Normalized Therapy Dose (EQD2) from management of locally advanced cervical cancer: comparison with ABS recommendation.

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Abstract: Optimal radiotherapy dose fractionation regime (DFR) for definitive management of cervical cancer is not well known. However, several investigators have demonstrated that the biologically equivalent dose in 2-Gy fractions(EQD2) required to achieve local control probability of more than 90% for advanced disease is about 87Gy to the high risk tumour volume. Patients with locally advanced cervical cancer (LACC) have been managed at the University College Hospital, Ibadan Nigeria with combination of external beam radiation and high dose rate (HDR) intracavitary brachytherapy using different DFR. This study is aimed at calculating EQD2 received by 250 patients with LACC managed with different DFR between 2008 and 2010. Patients' data were extracted from case files and mathematical method was used to calculate EQD2. Results obtained were compared with EQD2 values (80–90Gy) recommended by the American Brachytherapy Society (ABS) for LACC. Out of eleven different DFR employed at the centre, only five resulted in EQD2 values (81.00Gy, 87.60 Gy, 81.30 Gy, 88.80 Gy and 83.10 Gy) that are within ABS recommendation; five fell below (65.60 Gy, 70.30 Gy, 75.60 Gy, 78.40 Gy and 77.80 Gy) and one is higher (99. 80 Gy). It means out of 250 patients managed during this period, only 45% received recommended dose required to cure macroscopic disease. This study shows that to improve therapeutic ratio, total EQD2 for DFR(of choice) must be calculated before treatment. With the on-going follow-up, further study is aimed at assessment of late complications, 5- year survival and rate of recurrence in these patients.
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Introduction

Locally advanced cervical cancer remains a significant health problem for many countries in the developing world and for low-income populations of Western countries (Mohar A and Frias-Mendivil M., 2000). Carcinoma of the uterine cervix is the second most common cancer seen among women in developing countries, such as Nigeria and it accounts for 62.7 % of all malignancies seen at the University College Hospital (UCH) Ibadan (Babarinsa IA et al, 1998).

Radiotherapy is an effective treatment modality for all stages of carcinoma of the cervix and most especially at advanced stages III and IV, in which surgery is not possible (Saibishkumar EP et al, 2006). Radiotherapy is usually administered in the form of combination of external beam radiation and brachytherapy (low dose rate, pulse dose rate or High dose rate) and over the years, these combined treatment modalities have proven to be effective for patients with carcinoma of the cervix (Vandana SJ et al, 2007). The treatment outcomes of these modalities are often considered in terms of 5-year survival, local tumour control, and normal tissue late complication.

The conventional radiotherapy regimen, otherwise known as daily fractionation, is the preferred form of radiation therapy in the management of cancer of the cervix worldwide. However, between the year 1988 and 1992, hypo-fractionated radiotherapy was introduced into the management of patients with cancer of the cervix at UCH, Ibadan. This was meant to accommodate huge influx of patients requiring radiation therapy from the only functioning Teletherapy facility available at the centre (Campbell OB et al, 2000).

Since the introduction of this method, UCH has been able to maximize the use of its only functioning Teletherapy machine to manage large population of cancer patients. In addition to this, UCH has been able to reduce the waiting period of patients from 3 months to 6 weeks.

Brachytherapy in the form of low dose rate and high dose rate (HDR) seem to be relatively equivalent treatments in terms of survival outcomes (Akila NV et al, 2012). However, with high dose rate

(HDR) brachytherapy, there is a significant variation of the total tumour dose and dose delivered per fraction.

To achieve good therapeutic ratio in terms of target coverage and sparing of organs at risk, varieties of dose fractionation schedules and methods for integrating brachytherapy with external beam radiotherapy do exist. The best dose fractionation schedule would be the one that gives optimal tumour dose in 2-Gy per fraction equivalence (EQD2). Given the potential for short and long term complication to normal tissues from large HDR doses per fraction, the radiation oncologist must carefully assess and minimize normal tissue dose administered per fraction through prior calculation of total EQD2 from both external beam radiotherapy and brachytherapy.

The American Brachytherapy Society (ABS) in its latest publication (Akila NV et al, 2012) stated that to maximize local control of bucky diseases, that is, tumours larger than 4 cm at the time of brachytherapy, tumour dose escalation to EQD2 of 80 – 90 Gy is recommended to either point A or D_{90}. Point A is the standard reference point located at 2 cm above mucosa of lateral vaginal fornice and 2 cm lateral to mid-plane of the body (Meredith and Massey, 1997) and D_{90} is the minimum dose delivered to 90% of the volume of interest (Richard P et al, 2006). The ABS recommended EQD2 is the summation of EQD2 received from both external beam radiotherapy and HDR intracavitary brachytherapy.

The aim of this study is to estimate the extent to which local tumour control is achieved in 250 patients with locally advanced cervical cancer, who were managed with combination of external beam radiotherapy and high dose rate intracavitary brachytherapy at UCH and then compare the result with the ABS recommended EQD2 values.

Material and Methods

This is a retrospective study carried out at the Department of Radiotherapy, University College Hospital Ibadan (UCH), Nigeria. This centre is the first tertiary hospital in Nigeria to acquire high dose rate (HDR) brachytherapy machine through the support of the International Atomic Energy Agency (IAEA), Vienna Austria.

The HDR remote afterloading brachytherapy machine was manufactured by Bebig Germany. It is a five-channel Gynesource and housed Cobalt-60 radionuclide in contrast to the conventional Iridium-192 radioactive source. The machine was commissioned for clinical use in the year 2008.

In addition to HDR brachytherapy machine, UCH has one Cobalt-60 Teletherapy (Theratron 780C) machine manufactured by the Atomic Energy of Canada Ltd (AECL), Kanata, Ontario, Canada for external beam therapy.

The case files of patients with locally advanced cervical cancer, who were managed with external beam radiotherapy and HDR intracavitary brachytherapy between the year 2008 and 2010 were considered in this study. All information about patient, such as age, radiation dose per fraction from external beam therapy and HDR intracavitary brachytherapy, mobile phone number and contact address, were extracted from these case files. All radiation doses were prescribed by the Radiation Oncologist in charge of each patient.

All patients received external beam radiation therapy dose to the whole pelvic region over 4 weeks. Following the completion of external beam radiotherapy, patient received high dose rate brachytherapy, provided there are no contra-indication during post treatment follow-up visit. All HDR intracavitary brachytherapy doses were prescribed to point A, the Manchester system of dose reference point. The prescribed dose was delivered mostly in 3 fractions over three weeks. Only few patients had 4 fractions of HDR brachytherapy.

The software program developed by Nag and Gupta (Nag S and Gupta N, 2000) was used in this study to calculate EQD2 from administered external beam radiotherapy and all fractions of high dose rate brachytherapy. Both are summed up to obtain total EQD2. This program incorporates the linear–quadratic (LQ) formula to calculate both the biologically equivalent dose (BED) and tumour dose in 2-Gy per fraction radiobiological equivalence dose (EQD2) for tumour and late responding tissues. The LQ formula (Sudahar H et al, 2012) for calculating EQD2 is given below:

$$EQD\ \ 2\ =\ \frac{D\,[1\ +\ d\ /(\ \alpha\ /\ \beta\ )]}{[1\ +\ 2\ /(\ \alpha\ /\ \beta\ )]}$$

Where D is the total prescribed dose; d is the dose per fraction; and α/β (alpha/beta ratio) = 10 (for tumour) and 3 (for late responding tissue).

Results

The mean age of patients considered in this study was 55±10 years. The external beam radiation therapy dose received by patients ranged from 45–60 Gy given in either 12, 15 or 22 fractions, while the HDR intracavitary brachytherapy total dose ranged from 12 - 26 Gy delivered in 3 or 4 fractions.

The combination of treatment schedule received by patients from external beam therapy and HDR intracavitary brachytherapy are presented in

Table 1. Also presented in this table is the number of patient who received a particular dose fractionation regimen. Table 2 shows radiation dose in 2-Gy fractions equivalence (EQD2) for both the tumour and late responding tissues calculated for different dose fractionation regimen from external beam radiotherapy and HDR intracavitary brachytherapy.

The combined EQD2 obtained from different regimen of HDR intracavitary brachytherapy and external beam therapy are presented in Table 3. The total EQD2 values obtained in this study was compared with American Brachytherapy Society (ABS) recommended EQD2 value and is presented in Table 4.

Table 1: Dose Fractionation Regimen from External Beam Radiotherapy and HDR Intracavitary Brachytherapy

External Beam Radiotherapy	HDR Intracavitary Brachytherapy	No of patient
45 Gy in 12#	24 Gy in 3 #	20
45 Gy in 12 #	21 Gy in 3 #	17
45 Gy in 12 #	19.5 Gy in 3 #	20
45 Gy in 12 #	18 Gy in 3 #	15
45 Gy in 12 #	15 Gy in 3 #	80
45 Gy in 12 #	12 Gy in 3 #	44
45 Gy in 22 #	26 Gy in 4 #	18
50 Gy in 12 #	21 Gy in 3 #	3
50 Gy in 12 #	18 Gy in 3 #	18
50 Gy in 12 #	15 Gy in 3 #	12
60 Gy in 15 #	21 Gy in 3 #	3
Total		**250**

#: Fractions

Table2: EQD2 for different radiotherapy dose fractionation Regimen

	EQD2			EQD2	
EBRT	**Tumour (Gy)**	**Late responding tissue (Gy)**	**HDR**	**Tumour (Gy)**	**Late responding tissue (Gy)**
60 Gy in 15 #	70.00	84.00	26 Gy in 4#	35.80	49.40
50 Gy in 12 #	59.10	71.80	24 Gy in 3#	36.00	52.80
45 Gy in 12 #	51.60	60.80	21 Gy in 3#	29.80	40.40
45 Gy in 22 #	45.30	45.60	19.5 Gy in 3#	26.80	37.10
			18 Gy in 3#	24.00	32.40
			15 Gy in 3#	18.80	24.00
			12 Gy in 3#	14.00	16.80

#: Fractions; EBRT: External Beam Radiation Therapy

Table 3: **Combined EQD2 from different treatment regimen received by patient**

EBRT (A)	High Dose Rate Brachytherapy (B)	Combined EQD2 (from A + B)	
Fractionation Regimen	**Fractionation Regimen**	**Tumor Gy**	**Late Responding Tissue, Gy**
45 Gy in 12 #	24 Gy in 3 #	87.60	113.60
45 Gy in 12 #	21 Gy in 3 #	81.30	102.80
45 Gy in 12 #	19.5 Gy in 3 #	78.40	97.80
45 Gy in 12 #	18 Gy in 3 #	75.60	93.20
45 Gy in 12 #	15 Gy in 3 #	70.30	84.80
45 Gy in 12 #	12 Gy in 3 #	65.60	77.60
45 Gy in 22 #	26 Gy in 4 #	81.00	95.00
50 Gy in 12 #	21 Gy in 3 #	88.80	113.80
50 Gy in 12 #	18 Gy in 3 #	83.10	104.20
50 Gy in 12 #	15 Gy in 3 #	77.80	95.80
60 Gy in 15 #	21 Gy in 3 #	99.80	126.00

#: Fractions

Table 4: Comparison between EQD2 obtained in this study with ABS Recommended values

External Beam Radiotherapy Fractionation Regimen	HDR Intracavitary Brachytherapy Fractionation Regimen	Combined EQD2 from this study for Tumour, Gy	Combined EQD2 from this study for Late Responding Tissue, Gy	Variation from ABS Recom. Values (80 – 90 Gy)
45 Gy in 12 #	24 Gy in 3 #	87.60	113.60	Within
45 Gy in 12 #	21 Gy in 3 #	81.30	102.80	Within
45 Gy in 12 #	19.5 Gy in 3 #	78.40	97.80	Less than
45 Gy in 12 #	18 Gy in 3 #	75.60	93.20	Less than
45 Gy in 12 #	15 Gy in 3 #	70.30	84.80	Less than
45 Gy in 12 #	12 Gy in 3 #	65.60	77.60	Less than
45Gy in 22 #	26 Gy in 4 #	**81.0**	**95.00**	Within
50 Gy in 12 #	21 Gy in 3 #	88.80	113.80	Within
50 Gy in 12 #	18 Gy in 3 #	83.10	104.20	Within
50 Gy in 12 #	15 Gy in 3 #	77.80	95.80	Less than
60 Gy in 15 #	21 Gy in 3 #	99.80	126.00	Greater than

#: Fractions

Discussions

The conventional radiotherapy daily fractionation combined with brachytherapy is the preferred treatment modality in the management of locally advanced cervical cancer. However, in a low income resource radiotherapy centre, where few treatment machines are available for the management of large number of cancer patients, the introduction of hypo-fractionated radiotherapy would be necessary.

This practice will not only maximize the use of limited treatment facilities but it will also reduce the waiting period of patients. This is the situation in most developing countries of the world, where cancer incidence is on the increase but the available treatment facilities are not sufficient to meet the cancer challenges (Campbell OB et al, 2000). This is our experience at UCH, where one Cobalt-60 Teletherapy machine services about fifty patients per day.

Brachytherapy is an important component in the curative management of carcinoma of the cervix and significantly improves survival (Campbell OB et al, 2000). The success of brachytherapy, especially HDR, requires delivery of high radiation dose directly to the tumour, while sparing to some degree, the surrounding normal tissues (Shivkumar SS et al, 2002).

All patients considered in this study received both external beam radiotherapy and HDR brachytherapy but with different fractionation regimen. As seen in Table 1, the external beam fractionation ranged from 60 Gy in 15 fractions to 45 Gy in 22 fractions while brachytherapy dose fractionation ranged from 26 Gy in 4 fractions to 12 Gy in 3 fractions. The external beam radiotherapy dose was given within 4 weeks to the whole pelvic region of patients.

Most of the radiation dose was administered in hypo-fractionation regimen in contrast to daily fractionation schedule practice in developed countries (Wong FC et al, 2003; Petereit DG and Pearcey R, 1999; and Le PC et al, 1995). After completion of external beam radiotherapy sessions, the patients were planned for High Dose Rate (HDR) brachytherapy using Bebig Cobalt-60 remote afterloader machine. This practice is similar to the mode of administration of brachytherapy published in literature (Saibishkumar EP et al, 2006).

Radiation dose per fraction received by each patient from HDR brachytherapy depends on the total dose prescribed by Radiation Oncologists. Most of the patients received three fractions of intracavitary brachytherapy dose. Each fractional dose was prescribed to point A and delivered over three weeks. Both treatments (external beam radiotherapy and brachytherapy) were completed within seven weeks period. This is within the recommended total treatment period (less than 8 weeks) expected for better local tumour control and survival rate (Akila NV et al, 2012).

In order to estimate overall treatment outcomes and complication rate with respect to dose rates and fractionation schedules, the linear-quadratic model and biologically weighted EQD2 dose values are usually employed. The linear quadratic model is a useful tool for calculating physical dose of HDR brachytherapy fractions, taking into account the already delivered external beam radiation dose. This allows systematic assessment of radiation dose received by patients within a center and between different centers.

Several investigators have shown that in order to achieve local tumour control probability of more than 90% for advanced cervical cancer disease,

a biologically weighted total dose, EQD2, of at least 87 Gy must be delivered to the tumour volume (Yasir AB et al, 2011; Dimopoulos JC et al, 2009; and Dimopoulos JC et al, 2009).

Similarly, the American Brachytherapy Society in its latest publication (Akila NV et al, 2012) stated that to maximize local tumour control, the cervix and its surrounding region should be covered with EQD2 ≥ 80 Gy for patients with either a complete response or a partial response with residual disease less than 4cm. For non-responders or patients with tumours larger than 4cm at the time of brachytherapy, tumour escalation to an EQD2 of between 85 – 90 Gy is recommended to either point A or D_{90}.

In this study, the sum of EQD2 received by patient from external beam radiotherapy and HDR intracavitary brachytherapy was calculated and then compared with the ABS recommended values of 80 – 90 Gy. As seen in Table 4, out of eleven different combinations of treatment fractionation schedules (External beam and HDR brachytherapy) considered, only five were within ABS recommended EQD2 (87.60 Gy, 81.30 Gy, 81.0 Gy, 88.80 Gy and 83.10 Gy); five were below (65.60 Gy, 70.30 Gy, 75.60 Gy, 78.40 Gy and 77.80 Gy) and one was higher (99.80 Gy) than the recommended values.

The respective combinations of treatment (EBRT + HDR) schedule that achieved recommended EQD2 are namely, 45 Gy in 12 fractions + 24 Gy in 3 fractions; 45 Gy in 12 fractions + 21 Gy in 3 fractions; 45 Gy in 22 fractions + 26 Gy in 4 fractions; 50 Gy in 12 fractions + 21 Gy in 3 fractions; and 50 Gy in 12 fractions +18 Gy in 3 fractions. Their corresponding values for late responding tissues are 113.60 Gy, 102.80 Gy, 95.00 Gy, 113.80 Gy and 104.20 Gy respectively.

This shows that not all varieties of dose per fractionation schedules can be used to manage advanced cervical cancer. Therefore, the Clinicians need to choose the fractionation regime that would give adequate tumour dose and achievable tolerance dose to normal tissues. This can be achieved by subjecting their choice of DFR to EQD2 calculation.

In conclusion, this study has shown that out of 250 patients with locally advanced cervical cancer managed with combined external beam radiation therapy and HDR intracavitary brachytherapy, within two years of its (HDR machine) clinical use, only 45 % received optimal therapy dose recommended to cure macroscopic disease (Potter R et al, 2002).

In order to improve therapeutic ratio in the management of locally advanced cervical cancer, the Clinicians should endeavor to obtain EQD2 of their intended dose fractionation schedule before treatment execution.

The authors proposed treatment regimen of 45Gy in 22 fractions external beam radiation therapy combined with 26 Gy in 4 fractions HDR Intracavitary brachytherapy for management of patient with advanced cervical cancer. This is because these fractionation schedules offer optimal EQD2 (81 Gy) to early response tissue (tumuor) and tolerance dose (95 Gy) to late responding tissues (healthy tissues).

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