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Brachytherapy-A Brief Review with focus on Carcinoma Cervix

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Abstract: *Brachytherapy has been historically described as the first form of conformal technique where radioactive source is placed inside or very close to the tumour. With this modality of radiation a high dose could be delivered to the tumour with maximal sparing of adjacent normal structures. The dose gradient follows the inverse square law which states that the dose falls off sharply with increasing distance from the source. The evolution of this modality started with the use of radium initially, later development of numerous other sealed radioactive sources led to extensive use of this form of therapy in oncology. This has been most efficiently and extensively utilised in the treatment of carcinoma cervix. The earlier concept of point based treatment later changed to the development of volume based treatment.*

Key words: *Brachytherapy, carcinoma cervix*

I. Introduction

The term 'Brachytherapy' is derived from the Greek word "brachy" meaning "short", denoting the distance from which the action of this technique takes place and has been described as the first form of conformal radiation technique[1]. It is also known as endocurietherapy or plesiotherapy. Brachytherapy (BT) is a method of irradiation in which sealed radioactive sources are used to irradiate a tumour which is in contact with, or very close to, the radioactive source. Thus radiation is delivered at a short distance from the source. With this mode of therapy, a high radiation dose can be delivered locally to the tumour with rapid dose fall-off in the surrounding normal tissues.

In contrast to External Beam Radiotherapy (EBRT) where a relatively a homogenous dose distribution is achieved [2], the dose distribution achieved in BT is extremely heterogeneous, with isolated areas inside the tumour tissue even receiving more than 200% of the prescribed dose. This is achieved due to the dose gradient following the inverse square law which states that the dose fall off sharply with increasing distance from the source. As the dose falls off with distance, the surrounding normal tissue receives not only a reduced dose but also a reduced dose rate which results in enhanced normal tissue sparing.

Tumours with defined margins with a low risk of regional and metastatic spread potential are best treated by BT as a single modality; however, in modern day oncology, BT is more commonly used in conjunction with EBRT to give a highly localised tumour boost. In this scenario, EBRT is used to sterilise area of possible regional nodal and local microscopic spread, while BT is used for highly conformal dose escalation to the areas of gross disease. BT also finds use as a method for re-irradiation where a patient has received dose close to the normal tissue tolerance using EBRT.

Various forms of brachytherapy are sub-divided according to the body cavity or tissue being irradiated, viz. intracavitary; interstitial; surface moulds; intraluminal; and some special forms, like endovascular, ophthalmic plaques etc. The choice of one technique or the other is dictated primarily by the size and location of the tumour. For example, intracavitary therapy is used when applicators can be introduced into body cavities, like utero-cervix; interstitial therapy is indicated when the tumour is located inside organs or connective tissues and can be implanted directly according to accepted rules of distribution, such as carcinoma prostate, or soft tissue sarcoma; surface moulds are used to treat small superficial areas, such as carcinoma of the skin, the ear or the lip; intraluminal BT is used in the treatment of biliary channel tumours, bronchial tumours, or esophageal tumours.

Brachytherapy can be also divided into subtypes based on the dose rate at which the source delivers the doses. According to the International Commission on Radiation Units and Measurements (ICRU) report no. 38, low dose rate (LDR) implants deliver doses at no more than 2Gy/hr, medium dose rate (MDR) implants between 2 to 12 Gy /hr, while high dose rate (HDR) implants deliver doses at the rate of more than 12Gy/hr. Another brachytherapy method used is known as pulsed dose rate (PDR) which lies somewhere in between MDR and HDR in terms of dose rate and effects.The radiobiological properties of each of them varies according to the dose rate.

II. Radiobiological aspect

The dose rate is the key factor in determining the biological effects. Studies by Regaud were possibly the first to show the potential therapeutic advantages of dose fractionation in treatment of cancer[4,5].The mathematical description of dose rate effect in terms of chromosomal aberrations on the duration of exposure were given by Lea and Catcheside ., Marinelli and coworkers[6,7]. In general, the effects increase as the dose rate increases, predominantly due to decrease in sublethal damage repair; this being expressed in both the tumour and normal tissues. There is a theoretical advantage of re-assortment seen in LDR during the treatment time as the cells pass through the radio-resistant phases to the sensitive phase at late G2/M phase.

Transient hypoxia can also be overcome by LDR and PDR during the treatment which is not possible in the short duration that HDR treatment is delivered[8]. Chronic hypoxia can be overcome by fractionated HDR which allows tumour shrinkage, and thereby re-oxygenation, to occur during subsequent fractions.

The advantages of HDR over LDR are multiple. Due to the exclusive use of remote afterloading systems in HDR, it minimizes radiation exposure to the personnel; Owing to a relatively short duration of treatment, and the fact that the source size is smaller than in LDR, patient discomfort is minimized. For the specialized case of utero-cervical intracavitary brachytherapy (ICBT), the HDR tubes are thinner thus not needing wide cervical dilatation, and contributing to a more comfortable and pain-free procedure for the patient. The better patient compliance thus generated allows for better positioning and higher stability of applicators, thus affording a chance of higher precision in conforming the dose to the target. Moreover, a shorter treatment time allows less movement of normal tissues, hence there is a chance of better sparing of normal tissues too; this is an outpatient procedure, hospitalisation cost is reduced; thus, larger number of patients can be treated in a day; intra-operative procedures can be done more easily with HDR as duration is small.

However, HDR is not without its disadvantages. It does not allow for the repair of normal tissues or redistribution of cells in the cell cycle, hence dose reduction has to be done and multiple treatments are required; in vitro studies have shown a theoretical advantage of improved effect due to reassortment using LDR during treatment [9]; there is limited experience as compared to LDR; the HDR systems are more expensive. Pulsed dose rate (PDR) BT simulates the radiobiological advantages and dosimetric properties of LDR, while retaining the advantage of computerized dose optimisation, stepping source dosimetry, and remote afterloading of HDR.

III. Dosimetry Systems for Interstitial Brachytherapy

Various dosimetric systems exist for interstitial brachytherapy aiming to determine the distribution and type of radiation sources to provide optimum dose distribution, as well as to provide a complete dose distribution in the irradiated volume.These systems differ in source distribution, linear strength of sources, arrangement of crossing needles etc. The well-known Manchester system was published in 1934[10], followed by the Quimby system in 1944[11]; both these systems used radium as the radioactive source. Subsequently, the Paris system was developed which used Ir^{192} flexible wire sources [12].

IV. Intracavitary brachytherapy in carcinoma cervix

Cervical cancer brachytherapy constitutes a special case where a form of intracavitary brachytherapy (ICBT) has been used with very successful results.The unique anatomy of the pelvis, the position and anatomical relationships of the various organs (utero-cervix, bladder, rectum, bowel etc), combined with the physical advantage of separation being possible between target and normal tissues, as well as the relative radio-tolerance of the normal structures, altogether, confer on this site a specia lbiophysical opportunity to utilize BT in a very successful curative manner.

The various systems used in ICBT for carcinoma cervix are: Stockholm, Paris, or Manchester systems; all of them used radium as the radioactive source. Dose specification in Paris and Stockholm systems was made in milligram-hours of Radium exposure[13,14], whereas in the Manchester system dose prescription was done in Roentgen. The Manchester system is one of the oldest and the most extensively used systems in the world. It is characterized by doses to four points: point A, point B, a bladder point, and a rectum point. Point A was originally defined as 2 cm superior to the lateral vaginal fornix and 2 cm lateral to the centre cervical canal in the plane of uterus [15].Point B was defined to be 3 cm lateral to point A in the same plane. However, this led to the confusion whether these points were related to the patient anatomy (which changes with each fraction, and sometimes, even within a single fraction), or to the applicator set being used, and where exactly to prescribe the dose.

Clarification and a common terminology for prescription and reporting was provided by the ICRU 38 report, which recommended a system of dose specification that relates the dose distribution to the target volume, instead of the dose to a specific point. The dose was prescribed as the value of an isodose surface that just surrounds the target volume.Moreover, this report clarified that the reference points were related to the applicator set, and not to the patient anatomy, thus conferring a semi-rigid co-ordinate frame. However, these very same points turned out to be a disadvantage.

In external beam radiation therapy, one is used to visualizing the tumour/target tissues, and the normal organs, and then prescribing the curative doses to the target volumes, while trying to save as much of the normal organs is feasible. In order to translate these simple concepts to the BT setting, as well as to do away with the problem of the relationship of tumour and normal organs with motion (both inter- and intra-fraction), a European gynaecological working group, GEC-ESTRO, devised guidelines for three dimensional MRI-based target contouring and dose prescription for cervical cancer brachytherapy[16,17]. They explained that as tumour and normal organ topography change significantly during external beamtherapy, as well as in BT (both inter- and intra-fraction), there arises a clear need for a systematic, unambiguous and common description of target volumes at diagnosis, at the time of EBRT, and at the time of each BT application.

They formulated definitions of gross tumour volume(GTV-D) at diagnosis, and at each brachytherapy(GTV-BT) procedure, as well as high risk and intermediate risk clinical target volumes (HR-CTV,IR-CTV).A 'high risk' CTV (HR-CTV) includes residual macroscopic disease (if any), and at a minimum, includes the whole cervix. The intent is to deliver a total dose as high as possible, and appropriate, to eradicate all residual macroscopic tumour; the dose being iso-equivalent to 80-90+Gy. An 'intermediate risk' CTV (IR-CTV) corresponds to residual microscopic disease at time of BT. The intent is to deliver a total radiation dose appropriate to cure significant microscopic disease in cervix cancer, which corresponds to a dose of at least 60-70Gy.The dose to pelvic sidewall are 50-55Gy for smaller lesions and 55-60Gy for larger ones. The group also defined, for the first time, dose-volume constraints for normal organs; D_{2cc} to bladder and rectum being not more than 90Gy and 75Gy respectively.

In the end, the recommendation guidelines of the American Brachytherapy Society (ABS) are being given here [18,19]

ABS guidelines for LDR and PDR brachytherapy in carcinoma cervix

(1) ABS recommends use of two LDR or PDR applications. The first application should be performed within 4-6 weeks of initiation of EBRT and the second one should be done 1-2 weeks later to complete therapy within an overall treatment time (OTT) of 8 weeks.
(2) Optimal tandem and colpostat selection and application are essential for appropriate dose distribution.
(3) The tip of the tandem is often loaded with slightly higher activity than the distal tandem to provide adequate coverage to the lower uterine segment. Vaginal colpostats are loaded according to their diameter, keeping in mind the dose to tumour and critical structures.
(4) ABS recommends a therapeutic dose of 80-90Gy for locally advanced cervical cancer. After EBRT with a dose of 45Gy to pelvis, the remaining 35-40Gy should be given by BT with the dose rate of 0.4-0.6 Gy/hr. Prescription should include dose rate at point A in Gy/hr with D_{90} and $V_{100}$of HR-CTV being greater than 90% of the prescribed dose. The recommended normal tissue constraints for D_{2cc} for the sigmoid and rectum are less than 70-75Gy and that for bladder is 90Gy.

ABS guidelines for HDR brachytherapy in cancer cervix

(1) Complete treatment should be completed in less than 8 weeks, so HDR brachytherapy may be inter-digitated with EBRT to shorten the OTT.
(2) 3D imaging with CT/MRI should be performed when feasible to estimate tumour dimensions and ensure adequate coverage.
(3) Chemotherapy should not be administered on the day of HDR BT, given the risk of increased complications after a high dose.
(4) Achieving an acceptable dose distribution and simultaneously avoiding organ at risk with HDR and PDR requires proper insertion of applicator and a good optimization process.
(5) Dose recommendation: Good tumour coverage with EQD2 $\geq$80Gy for patients with residual disease less than 4 cm in diameter. For tumours more than 4cm, to maximize tumour control, dose escalation to EQD2 85-90Gy is recommended to either the point A or the D_{90}. For the normal tissues, for each fraction, DVH values are calculated and final dose is then calculated.

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