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Outcome and toxicity of chemoradiation using volumetric modulated arc therapy followed by 3D image-guided brachytherapy for cervical cancer: Vietnam National Cancer Hospital experience

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ABSTRACT

Background: Volumetric modulated arc therapy (VMAT) and 3D image-guided brachytherapy (3D-IGBT) have recently been introduced in Vietnam for the treatment of locally advanced cervical cancer. This study aims to assess the outcomes and toxicities of chemoradiation using VMAT followed by 3D-IGBT in Vietnamese cervical cancer patients.

Materials and methods: A prospective interventional study on 72 patients with 2018 International Federation of Gynecology and Obstetrics (FIGO) stage IB3–IIIC2 disease who underwent concurrent chemoradiation using VMAT, followed by 3D-IGBT according to EMBRACE-II protocol. Primary endpoints were locoregional control; secondary endpoints were systemic control and toxicity.

Results: Median body volume received 43 Gy was 1589.1 cm^3 (range 1214.8–2574.8). Median high-risk clinical target volume (CTV-HR) was 18.8 cm^3 (range 8.6–61.2) with a median dose to 90% (D90) of CTV-HR of 90.6 Gy (range 86.8–99.6). Mean doses to 2cc (D2cc) of bladder, rectum, and sigmoid were 75.8, 55.2, and 62.1 Gy, respectively. At median 19-month follow-up (range 12–25), locoregional control and systemic control were 95.8% and 81.9%, respectively. Systemic control was the lowest in N2 disease (54.5%). Grade ≥ 3 acute toxicities were less than 10%, except neutropenia (31.9%). Extended-field radiation increased significantly nausea, fatigue, and thrombocytopenia. No grade ≥ 3 proctitis or cystitis; 8.3% had grade 3 vaginal stenosis.

Conclusions: VMAT-based chemoradiation therapy followed by 3D-IGBT achieved high locoregional control with manageable toxicities in locally advanced cervical cancer. Systemic control correlated with disease stage.

Key words: cervical cancer; chemoradiation; volumetric modulated arc therapy (VMAT); 3D image-guided brachytherapy (3D-IGBT)

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Introduction

Cervical cancer is globally ranked as the fourth most prevalent cancer and is the fourth leading cause of cancer-related deaths in women worldwide according to Globocan 2020. In low- and middle-income countries, cervical cancer holds the second position in terms of both incidence and mortality rates among women, following breast cancer [1].

In Vietnam, specifically in the country's largest cities, Ho Chi Minh city and Hanoi, cervical cancer stands as the leading cause of cancer-related deaths among women in Ho Chi Minh City and holds the second position in Hanoi [2].

According to a global systematic literature review, locally advanced cervical cancer represented 37% of cases, with the highest prevalence found in Asia [3]. Patients with locally advanced cervical cancer (stage IB3 to IVA) have a higher rate of recurrence and worse survival compared to those with early-stage disease (stage IA to IB2) [4].

The choice of treatment for cervical cancer varies depending on the stage of the disease. For locally advanced cervical cancer, concurrent chemoradiation therapy including external beam radiation therapy (EBRT) concomitant with chemotherapy and brachytherapy has been the standard treatment since 1999 based on several large clinical trials [5]. Over the past two decades, there have been significant advances in equipment and techniques for radiation therapy, including the application of intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and 3D image-guided brachytherapy (3D-IGBT) in the treatment of cervical cancer. There is evidence that IMRT reduces the risk of acute and late morbidity [6]. VMAT represents a novel technology with treatment plans comparable to IMRT, but offers shorter treatment delivery time [7]. Furthermore, image guided radiotherapy (IGRT) allows tight treatment margins which enables the overall volume irradiated with EBRT [8] to be reduced. The impressive results achieved with 3D-IGBT have been demonstrated in various single-institution reports as well as in the retroEMBRACE study and EMBRACE I study [8]. This approach has become the gold standard in the definitive management of locally advanced cervical cancer. Groupe Européen de Curiethérapie/European Society for Radiotherapy & Oncology (GEC-ESTRO) recommendations I–IV, incorporated into the International Commission on Radiation Units and Measurement (ICRU) 89, have served as a fundamental framework for the implementation of IGBT [9]. In 2016, EMBRACE II study was initiated as a prospective interventional study which used advanced EBRT (IMRT and IGRT) and brachytherapy (IGBT) technique with the aim to benchmark a high level of loco-regional control while minimizing morbidity [8]. In 2021, the Chilean consensus of the Society of Radiation Oncology endorsed the use of the EMBRACE II protocol [10]. By 2023, this protocol has gained recognition as a reference template in the European Society of Gynaecological Oncology (ESGO)/ESTRO/the European Society of Pathology (ESP) guidelines for the management of patients with cervical cancer [11]. At the Vietnam National Cancer Hospital, VMAT technique and IGBT have been used in treating cervical cancer since 2018; however, the implementation of the EMBRACE II protocol in the management of cervical cancer has taken place only recently. Moreover, cervical cancer patients in Vietnam may have different characteristics compared with similar patients in other populations, but data on efficacy and toxicity of these techniques in the Vietnamese patient population is currently not available. Therefore, we conducted this study using chemoradiation therapy with VMAT technique and 3D-IGBT to evaluate the outcome and toxicity of these new techniques in the treatment of locally advanced cervical cancer.

Materials and methods

Study design and participants

This was a prospective, non-control clinical interventional study done at the Vietnam National Cancer Hospital. Eligibility criteria were biopsy-proven squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix, FIGO (2018) stage IB3, IIA2, IIB, IIIA, IIIB, IIIC1, IIIC2, Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, white blood cell count over 3000/dL, haemoglobin (Hb) level over 95 g/L, platelets count above 100,000/dL, normal liver function, and creatinine clearance above 50 mL/minute). Exclusion criteria were other primary malignancies, previous pelvic

or abdominal radiotherapy, previous total or partial hysterectomy, contraindications to magnetic resonance imaging (MRI), human immunodeficiency virus (HIV) infection, active hepatitis B and C virus or severe medical conditions endangering treatment delivery.

Procedures

Gynecological examination, pelvic MRI, abdominal computed tomography (CT), chest X-ray, neck lymph node ultrasound at diagnosis for staging were mandatory for all patients. Positron emission tomography (PET)/CT can be used in the evaluation of lymph nodes and distant metastasis.

All patients received concurrent chemoradiation therapy with cisplatin 40 mg/m^2 per week.

External beam radiation therapy (EBRT): patients received whole pelvic radiation therapy or extended-field radiation therapy in case of metastasis ≥ 3 pelvic lymph nodes, and/or common iliac lymph node metastasis, and/or para-aorta lymph node metastasis. The target volume delineation and prescription dose and dose constraint of organs at risk were applied according to the protocol of EMBRACE-II. The total radiation dose was 45 Gy in 25 fractions, 5 fractions per week. Simultaneous integrated boost to 55 Gy in 25 fractions for the pelvic lymph node and 57.5 Gy in 25 fractions for the common iliac node and/or para-aortic lymph node. External beam radiation therapy used the VMAT technique with CT simulation. Bladder protocol was applied for all patients (patients needed to empty their bladder first, drank 500 ml water and waited for 1 hour to take a CT simulation). Patients received laxatives before CT simulation and during treatment to soften stools. Cone-beam computed tomography (CBCT) was performed every fraction to check the patient's position.

Brachytherapy (BT): brachytherapy was performed after completing EBRT or at the 5th week of EBRT. All patients received pelvic MRI before the first fraction of BT to evaluate the tumor response. Patients underwent CT simulation of 2 mm slice thickness with applicator in situ. Intracavity BT or intracavity BT combined with interstitial BT (needle insertion) in case of bulky tumor or invasion of parametrium at the time of BT. The target volume delineation and prescription dose were applied according to GEC-ESTRO/ICRU 89. The 2-Gy equivalent dose (EQD2) of EBRT and BT was calculated with $\alpha/\beta = 10$ for tumor and $\alpha/\beta = 3$ for late toxicity of organs at risk. The total treatment time was limited to less than 50 days [12].

Follow-up and assessment of toxicity: patients were assessed for acute toxicity weekly during radiation therapy. Patients underwent a clinical examination, pelvic MRI at three months after treatment and then follow-up every 3 months by clinical examination and imaging to monitor recurrence and late complications of radiation therapy.

Outcomes

The primary endpoint of the study was locoregional control. Systemic control and toxicity were secondary endpoints. Locoregional control was defined as absence of any recurrent or progressive disease in the radiation field. Systemic control was defined as absence of any recurrent or progressive disease outside the radiation field. Acute toxicity was defined as that occurring during the treatment. Late toxicity was defined as any morbidity at 3 months or longer after the end of treatment. Acute and late toxicities were recorded and graded according to CTCAE v5.0 [13].

Statistical analysis

Medians and ranges were calculated for metric variables [age, tumor size, dose parameters, high risk clinical target volume (CTV-HR) volume] and absolute and relative frequencies were calculated for categorical variables [histology, The International Federation of Gynecology and Obstetrics (FIGO) stage, nodal status, and treatment characteristics]. Disease events were reported by location (local, nodal, and systemic). Time-to-event intervals were calculated from the date of diagnostic biopsy until the respective event. Patients without events were censored at the date of last follow-up. For time-to-event outcomes, the probability of a patient remaining event-free within a given time period was calculated using the Kaplan-Meier method. Time-to-event curves were compared between groups using the log-rank test. Patients lost to follow-up were censored at the timepoint when they were lost to follow-up. Morbidity was reported as absolute number of events and patients and actuarial cumulative incidence rate for grade 1–5 morbidity, for gastrointestinal tract, genitourinary tract, hematotoxicity, vagina. χ^2 and Fisher's

exact tests were used to compare the proportion of morbidity between two groups (whole pelvis and extended-field). Statistical analysis was conducted using SPSS 25.0.

Results

Our study recruited patients from July 2021 to December 2021 with 72 locally advanced cervical cancer patients who met the inclusion and exclusion criteria. The final analysis was based on data updated as of July 03, 2023. Patient characteristics are summarized in Table 1. The most frequent FIGO stage was IIIC1, which was observed in 41 patients (56.9%). Squamous cell histology accounted for 83.3% of the tumors. Para-aortic lymph node metastasis was observed in 11 patients (15.3%).

In our study, a majority of patients (94.4%) received a complete course of 5 weekly cycles of cisplatin, and only 4 patients (5.6%) received 4 cycles of cisplatin. Nineteen patients (26.4%) were treated by extended-field radiation therapy. Most patients received intracavity brachytherapy, while 5 patients (6.9%) were treated with a combination of intracavity BT and interstitial BT. The details of dosimetric data were outlined in Table 2.

The median follow-up was 19 months (range 12–25). The crude locoregional control rate in our study was 95.8% (3/72 locoregional failures). Only one patient experienced local recurrent, one patient had nodal recurrent, and one patient experienced both local and regional recurrent as well as distant metastasis at multiple sites. The locoregional control curve was provided in Figure 1.

The systemic control rate was 81.9% (13/72 systemic failures). This rate differed significantly between patients with stage N2, N1 and N0 disease, accounting for 54.5%, 76% and 100%, respectively ($p = 0.004$) (Fig. 2).

All patients in our study experienced acute toxicities, such as anorexia, nausea, vomiting, diarrhea, fatigue, and insomnia, primarily in grade 1 and 2. Thrombocytopenia and neutropenia were two common hematotoxicities observed during concurrent chemoradiotherapy (Tab. 3).

There was no significant difference between whole-pelvic radiation and extended-field radiation groups in the rates of grade 2 anorexia, vomiting, diarrhea and insomnia, and grade 3 and 4 of neutropenia. However, the extended-field irradiation group had higher rates of grade ≥ 2 nausea, fatigue, and thrombocytopenia than the whole-pelvic radiation group (Tab. 4).

After a median follow-up of 19 months (range 12–25), 10 patients (13.9%) reported mild rectal bleeding (grade 2 proctitis), 8 patients reported discomfort in the abdomen and 2 patients experienced abdominal pain. No patient reported cystitis. A small percentage (8.3%) of patients had grade 3

Table 1. Patient characteristics

Characteristics	Number of patients (%)
Age [years]	50 ± 11
Median tumor size [mm]	44.5 (30–70)
Tumor > 4 cm	52/72 (72.2%)
Parametrial invasion	
No invasion	35 (48.6 %)
Invasion one side	22 (30.6 %)
Invasion two side	15 (20.8 %)
Vaginal invasion	
No	19 (26.4 %)
Invasion 2/3 proximal vagina	51 (70.8 %)
Invasion 1/3 distal vagina	2 (2.8 %)
Pelvic fixation	
No	67 (93.1 %)
One side	4 (5.6 %)
Two side	1 (1.4%)
Hydronephrosis	2 (2.8%)
Uterine corpus invasion	13 (18.1%)
Median lymph node size [mm]	10 (5-35)
Lymph node size ≥ 20 mm	8/52 (15.4 %)
Number of pelvic lymph nodes involvement	
< 3 nodes	37 (51.4 %)
≥ 3 nodes	15 (20.8 %)
Common iliac lymph nodes involvement	14 (19.4%)
Para-aortic lymph nodes involvement	11 (15.3%)
FIGO stage 2018	
IB3	6 (8.3%)
IIA	5 (6.9%)
IIB	8 (11.1%)
IIIB	1 (1.4%)
IIIC1	41 (56.9%)
IIIC2	11 (15.3%)
Histopathologic type	
Squamous cell carcinoma	60 (83.3%)
Adenocarcinoma	11 (15.3%)
Adenosquamous	1 (1.4%)

FIGO — International Federation of Gynecology and Obstetrics

Table 2. Treatment characteristics

Treatment characteristics	Number of patients (%)
Median of total treatment time (days)	45 (41–57)
≤ 50 days	67 (93.1%)
> 50 days	5 (6.9%)
Cycles of cisplatin	
4 cycles	4 (5.6%)
5 cycles	68 (94.4%)
Extended-field radiation therapy	19 (26.4%)
Volume InitHR CTV-T [cm^3]	62 (24.9–248.4)
Volume InitLR CTV-T [cm^3]	252.2 (133.9–4353.7)
Bowel bag [cm^3]	
V15 Gy	757.5 (87.6–2037.5)
V30 Gy	347.3 ± 123.2
V40 Gy	147.2 ± 68.4
V50 Gy	0.3 (0–32.3)
Sigmoid (%)	
V30 Gy	97.6 (65–100)
V40 Gy	83.6 (17.6–99.9)
V50 Gy	0 (0–30.2)
Bladder (%)	
V30 Gy	94.4 (64–100)
V40 Gy	67.9 ± 11.9
V50 Gy	0 (0–23.1)
Rectum (%)	
V30 Gy	97.4 (74.3–100)
V40 Gy	92 (67.1–100)
V50 Gy	0 (0–17.6)
Mean bone marrow dose [Gy]	27.8 ± 1.5
Median V43 Gy body [cm^3]	1589.1 (1214.8–2574.8)
Median V50 Gy body [cm^3]	89.6 (0–625.8)
Intracavity	67 (93.1%)
Intracavity + interstitial	5 (6.9%)
Volume CTV-HR at brachytherapy [cm^3]	18.8 (8.6–61.2)
EQD2	
D50 CTV-HR [Gy]	128.9 (120–162.2)
D90 CTV-HR [Gy]	90.6 (86.8–99.6)
D98 CTV-HR [Gy]	81.7 ± 1.8
D98 CTV-IR [Gy]	62.2 (59.3–68)
D0.1 cm^3 Bladder [Gy]	90.6 ± 8.7
D2cm^3 Bladder [Gy]	75.8 ± 6.1
D0.1cm^3 Rectum [Gy]	63.6 ± 8.8
D2cm^3 Rectum [Gy]	55.2 ± 5.3
D0.1cm^3 Sigmoid [Gy]	73.1 ± 5.8
D2cm^3 Sigmoid [Gy]	62.1 ± 4
D2cm^3 Bowel [Gy]	54 ± 4.7
PIBS point [Gy]	50 (7.5–76.6)
Recto-vaginal point ICRU [Gy]	59.7 ± 3.8

ICRU — International Commission on Radiation Units and Measurement; CTV HR — high-risk clinical target volume; EQD2 —equivalent dose in 2 Gy

vaginal stenosis, which that interfered with clinical examination (Tab. 5).

Discussion

Volumetric-modulated arc therapy (VMAT), a more advanced form of IMRT, was introduced in 2007. VMAT employs continuous rotation of the accelerator head, alterations in gantry rotation speed, adjustments in the radiation field's shape through the movement of the multi-leaf collimator, and the modulation of radiation dose rate which allows improvement of the conformal dose distribution to the tumor shape, while decreasing radiation exposure to critical organs as well as reducing radiation time and radiation dose emitted by the machine (referred to as machine units — MU) [14].

V43 Gy is a parameter which was shown to be related with acute and late toxicities [15]. In 2021, a study conducted by Seppenwoolde et al. investigated 48 patients with locally advanced cervical cancer to compare the irradiated volume [16]. The findings revealed that with the 3D-CRT technique, V43 Gy was about 2500 cm^3. However, when employing the VMAT technique using EMBRACE-I protocol, V43 Gy went down to approximately 2000 cm^3, and for the VMAT technique with EMBRACE-II protocol, it further decreased to about 1800 cm^3. Our study used the EMBRACE-II protocol, therefore the volume received 43 Gy was relatively low. Specifically, for patients receiving extended-field radiation (n = 19), the median V43 Gy was 1945.3 cm^3 (1469.1–2574.8), while for patients treated with the whole pelvic radiation (n = 53), the median V43 Gy was 1448 cm^3 (1214.8–2290.9). Similarly, in 2021, Schulz and Potter demonstrated in the EMBRACE experience that the mean V43 Gy in EMBRACE-I, EMBRACE-II was 2390/1412 cm^3 for the whole pelvis and 2895/1765 cm^3 for the extended-field. The application of the EMBRACE-II protocol for external beam radiation significantly reduced the V43 Gy received by the body [17].

The use of 3D image-guided brachytherapy has marked a major advance in brachytherapy for cervical cancer. Our study demonstrated that this approach allowed for the delivery of a relatively high total dose of EQD2 radiation to the high-risk clinical target volume (CTV-HR), with a median of 90.6 Gy and a minimum dose of 86.6 Gy. The median volume of CTV-HR in our study was

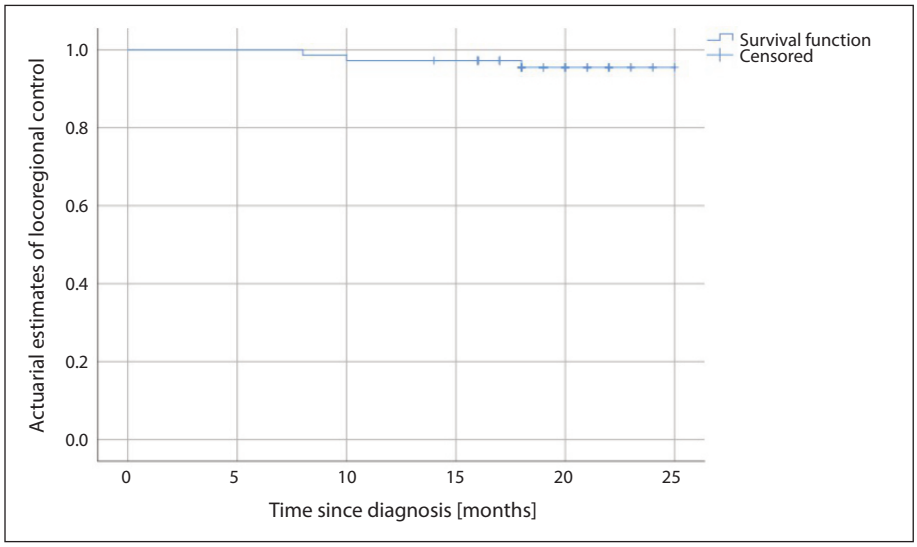

Figure 1. Locoregional control

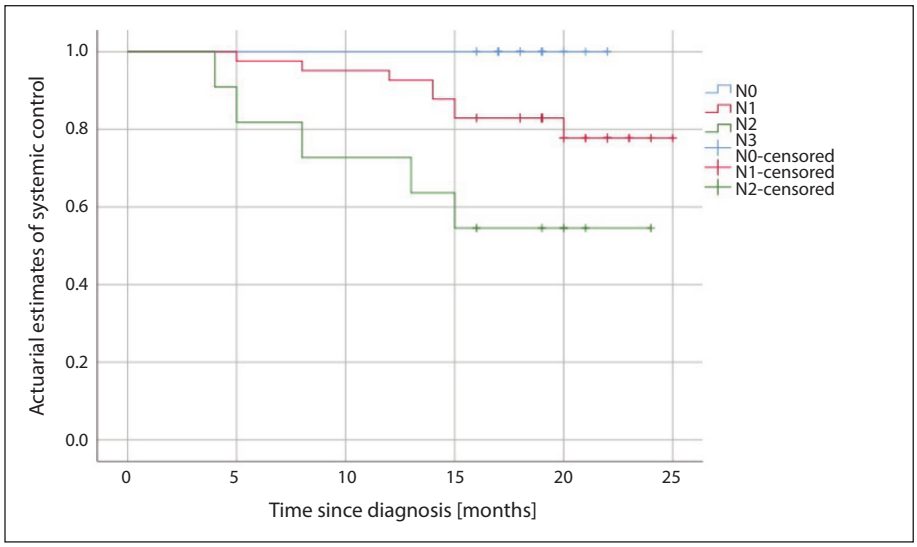

Figure 2. Systemic control and stage

Table 3. Acute toxicities

Acute toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anorexia	16 (22.2%)	50 (69.4%)	4 (5.6%)	0	0
Nausea	19 (26.4%)	41 (56.9%)	1 (1.4%)	0	0
Vomiting	20 (27.8%)	10 (13.9%)	2 (2.8%)	0	0
Diarrhea	17 (23.6%)	14 (19.4%)	1 (1.4%)	0	0
Fatigue	39 (54.2%)	26 (36.1%)	7 (9.7%)	0	0
Insomnia	31 (43.1%)	30 (41.7%)	2 (2.8%)	0	0
Thrombocytopenia	37 (51.4%)	3 (4.2%)	0	0	–
Neutropenia	16 (22.2%)	20 (27.8%)	18 (25%)	5 (6.9%)	–
Elevated AST/ALT	10 (13.9%)	1 (1.4%)	0	0	–
Elevated creatinine	6 (8.3%)	0	0	0	–

AST — aspartate transaminase; ALT — alanine transaminase

Table 5. Late toxicity

Late toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Proctitis	1 (1.4%)	10 (13.9%)	0	0	0
Cystitis	0	0	0	0	0
Enteritis	8 (11.1%)	2 (2.8%)	0	0	0
Vaginal stenosis	43 (59.7%)	23 (31.9%)	6 (8.3%)	-	-

Table 5. Late toxicity

Late toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Proctitis	1 (1.4%)	10 (13.9%)	0	0	0
Cystitis	0	0	0	0	0
Enteritis	8 (11.1%)	2 (2.8%)	0	0	0
Vaginal stenosis	43 (59.7%)	23 (31.9%)	6 (8.3%)	–	–

18.8 cm^3 (range 8.6–61.2). Additionally, this treatment approach resulted in a relatively low total dose of EQD2 radiation to critical organs, with the mean D2cc of the bladder below 80 Gy and mean D2cc of the rectum and sigmoid below 65 Gy [18, 19]. In the EMBRACE experience report, the volume of CTV-HR in EMBRACE-I and EMBRACE-II were 33 ± 19 and 30 ± 16 cm^3, respectively. The mean D90 CTV-HR was overall 89 ± 9, 93 ± 4 Gy; mean D2cc for bladder was 76 ± 10, 75 ± 9 Gy; rectum 63 ± 7, 59 ± 6 Gy; sigmoid 64 ± 7, 62 ± 7; bowel 63 ± 10, 59 ± 9; rectovaginal point 66 ± 9, 62 ± 7 Gy [17] . However, the study of Okonogi et al. (2020) which reported on the current patterns of 3D-IGBT in the treatment of locally advanced cervical cancer in East and Southeast Asia, showed a wide range of CTV-HR and organ at risk (OAR) doses across different institutions [20].

According to the Pitchaya Thongkhao's 2022 report, which analyzed 1658 patients with locally advanced cervical cancer undergoing concurrent chemoradiation therapy with brachytherapy based on point A, it was found that roughly 75% of recurrence cases occurred within two years after completing treatment, and an approximate locoregional recurrence rate of 18% [21]. With a median follow-up time of 19 months, we observed 3 cases of locoregional recurrence (accounting for 4.2%) and the locoregional control rate in our study was 95.8%. In 2021, Shiao et al. reported the excellent outcomes with CT-based brachytherapy for 114 locally advanced cervical cancer patients, with only one patient experiencing local recurrence and nine patients had regional recurrence within the pelvis (locoregional control was 91.2%) during 16.8 months of follow-up (range 0 to 90) [22]. A meta-analysis conducted by Vasha Hande et al. (2022) showed that the three-year local control rates for point-A and volume-based studies were 86% and 92%, respectively (p = 0.01). Another systematic review by Fei Li et al. (2021) focused on 3D-IGBT combined with intracavity and interstitial brachytherapy in cervical cancer, found a significant relationship between D90 CTV-HR and local control (p = 0.03). The planning aim dose of 90 Gy for D90 CTV-HR, recommended in the EMBRACE-II protocol, corresponded to 90.5% local control [23]. Similarly, the result from EMBRACE-I (2021) reported a 92% 5-year local control rate in locally advanced cervical cancer using MRI-guided adaptive brachytherapy [24]. Furthermore, in our study, we used simultaneous integrated boost (SIB) for pathologic nodes to 60 Gy EQD2 during EBRT. A study by Richa Tiwari et al. (2021) showed the significant improvement of the 3-year regional control in patients with node-positive cervical cancer treated with nodal boost irradiation and MRI-based brachytherapy compared to the non-boost arm (93% *vs.* 80%, p = 0.035) [25].

Despite the high local and regional control rate, the systemic control rate in our study was lower and depended on the stage of the disease (54.5% for N2, 76% for N1 and 100% for N0 stage). In 2019, Queiroz et al. studied the risk

factors for pelvic and distant recurrence in locally advanced cervical cancer and confirmed that positive lymph nodes were related to shorter distant-metastasis-free survival [26]. In the EMBRACE-I study, while there was no difference in local control between stages due to use of MRI-based brachytherapy, there remained a difference in disease-free survival and overall survival between limited stage and advanced stage due to limited nodal and systemic control [24]. This posed the question of systemic treatment to improve the systemic control in high-risk cases of distant metastasis.

In terms of toxicities, acute gastrointestinal and hematologic toxicity were common complications associated with chemotherapy and radiotherapy in the treatment of cervical cancer. Our study found that the symptoms including anorexia, nausea, vomiting, diarrhea, fatigue, and insomnia often appeared during concurrent chemoradiation, but were mild and can be tolerated. NRG Oncology/RTOG 1203 reported that pelvic IMRT was associated with significantly less gastrointestinal toxicity than standard radiation therapy [27].

Acute hematologic toxicities, including neutropenia and thrombocytopenia, were the two most common symptoms. Thrombocytopenia was mainly grade 1 and 2, while neutropenia could reach grades 3 and 4. Many studies have shown that IMRT/VMAT techniques can protect bone marrow, reduce bone marrow dose and decrease the rate of hematologic toxicity [28, 29]. In our study, the average dose of bone marrow was relatively low, at 27.8 ± 1.5 Gy. According to Kumar et al (2019), grade 4 hematological toxicity was related to a mean pelvic bone marrow dose greater than 31 Gy [29]. However, we did not find a significant relationship between bone marrow and neutropenia and thrombocytopenia in our study.

When comparing the two groups of radiation therapy, extended-field, and whole pelvis, regarding toxicity, only nausea, fatigue, and thrombocytopenia showed statistical significance. However, the majority of toxicities were grade 2 nausea and fatigue and grade 1 thrombocytopenia. These finding are similar to previous studies on extended-field radiation therapy [30, 31]. A study by Ballari et al. (2021) also reported an acceptable acute toxicity profile in prophylactic para-aortic extended-field VMAT with SIB technique in locally advanced cervical cancer [32].

In our study, with a median follow-up time of 19 months, no patient experienced grade 3 proctitis or any grade of bladder late toxicity. Six patients (accounting for 8.3%) experienced grade 3 vaginal stenosis, of whom three had tumors invading the middle and lower third of the vagina at diagnosis. According to two large-scale multicenter studies, retroEMBRACE and EMBRACE-I, on 3D-IGBT in cervical cancer, actuarial cumulative 5-year incidence of grade 3–5 morbidity on the bladder, gastrointestinal, and vaginal are 5%, 7%, 5% and 6.8%, 8.5%, 5.7%, respectively [24, 33]. These studies indicated that 3D brachytherapy reduced the late complications of radiation therapy by decreasing the dose to critical organs. In our study, D2cc of the bladder, rectum, and sigmoid colon were low (the total dose of EQD2 was 75.8, 55.2, and 62.1 Gy, respectively), which might predict the low rate of late toxicity. However, the study's limitation was the short follow-up time. It needs more time of follow-up to confirm the role of VMAT combined with 3D brachytherapy in reducing the late toxicity of radiotherapy in cervical cancer.

Conclusion

Concurrent chemoradiation therapy using VMAT and 3D-IGBT resulted in a high locoregional control rate with manageable toxicities in patients with locally advanced cervical cancer. The systemic control depended on the stage of the disease. Failures primarily occurred outside the irradiated area in stage IIIC2, which might indicate the need for additional treatment to improve systemic control.

Conflicts of interest

The authors declare no financial or other conflicts of interest.

Funding

None declared.

Ethical permission

Informed consent was obtained from all patients. The study was approved by the Hanoi Medical University ethics committees, IRB-VN01.001/IRB00003121/FWA 00004148.

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