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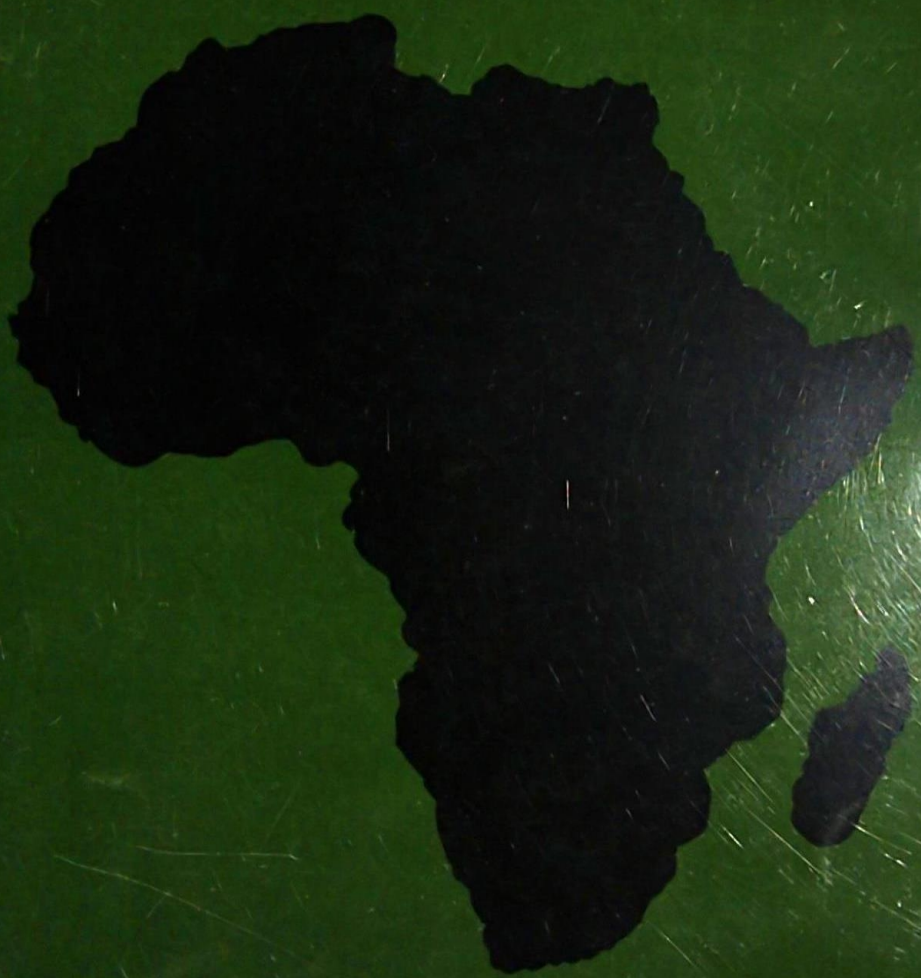

EDITOR:
B. O. OSOTIMEHIN

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Comparative evaluation of hypofractionated radiotherapy and conventional fractionated radiotherapy in the management of carcinoma of the cervix in Ibadan, Nigeria

OB Campbell[1], IB Akinlade[1], A Arowojolu[2], IA Babarinsa[2], RI Agwimah[3] and IF Adewole[2]
[1]Department of Radiotherapy, [2]Department of Obstetrics & Gyneacology, University College Hospital, Ibadan and [3]Department of Physics, University of Ibadan, Ibadan, Nigeria.

Summary
Four hundred and eighty patients with histologically confirmed carcinoma of the uterine cervix were randomized into 2 groups to either receive hypofractionated radiotherapy (HF – 230 patients – study group) or conventional fractionated radiotherapy (CFR – 250 patients – control group) between December 1988 and November 1992 at the Radiotherapy Department, University College Hospital, Ibadan.The 5- year survival rate for HF patients in Stages I, II, III and IV were, respectively, 91.3%, 67.2%, 40.2% and 18.0% while for CFR patients in Stages I, II, III and IV were respectively, 92.8%, 69.2%, 42.5% and 19.6%. Though early radiation adverse effects were similar in CFR and HF patients, marked late adverse radiation effects were observed in HF patients than in CFR patients. Complete response rate and local tumour controls were found to be similar in the HF and CFR patients. This study revealed that with similar 5- year survival, complete response rate and local tumour control in HF and CFR patients while a significantly higher late radiation adverse effects were recorded in HF patients, conventional fractionated radiotherapy is the preferred form of radiation therapy in the management of carcinoma of the uterine cervix. Administration of hypofractionated radiotherapy for cervical cancer patients with the aim of maximizing the use of few available radiotherapy facilities, as currently obtained in some radiotherapy centres in Nigeria will result in high post treatment morbidity.

Keywords: *Cervical cancer, Fractionated radiotherapy.*

Résumé
Quátre cent quatre vingts malades sonffrant de la carcinomie de l'utérine cervix ont été arbitrairement divisé en deux groupes pour soit recevoir la Radiogahic hypofactionnée (HF = 230 malades – groupe d'étude). Soit la Radiographic fractionnée conventionelle (CFR – 250 malades – groupe de control) entre Décembre 1988 et Novembre 1992 au Department de la Radiographic di Centre Hospitalier Universitaire, d'Ibadan.Les 5 ans de taux de survie pour les malades HF aux stades I, II, III et IV étaient 91,3%, 67,2%, 40,2%, et 18,0% respectivement alors que ceux des malades CFR aux stadesI, II, III et IV étaient de 92,8%, 69,2%, 42,5% et 19,6% respectivement. Bien que les effets secondaires des premiéres radiations étaient similaires cheq les malades CFR et HF, les radiations marquées á effets secondaires retarde's étaient plus observées cheq les malades HF que les CFR. Le taux de réponse compléte et le control de tumeur local étaient similaire cheq les malades HF et CFR.Cette étude montre que avec les mêmes 5 ans de taux de survie, le taux de réponse complete et le control de tumur local cheq les malades HF et CFR, pendant que les effets des radiations secondaires futures trés significatives étaient notés cheq les malades HF, la radiographe fractionnée conventional est la forme préférée des soins radiographiques pour le traitement de la carcinomie dde l'utérine cervix. L'administration de la radiographie hypofractionnée pour les malades sonffrant du cancer cervical dans lé but de maximiser l'utilisation de qulques facilities radio graphiques, tel que conramment obtenne dans certains centre Radiographiques du Nigeria, resultera á un frant aprés traitement morbide.

Correspondence: Dr. O. B. Campbell, Department of Radiotherapy, University College Hospital, Ibadan, Nigeria.

Introduction

Cervical cancer is the commonest gyneacological tumour in Nigeria and sub-Saharan West Africa [1,2] and accounts for 62.7% of all malignancy seen at the University College Hospital (UCH), Ibadan, Nigeria [3].

This malignant tumour is the most frequent cancer among women in Africa, Asia and South America [4].

Between December 1988 and November 1992, this malignancy was diagnosed in 580 patients who attended the Radiotherapy Clinic at the UCH, which had only functioning radiotherapy (teletherapy) facility the Telecobalt Theratron 780C unit during the stated period.

The huge influx of patients requiring radiation therapy during the period of study led to the need to introduce hypofractionated radiotherapy in order to maximize the use of the only functioning teletherapy facility.

In this study the role of hypofractionated radiotherapy (HF) by comparing this treatment (HF) with conventional fractionated radiotherapy (CFR) in the management of carcinoma of the uterine cervix in Ibadan is discussed and assesssed.

Table 3a: Early radiation adverse effects in CFR and HF patients early radiation adverse effects

Stage						
CFR patients	Proctitis	Enteritis	Cystitis	Vagino-Vulvitis	Total	P-value
I	3	4	2	4	145pts 58%	0.05 X^2=3.6
II	6	8	11	6		
III	14	10	14	8		
IV	16	11	17	11		
HF patients	Proctitis	Enteritis	Cystitis	Vagino-Vulvitis	Total	P-value
I	2	3	4	6	142pts 61.7%	0.05 X^2=3.6
II	4	6	10	4		
III	10	14	10	12		
IV	11	17	16	13		

Table 3b: Late radiation adverse effects in CFR and HF patients late radiation adverse effects

Stage								
CFR patients	Rectal Ulceration	Rectosigmoid Constriction	Late Cystitis	Late Enteritis	Vaginal Stenosis	Pelvic Fibrosis	Total	P - Value
I	Nil	Nil	1	1	1	1	}	
II	1	1	1	1	1	1	}	
III	1	1	2	2	2	1	} 12.8%	0.05
IV	2	3	2	2	2	2	} 32pts	X^2=4.3
HF patients	Rectal Ulceration	Rectosigmoid Constriction	Late Cystitis	Late Enteritis	Vaginal Stenosis	Pelvic Fibrosis	Total	P - Value
I	2		3	3	2	2	}	
II	3		5	4	3	3	}	
III	3		7	6	5	5	} 42.6%	0.05
IV	5		8	8	8	7	} 98pts	X^2=4.3

Table 4: Response to therapy

Response	HF Patients N = 230 Study Group		CFR patients N = 250 Control Group	
Complete Response	Stage	%tage Response	Stage	%tag Response
	I	- 95.5%	I	- 96.8%
	II	- 80%	II	- 83.2%
	III	- 74%	III	- 76%
	IVa	- 53.8%	IVa	- 56.2%
Local Tumour Control	I	- 92.5%	I	- 93.4%
	II	- 77%	II	- 79.3%
	III	- 73.4%	III	- 75.8%
	IVa	- 52.7%	IVa	- 55.9%
5 year survival	I	- 91.3%	I	- 92.%
	II	- 67.2%	II	-69.2%
	III	- 40.2%	III	-42.5%
	IV	- 18.0%	IV	- 19.6%

put at $P = 0.05$. Statistical analysis level of significance between the variables (study and control groups) were calculated using the chi-square test.

Table 5: Summary and comparison of NSD and BED for CFR and HF Patients

	CFR (Stages I, II, III)	HF (Stages I, II, III)
NSD	15.62Gy	17.66Gy
Bed Early	60Gy	66.6Gy
Bed Late	90Gy	116.6Gy

Results

The age range for patients in the study group (HF) was 21 years to 75 years with a median of 46 years and in the control group (CFR) was 22 years to 76 years with a median of 45 years. The ages in the two groups were similar.

Ten percent (10%) (23 patients) in the study group (HF) presented in stage I, 28% (64 patients) in

Table 1:Stage of disease and frequency

Stage of Disease	No of patient and Percentage		No of patient and Percentage	
	HF (Study Group)		CFR (Control Group)	
I	23pts	10%	28pts	11%
II	64pts	28%	65pts	26%
III	87pts	38%	100pts	40%
IVa	56pts	24%	56pts	23%

Table 2: Tumour cell type and frequency

Tumour cell type	HF Patients		CFR Patients	
Squamous Cell Carcinoma	209pts 90.8%		230pts	92%
Adenocarcinoma	12pts	5.2%	15pts	6%
Adenosquamouscell carcinoma	7pts	3.0%	5pts	2.0%
Oat cell carcinoma	2pts	1.0%	Nil	0%

Patients and methods

(I) Patients

This is a prospective study, which was carried out between 1988 and November 1992 at the University College Hospital, Ibadan. About 480 patients with histologically diagnosed carcinoma of the uterine cervix were entered into the study. The inclusion criteria were the following:

- Histological confirmation of malignancy of the uterine cervix.
- No previous history of radiotherapy or surgery
- No evidence of concomitant malignancy
- The full blood count, liver functions (SGPT, SGOT), blood urea and creatinine must be of normal range.
- Chest X-ray must be normal.
- Karnofsky performance must be above 70%
- All patients were staged according to FIGO (International Federation of Obstetrics and Gyneacology) staging. Only patients with stages I, II, III and IVa were entered into the study (since stage IVb patients have disseminated metastatic disease).

The patients were then randomized into two treatment group- the study group (230 patients) to receive hypofractionated radiotherapy (HF) and the control group (250 patients) to receive conventional fractionated radiotherapy (CFR).

(II) Administration of Radiotherapy and Follow Up

External radiotherapy was delivered by Telecobalt Therapy 780C, 1.25Mev (Theratronics manufacturers, Kanata, Ontario, Canada). A mid-pelvic dose of 50Gy in 15 fractions on alternate days over 5 weeks was delivered to patients with stages I, II, III on hypofractionated radiotherapy (HF). Patients with stage IVa on HF received palliative dose of 30Gy in 9 fractions over 3 weeks.

Patients in the control group (conventional fractionated radiotherapy CFR) – in stages I, II, III received mid-pelvic dose of 50Gy in 25 fractions over 5 weeks.

Ten days following external radiotherapy, all patients (in study and control groups) received radioactive Caesium brachytherapy, which delivered a dose of 30Gy to a point A [5]. Point A is the standard referral point located at 2cm above mucosa of lateral vaginal form and 2cm lateral to midplane of the body [5].

Patients in stage IVa (who have been confirmed not to have recto or vesco vaginal fistulae) initially had debulking external pelvic irradiation. A mid pelvic dose of 30Gy in 15 fractions over 3 weeks was delivered – followed by radioactive caesium brachytherapy, which delivered a dose of 30Gy to point A. A combination of external pelvic radiotherapy which initially debulks the tumour followed by intracavitary caesium therapy is being administered for patients with stage IVa cervical cancer (who do not have vesico or recto-vaginal fistulae) as reported by Couller, C. and Mason, P. [6].

Following completion of radiotherapy, all the patients were seen at the Radiotherapy and Gyneacologic Oncology Clinics after 6 weeks, then at 3- month intervals or as soon as the patients presented with complaints/complications. At the follow up clinics, physical examinations, biochemical, haematological and radiological investigations such as abdomino-pelvic ultrasonography were carried out.

Complete response (CR), and partial Response (PR) were noted and recorded [7]. Early and late toxicities, the local tumour control, disease free survival and the 5-year survival were documented. The 5-year survival was calculated for different stages of the disease in the study and control group.

In the study group, the 5- year survival was calculated and recorded as following: stage I – 21(91.3%) out of total 23 patients, stage II – 43(67.2%) out of total 64 patients, stage III – 35(40.2%) out of total 87 patients and stage IV – 10(18%) out of total 56 patients. (Table 4).

In the control group, the 5- year survival was calculated and recorded as following: stage I –26(92.8%) out of the total 28 patients, stage II – 45(69.2%) out of the total 65 patients, stage III – 43(42.5%) out of the total 101 patients and for stage IVa – 11(19.6%) out of the total 56 patients. (Table 4).

Intensive counseling of the cancer patients before and while undergoing radiotherapy about the importance of reporting at our post-therapy follow up clinic helped considerably in minimizing to a very low rate the loss to follow up which is a common feature amongst the patients in our community.

Values obtained for the two groups were compared using test and level of statistical significance

10Gy for early responding tissue [11] (early radiation adverse effects).

BED calculation:

Early radiation adverse effects for:

(a) CFR patients in stage I, II & III: 50Gy in 25 fractions

BED = D (1 + d/ œ/ß)

Where œ/ß for early effect is 10Gy and d for all CFR patients is 2Gy.

BED = 50(1 + 2/10)
= 50(1.2)
= 60Gy.

Early Radiation adverse effects for:

(b) CFR patients in stage IVa: 30Gy in 15 fractions

BED = D (1 + d/ œ/ß)
= 30(1 + 2/10)
= 30(1.2)
= 36Gy.

Late radiation adverse effects for

(c) CFR patients in stages I, II & III: 50Gy in 25 fractions

BED = D (1 + d/ œ/ß)

œ/ß for late radiation effect is 2.5Gy

BED = 50(1 + 2/2.5)
= 50(1.8)
= 90Gy

Late radiation adverse effects for CFR patients in stage IV: 30Gy in 15 fractions

BED = D (1 + d/ œ/ß)
= 30(1 + 2/2.5)
= 30(1.8)
= 54Gy.

Early radiation adverse effect for:

(a) HF patients in stages I, II & III: 50Gy in 15fractions

BED = D (1 + d/ œ/ß)

œ/ß for early effect is 10Gy; d, for all HF patients is 3.33Gy

BED = 50(1 + 3.33/10)
= 66.67Gy

Early radiation adverse effect for:

(b) HF patients in stage IVa

BED = D (1 + d/ œ/ß)
= 30(1 + 3.33/10)
= 30(1.33)
= 40Gy.

Late radiation adverse effect for:

(a) HF patients in stages I, II & III

BED = D (1 + d/ œ/ß)
= 50(1 + 3.33/2.5)
= 116.6Gy

(b) HF patients in stage IVa: 30Gy in 9 fractions

BED = 30(1 + 3.33/2.5)
= 30(2.332)
= 70Gy.

Table 5 is a summary and comparison of the Nominal Standard Dose (NSD) and Biological Effective Dose (BED) for patients with uterine cervix who had CFR and HF. The NSD for CFR and HF patients were similar. Also BED for early radiation adverse effects for CFR and HF patients were similar. But the BED for late effects was higher in HF patients compared to CFR patients. This accounts for the fact that hypofractionated radiotherapy was accompanied by more marked late radiation adverse effects than obtained for CFR patients. Hypofractionated radiotherapy in the management of uterine cervical cancer has been instituted at the only two radiotherapy centers in Nigeria (Lagos University Teaching Hospital and University College Hospital, Ibadan) within the past 10 years.

Though hypofractionated radiotherapy has reduced the waiting period from 3 months to 6 weeks at the University College Hospital during the stated period and has the same rate of early radiation adverse effects, local tumour control and 5- year survival with CFR however, the marked late radiation adverse effects recorded in patients with uterine cervical cancer on hypofractionated radiotherapy as shown in this study makes HF an unacceptable modality of radiation therapy in the management of cervical cancers. Continuous efforts have to be made to procure more Teletherapy and Brachytherapy facilities to cope with the management of patients with cervical cancers – a neoplasia with increasing high prevalence in the West African subregion.

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stage II, 38% (87 patients) in stage III and 24% (56 patients) in stage IVa (Table 1).

In the control group (CFR), 11% (28 patients) presented in stage I, 26% (65 patients) in stage II, 40% (100 patients) in stage III and 23% (57 patients) in stage IVa (Table 1).

The histological patterns were similar in the study and control groups. In the HF group, squamous cell carcinoma constituted 90.8% (209 patients), adenocarcinoma – 5.2% (12 patients), adenosquamous carcinoma – 3.0% (7 patients) and oat cell carcinoma – 1.0% (2 patients) (Table 2).

In the control group (CFR patients), squamous cell carcinoma constitute 92% (230 patients), adenocarcinoma - 6% (15 patients) and adenosquamous cell carcinoma – 2% (5 patients).

Early radiation adverse effects were observed in 61.7% (142 patients) in study group (HF) patients and in 58% (145 patients) in control group (CFR). At the $P = 0.05$ level of significance, the chi-square $X^2 = 3.6$ obtained for early radiation adverse effects in the two reveals that there is no difference in early radiation effects in the two groups (Table 3A). Late radiation adverse effects were observed in 42.6% (98 patients) of the study group and 12.8% (32 patients) of the control group. At the $P = 0.05$ level of significance, the chi-square, $X^2 = 4.3$ obtained for late radiation adverse effects in the two group, reveals that there are significantly more marked late radiation effects in the hypofractionated patients (study group) (Table 3B).

Response to treatment according to the clinical disease stages is as shown in Table 4. In the study group, complete response was seen in 96.8% of patients with stage I and 83.2% of those with stage IV, 76% - stage III, and 56.2% - stage IVa. Local tumour control according to the clinical disease stage were 92.5% for stage I, 77% for stage II, 73.4% for stage III, and 52.7% for stage IVa in the study group. In the control group, local tumour control was 93.4% for stage I disease, 79.3% for stage II, 75.8% for stage III and 55.9% for stage IVa. There was no difference in the complete response to treatment or local tumour control in the two groups.

The five-year survival in the two groups according to the clinical stages was also similar as shown in Table 4.

Discussion

In radiotherapy, hypofractionation refers to irradiation schemes with less than 5 fractions per week and larger doses per fraction than 2Gy. It was initiated to ease the burden for patients who had to come to the hospital to be treated everyday and save the (treatment) machine time [8]. Hypofractionated radiotherapy was introduced into the management of patients with carcinoma of the uterine cervix at the University College Hospital, Ibadan between 1988 and 1992 in order to accommodate more of these patients on the only functioning teletherapy machine in our department while easing the burden on the treatment facility.

In our study, cervical cancer patients in stage I, II, III on CFR received tumour dose of 50Gy in 25 fractions over 5 weeks (external radiotherapy) while stage IVa patients on CFR received 30Gy in 15 fractions over 3 weeks. Patients in stage I, II and III on HF received 50Gy in 15 fractions over 5 weeks, while stage IVa patients on HF received 30Gy in 9 fractions over 3 weeks. The Nominal Standard Dose (NSD) and the Biological Effective Dose (BED) in the two treatment schedules (CFR and HF) in this study were determined in order to present the radiobiological basis for the rate of early and late post-radiation adverse effects obtained in CFR and HF patients. The expression:

$NSD = D \times N^{-0.24} \times T^{-0.11}$ [7, 8, 9, 10] describes the relationship between the total dose (D), number of fractions (N) and overall treatment time (T), where NSD is a constant and is termed the Nominal Standard Dose.

The NSD in CFR and HF patients are determined and a comparison is carried out.

NSD for CFR patients in stages I, II & III

$NSD = D \times N^{-0.24} \times T^{-0.11}$
$= 50 \times 25^{-0.24} \times 35^{-0.11}$
$= 50 \times 0.4618 \times 0.6763$
$= 15.62Gy.$

NSD for CFR patients in stage IVa

$NSD = D \times N^{-0.24} \times T^{-0.11}$
$= 30 \times 15^{-0.24} \times 21^{-0.11}$
$= 30 \times 0.5221 \times 0.7154$
$= 11.21Gy.$

NSD for HF patients in stages I, II & III

$NSD = D \times N^{-0.24} \times T^{-0.11}$
$= 50 \times 15^{-0.24} \times 35^{-0.11}$
$= 50 \times 0.5221 \times 0.6763$
$= 17.66Gy.$

NSD for HF patients in stage IVa

$NSD = D \times N^{-0.24} \times T^{-0.11}$
$= 30 \times 9^{-0.24} \times 21^{-0.11}$
$= 30 \times 0.5902 \times 0.7154$
$= 12.67Gy$

The Biological Effective Dose (BED) in the CFR and HF patients are determined and compared:

$BED = D(1 + d/\alpha/\beta)$

Where D = Total radiation dose in Gy
d = fractionation dose in Gy
α/β = an important parameter describing the dose rate and fractionation sensitivity of the tissue.

α/β in terms of tumour control is 2.5Gy for late responding tissue (late radiation adverse effects) and is

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