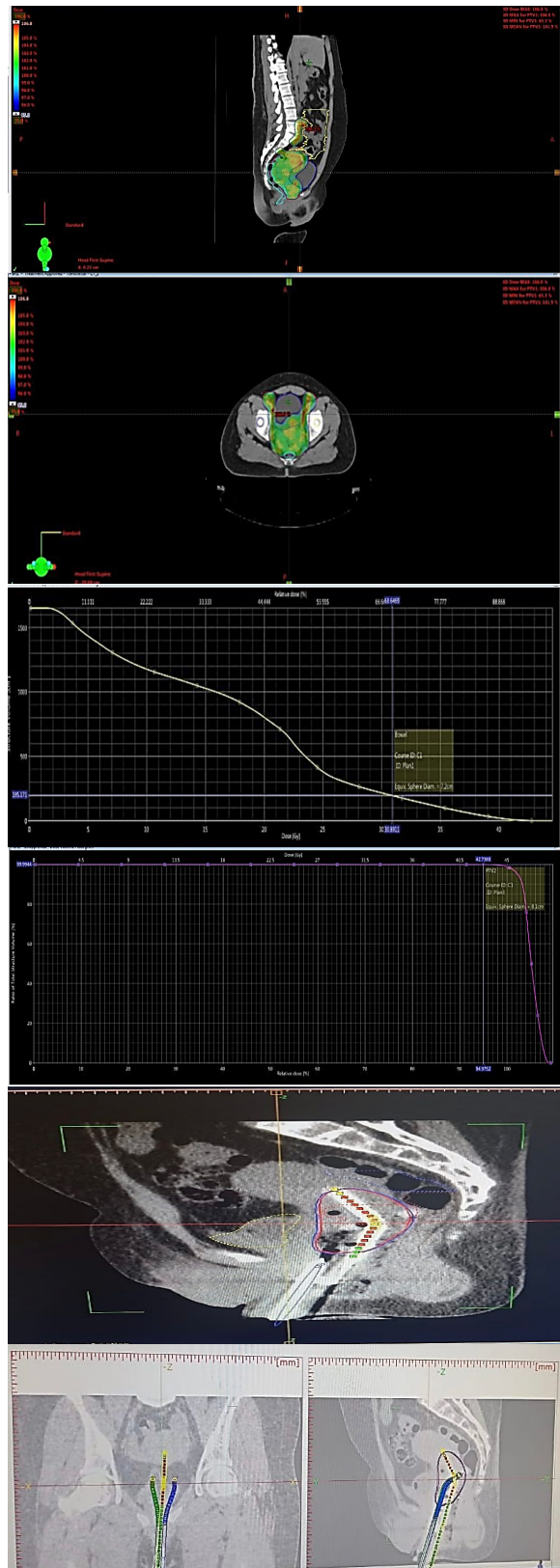


**Figure 2.** Stage 3B cervical cancer for definitive CCRT with cisplatin, Dose of IMRT 45GY/1.8Gy, then received boost brachytherapy with dose 7Gy/4fr, prescription dose 7Gy , for one fraction ; CTVHR D90 = 6 GY, Bladder D2cm2 = 3Gy, Rectum D2cm2 = 4.4Gy, Sigmoid D2cm2 = 2.8Gy

Regarding acute GIT toxicity in our result; grade 2&0 were the highest being (33.3%) for each, followed by grade 1 (20%) then grade 3 (13.3%), while in Sadia Sadiq et al., Abubaker Shahid et al. (Sadiq, Shahid et al. 2020) GIT toxicity, Grade 1 was the highest being 30cases (54.5%) followed by Grade-0 toxicity which was observed in 21cases (38.2%) patients. Regarding acute urinary tract toxicity; grade 1 was the highest being (60%), followed by grade 0 (30%) , while in Sadia Sadiq, Abubaker Shahid et al, (Sadiq, Shahid et al. 2020) Grade-1 genitourinary toxicity was most Common, 43 cases (78.2%) followed by Grade-II 9 cases (16.2%). Regarding acute vaginal toxicity; grade 2 was the highest being (43.3%), followed by grade 1 (33.3%) while vaginal toxicities of Grade-2 and 3 were commonly seen 29 (52.7%) and 16 (29.1%), respectively (Sadiq, Shahid et al. 2020). Patients with GIT grade 0 toxicity all were married (100%), while patients with GIT grade 2 toxicity (80%) of them were married with significant difference 0.015 & patients with grade 0 GIT toxicity was at median age 57 years, grade 2 GIT toxicity was at median age 61 years followed by grade 1 was at age 66.5

There was a significant difference regarding the dose of brachytherapy (P value = 0.016). All patients received 7GY/4Fx except 2 patients who received less than 4 fractions due to severe toxicity (Grade 3), 10 patients had no toxicity, 10 patients had grade 2 toxicity, 6 patients had grade 1 toxicity and only 2 patients showing grade 3.

In comparable with a recent study (Sadiq, Shahid et al. 2020) stratification of grades of acute side effects with respect to age groups revealed that age was not significantly related with severity of acute toxicities, no significant difference was observed in GU, lower GIT and vaginal toxicities with respect to age .

Tumor size also had no significant effect on GU and lower GIT toxicities which was like our result.  Also, in comparable with a previous similar study (Yildirim, Ozsaran et al. 2008), potential factors which could influence the toxicity rate included age, diabetes, obesity, prior surgery, total ERT dose and BT. In our result, Grade 0 and 2 toxicities were more common at the median doses of sigmoid 2.76gy

and 3.15gy respectively, Grade 1 toxicity occurred at the median dose of sigmoid 2.3gy and grade 3 at median dose of sigmoid 3.13gy with significant difference (*P* value 0.045). Grade 2 toxicity was more common at the median dose of rectum 3.65gy, Grade 1 toxicity at the median dose of rectum 3.7gy and grade 3 toxicity at the median dose 3.9gy with no significant difference. While in the results of Vicky Koh et al. (Koh, Choo et al. 2017); the rectal doses to 2 cm$^3$ (D2cc) EQD2 and bladder D2cc EQD2 were 74 Gy (SD, 6) and 79 Gy (SD, 15), respectively. Twenty-two patients (23%) had grade 2 proctitis and 10 patients (11%) had grade 3 proctitis. Four patients (4%) had grade 2 cystitis and two patients (2%) had Grade 3 cystitis. No patients had ≥ grade 4 toxicity.

Regarding nausea, there was 19 (63.33%) patients complained from it; with 10(52.6%) had grade 1 while 9(47.36%) had grade 2, with no significant difference regarding relations between nausea and demographic data, but there was significant difference (P value 0.022) with dewall time. Regarding vomiting, there was 12 (40%) patients complained from it; with 9(75%) had grade 1 while 3(25%) had grade 2; there was no significant difference with tumor size or stage or treatment parameters.

Regarding diarrhea; there was 15 (50%) patients complained from it; with 8(53.33%) had grade 1 while 7(46.66%) had grade 2; with statistically significant difference between diarrhea and the dose of brachytherapy (*P* value =0.048) and the volume of the rectum (*P* value = 0.041).

Regarding abdominal pain/ discomfort; almost all patients suffered from it, half of them had grade 1 and another half-had grade 2. There was statistically significant difference with comorbidity as HTN with P value=0.008).

In our result, diarrhea was the third most common acute toxicity after abdominal pain / discomfort and nausea.  In comparable to Atara ntekim et al. (Ntekim, Adenipekun et al. 2010) diarrhea was the second most common acute reaction experienced by the patients with 32 (46%) having grade 1 while 9 (13%) had grade 2. Grade 3 diarrhea was the worst reaction noted among all the patients and this occurred in 2 (3%) of the patients.

Limitations of our study were small sample size, single center study, chemotherapy regimens differ according to institution, the follow up time is not long enough, we did not control variations in applicator placement accuracy, target volume size, or differences in systemic therapy and scoring systems for toxicity are inconsistent across series and other series may report their data using different toxicity scales.

## CONCLUSION

The most common acute gastrointestinal toxicity after definitive chemo radiotherapy followed by intracavitary brachytherapy in the treatment of locally advanced cervical cancer were abdominal pain / discomfort, nausea and diarrhea. There was significant relation between gastrointestinal toxicity and the dose and the site of brachytherapy, which nausea toxicities were related to dose of sigmoid. Also, diarrhea toxicities related with median volume of rectum. The mean time of the progression free survival was 10.18 months and % at the end of study was 76.7.

## CONFLICT OF INTEREST

All authors declare no conflicts of interest.

## FUNDING

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