PROPOSAL FOR ANNUAL QA ASSESSMENT OF SAFETY AND CONSISTENCY OF OARS DOSES IN TREATMENT OF CANCER BY BRACHYTHERAPY

P.K. Ndonye[1], S.N.A. Tagoe[2]

[1] The Nairobi Hospital, Cancer Treatment Center, Nairobi, Kenya.
[2] University of Ghana, School of Biomedical & Allied Sciences, Accra, Ghana.

Abstract

The aim of the study was to assess the safety and consistency of organs at risk (OARs) doses received by the rectum, bladder and urethra during cervical and prostate cancer treatments by brachytherapy and thereafter propose the procedure for annual QA assessment of all radiotherapy treatments in an institution. The cervical cancer patients considered in the study received both EBRT and brachytherapy treatment in 2017 and were assessed for their bladder and rectal OARs doses received during the treatment. Only prostate cancer patients who received I-125 permanent seed implants brachytherapy doses alone were assessed for their rectal and urethra doses. The same study was again repeated in 2022 for consistency comparison with the 2017 results. The combined OARs doses for cervical cancer treatment by both EBRT and brachytherapy were below the recommended maximum doses for the respective OARs. Rectum and urethra doses in prostate brachytherapy treatment indicated doses below the target prostate dose, D90%, and thus received safe doses within acceptable limits. A similar safety assessment repeated in 2022 after five years did not reflect significant difference from those for 2017, a confirmation of consistency in the treatment practice at the hospital. The study results revealed that for all the cervical and prostate cancer brachytherapy treatments considered in 2017 and 2022, the OARs doses were below the recommended maximum dose limits for the respective OARs, and thus safe. There was no significant difference in the safety results realized in the repeat study after five years, a confirmation that the brachytherapy treatment practice at the institution was consistent. The safety and consistency assessment demonstrated in the study was thus proposed as an annual QA procedure in brachytherapy treatment of cancer and can be extended to cover all radiotherapy treatment modalities in an institution.

Keywords
Brachytherapy, Organs at risk, Safety, consistency, Cancer

I. INTRODUCTION

Brachytherapy is applicable for the treatment of tumors where applicators and radioactive sources can be placed within a body cavity (intra-cavitary, e.g., the uterine canal or vagina), into a lumen (trans-luminal, e.g. bronchus or esophagus), into an artery (intravascular e.g. Coronary or peripheral arteries, prevention of restenosis) and also where the tumor is accessible to needle or catheter sources being placed within or directly into tissue, interstitial, intra-cavitary or surface application. A major advantage of this mode of treatment, as opposed to EBRT, is because a high radiation dose can be delivered locally to the tumor with rapid dose fall-off in the surrounding normal tissues.

Currently, artificially produced radionuclides such as Cs-137, Ir-192, Au-198, I-125, Pd-103 and Co-60 are used. Radionuclide sources for brachytherapy are now available with many radionuclides and in various shapes and sizes. Different sources have different applications depending on their emission type, radiation energy and how they are constructed. Below is a table of the most common radionuclides applicable in brachytherapy treatment.

Treatment of cervical cancer by brachytherapy can be done by application of high dose-rate (HDR) treatment equipment which use Iridium-192 sources, and of late, Cobalt-60 sources. Low dose-rate (LDR) equipment that use Caesium-137 source or a similar applicable LDR radioisotope are also applicable, although the HDR equipment are the most common now and currently recommendable due to their advantages of use. [1].

Brachytherapy treatment of prostate cancer can use LDR radioactive permanent seed implants for the treatment. The current commonly used LDR radioisotope seeds in this case are I-125 and Pd-103 isotopes; which are also recommended by the American Brachytherapy Society, since they have demonstrated excellent long-term outcomes [2].

HDR treatments normally take a few minutes, depending on the activity of the source at the time of treatment; while those for LDR can take several hours. HDR brachytherapy for cervical cancer is currently more preferable to LDR. This part of the study was done at a selected hospital in Kenya where there is a Varian GammaMedplus HDR system. The system uses an Iridium-192 source, with a half-life of 73.831days. The source would be used for three months (90 days) and then changed for a new one with an initial activity of about 10Ci.

The cervical cancer treatment itself by HDR brachytherapy would take a few minutes, but the whole process from applicator insertion, CT imaging, treatment planning, treatment delivery, and applicator removal may take about two hours per patient.

The external beam radiation therapy (EBRT) treatment planning system was a Varian Eclipse and compatible to CT or MRI-based images for treatment planning. The applicators are platinum made Ring and Tandem or Tandem and ovoids, with variety of Tandem lengths, example 2, 4, and 6cm. The ovoids can be small or medium size. Another type of applicator is in the form of a Cylinder, of different diameters (1.4cm, 2.1cm, 2.3cm, 2.6cm, 3.0cm and 3.5cm).

The Clinical Oncologist performing a brachytherapy treatment would physically examine the patient first. Then choose a type of applicator for a particular patient depending on the patient's body anatomy and extent of the disease. The applicators would then be inserted after simple premedication of the patient. CT scan of the pelvic area of the patient would then be done for treatment planning purpose. Treatment planning Guidelines are available for planning cervical cancer treatment by different types of applicators.

The dose prescription protocol for the delivery of the brachytherapy dose was a boost dose of 16Gy delivered in two fractions of 8Gy a week apart.

As opposed to EBRT where the treatment dose is delivered externally and can be verified before entering into the patient, brachytherapy treatments are normally executed internally and verification using a diode for EBRT purpose may not be possible.

The approach for verification of cervical or prostate cancer brachytherapy treatment was attained by use of the treatment plan dose volume histogram (DVH). European Society for Therapeutic Radiology and Oncology (GEC Estro), in 2006, gave the recommended dose calculations based on three-dimensional image of the patient obtained from dose volume histogram (DVH) and the volume histogram connecting organ with the radiation dose received [3]. So, the DVH has now become a common tool to express the dose that is delivered to targets and OARs. It contains information about the doses delivered to partial volumes (either absolute or relative) of targets or OARs. So, the dose to OARs for each patient considered for the study was acquired from the patient's treatment plans and the data for the cervical cancer brachytherapy treatments compiled and presented in graphical form.

Radiation can be harmful to health if not used properly and all radiation administration to humans for treatment purposes need to be done by qualified professionals and the dose delivery verified for safety purpose.

Our study was in a selected hospital and assessed safety and consistency in OARs doses realized during cervical and prostate cancer brachytherapy treatment in comparison to the delivered tumor dose and the maximum recommended dose limits to the OARs. If the results are within the recommended values, the procedure would be recommended as an annual QA in radiotherapy treatments.

II. MATERIALS AND METHODS

A. Cervical cancer brachytherapy data

The study involved a total of 41 cervical cancer patients who received brachytherapy treatment at the hospital in both 2017 and 2022. The treatment applicators used for the patients were either a 'Tandem and Ovoids', 'Ring and Tandem' or a 'Vaginal Cylinder'. The applicator selection for a particular patient would depend on the clinical condition of the patient.

After insertion of the applicators in the brachytherapy theatre, the patient would then have CT scans of the pelvis for the purpose of treatment planning on the TPS. During treatment planning, the doses to the target volume, the rectum or bladder would be altered appropriately so that doses would not exceeded the maximum limits on the protocols. The final treatment plan would then be exported to the HDR Treatment system for execution of the treatment.

The doses received by the bladder and rectum during the cervical cancer treatment were taken from the treatment planning TPS 'dose statistics' and also through the TPS protocols for the OARs (D20, Gy); and the results presented graphically. Another graph plotted involved the brachytherapy OARs data with the EBRT OARs doses received previously before the brachytherapy boost dose.

The average dose for the bladder and rectum of all the 41 patients assessed were also determined and the results presented on a table.

B. Combined EBRT and brachytherapy treatment of cervical cancer

Bladder and rectum were targeted as the main organs at risk in cervical cancer treatment in both EBRT and brachytherapy.

We investigated the total bladder and rectum doses for the 41 cervical cancer patients treated at the hospital by both EBRT linac photon energies (6 MV and 15 MV) and Ir-192 HDR brachytherapy. Recommended EBRT 3D-CRT prescription total tumor dose is 45-50 Gy to be delivered in 25 daily fractions while brachytherapy need to be delivered as 6-8 Gy fraction dose weekly, 2-3 times depending on the patient's clinical condition. At the hospital, EBRT doses were delivered as 50 Gy in 25 fractions of 2 Gy daily while the protocol used for the delivery of the brachytherapy dose was a total boost dose of 16 Gy delivered in two fractions of 8 Gy a week apart.

C. Prostate brachytherapy treatment and data

Forty-two prostate cancer patients treated by LDR brachytherapy using I-125 permanent seed implants were also assessed. The treatment applies trans-rectal ultrasound-guided permanent prostate brachytherapy technique which is

an outpatient procedure associated with a rapid recovery and return to normal activity.

The Ultrasound equipment is a 'bk Medical flexFocus 400' model, used together with a C-Arm X-Ray Image Intensifier. A Treatment Planning System (TPS) is also available and linked to both the Ultrasound Guidance and the Image Intensifier.

The procedure is acknowledged by many brachytherapy institutions, including the National Cancer Institute [4], American Cancer Society [5], American Urological Association [6] and many others.

In Kenya, about 70% of cancer patients are diagnosed at late stages due to a combination of many diverse reasons.

Thus, majority of our prostate cancer patients are of 'High-Risk' classification and thus recommended to receive combined treatment with EBRT 'boost dose' in 6-12 weeks after receiving the LDR brachytherapy treatment [7], [8].

In our study, we only assessed the OARS doses resulting from the brachytherapy treatment by LDR I-125 permanent seed implants only.

III. RESULTS AND DISCUSSION

A. OARs doses in cervical cancer brachytherapy treatment

Table 1 below shows the protocols implemented on the Varian HDR brachytherapy TPS for treatment planning control of the doses to OARs.

Table 1. Varian TPS Protocols used for control of doses to the major OAR during HDR brachytherapy treatment planning of cervical cancer.

Results of the OARs doses (two fractions) realized by the 41 cervical cancer patients during the brachytherapy treatment in 2017 were presented in Figure 1A and 1B below. The maximum dose limit of 8 and 10 Gy for the D20 rectum and bladder OARs two fraction treatments were also plotted with 16 Gy for the two-fraction total tumor dose.

Structure	Index		Target Value	Actual Value
Bladder	D0.10cc (% of dose)	Is less than	125	
Bladder	D2.0CC (% of dose)	is less than	75	
Bladder	D20.0 (Gy)	is less than	5	
Rectum	D0.10cc (% of dose)	is less than	125	
Rectum	D2.0cc (% of dose)	is less than	75	
Rectum	D20.0 (Gy)	is less than	4	
Rectum	D1.0cc (% of dose)	is less than	95	
Rectum	D1.0cc (% of dose)	is less than	95	

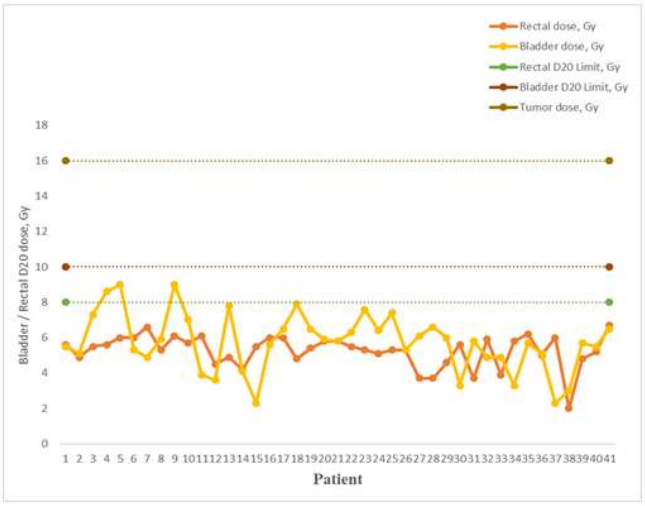

Figure 1A. Graph of D20 (Gy) bladder, rectum and total tumor dose for the 41 cervical cancer patients treated at the hospital in two fractions by I-192 HDR brachytherapy in 2017.

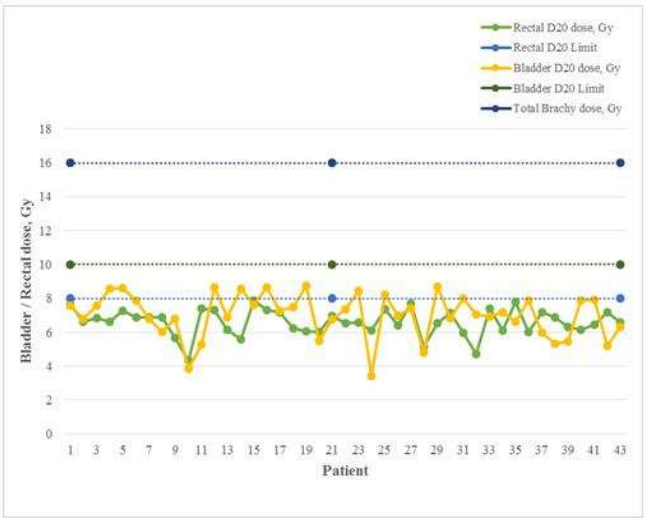

Figure 1B. Graph of D20 (Gy) bladder, rectum and total tumor dose for 43 cervical cancer patients treated (two fractions) by I-192 HDR brachytherapy in 2022.

For both assessments done in 2017 and 2022 for the brachytherapy treatment of cervical cancer, a mean dose of the bladder and rectum doses received were determined and a summary of the results presented on Table 2, below. All the treatments in the institution were based on 3-dimensional (3D) CT imaging and also 3D treatment planning and treatment.

The mean dose to both OARs for the 2017 and 2022 assessments were below the recommended maximum limits for the bladder (5 Gy) and rectum ((4 Gy) in a single fraction treatment. Also in accordance with the American

Brachytherapy Society (ABS) recommendation, [2], the dose to the bladder and rectum must be below 80% of the prescribed dose to the cervix. For a prescribed dose of 8 Gy per fraction to the cervix in our case, the bladder and rectum must not receive doses above 6.4 Gy. This means that our brachytherapy cervical cancer treatments are not only not harmful to the patients but also that the treatment practice has been consistent. These results were also in agreement with other related published results, [9].

Table 2. Two fraction mean doses to OARs in cervical cancer brachytherapy treatment in both 2017 and 2022 assessments.

OAR	Mean Dose, Gy, (2017)	Mean D20 Dose, Gy, (2022)	Max Dose Limit, Gy
Bladder	5.8	7.0	10
Rectum	5.2	6.6	8

B. Demonstration of combined OARs doses in cervical cancer treatment

Late-stage treatment of cervical cancer by radiotherapy at the hospital is normally a combination of EBRT and brachytherapy. First, an EBRT dose of 50 Gy in 25 fractions is administered, followed by a boost dose of brachytherapy, given in two fractions of 8 Gy, a week apart.

Since the two brachytherapy fraction doses applied during the treatment of cervical cancer by both EBRT (2 Gy) and brachytherapy (8 Gy) are different from the EBRT dose, the brachytherapy dose needs to be converted to match that of EBRT. The brachytherapy fraction dose of 8 Gy will need to be converted to equivalent dose to that EBRT fraction dose of 2Gy. The conversion will utilize α/β ratio which is dependent on the type of tumor. For cervical cancer, a ratio of α/β =10, [10], [11], [12], has been used and the following equations applied to determine the brachytherapy fraction dose.

$$BE\ D = [nxd[1+(d/(\alpha/\beta)] \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where n = number of treatment fractions,
d = dose per fraction, in Gy,
α/β = dose at which the linear and quadratic components of cell kill are equal.

Also, α is the linear dose damage response, and β the quadratic dose response in tissue.

BED is the biologically effective dose and is a measure of the true biological dose delivered by a particular combination of dose per fraction and total dose to a particular tissue, in this case, the cervix.

The biologically equivalent dose (EQD_2) is the dose delivered in 2Gy fractions that biologically equivalent to a total dose.

$$So,\ EQD_2 = BED/[1+2/(\alpha/\beta)] \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

So, the cervical cancer brachytherapy dose to be added to the 50 Gy dose delivered by EBRT will be 12Gy per fraction as determined from Equation 2. The total EBRT and brachytherapy (two fractions) treatment dose in our case was 74 Gy.

Below (Figure 2) is the graphical presentation of the OARs dose data for the 41 patient treatments by EBRT. The maximum limit for the rectum, which is more sensitive to radiation than the bladder, is also plotted at 50Gy.

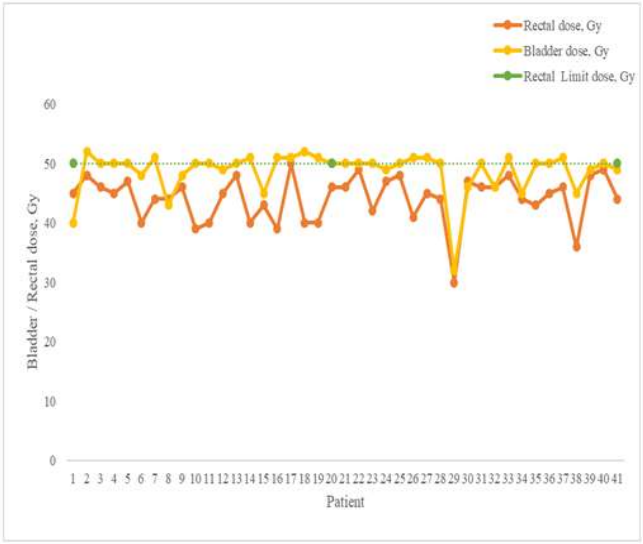

Figure 2. EBRT dose to the bladder, rectum and maximum rectal dose limit for the 41 cervical cancer patients treated at the hospital in 2017.

The maximum limit dose to OARs in both EBRT and brachytherapy treatments are normally controlled by the quality assurance (QA) process during the treatment planning stage. From the data of the 41 cervical cancer patients treated then on Figure 3 below, the mean total dose to OARs were below the maximum limit dose of 62 Gy for the rectum and 65 Gy for the bladder. Also reflected on the graph is the total tumor dose received for the combined EBRT and two fractions of brachytherapy treatment of 74 Gy. The recommended total dose for both EBRT and brachytherapy in high-risk cervical cancer treatment is 80-90 Gy, received in 50 Gy of EBRT plus three fractions of equivalent brachytherapy total dose of 36 Gy. For 50 Gy of EBRT combined with two fractions of HDR brachytherapy treatment, a total of 70-80 Gy tumor dose was recommended.

Figure 3. Combined EBRT and brachytherapy doses to the target tumor and OARs (bladder and rectum) for the 41 cervical cancer patients treated in 2017. The maximum dose limits realized in both treatments to the OARs are also plotted.

C. OARs doses in prostate cancer brachytherapy treatment

Brachytherapy DVH has now become a common tool to express the dose that is delivered to targets and OARs and contains information about the doses delivered to partial volumes of targets or OARs. So, the dose to OARs for each patient considered for the study was acquired from the patient's treatment plan.

Analysis of rectal and urethra (OARs) doses from the plans DVH data of the 42 prostate cancer patients treated by I-125 permanent seed brachytherapy implants in 2017-2018 was done.

With a prescribed dose of 110 Gy, the protocol used for the LDR brachytherapy treatment with I-125 permanent seed implants recommends that the target dose to the prostate should be above 140 Gy [2]. The mean/average 'Day zero' dose, D90%, (dose that covers 90% of the prostate volume) for the 42 patients treated was 139 Gy. D90, also described as the dose that covers 90% volume of the CTV and would be larger than the prescription dose, D90>100% of prescription dose [13], [14]. The mean prostate dose realized in our study was 139 Gy and was within the acceptable ±5% uncertainty for radiotherapy dose delivery of 140 Gy. The mean urethra and mean rectal dose were 89.9 Gy and 56.3 Gy respectively. The urethra appears to be more resistant to radiation, compared to the rectum, since no significant radiation-related issues have been reported for the urethra. Also, being central to the prostate gland, restricting the urethra to low OAR dose would prevent the targeted prostate volume from getting the required tumor dose. The maximum dose received by the two major OARs, rectum and urethra, during prostate brachytherapy treatment with I-125 is recommended to be below the target prostate tumor dose (140 Gy). So the mean dose received by the rectum and urethra in our case, were within the acceptable limits.

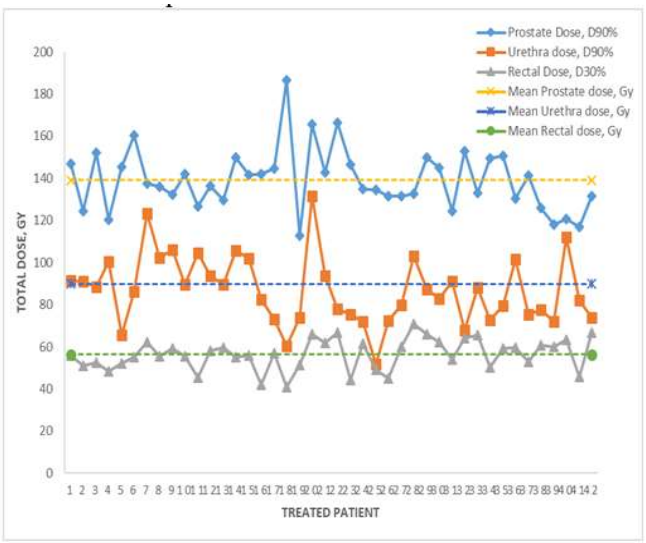

Figure 4A. Target and OARs doses for 42 prostate cancer patients treated at the hospital by brachytherapy using I-125 permanent seed implants in 2017-2018.

A 'learning curve' plot of the Day zero prostate dose, D90%, against the respective patients treated had a mean prostate dose of 139±15 Gy as reflected on Figure 4A. Based on published literature, an acceptable dose range for post-implant D90% for I-125 may be 130-180 Gy as long as normal structures are not overdosed [2]. This confirms that our treatment results were within acceptable limits and similarly confirmation that the quality of our past treatments were satisfactory.

A repeat study of 31 prostate cancer patients treated by I-125 permanent seed implants in 2021-2022 was done to assess the consistency of the treatment practice. The results were presened graphically on Figure 4B for comparison with those for 2017-2018 on Figure 4A

Table 3 below gives a summary of results for the prostate brachytherapy treatment by trans-perineal I-125 permanent seed implants.

Table 3. Results of prostate cancer brachytherapy treatment by I-125 permanent seed implants in 2017 and 2022, showing the prostate target and OARs doses.

Organ	Mean dose, Gy, (2017)	Mean dose Gy, (2022)	Max dose limit, Gy
Prostate (Target)	139	137	130-180
Rectum (OAR)	56	62	<140
Urethra (OAR)	90	116	<140

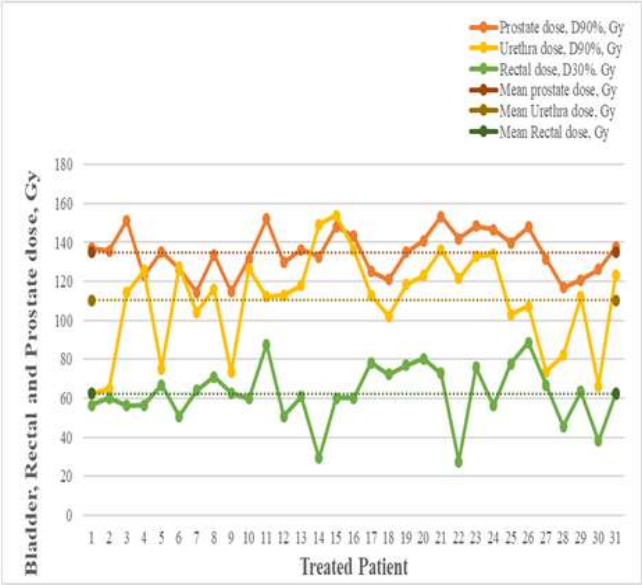

Figure 4B. Target and OARs doses for 31 prostate cancer patients treated by brachytherapy using I-125 permanent seed implants in 2021-2022.

IV. CONCLUSION

OARs doses in both EBRT and brachytherapy treatment of cervical cancer were assessed, while rectal and urethra (OARs) doses in prostate cancer treated by I-125 permanent seed implants were assessed from the DVH of the treatment plans.

The mean dose to both bladder and rectum in brachytherapy treatment of cervical cancer in 2017 and 2022 assessments were below the recommended maximum limits for the bladder (5 Gy) and rectum (4 Gy) in a single fraction treatment. Also in accordance with the American Brachytherapy Society (ABS) recommendation, [2], the dose to the bladder and rectum must be below 80% of the prescribed dose to the cervix. For a prescribed dose of 8 Gy per fraction to the cervix in our case, the bladder and rectum must not receive doses above 6.4 Gy. Our means single fraction doses to the bladder and rectum for 2017 and 2022 were below 6.4 Gy (Table 2), a confirmation that the doses to the OARs in brachytherapy treatment of cervical cancer were safe and consistent. These results were also in agreement with other related published results, [9].

In a combined treatment of EBRT and brachytherapy in treatment of cervical cancer, the combined doses to to the OARs were also demonstrated as below the recommended maximum limits and safe.

A plot of the 'Day zero' prostate dose, D90%, against the respective patients treated had a mean prostate target dose of 139 Gy and 137 Gy, in the respective years of assessment, 2017 and 2022. The doses to the OARs as summarized on Table 3 are below the recommended target prostate dose. Based on published literature, an acceptable dose range for post-implant D90% for I-125 may be 130-180Gy as long as normal structures are not overdosed [2]. The maximum dose received by the two major OARs, rectum and urethra, during prostate brachytherapy treatment with I-125 is recommended to be below the target prostate tumor dose (140 Gy). So the mean dose received by the rectum and urethra in our case, were within the safe and acceptable limits.

The repeat similar study after five years produced results that were similarly safe and a confirmative demonstration of a consistent radiotherapy practice for treatment of cervical and prostate cancer by brachytherapy at the referred hospital.

The safety and consistency assessment demonstrated in the study is thus proposed as an annual QA procedure in brachytherapy treatment of cancer and can be extended to cover all radiotherapy treatments in an institution.

VI. ACKNOWLEDGEMENTS

I acknowledge my Institutions' Ethics and Research Committee (Kenyatta National Hospital, University of Nairobi, and The Nairobi Hospital) for accepting and allowing me to do my PhD research project at the institutions.

CONFLICT OF INTEREST

No conflict of interest

REFERENCES

1. Khan F.M. (2003). The physics of radiation therapy. Third Edition. Philadelphia, USA.
2. Davis B.J, Horwitz E.M., Robert Lee W, et al, (2012). American Brachytherapy Society consensus guidelines for trans-rectal ultrasound-guided permanent prostate brachytherapy. Brachytherapy.11: 6-19.
3. Pötter R, Haie-Meder C, Limbergen E.V. et al. (2006). Recommendations from gynecological (GYN) GEC Estro working group (II) Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology *Rad and Oncology* 78: 67-77
4. NCI (2011). Prostate cancer treatment, --treatment option overview. National Cancer Institute. Available at: http://www.cancer.gov/cancertopics/pdg/treatment/prostate/patient/pag4
5. American Cancer Society. (2011). Initial treatment of prostate cancer. American Cancer Society. Available at: http://www.cancer.org/cancer/prostate Cancer/Detailedguide/prostate-cancer-treatment-by-stage.
6. Thompson I, Thasher J.B, Aus G, et al. (2007). Guideline for the management of clinically localized prostate cancer. J Urol: 177: 2106-2131.
7. Horwitz E.M, Bae K, Hanks G.E, et al. (2008). Ten-year follow-up of radiation therapy oncology group protocol 92-02: A phase III trial of the duration elective androgen deprivation in localized advanced prostate cancer. J Clin Oncol: 26: 2497-2504.

8. Bolla M., Van Tienhoven G, Warde P, et al. (2010). External irradiation with or without iong-term androgen suppression for prostate cancer with high metastatic risk: 10 year results of an AORTC randomized study. The Lancet Oncology: 11: 1066-1073.
9. Wibowo A, Haris B, and Islamiyah D.I, (2017). Dose evaluation of organs at risk (OAR) cervical cancer using dose volume histogram (DVH) on brachytherapy. J. Phys.:Conf. Serv. 853012013.
10. Fowler J.F, (1989). The linear quadratic formular and progress in fractionated radiotherapy. Br j Radiol; 62(740): 679-894.
11. Jones B., Dale R.G. Deehan C, et al. (2001). The role of biologically effective dose (BED) in clinical oncology. Clin Oncol (RollRadiol): 13(2): 71-81.
12. Fowler J.F. (2010). 21 years of biologically effective dose. Br J Radiul: 83 (991): 554-568.
13. Crook J.M, Potters L., Stock R.G. and Zelfsky M.J. (2005). Critical organ dosimetry in permanent seed prostate brachytherapy: Defining the organs at risk. Brachytherapy; 4: 186-194.
14. Nath R, Bice W.S, Butler W.M, et al. (2009) AAPM recommendations on dose prescription and reporting methods for permanent interstitial brachytherapy for prostate cancer: Report of Task Group 137; Medical Physics; 36: 11, 5310-5322.

Contacts of the corresponding author:

Philip Kioko Ndonye,
Oncology & Cancer Treatment Centre,
The Nairobi Hospital,
P.O Box 30026, Code-00100,
Tel. +254 020 2845000,
Cell phone +254 711150081,
NAIROBI, KENYA.
Email; pkndonyeh@gmail.com