DOSE RATE AND FRACTIONATION ISSUES IN INTRACAVITARY BRACHYTHEARPY

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DOSE RATE AND FRACTIONATION ISSUES IN INTRACAVITARY BRACHYTHEARPY

HISTORY

1896. Soon after the discovery of radioactivity, radioactive isotopes used for cancer cervix treatment.

Next 60 years treatment exclusively by LDR.

1940- 50 high activity sources available.

Early 60's advent of afterloading.

1964 first RAL unit for HDR – Brachytron by Henschke.

Then first RAL unit for LDR – Cervitron and Curietron.

Mid 80s RAL for LDR and HDR commonly used.

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According to ICRU Report 38

Dose Rate	Definition
LDR	0.4 – 2 Gy/hr.
MDR	2-12 Gy/hr.
HDR	> 0.2 Gy/min (12 Gy/hr.) but usually 2.5 Gy/min.

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According to Clinical Practice

Dose Rate	Definition
LDR	: 0.5-0.6 Gy./hr. (< 1Gy/hr.)
MDR	: Usually 3 times higher than conventional LDR. Any dose rate where correction has to be made. 1- 3 Gy./hr.(ICRU-LDR) is in the dose rate region in which changes in effectiveness per gray do occur.
HDR	: Usually 100-300 Gy/hr.

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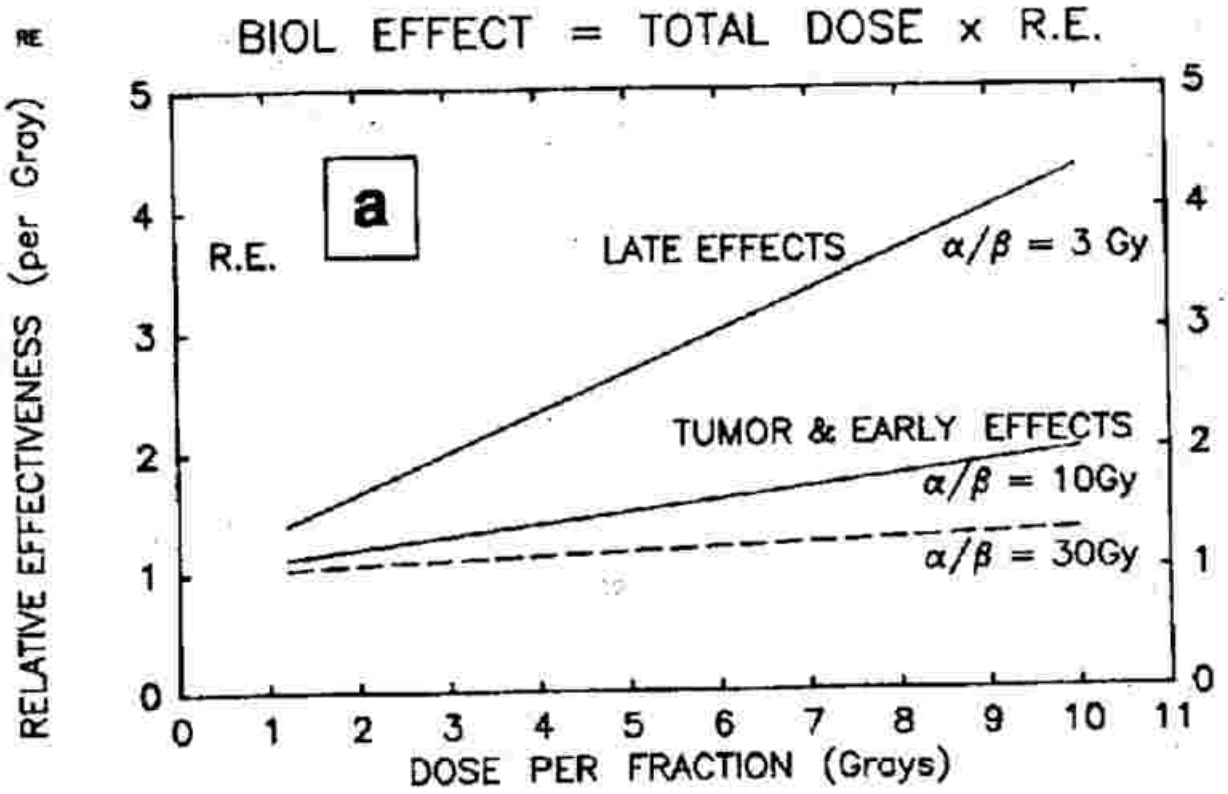

Fowler, Brachytherapy in HDR & LDR, 1989

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CONVERTING LDR TO HDR

Loss of Therapeutic Ratio with HDR.

Overdose late reactions by 25% or underdose tumours by 20%..

Doses should be equated to the tumour ($Gy._{10}$)
or late-responding tissues ($Gy._{3}$) ?

LQ model is the best working model
α/β early=10, α/β late=3, repair half times ?

Dose reduction ? **HDR 0.54 ± 0.06; MDR ?**
No. of fractions ?
Dose per fraction ?

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LDR / HDR

* Two meta-analyses – Orton 1991,1993
  - Compared published results of HDR – 4283, pts. LDR – 5100 pts.

* Review – Fu & Phillips 1990

* Three randomized studies
  - Shigematsu, 1983
  - Patel, 1993
  - Prasert , 2004

* More than 22 articles

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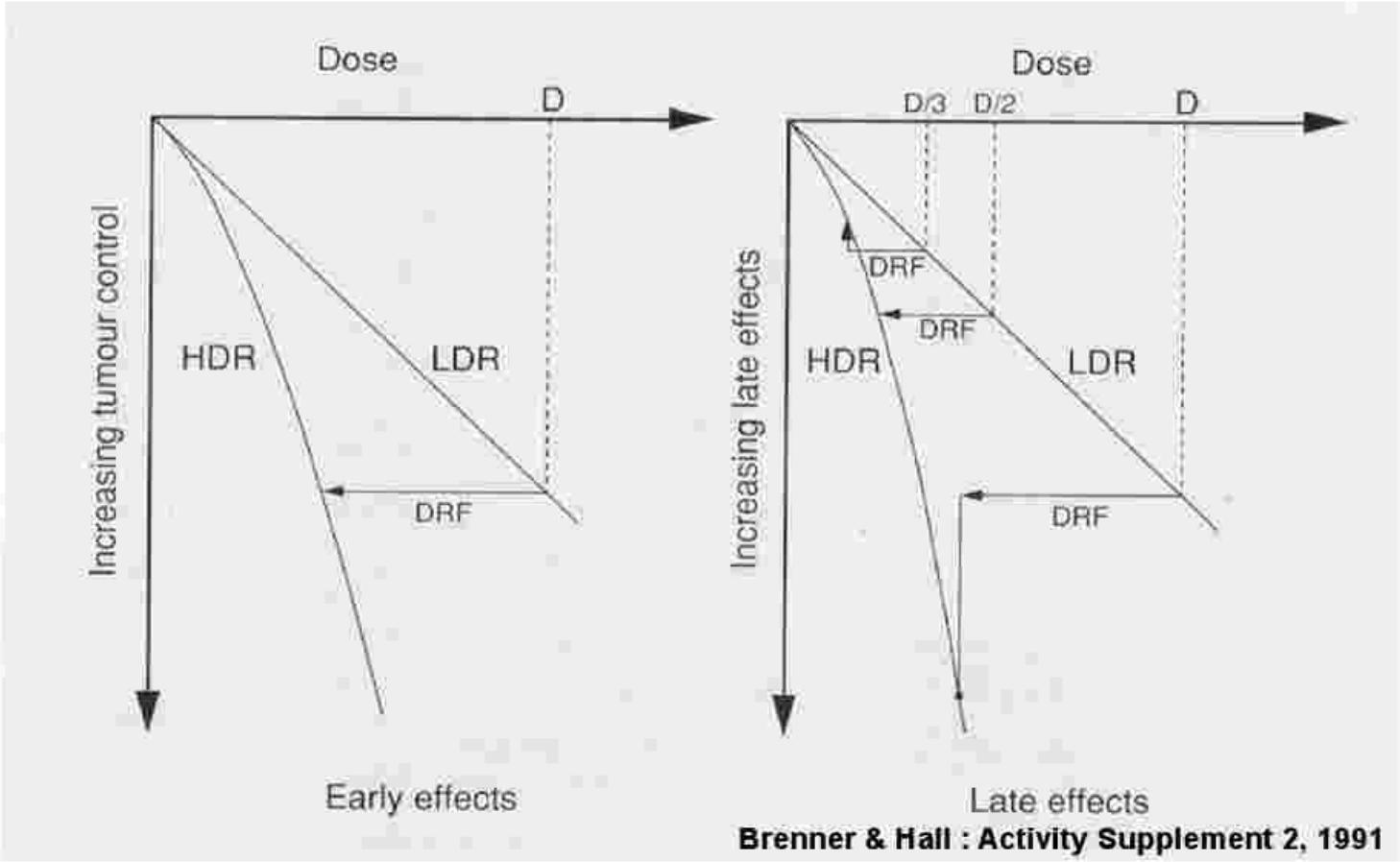
Doses should be equated to the tumour ($Gy._{10}$) or late-responding tissues ($Gy._{3}$) ?



Brenner & Hall : Activity Supplement 2, 1991

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RADIOBIOLOGY

* If dose to critical normal tissues (Bladder Rectum) is less than 75% of prescribed dose, for equal tumour control HDR results in comparable (or less) late effects than LDR.

* HDR LDR protocols should be matched for early effects for Carcinoma Cervix

LDR-HDR BRACHYTHERAPY IN CANCER CERVIX

To compensate for loss of T.R. HDR should be fractionated like Ext. RT. 16-20 Frs.

Author	No.of Frs.	Dose/Fr.(Gy.)
ARAI,	4 - 5	5 – 6
ROMAN	1 - 2	8 – 10
JOSLIN	4	10
UTLEY	4	8 – 10
SHIGEMATSU	3	8 - 10
PATEL	2 - 4	9 – 9.5
SOOD	2 - 4	9 – 9.4
PRASERT	2	7.5 – 8.3
HAN	8-12	3.86

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RESULTS LDR/HDR – Dose/F

Authors	Local Control	Complication
Han.	80%	3.4%
8-12 F of 3.86 Gy/F		
Patel	75.8%	2.4%
2-4 F of 9 Gy/F		
Sood	77%	5% gr2
2-4 F of 9Gy/F		
Prasert (3 yrs.)		
2 F of 7.5 – 8.3	86.4%	7.1%

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LDR Brachytherapy in Cancer Cervix --"Gold Standard"

To replace LDR by HDR/MDR :-

1. **Disease control rates & survival rates with HDR /MDRshould be at least equal to if not better than LDR.**

2. **Morbidity of HDR/MDR should be either equal to or preferably less than LDR.**

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RESULTS

STAGE	HDR	LDR
I	82.7%	82.4%
II	66.6%	66.8%
III	47.2%	42.6%
IV	20.4%	14.3%
ALL	60.8%	59.0%

Orton -1991

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RESULTS - 5 YRS SURVIVAL

	OSAKA		PGIMER		Bankok (3yrs.)	
	LDR	HDR	LDR	HDR	LDR	HDR
Stage – I	89	66	73	78	--	--
Stage – II	73	61	62	64	74	65
Stage- III	45	47	50	43	63	71

LDR-HDR BRACHYTHERAPY IN CANCER CERVIX

5 YEAR SURVIVAL LDR/HDR

Reference	LDR			HDR		
	I	II	III	I	II	III
Vahrson	74	53	24	71	76	62
Cikarie	--	70	43	--	54	37
Akine	--	56	38	--	60	54
Kupiers	80	68	48	76	74	36
Joslin	--	--	--	94	62	37
Newman	--	--	--	81	57	27
Utley	--	--	--	89	58	33
Shigematsu	89	73	45	66	61	47
Patel	73	62	50	78	64	43
Sood					78	
Prasert (3yrs.)	--	74	63	--	65	71

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RADIATION MORBIDITY-(Bladder)

Author	HDR	LDR
Vahrson	3.0	2.0
Cikarie	5.0	9.6
Akine	1.2	11
Kupiers	3.5	3.3
Sato	9.2	7.5
Rotte	0.8	2.5
Shigematsu	2.0	7.0
Patel	3.8	3.7
Prasert	0.9	2.7

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RADIATION MORBIDITY (Rectal)

Author	HDR	LDR
Vahrson	3.0	2.0
Cikarie	7.1	16.6
Akine	24.0	36.0
Kupiers	7.0	6.6
Sato	14.9	13.6
Rotte	2.6	10.5
Shigematsu	5.0	3.0
Patel	1.6	2.4
Prasert	4.5	0.9

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DEPENDENCE OF DOSE / FRACTION

	≤ 7 Gy./F.	> 7 Gy./F	L.D.R.
Cure Rates	Equivocal		
Severe Morbidity	1.28%	3.44%	5.34%
Moderate + Severe Morbidity	7.58%	11.22%	20.66%

Orton 1991 : Int. J. Rad. Oncol. Biol. Phys.

DOSE RATE AND FRACTIONATION ISSUES IN INTRACAVITARY BRACHYTHEARPY

ABS RECOMMENDATIONS

- HDR brachytherapy although use successfully for over 30 years has encountered considerable resistance in the United States because of concerns regarding its potential toxicity.

- Primary disadvantage of HDR brachytherapy is the potential late toxicity of large doses per fraction.

DOSE RATE AND FRACTIONATION ISSUES IN INTRACAVITARY BRACHYTHEARPY

ABS RECOMMENDATIONS

- HDR dose per fraction should be kept to < 7.5 Gy. due to reports of higher toxicity with larger fractions sizes.
  (Orton 1991 & 1998)

- Number of HDR fractions range from 4 to 8 – caution was included "it should be noted that these schedules have not been thoroughly tested clinically".

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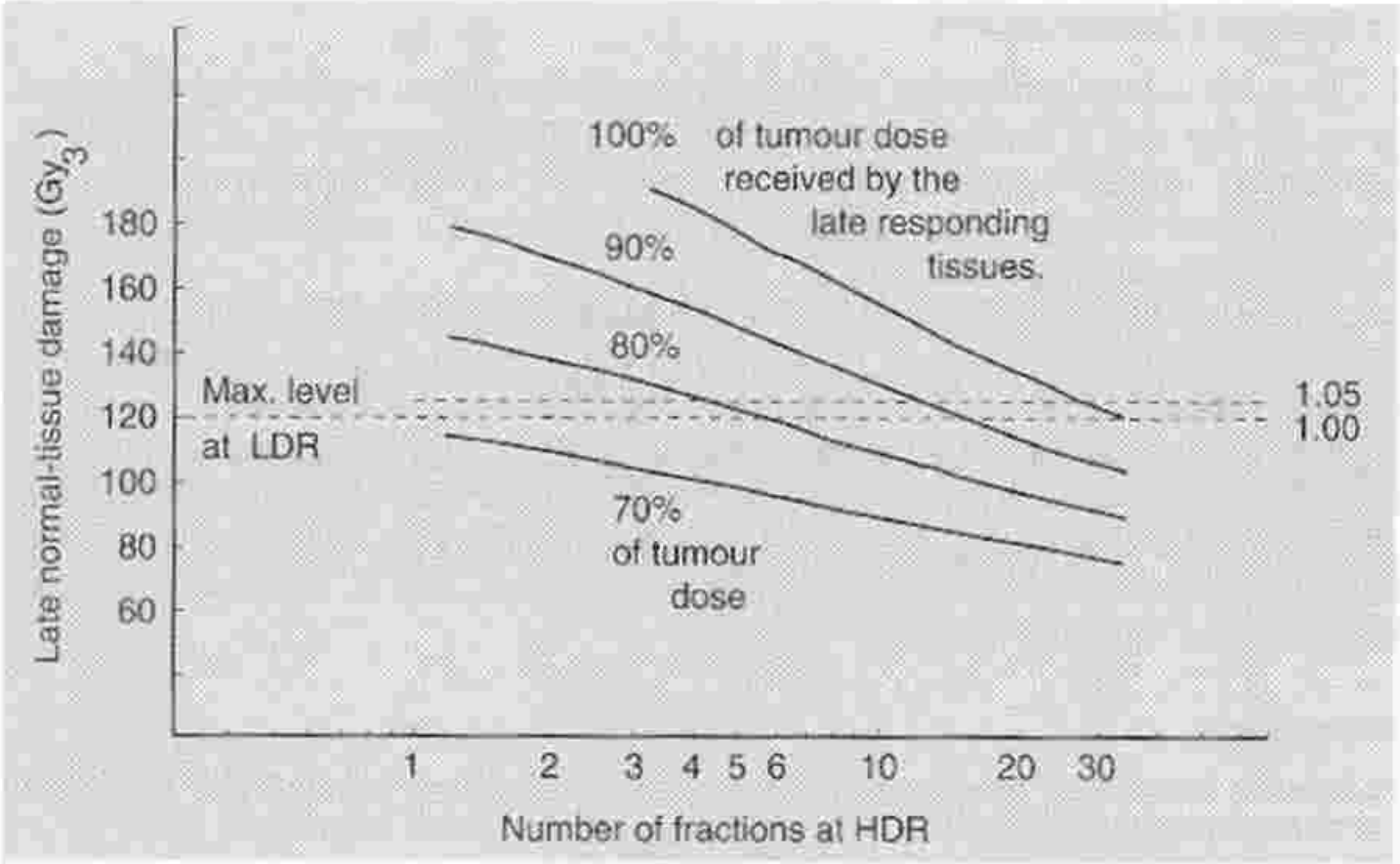

Figure 1. Increase of late damage with fewer HDR fractions: calculated for equal tumour effect to LDR 70 Gy in 140 hours.

Fowler & Stitt : International Brachytherapy , November, 1995

DOSE RATE AND FRACTIONATION ISSUES IN INTRACAVITARY BRACHYTHEARPY

"HDR BRACHYTHERAPY MAY BE RADIOBILOGICALLY SUPERIOR TO LDR DUE TO SLOW REPAIR OF LATE RESPONDING NORMAL TISSUE CELLS" **Orton; Int J. of Rad. Oncol Biol Phys;2000**

Clinical observations are incompatible with previous L-Q model predictions, where repair half time for late responding tissues is taken as a 1.5 hrs.

Recent data suggest repair half time for late responding tissues as high as 5 hrs.

Hence, slow repair of late-reacting normal tissue cells, works to the detriment of LDR but not HDR.

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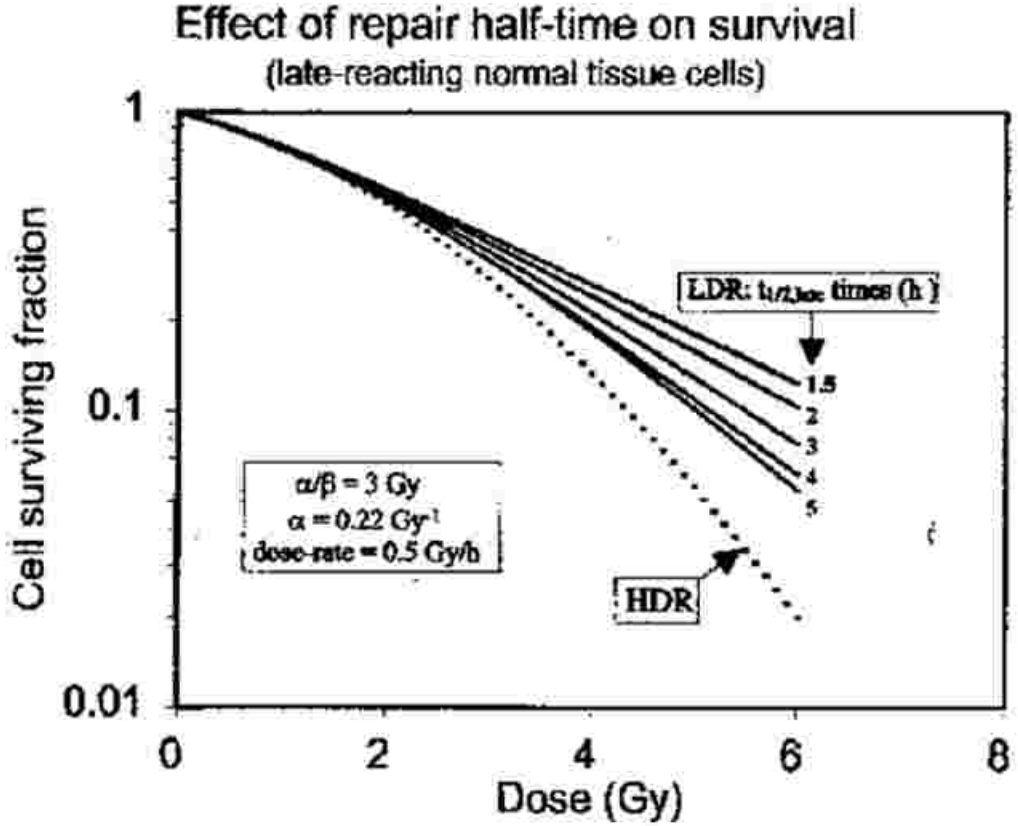

Fig. 1. Illustration of how increasing repair half-time decreases cell survival for low-dose rate (LDR) irradiation and reduces the difference between LDR and high-dose-rate (HDR) (which is not affected by repair rate). The linear–quadratic (L–Q) model was used to construct these curves with the parameters shown (22).

Orton : Int. J. Rad. Oncol. Biol. Phys. Vol. 49, 2001

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LDR / MDR

*ICRU MDR 2-12 Gy/hr

*Clinically MDR – Above 1 Gy / hr

*Magnitude of dose to be reduced is highly dependent on dose rate used.

*Radiobiology – 33% Correction

*Clinical studies – 9-30% Correction

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	LDR / MDR	COMPLICATIONS
MANCHESTER		
Radium	53cGy/hr	11-15%
Selectron	180-140cGy/hr	
0% Red.		57%
6% Red.		36%
12.5-19% Red.		No Diff.
GLASGOW		
Manual	55cGy/hr	4%
Selectron	140-120cGy/hr	
25% Red.		9.3%

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LDR / MDR P.G.I. STUDY – I

	LDR	MDR-30	MDR-12.5
Local Control	76.8%	74.7%	74.4%
Total Morbidity	24.3%	26.4%	41.8%
Grade III & IV	2.7%	5.7%	8.1%

LDR / MDR P.G.I. STUDY – II

	MDR-30	MDR-20
Local Control	69.6%	77.3%
Total Morbidity	23.9%	27.3
Grade III & IV	4.3%	6.8

At 220±10cGy./hr. at point A dose should be reduced around 30%.

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LDR / MDR P.G.I. STUDY – II

Rectal BED Vs. Complications

BED Gy_3	No.of Pts.	Pts.with Complications(%)
100 < 120	129	13 (10.0)
120 < 140	34	18 (52.9)
140 < 160	16	10 (62.5)
160 < 180	1	1 (100.0)

Rectal BED should be around 125 Gy_3 to keep the rectal morbidity low.

30% reduct, critical organs can receive 68% of point A dose

12.5% reduct, critical organs can receive 58% 0f point Adose

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CONCLUSIONS

- HDR/MDR brachytherapy is an established alternative to conventional LDR brachytherapy in Ca. Cervix.

- The local control, 5 year survival and morbidity are comparable with those of LDR.

- The ideal number of fractions & dose per fraction are not fully optimized.

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CONCLUSIONS

- It is not the dose per fraction that is important but the proportion of prescribed dose received by critical organs that is important.

- LQ model predictions must be reviewed with clinical experience.

- Stop comparing HDR/MDR to LDR brachytherapy but consider it as a completely new therapeutic field.