

High Dose Rate Brachytherapy (HDR) - Its Role in Malignant Tumours

S.C. SHARMA

Department of Radiotherapy, Post Graduate Institute of Medical Education & Research, Chandigarh-160012 (India)

Abstract: Introduction of remote control afterloading machines and production of high specific activity radioactive source of cobalt-60 and later on Iridium-192 led to introduction of high dose rate brachytherapy, which has advantages of short treatment time and therefore, comfortable to patient, maintenance of geometry, individualization of treatment and no radiation hazard. All the applicators used with low dose rate brachytherapy have been modified to be used with HDR. Calibration of sources is of utmost importance and computerized treatment planning should be carried out either in 2-D or 3-D format. Quality of high dose brachytherapy should be ensured. Linear quadratic model is useful for conversion of doses from low dose rate to high dose rate brachytherapy. HDR brachytherapy is to be used in fractionated manner to minimize late radiation morbidity with effective control of disease.

All types of brachytherapy can be practiced using high dose rate which includes intracavitary, interstitial, intraluminal and surface moulds. The treatment of each patient can be individualized and optimized which gives better control of disease with reduced morbidity. High dose rate brachytherapy is being commonly used in the treatment of carcinoma cervix and endometrium where it has been optimized and produces results which are similar to low dose rate brachytherapy and has additional advantage of reduced morbidity to rectum. HDR brachytherapy is being used with increased frequency in interstitial setting for treatment of head and neck and other carcinomas but still needs to be optimized. The introduction of HDR brachytherapy has made it simple and comfortable to the patient for treatment of carcinoma bronchus and esophagus in form of intraluminal brachytherapy due to short treatment time and gives best palliation. Surface moulds can also be practiced using high dose rate brachytherapy. Endovascular brachytherapy using HDR has made it possible to use it for preventing stenosis following angioplasty in coronary heart disease. Therefore in conclusion HDR brachytherapy is slowly replacing low dose rate brachytherapy and will be used with increasing frequency in future.

Key Words : *Brachytherapy, High Dose Rate, Individualization.*

Introduction

Radium was discovered in 1898 by Marie and Pierre Curie and was successfully used for brachytherapy treatment within five years of its discovery. Brachytherapy delivers very high dose of radiation in short time with sharp fall off of dose leading to best tumour control and minimum radiation morbidity. Manchester system of Paterson and Parker¹ was devised in 1930 and became most popular way of prescribing dose in brachytherapy for next 30-40 years. The technical advances in 60s and 70s led to introduction of Paris method of Ir-192 wire sources. All these methods of brachytherapy were practiced at low dose rate, (LDR) which gives better dose distribution, radiation is delivered continuously over a period of 7-10 days, helps in repair of sub-lethal damage thereby maximizing differential between early and late responding tissues and is considered to be treatment par excellence. However, limitation of this treatment include long treatment time and, therefore, discomfort to the patient, improper dosimetry due to haste in application being a loose system and radiation hazard as most of the low dose rate systems were pre-loaded.

The technological development in the form of remote control afterloading machines and production of high specific activity radiation sources of Cobalt-60 led to introduction of high dose rate (HDR) brachytherapy in 1965², which has advantage of short treatment time per application and, therefore, highly comfortable to patient, better maintenance of geometry leading to uniform dose distribution and this also made it possible to individualize the treatment. There is no radiation hazard associated with HDR brachytherapy as it is imparted through remote control afterloading machines and the treatment can also be done from out patient, thereby minimizing hospital stay and cost.

Physics of HDR Brachytherapy

HDR brachytherapy can only be practiced using remote control afterloading system, which should have shielding safe for sources, source position system, safety system to ensure operations, emergency system to withdraw sources and computerized control console to co-ordinate operations of the unit. High intensity radioactive sources of either Cobalt-60 in form of pellets in earlier days and now Iridium-192 is used, which is placed at the end of a drive cable and is transferred to applicator inside the patient through transfer catheters and the proposed unit should conform to international standards of safety and quality set forth by international standards organization-ISO-9000. Virtually all types of applicators used in low dose rate are modified for use with HDR brachytherapy of any type. The system should be closed so that there no possibility of any part of HDR sources getting dislodged in the patient³. Calibration of sources is of utmost importance. The dose calculation should be computer based in 2-D or 3-D format to get exact dose distribution. HDR gives the opportunity of optimization of dose distribution for an individual patient by manipulating the dose distribution by controlling the dwell times used at each dwell position. Quality control of HDR afterloading system, HDR brachytherapy planning computer and treatment planning as well as dose delivery should be ensured by the Medical Physicist.

Radiobiology of HDR Brachytherapy

HDR brachytherapy is a relatively new modality of radiation therapy, where documented expression or personal experience is lacking today. Radiation oncologist must commonly resist to use the bio-effect dose models to convert dose from LDR to HDR brachytherapy. Now-a-days linear quadratic model is used for

conversion of biological equivalent doses by calculating BED values commonly used for usch conversions⁴. High dose rates are high enough to delivered dose in the tissues which is less than the half time for repair for sub lethal radiobiological damage and the duration of treatment is less than few minutes. For long exposures, repair takes less time to occur and biological effects becomes less. Late responding tissue has great capability for repairing than the tumour or early responding tissue. But this repair does not take plaes as fully with HDR Large doses per fraction cause relatively more severe late damage then the tumour cell kill during HDR Brachytherapy and carries radiobiological risk of late complications for the same control rate. This risk can be minimized by altering the total HDR dose or distribution of dose. Therefore, it is necessary to use multiple HDR fractions and to decrease the dose to late responding tissue. If critical organs like rectum and bladder in carcinoma cervix treatment are kept at 80% of prescribed dose by displacing these structure away, 4-6 fractions of HDR can be given leading to minimum late radiation morbidity. Radiobiological consideration favour a large number of fractions which are not feasible in clinical practice⁵.

Clinical Application of HDR Brachytherapy

All forms of brachytherapy techniques are practised using high dose rate which include intracavitary, interstitial, intraluminal and surface mould brachytherapy and are discussed below :

Intracavitary HDR Brachytherapy

a) **Carcinoma Cervix** : Brachytherapy plays a sheet anchor role in the treatment of carcinoma cervix and is responsible for high degree of control rate and survival. Brachytherapy was practiced at low dose rate devised by Paterson and Parker at Machester, U.K. and is standard of care even today. Joslin et al in 1972 introduced high dose rate brachytherapy in the treatment of carcinoma cervix and is being practiced since then with increasing frequency⁶. He started with dose of 10 Gy.* per fraction weekly for 4 weeks but encountered high morbidity particularly to small bowel. But when the dose was reduced to 8 Gys. per fraction and a number of fraction increased to 5, this resulted in similar control rate and complications when compared with low dose rate brachytherapy^{7,8}. Since then dose ranging from 6-10 Gys. per fraction for a total of 3-7 fractions has been used by various workers. Early stage patitns are treated with 4-7 fractions of 7-9 Gys. per fraction on weekly basis with external supplement to parametrium only. Late stage patients are treated with external radiation to whole pelvis delivering a dose of 45-50 Gys. followed by 2-3 fractions of HDR brachytherapy. This produces the results which are comparable to LDR both for local control and late radiation morbidity. Meticulous treatment planning in 2-D or 3-D formatting is necessary and individualized optimization of dose distribution can be achieved particularly with Ir-192 source by altering the dwell time accordingly. Manchester or Fletcher Suite appliator used for LDR have been modified for use with HDR maintaining the same geometry.

*Gy=1 GRAY is a S.I. unit of radiation, named after a British scientist Dr. Hal Gray. 1 Gy = 100 cGy (centiGray)

Mostly non-randomized trial were carried out using HDR brachytherapy in cancer cervix which produced results similar to LDR brachytherapy^{6,7,8,9}. However, 3-4 randomized study have been carried out to assess and compare results of HDR with that of LDR brachytherapy^{10,11}. These studies have produced similar control rate of disease in the pelvis with similar or reduced morbidity with HDR. With increasing popularity of remote control after loading machines using high intensity Ir-192 source is likely

to become standard of care for treatment of carcinoma cervix due to its inherent advantages over LDR brachytherapy as discussed earlier.

b) **Carcinoma Endometrium** : Total abdominal hysterectomy with bilateral salpingoofrectomy is treatment of choice for endometrium carcinoma. There is 5-15% chances of recurrence at vault or in the vagina, therefore, surgery is followed by post-operative intravaginal irradiation, when there is invasion of myometrium more than 1/2 and tumour is of undifferentiated variety and reduces the chances of recurrence to 1-3%¹². The intravaginal radiation is delivered by a sorbo applicator using low dose rate. Introduction of HDR intravaginal brachytherapy has made it most suitable for these elderly patients because it prevents prolonged immobilization required for LDR and treatment is usually done on outdoor basis. HDR also provides opportunity for individualized treatment, which is necessary in this cancer. 3-4cm of upper part of vagina is treated and dose is prescribed at 0.5cm from mucosal surface. The vaginal applicator of diameter 2-3cm. can be used depending upon individual requirement. The fractionated dose ranging from 4.5 to 9.5 Gy per fraction has been used by different centers to a total dose of 21-36Gy. Dose of 5Gy per fraction daily for 5 days has been found to be most suitable, which gives good control with least morbidity. The 5 year survival rates have been reported to be more than 90% in most of the studies with late radiation morbidity of 3.7% to 11.2%^{12,13}. Higher dose of more than 6Gy per fraction increases the chances of late radiation morbidity¹². The Stage-II patient with involvement of cervix are best treated by whole pelvic external radiation of 45-50Gy to be followed by intravaginal application of 8Gy per fraction weekly for 2-3 treatment. HDR brachytherapy can also be used in pre-operative settings or in those patients, who are inoperable. The intracavitary application with vaginal sorbo is used and a dose of 8.5 Gy per fraction is delivered to a total fractions of 4-5 and gives good control of disease in such advanced disease. The intracavitary hgih dose brachytherapy can also be used for treatment of primary vaginal carcinoma, nasopharyngeal carcinoma or rarely in carcinoma of maxillary antrum but the experience in these areas is limited.

2. Interstitial HDR Brachytherapy

a) **Head & Neck Cancer** : Interstitial brachytherapy is often used in the treatment of early, locally advanced or recurrent carcinoma of head and neck more so in cancers arising from oral cavity and oropharynx. Low dose rate brachytherapy using radium was most successful and was governed by Manchester System devised by Paterson and Parker¹ and is standard of care. With introduction of remote control after loading machiens using high intensity iridium-192 sources is being used for high dose rate brachytherapy at present in all the above mentioned sites. It is used as the only curative treatment in early stage T1, T2 lesions or as boost treatment following external radiation in locally advanced disease. Plastic catheter are implanted in tumour area with adequate margin all around the tumour using single or double plane implants. These catheters are connected through transfer tube to the machine for treatment. The Treatment Planning should be done in 2-D or 3D format in treatment planning system and the machine is programmed accordingly to deliver the prescribed dose. The dose is usually delivered twice daily (6 hours apart) over a total period of 3-7 days depending upon intention of treatment whether radical or as boost. Dose of 3-6.5 Gys. per fraction has been used delivering total dose of 40-60 Gys. for curative therapy and 15-25 Gys. as boost treatment. However, the dose per fraction and the total dose needed for curative therapy still needs to be optimized. Higher the total dose and dose per fraction, more are the chances of late

radiation morbidity. It has been seen that dose of 3-4.5Gy per fraction gives similar control rate and radiation morbidity compared with low dose rate brachytherapy. Leung¹⁴ reported comparable and encouraging results using HDR brachytherapy in treatment of anterior 2/3rd of tongue. Quantitative assessment of HDR implant can be done using dosimetry procedure such as volumetric irradiation indices, dose non uniformity ratio and offer quantitative data on the extent to which the implant delivers the prescribed dose to the target volume and also determines the dose homogeneity within target volume and irradiation of tissue outside the target volume which helps in predicting the tumour control and late radiation morbidity¹⁵.

b) **Other Areas** : The HDR interstitial brachytherapy has also been extended to the treatment of parametrium in carcinoma cervix, prostate, soft tissue sarcomas, skin cancer and in carcinoma breast following conservative surgery and external radiation as boost treatment. Intraoperative implants are practiced in the treatment of carcinoma breast and soft tissue sarcomas using HDR brachytherapy.

3. Intraluminal HDR Brachytherapy

The intraluminal HDR brachytherapy is being used in the treatment of carcinoma bronchus, carcinoma esophagus, carcinoma bile duct and carcinoma of the nasopharynx as discussed below :-

a) **Endobronchial HDR Brachytherapy** : Surgery is the treatment of choice for carcinoma bronchus. However, only a small fraction of < 15% cases are suitable for surgery. Majority are treated with radiation using external radiation, rarely for cure being the intent in most patients. Patients with endobronchial disease are highly symptomatic and cough, dyspnoea and haemoptysis. External radiation provide slow relief of symptoms in a small number of cases. However, endobronchial brachytherapy in such patient usually produce quick and early control for symptoms and therefore, better quality of life. Endobronchial brachytherapy was started initially using low dose or intermediate dose rate brachytherapy which was not popular and uncomfortable to the patient due to long treatment time. Introduction of high dose brachytherapy by Spieser et al¹⁶ has made it easier to practice this form of treatment in carcinoma bronchus presenting with endobronchial obstruction

and is being used with great frequency. A 6F plastic catheter is introduced into the bronchus on bronchoscopy and is placed covering the growth with 2-3 cm margin on either side of the lesion. This catheter is directly connected to remote control after loading machine to deliver the treatment. A length of 6-10 cm can be treated effectively. The dose is prescribed at 1cm from central axis of the catheter. A dose of 5-20 Gy. per fraction has been in practiced. The endobronchial brachytherapy is used either alone or in combination with external radiation for palliative treatment of carcinoma bronchus¹⁶⁻²². The results of endobronchial brachytherapy are summarized in Table-1.

b) Intraluminal HDR Brachytherapy in Carcinoma Esophagus :

The rationale of using brachytherapy in carcinoma esophagus is that the dose of external radiation is limited by tolerance of perioesophageal tissue but with brachytherapy higher dose can be delivered to tumour and there is sparing of tissue outside the esophagus due to sharp fall off of dose. It was first practiced using low dose rate brachytherapy but did not become popular because of long treatment time and discomfort to the patient. Introduction of HDR has made it easier to deliver intraluminal brachytherapy in carcinoma esophagus. It is rarely being used with radical intention along-with external radiation in early stages; however is excellent for palliation in advanced carcinoma esophagus. HDR brachytherapy delivers high dose of radiation to the intraluminal tumour and produces extensive necrosis of tumour and therefore, quick relief of dysphagia. The plastic catheter is placed under endoscopy guidance in the esophagus covering the lesion with 2-3 cm margin on either side. A length of 6-10 cm can be treated effectively. A single dose of 15 Gys or 12-18 Gy. in 2-3 fractions is used commonly. External radiation dose of 30-40 Gys. is delivered in 2-3 weeks followed by intraluminal HDR brachytherapy delivering 12-15 Gys. in 2-3 fraction. More than 50% of cases achieve good relief of dysphagia with marginal increase in the median survival compared to external radiation alone²³⁻²⁶. The complications and radiation morbidity is within acceptable limits. 15% of patients developed stenosis, 5% fistulae and 10% ulceration of the wall of the esophagus²²⁻²⁵. Results reported in the literature are summarized in Table-2.

Table 1 : Relief of Symptoms following H.D.R. Endobronchial Brachytherapy.

Worker	Dose of I/L BRT	Improvement in Symptoms Disease (%age)				
		Overall	Cough	Dyspnoea	Haemoptysis	Pneumonia
1. Speiser, 16 1993	30Gys.x3F	87	85	86	99	99
	22.5Gys.x3F	84	-	-	-	-
2. Chang, 17 1994	27Gys.x3F	87	79	87	95	88
3. Gollin, 18 1994	15-20 Gys.x1F	8	62	60	88	46
4. Taullette, 19 1998	24-40Gys.x3.4F	74	54	54	75	-
5. Kelly, 20 2000	15Gysx5F	85	76	85	34	-
6. Gejerman, 21 2002	15Gysx3F	95	71	95	22	-
7. Sharma, 22 2002	-	-	50	66	81	57
	18Gysx2F	-	65	66	100	62
Dose of EXRT	37.5Gy/sx18F; 30Gys.x10F					

Table 2 : Relief of Dysphagia Following HDR Intraluminal Brachytherapy in Carcinoma Esophagus

Worker	Dose of EXRT	Dose of I/L BRT	Relief of Dysphagia (%age)	Dysphagia free Median Survival (Mos)
1. Sur, 23 1992	35Gys.+25Ys.	-	37.5	
	35Gys.x15F	12Gys.x2F	70.6	
2. Jagar, 24 1995	-	15Gys.	67.0	5.5
3. Sur, 25 2002	-	18Gys.x3F	-	9.1
	-	16Gys.x2F	-	6.9
4. Vinay, 26 2002	-	12Gys.x2F	48.0	10

4. H.D.R. Surface Mould Therapy

Surface mould therapy, which is used for the treatment of superficial surface tumour and has the advantage of control over depth of radiation and thereby sparing the tissue beyond certain depth. It did not become very popular at low dose rate because of associated radiation hazard. Introduction of HDR brachytherapy has renewed the interest of radiation oncologist in the application of surface mould therapy. It is delivered in a fractionated manner over a period of time using 5-8 Gys. per fraction for a total of 6-8 treatments given daily and gives excellent control. It is highly useful for treatment of superficial chest wall recurrences in post-mastectomy patients of carcinoma breast²⁷.

Conclusion

HDR brachytherapy is slowly replacing all forms of low dose rate brachytherapy due to its inherent advantages and will be standard of care for the treatment of various cancers.

References

1. Paterson R. The treatment of malignant disease by radiotherapy. Edward Arnold: London, 1963.
2. Connell OD, Howard N, Joslin CAF, Ramsey NW et al. A new remotely controlled unit for the treatment of uterine carcinoma. Lancet 1965;2:570-571.
3. Williamson J, Thomasden B, Nath R eds. Brachytherapy physics. Medison WI, Medical Physics publishing, 1995.
4. Dale RG. The use of small fraction number in high dose rate gynaecological afterloading. Some radiobiological consideration. Brit. J. of radiology 1991;64:133-144.
5. Fowler JF. The radiobiology of brachytherapy HDR & LDR. Martinez AA, Orton CG, Mould RF (eds) Nucletron Colombia 1990;page 121-137.
6. Joslin CAF, Smith CW, Mallik A et al. The treatment of cervix cancer using high activity Cobalt 60 Sources. Br. J. Radiol. 1972;45:257-270.
7. Akine Y, Arimoto H, Ogino T et al. High dose rate intracavitary irradiation in the treatment of carcinoma of the uterine cervix: Early experience with 84 patients. Int. J. Radiation Oncology Biol. Phys. 1988;14:893-898.
8. Joslin CAF: High-activity source afterloading in gynecologic cancer and its future prospects. Endocuriether. Hyperther. Oncol, 1989;5:69-82.
9. Sood BM, Goirla G, Gupta S et al. Two fractions of high dose rate brachytherapy in the management of cervix cancer: Clinical experience with and without chemotherapy. Int. J. Radiation Oncology Biol. Phys. 2002;53:702-706.
10. Patel FD, Sharma SC, Negi PS et al. Low dose rate vs. high dose rate brachytherapy in the treatment of carcinoma of the uterine cervix: A clinical trial. Int. J. Radiation Oncology Biol. Phys. 1994;28:335-341.
11. Sarkaria JN, Peterit DG, Stitt JA et al. A comparison of the efficacy and complication rates of low dose rate versus high dose rate brachytherapy in the treatment of uterine cervical carcinoma. Int. J. radiation Oncology Biol. Phys. 1994;30:75-82.
12. Rotte K, et al. HDR brachytherapy for endometrial cancer. IN Mould RF Battermann JJ, Martinez AA, et al. Brachytherapy from radium to optimization, 1994:pp91-100, Veenendaal, The Netherlands, Nucletron International BV.
13. Sorbe BG, Smeds A-C, et al. Postoperative vaginal irradiation with high dose rate afterloading technique in endometrial carcinoma stage-I. Int. J. Radiation Oncology Biol. Phys. 1990;18:305-314.
14. Leung Tw, Wong VYW et al. High dose rate brachytherapy for carcinoma of the oral tongue. Int. J. radiation Oncology Biol. Phys., 1997;39:1113-1120.
15. Saw BC, Sunthralingam N: Quantative assessment of interstitial implants: Int. J. Radiation Oncology Biol. Phys., 1994;20:135-139.
16. Speiser BL, Spartling L: Remote afterloading brachytherapy for the local control of endobronchial carcinoma. Int. J. Radiot Oncol Phys 1992;25:579-587.
17. Chang ii, Horvath J, Peyton W, et al.: High dose rate afterloading intraluminal brachytherapy in malignant airway obstruction of lung cancer. Int. J. Radiot Oncol Phys 1993;28:589-596.
18. Gollins SW, Burt PA, Barber PV et al. High dose rate intraluminal radiotherapy for carcinoma of the bronchus outcome of treatment of 406 patients. Radiother Oncol 1994;33:31-39.
19. Taulelle M, Chauvet B, Vincent P et al. High dose rate endobronchial brachytherapy: results and complications in 189 patients. Euro. Respi. J. 1998;11:162-168.
20. Kelly JF, Delclos ME, Morice RC et al. High dose rate endobronchial brachytherapy effectively palliates symptoms due to airway tumours; the 10 year M.D. Anderson Cancer Centre experience Int. J. Radiat Oncol Phys, 2000;48:696-702.
21. Gejerman G, Mullokandov EA, Bagiella E et al. Endobronchial brachytherapy and external beam radiotherapy in patient with endobronchial obstruction and extrabronchial extension. Brachytherapy. 2002;1:204-210.
22. Sharma SC, Behra D, Beriwal S, et al. Evaluation of addition of endobronchial brachytherapy for the symptoms relief in locally adanced bronchogenic carcinoma. A prospective, randomized study. J. Clinical Radiotherapy & Oncol., 2002;2:14019.
23. Ranjan Sur RK Sharma SC, Deepinder PS et al. Radiation therapy of esophageal cancer role of high dose rate brachytherapy. Int. J. radiot Oncol Biol. Phys. 1992;22:1043-1046.
24. Jager J, Langendijk H, Pannebakker M et al. A single session of intraluminal brachytherapy in palliation of oesophageal cancer. Radiotherapy & Oncology. 1995; 37: 237-240.
25. Ranjan KS, Victron C, Bernard SA, Sharma V, et al.: Prospective randomized trial of HDR brachytherapy as a sole modality in palliation of advanced esophageal carcinoma - An international atomic energy agency study. Int. J. Radiot Oncol Biol. Phys; 2002;53:127-133.
26. Sharma V, Mahantshetty U, Dinashaw A, et al: Palliation of advanced/ recurrent esophageal carcinoma with high dose rate brachytherapy. Int. J. Radiot Oncol Biol. Phys. 2002;52:310-315.
27. Sharma SC, Negi PS, Singh DP, et al. High dose rate surface mould brachytherapy for superficial localized chest wall recurrences in postmastectomy carcinoma breast patients. J. Clin. Radiation Oncology. 1997;12:1-6.

ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the critical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory *clinical trails* on new drugs, a number of *diagnostic procedures, therapeutic interventions and prevention measures* including the use of vaccines, are being introduced which involve human subjects. Further the advent of *new medical devices and radio-active materials* and therapeutic benefits of *recombinant DNA products* have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in

mind the following principles of : i) **essentiality**, (ii) **voluntariness**, **informed consent**, (iii) **non exploitation**, (iv) **privacy and confidentiality**, (v) **precaution and risk minimisation**, (vi) **professional competence**, (vii) **accountability & transparency**, (viii) **maximisation of public interest** and **distributive justice** (ix) **institutional arrangements** (x) **public domain** (xi) **totality of responsibility** and (xii) **compliance**.

Recent advances in the field of **Assisted Reproductive technologies, organ transplantation, Human genome analysis, and gene therapy** promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMR Publication 2000)