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DEMOGRAPHIC PROFILE AND CHEMORADIOTHERAPY TREATMENT OUTCOME OF CERVICAL CANCER PATIENTS: A LOW-RESOURCE SETTING PERSPECTIVE

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ABSTRACT

Introduction: Cervical cancer is a leading cause of morbidity and mortality especially in developing countries with steady rise in its incidence and mortality over the years. Most women with cervical cancer in sub-Saharan Africa present late with locally advanced disease and require external beam radiotherapy and brachytherapy for effective curative treatment.

Methods: The records of 243 cervical cancer patients that received treatment between January 2008 and December 2012 were retrospectively reviewed, only patients with locally advanced disease (FIGO stage IIA – IVA) were included in the study. Patients' socio-demographic information and response to treatment were extracted and documented in a semi structured proforma questionnaire.

Results: The mean age of cervical cancer patients was 50.7 ± 11.1 years. Majority of the patients were multiparous (95.1%) and full-time housewives (68.3%) and presented late. Mean duration of symptoms was 9.5 months (range:1-48months). Majority of the patients received induction chemotherapy (70.8%) and few had standard concurrent

chemoradiation (7.8%) and brachytherapy (10.3%). Almost all the patients had curative dose of external beam radiotherapy (90%) but less than half (46.7%) had complete response following treatment.

Conclusion: Most of the cervical cancer patients presented late. Treatment outcome as evaluated by tumor response was relatively poor due to inability to access standard concurrent chemoradiation and brachytherapy treatments. Early detection of disease and timely access to treatment would improve the treatment outcome.

KEYWORDS: Radiotherapy, Brachytherapy, Chemotherapy, Outcome, Response

INTRODUCTION

Cervical cancer is a leading cause of morbidity and mortality especially in developing countries with steady rise in its incidence and mortality over the years.[1-4] There was an estimated 662,301 new cervical cancer cases and 348,874 deaths globally in 2022.[5] Despite contributing 14.7% to the total female population globally, the Sub- Saharan Africa contributed 16.9% to the global incidence and 21.8% of global death from cervical cancer. [5,6] This unfavorable disproportionate burden of cervical cancer relative to its population highlights the fact that cervical cancer is very much prevalent in Sub- Saharan Africa with its associated morbidity and mortality.[6,7]

In Nigeria, it is the second most commonly diagnosed cancer and third leading cause of cancer death, accounting for 127,763 new cases and 79,542 deaths in 2022.[8] Reports from population-based cancer registries in Nigeria (Ibadan and Abuja cancer registries) showed that cervical cancer is the second most common cancer in females after breast cancer.[9] It is the leading cause of gynecological cancers in Nigeria, accounting for about 65-75% of all gynecological cancers, incurring heavy burden on patients.[10- 13]

A large proportion of cervical cancer can be characterized as a sexually transmitted disease, with early age of first intercourse, history of multiple sexual partners, and large number of pregnancies as risk factors. [14] The role of human Papilloma virus (HPV) as a causative agent of cervical cancer is well established and the detection of HPV types 16 and 18, predominantly, carries prognostic importance in some studies. Notably, HPV 16 predominated in squamous-cell carcinoma, whereas in adenocarcinoma and adenosquamous carcinoma, HPV 18 predominated.[14]

Most women with cervical cancer in sub-Saharan Africa present late with locally advanced disease and require external beam radiotherapy and brachytherapy for effective curative treatment.[15]

Concurrent chemoradiotherapy (CRT) represents the standard of care for locally advanced cervical cancer. [16] An individual patient data meta-analysis of CRT showed that the benefit of adding chemotherapy to radiation improves 5-year overall survival (OS) by 6%, the observed 5-year disease- free survival (DFS) rate of 58%.[16] The use of neoadjuvant sequential chemotherapy (NACT) has already been evaluated in cervical cancer.[16,17] The rationale of induction /neoadjuvant chemotherapy (NACT) in cervical cancer is that it might reduce tumor volume while controlling micro metastatic disease before the definitive treatment.[16,17] Also neoadjuvant chemotherapy for patients with locally advanced cervical cancer has comparable benefits to concurrent chemoradiotherapy (CCRT), but with fewer

side effects.[17] The National Cancer Institute showed that in addition to radiotherapy, cisplatin chemotherapy produced a therapeutic effect in women with locally advanced cervical cancer (LACC) in five randomized trials.[18]

Of course, the standard treatments for early cervical cancer have traditionally comprised radical hysterectomy with lymph node dissection or cisplatin - based chemoradiation.[17] Unfortunately, poor prognosis was observed in patients with tumors more than 4cm in diameter and a poor survival rate of 50% – 60% was noted in patients with large tumors.[17] To improve the therapeutic results, a new approach with neoadjuvant chemotherapy (NACT) followed by radical surgery or chemoradiation has been introduced.[17]

In some Radiotherapy centers in Nigeria and other low- and middle-income countries of Sub-Saharan Africa, most patients with locally advanced carcinoma of the cervix undergo neoadjuvant sequential chemotherapy while waiting for long period of radiotherapy.[19]

This study therefore aims to evaluate the demographic profile and outcome of chemoradiotherapy among cervical cancer patients being managed in Department of Radiotherapy and Oncology of Ahmadu Bello University Teaching Hospital, Zaria with a view of finding ways to improve its management in a low resource setting.

METHODOLOGY

Study design

This was a retrospective cross- sectional descriptive study.

Study Area

The study was carried out in the Radiotherapy and Oncology Department of Ahmadu Bello University Teaching Hospital (ABUTH) Zaria, Nigeria. This is a tertiary health institution located in Zaria, Kaduna State, North-Western part of Nigeria.

Study Population

The study population included all patients with locally advanced cervical cancer treated with radiotherapy at the Department of Radiotherapy and Oncology within a 5- year period from January 2008 to December 2012.

Inclusion criteria

All histologically confirmed locally advanced cervical cancer (FIGO Stages IIA-IVA) patients, who had received at least three cycles of chemotherapy and had received radiotherapy to the primary site.

Exclusion criteria

Patients who started primary treatment before being referred to the facility, those who received palliative doses of radiotherapy, and those with missing information on treatments received were excluded from the study.

Data Description and Method of Collection

All available radiotherapy case notes and treatment records of locally advanced cervical cancer patients that had radiotherapy seen from January 2008 to December 2012 were retrieved and analyzed. Information obtained from radiotherapy case notes and treatment records included patients' bio-data: including age at presentation, patient's and relative's telephone numbers, ethnic group, occupation, marital status, employment, educational level and socioeconomic level. Risk factors including age at first sexual intercourse,

menopausal status at diagnosis, and retroviral status at diagnosis. Clinicopathological characteristics including duration of illness, size of tumor measured using trans-abdominal ultrasound scan by trained radiologist, stage at presentation, nodal status, histology type and grade of tumor. These were determined from history, physical examination, radiological and blood test during pretreatment evaluation, and follow up periods. The patients were retrospectively restaged at time of presentation using the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system.

The details of treatment received was taken into consideration; radiotherapy (total dose, and duration), chemotherapy regimen and number of cycles received, or combination of these. Radiotherapy was administered using Cobalt-60 teletherapy unit while brachytherapy (BRT) was delivered using low dose rate remote after loading Cesium-137. Chemotherapy was administered 3-weekly as neoadjuvant, concurrent or adjuvant to radiotherapy as single agent cisplatin or combination chemotherapy using cisplatin or carboplatin with other agents including 5-FU, paclitaxel and doxorubicin commonly. Also, treatment outcome was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) which measured outcome as complete response (disappearance of all target and nontarget lesions, pathological lesion reduced to < 10mm, no new lesion); partial response (at least 30% decrease in diameter of target lesion compared to baseline, non-progressive disease of non-target lesion, no new lesion), progressive disease (appearance of new lesions or 20% increase in diameter of lesion or 5mm absolute increase diameter); or stable disease (not meeting criteria for partial response or progressive disease).

Data Management and Analysis

The data obtained were analyzed using SSPS version 20.0. Sociodemographic, clinical and treatment variables of patients were presented in tables and graphs using frequency and percentages.

Ethical Consideration

Ethical approval was obtained from Ahmadu Bello University Teaching Hospital Health Research and Ethical Committee. Care was taken to ensure confidentiality of information obtained from patients' case notes. Unique identifiers of patients were not included among the data collected. The data was stored in a password protected computer, only accessible to the lead researcher or his research team upon authorization.

RESULTS

A total of 243 cervical cancer patients were included in the study. Table 1 shows the socio-demographic characteristics of the patients. The age of cervical cancer patients ranged between 25.0-80.0 years with the mean age being 50.7± 11.1 years. Majority of the patients 231 (95%) were married. About a third 80 (32.9%) had sexual debut at age of 17 years or less, while about half 120 (49%) had sexual debut between 18 to 20 years. Only 19(7.8%) of patients were retroviral positive at the time of diagnosis, while about one-fifth 50 (20.6%) of the patients had at least one Pap smear done prior to diagnosis of cervical cancer.

Table 1: Sociodemographic characteristics of respondents

Variable	Frequency (%)
Age (years)	
< 40	35 (14.4)
40- 49	69 (28.4)
50- 59	83 (34.4)
≥ 60	56 (23.0)
Marital status	
Married	231 (95.0)
Single	6 (2.5)
Widowed	6 (2.5)
Age at sexual debut (years)	
≤ 17	80 (32.9)
18- 20	120 (49.0)
≥ 21	43 (17.7)
Parity	
Nulliparity	12 (4.9)
Parous	231(95.1)
Education	
Non- formal	148 (60.9)
Formal	95 (29.1)
Occupation	
Civil servant	5 (2.1)
Farming	15 (6.2)
Trading	13 (5.3)
Others	44 (18.1)
Not employed	166 (68.3)
Retroviral status	
Positive	19 (7.8)
Negative	224 (92.2)
Pap smear prior to diagnosis	
Yes	50 (20.6)
No	193 (79.4)

Table 2. Clinicopathological characteristics of patients

Variable	Frequency (%)
FIGO stage	
IIA	18 (7.4)
IIB	106 (43.6)
IIIA	39 (16.0)
IIIB	70 (28.8)
IVA	10 (4.1)
Histology type	
Squamous cell carcinoma	213(87.7)
Adenocarcinoma	11 (4.5)
Others	19 (7.8)
Histology grade	
Well differentiated	12 (4.9)
Moderately differentiated	7 (2.9)
Poorly differentiated	31 (12.8)
Undocumented	193 (79.4)
Width of tumor at diagnosis	
≤ 4 cm	60 (24.7)
➢ 4cm	183 (75.3)

Only 18 (7.4%) presented with early disease (FIGO stage IIA), most 225 (92.6%) had locally advanced disease at diagnosis (FIGO stage IIB – IVA) (Table 2). Most of the patients 223 (91.8%) received platinum-based chemotherapy while 20 (8.2%) received other forms of chemotherapy. Most of the patients 172 (70.8%) received induction (neoadjuvant) chemotherapy (Figure 1), while only 19 (7.8%) of the patients received concurrent chemoradiation as a form of radiotherapy treatment (Figure 2). Only 25 (10.3%) of the patients received low-dose brachytherapy following external beam radiotherapy (Figure 3). Majority 159 (64.5%) received 50Gy of External Beam Radiotherapy, while 59 (24.3%) received external beam radiotherapy of 54Gy (Figure 3).

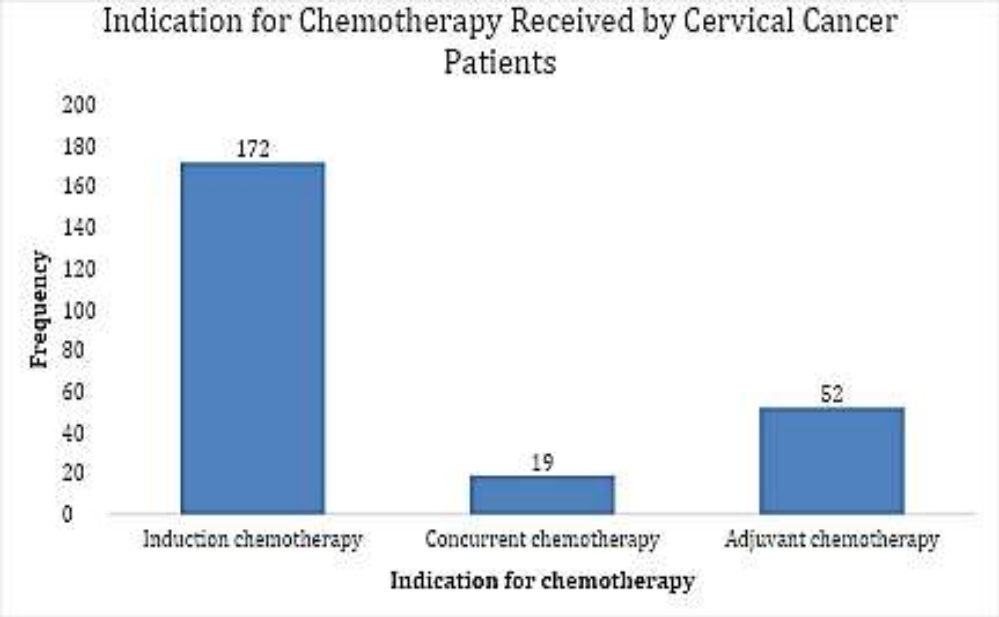

Figure 1. Indication for chemotherapy for cervical cancer patients

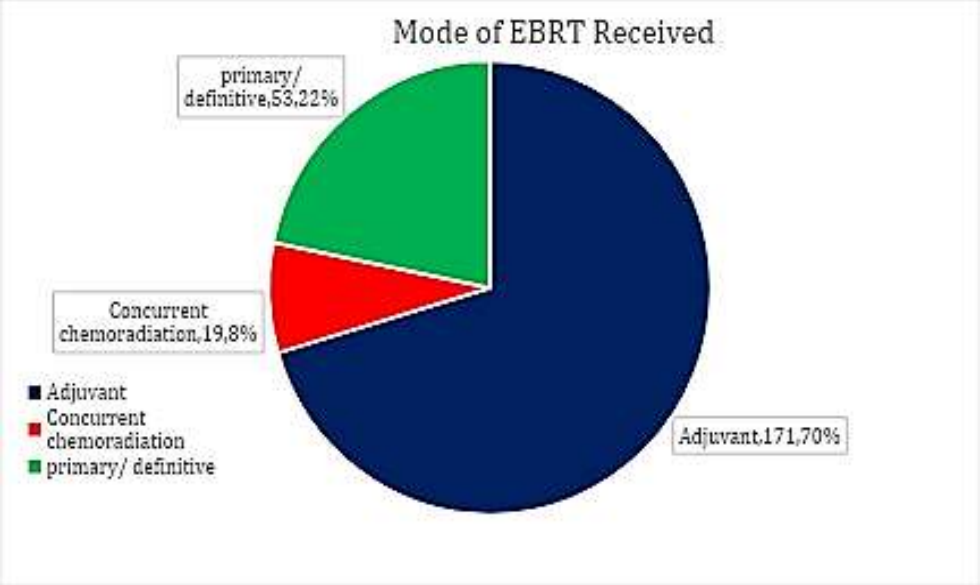

Figure 2. Mode of External Beam Radiotherapy (EBRT) Received by Cervical Cancer Patients (Primary/definitive EBRT means EBRT given first before any other treatment; adjuvant EBRT given following chemotherapy, concurrent chemoradiation EBRT along with chemotherapy)

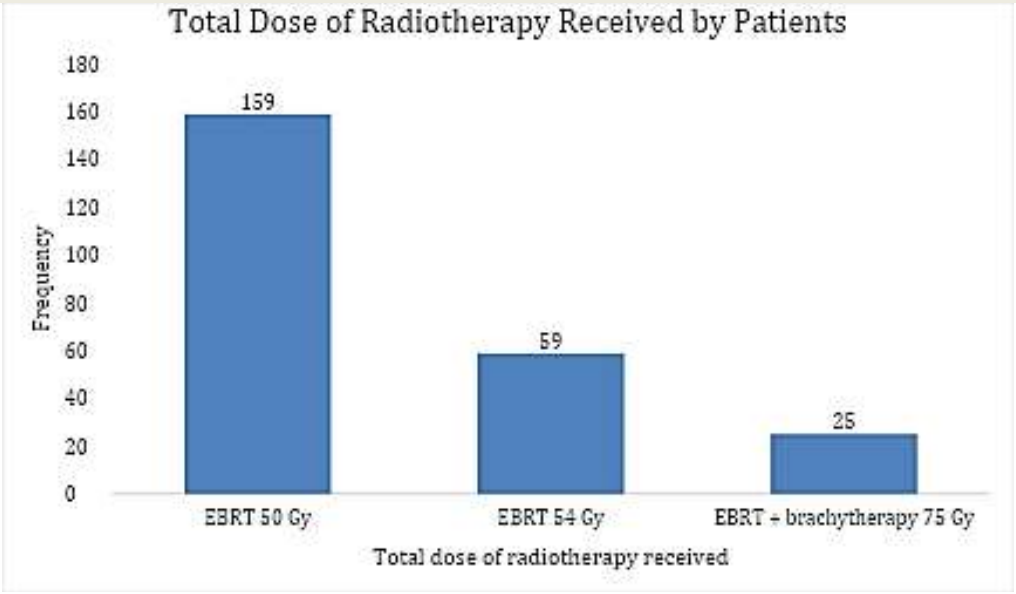

Figure 3. Total Dose of Radiation Received by Cervical Cancer Patients

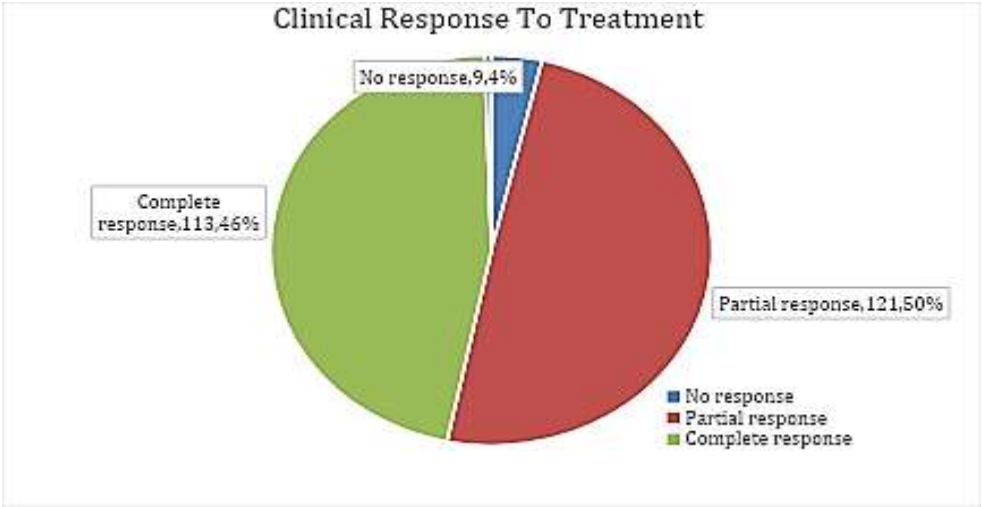

Figure 4. Clinical Response of Cervical Cancer Patients Following Treatment (NB No response = RECIST stable disease or progressive disease)

There were 113 (46%) of patients who had complete response following treatment while 121(50%) had partial response and 9 (4%) had no response to treatment (Figure 4).

DISCUSSION

The average age of cervical cancer patients in this study was 50.7 years which was consistent studies in other regions of Nigeria,[20-22] Sub-Saharan Africa [23,24] and other developing countries,[25,26] where the mean age of cervical cancer patient ranged from 40 to 51 years. This demonstrates that cervical cancer in low resource countries affects women at their

prime when they play vital roles in their families.

Most of the women in this study were multiparous (95.1%) and significant number had coitarche age less than 18 years, with majority between ages of 18-20 years. This is consistent with other studies that demonstrated that established risk factors are very much prevalent among cervical cancer patients in low resource settings.[24,27-29] Furthermore, the HIV prevalence among cervical cancer patients in this study was 7.8% which was quite low compared to South African studies with a high prevalence ranging from 28% 52.4%.[30,31] The significance of HIV infection in cervical cancer was stated by the World Health Organization; women with HIV infection have six -fold increased risk of cervical cancer compared to those without HIV. This is so because they have increased risk of acquiring human Papilloma virus, increased likelihood of progression of premalignant lesions to cancer and high rate of recurrence following treatment.[32]

Only about a one- fifth of patients ever had Pap smear screening for cervical cancer prior to diagnosis. It is important to note that having a Pap smear done at least once does not represent the standard recommended by the WHO which pegs frequent Pap smear screening in low resource setting once every three years for women aged 30 years and above, and even shorter interval for those considered at high risk.[33] Despite these, having prior Pap smear in only about 20% of cervical cancer patients is far below the target of the global strategy for elimination of cervical cancer which states that at least 70% of women globally should be screened for cervical cancer regularly.[34] The finding in this study is generally in tandem with other studies in Nigeria which showed poor uptake of cervical cancer screening among women in the general population.[35-37] Effective population-based screening helps to detect premalignant lesions and early cervical cancer which can be treated easily using cost-effective approaches.[37] Furthermore, it helps to raise the awareness and knowledge levels of women in the society about cervical cancer and its management.[36] This will help reduce the presentation delays and late presentation predominantly experienced by cervical cancer patients in low-resource settings.[38]

The commonest stage at diagnosis was FIGO stage IIB while over three- quarter of patients had tumour size of more than 4 cm in diameter. These findings indicate that most of the cervical cancer patients have advanced and bulky disease; usually managed using multiple modalities of treatment. Most of the patients (70%) in this study received induction/neoadjuvant chemotherapy. In practice, neoadjuvant chemotherapy in resource poor settings, like obtainable in this study, is usually given to patients with bulky disease to reduce tumor size before commencing radiotherapy.[16-18] However, in our clinical practice, it is given to patients who either are unable to afford radiotherapy straight away as a form of treatment while sourcing for funds; or those who are on a long queue awaiting their turn for definitive treatment, or during prolonged periods of radiotherapy machine breakdown. Further studies are recommended to demonstrate the effectiveness of neoadjuvant chemotherapy use in treatment of cervical cancer in low resource settings.

Though, concurrent chemoradiation is the gold standard in the management of predominantly locally advanced disease, only 7.8% of patients

in this study received this combination of treatment.[39] The study demonstrated the effective role of radiotherapy in the management of cervical cancer as 96% of patients who received radiotherapy had some form of clinical response to treatment. This finding has been affirmed by several other studies that clearly demonstrated that radiotherapy was effective in the management of cervical cancer. [40,41] The stipulated total dose for treatment of cervical cancer is 80 to 90Gy given as a combination of external beam radiotherapy (EBRT) and brachytherapy.[42,43] Most of the patients (92.8%) received EBRT only with a total dose of 50Gy or 54Gy, while only a few (7.8%) received the combination of EBRT and brachytherapy with a total dose of 75Gy. The optimum dose for treatment for cervical cancer patients in this context could not exceed 75Gy because the machine used for EBRT was Cobalt-60 machine with 2D planning. These findings point to the fact that most patients neither benefitted from the gold standard of care, nor the optimal total dose of radiation for their treatment. Many reasons may be adduced for these findings from our clinical practice. Firstly, not all patients have good performance status to withstand the rigors of standard of care. Secondly, some patients, after undergoing EBRT still retained bulky diseases and were likely to be ruled out from brachytherapy. Thirdly, some patients were unable to proceed with brachytherapy after EBRT due to financial toxicity, as out-of-pocket expenditure was the predominant mode for funding cancer care. Patients usually rely on support and contributions from family members, friends and organizations. While some patients simply did not feel the need for further treatment after gaining significant symptomatic improvement. In the context of the above highlighted challenges, it is therefore quite unsurprisingly that only 46% of patients with potentially curable tumors had complete response following treatment.

The strength of this study is that it accrued a large number of patients across Northern Nigeria over a 5-year period thereby giving it a good generalizability (external validity) in the Nigerian context.

Limitation of the study

It was a retrospective study and many patients were excluded due to grossly inadequate data. This could potentially mean excluding patients with peculiar characteristics from the study thereby introducing recruitment bias.

CONCLUSION

This study highlighted the outcome of chemoradiotherapy in the management of locally advanced cervical cancer; while the treatment outcome is optimistic as shown by the complete clinical response of around 46%, it is still inadequate, and this is due to the sub-optimal utilisation of concurrent external beam chemoradiation and brachytherapy. Therefore, efforts must be concentrated on the optimal application of chemoradiotherapy, creating awareness of the disease, cervical cancer screening programs and early presentation. A further study on long-term follow up and survival analysis would provide comprehensive information on the treatment outcome of patients with cervical cancer treated with chemoradiotherapy.

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