Radiobiological quality of high dose rate interstitial brachytherapy treatments of carcinoma of the cervix

Sanjay S. Supe[1 ACDEF], **K. M. Ganesh**[1 BCDE], **Hema Vaithianathan**[1 BD], **B. N. Sankar**[2 DE]

[1] Department of Radiation Physics, Kidwai Memorial Institute of Oncology, Bangalore, India
[2] Department of Physics, Anna University, Chennai, India

Summary

Aim

The aim of the present study was to apply the Figure of Merit (FOM) concept to High Dose Rate (HDR) interstitial brachytherapy treatments delivered for carcinoma of the cervix at the Kidwai Memorial Institute of Oncology, Bangalore, in order to evaluate the radiobiological quality of the implants.

Materials/Methods

Twenty seven patients received external beam radiotherapy, as 50Gy in 25 fractions over five weeks, followed by interstitial brachytherapy by the HDR template technique on a Gammamed HDR machine. Doses were delivered 5mm from the periphery of the implant along the transverse plane. Points in the bladder and rectum, receiving the maximum dose rate, were used for the evaluation of total dose received by these critical organs. BED and FOM values were evaluated for all patients.

Results

Two patients had a rectal FOM value greater than 10. A FOM bladder value of higher than 10 was observed in six patients. Only in one patient were FOM values for both the rectum and bladder found to be above 10. The relationship between FOM values for the rectum and the bladder indicated that most FOM values were clustered near the initial portion of the scattergram obtained. For one patient the rectal FOM value was above 10, while the FOM for the bladder was significantly smaller. In another patient, having a high FOM value for the bladder, the FOM value for the rectum was also above the critical value of 10.

Conclusions

Good physical optimization can lead to good radiobiological optimization, as observed in our study. Radiobiology can not improve a bad quality implant. HDR interstitial brachytherapy, which gives better geometrical sparing for critical normal organs such as the rectum and bladder, should be the treatment of choice for patients with carcinoma of the cervix. In optimizing treatment for a patient, the maximizing of FOM should be supplemented by a comparison of reference BED values and new treatments for the tumour, rectum and bladder.

Key words

HDR • brachytherapy • treatment

BACKGROUND

Cancer of uterine cervix is one of the commonest cancers in developing nations. It comprises 45% of cancers in women and 25% of all cancers, as documented by the cancer registry of the Kidwai Memorial Institute of Oncology [1]. Seventy percent of these patients present in advanced stage IIIB. Brachytherapy plays an important role in the radiotherapeutic management of this malignancy. Intracavitary brachytherapy has been practiced since the emergence of radiation oncology. However, intracavitary brachytherapy for carcinoma of the cervix does not give satisfactory dose-volume coverage in the sense that the lateral pelvic wall does not receive adequate dosage. Interstitial brachytherapy with a gynaecological template overcomes this drawback and has been widely utilized as an important aspect of radiotherapy.

Interstitial implants generally involve a range of dose rates where variations in the biological effects of the dose rate are substantial and important. In the case of interstitial implants in a clinical setting, the limiting factor is the normal-tissue tolerance, which should be used fully to maximize the possibility of tumour control. The maximum dose that can be delivered without unacceptable damage to surrounding normal tissue depends, critically, on the dose rate and also on the volume of tissue irradiated [2].

High Dose Rate (HDR) brachytherapy was developed to overcome some of the potential disadvantages of low dose rate brachytherapy, such as exposure of the professional staff to radiation, prolonged treatment times, the need for hospitalisation, the risks of anaesthesia, bed immobilization that can lead to thromboembolism, the discomfort of vaginal packing and applicators during bed immobilization and displacement of the applicator [3–8]. HDR brachytherapy has been used for more than 30 years world wide. Template guided interstitial brachytherapy has been routinely utilized in the management of carcinoma of the cervix and has been extended to HDR brachytherapy techniques. Although three decades of experience and literature reports on the use of HDR brachytherapy for the treatment of cervical cancer are available, a wide range of fractionation schedules exist and the treatment optimisation scheme remains unclear [3–8].

The empirical concepts of NSD, CRE and TDF were proposed and utilised for many years in spite of their limitations [9]. Now, the linear quadratic model (LQ) is being used increasingly, to predict the biological effects of fractionated radiotherapy using different parameters for particular tissues, such as α/β, μ, K and T(0) [10–14]. Dale [10] has proposed LQ equations for external beam therapy, intracavitary brachytherapy and interstitial brachytherapy.

Within the context of the linear-quadratic (LQ) model, the parameter which quantifies the overall biological effect on a given tissue is the biologically effective dose (BED). At least two BEDs are associated with each treatment and, in principle, two or more treatments may be compared by reference to their respective tumour and late-reacting BED values. The BED concept is also of potential value in deciding how best to reschedule an interrupted treatment.

The parameters which are more directly linked with the all important concept of therapeutic ratio are, however, the tumour cure probability (TCP) and the normal tissue complication probability (NTCP), neither of which are simply related to their respective BEDs. Whilst any treatment which (relative to a reference regime) increases the tumour BED and reduces the critical tissue BED is clearly an improvement over the original treatment, the benefits of an increased tumour BED which can only be achieved by allowing an increase in the late-reacting BED, is much more difficult to judge. The biological "worth" that should be attached to changes in pairs of BED values is by no means obvious, as there is a secondary dependence on other (usually unknown) biological parameters. Dale and Sinclair [11] have proposed the Figure of Merit (FOM) concept with which to rank different treatment options. FOM takes into account the BED values for tumours and critical organs. Those alternative treatments which are most like a given reference treatment will have FOM values close to 10.0. FOM values higher or lower than 10.0 respectively correspond to treatments which overall are likely to be better or worse than the reference. No special robustness is claimed for the proposed scoring system, but the method nevertheless allows the ranking of treatment options such that the least satisfactory may be identified and rejected.

AIM

The aim of the present study was to apply the FOM concept to high dose rate interstitial

Table 1. LQ model parameters utilized in the evaluation of BED values [1,4,10,13,18].

Criteria	α/β (Gy)	µ (hr⁻¹)	K (Gy/day)
Prescription point (Tumour)	10.0	0.693	0.5
Rectum	3.87	0.46	0.0
Bladder	4.00	0.46	0.0

brachytherapy treatments delivered for carcinoma of the cervix at the Kidwai Memorial Institute of Oncology, Bangalore, in order to evaluate the radiobiological quality of the implants.

MATERIALS AND METHODS

Twenty seven patients diagnosed with stage IIIB carcinoma of cervix, and who had received curative radiotherapy in the form of a combination of external beam radiotherapy followed by HDR interstitial brachytherapy, were prospectively included in this study. External beam radiotherapy was delivered as 50Gy in 25 fractions over five weeks on a Cobalt-60 teletherapy machine, without mid-line shielding. 10–15 days after completing external beam radiotherapy, interstitial brachytherapy was delivered by the HDR technique using a Modified Multipurpose Perineal Interstitial Template (M-MUPIT) on a Gammamed HDR machine. Implantation was carried out under general anaesthesia. Sixteen to twenty two needles were implanted in these cases.

Semi-orthogonal simulation was utilised for reconstructing the implant. A rectal marker tube containing lead balls, and 7cc of contrast medium in a Foley bladder catheter were used for simulating these critical organs. Computation of dose distribution was carried out on an Abacus treatment planning system. Doses were delivered 5mm from the periphery of the implant along the transverse plane. Points in the bladder and rectum, receiving the maximum dose rate, were used for the evaluation of total dose received by these critical organs. Patients received HDR interstitial brachytherapy in 3 to 4 fractions of 4.5 to 6.0Gy/fraction over 2 to 14 days.

BED values for the prescribed points of the rectum and bladder were evaluated for an LDR reference treatment with the help of an LDR interstitial brachytherapy equation proposed by Dale [10] and the parameters given in Table 1. [3,9,14,15,16] The LDR reference treatment was taken as 25Gy at a dose rate of 0.4Gy/hr

(equivalent to 4.5Gy x 4 fractions of HDR). The BED to the rectum and bladder was evaluated from the mean rectal dose rate/mean prescription dose rate ratio and from the mean bladder dose rate/mean prescription dose rate ratio obtained from our earlier study [17].

$$BED = (Total\ dose \times RE) \qquad (1)$$

$$RE = 1 + (2R_0\lambda/\mu - \lambda)\ (\beta/\alpha)\ [1 - e^{-\lambda T}]^{-1}$$
$$\{1/2\ \lambda[1 - e^{-2\lambda T}] - 1/(\mu + \lambda)\ [1 - e^{-T(\mu + \lambda)}]\} \qquad (2)$$

The RE value for HDR interstitial brachytherapy was evaluated with the following equation and the parameters given in Table 1.

$$RE = 1 + d/(\alpha/\beta) \qquad (3)$$

Where,
RE = Relative Effectiveness per unit dose;
R_0 = initial dose rate in Gy/hr;
$\lambda = 0.693/T_{1/2} = 0.00038915\ hr^{-1}$;
μ = repair constant (hr⁻¹);
α/β = tissue specific radio-sensitivity parameter (Gy);
d = dose per fraction of HDR treatment.

BED values were corrected for re-population with a correction factor:

$$RCF = KT \qquad (4)$$

Where,
K = re-population coefficient in Gy/day;
T = overall treatment time in days.

FOM was evaluated with the following methodology [11]:

$$FOM = [10\ (BEDnew/BEDref)tum^Z]^X \qquad (5)$$

Where,
Z = 2.5 when (BEDnew/BEDref)tum ≥1.0;
Z = 8.0 when (BEDnew/BEDref)tum <1.0;
and X = [(BEDref/BEDnew)crit^Y];
with Y = 2.0 when (BEDnew/BEDref)crit ≥1.05;
Y = 1.0 when (BEDnew/BEDref)crit <1.05.

RESULTS

The relationship between the dose per fraction of HDR interstitial brachytherapy and BED to the prescription point is shown in Figure 1. As the dose per fraction increased from 4.5Gy to 6Gy, the BED to the prescription point increased slightly. One patient with a dose per fraction of 4.5Gy received a BED of 31.1Gy to prescription point. Table 2 shows the BED values for the prescription points, the rectum and the bladder and FOM values for the rectum and bladder. The BED values for the prescription point varied from 19.3Gy to 31.1Gy (Mean 24.3Gy, SD 2.6Gy) for new treatments. BED values for the rectum and bladder varied from 12.2Gy to 37.8Gy (Mean 24.7Gy, SD 7.4Gy) and from 14.8Gy to 39.4Gy (Mean 25.4Gy, SD 7.5Gy) respectively. The BED values for reference treatments to the prescription point, rectum and bladder were 27Gy, 22Gy, and 23Gy respectively.

The relationship between the rectal dose versus BED (rectum) and bladder dose versus BED (bladder) are highlighted in Figures 2 and 3 respectively. The rectal and bladder BED values increased with increases to the total cumulative dose delivered to these critical organs. The FOM values for the rectum and bladder are tabulated in Table 2. Two patients had rectal FOM values greater than 10. A FOM value higher than 10 for the bladder was observed in six patients. Only in one patient were values for both the FOM for the rectum and the FOM for the bladder above 10. Figures 4 and 5 depict the relationship between the critical organ dose – prescription dose ratio and FOM values for the rectum and bladder respectively. The FOM values maximized with decreases to the above said ratio for both the rectum and the bladder.

The relationship between the FOM for the rectum and the FOM for the bladder is shown in Figure 6. Most of the FOM values were clustered near the initial portion of this scattergram. For one patient, the FOM for the rectum was above 10, while the FOM for the bladder was significantly smaller. For another patient, having a significantly higher FOM value for the bladder, the FOM value for the rectum was also above the critical value of 10.

DISCUSSION

The use of the LQ model for the intracavitary brachytherapy of cervical cancer is frequent
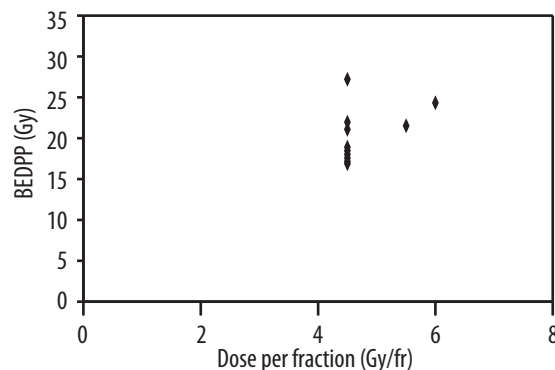

Figure 1. Dose per fraction vs. BED (presription point).
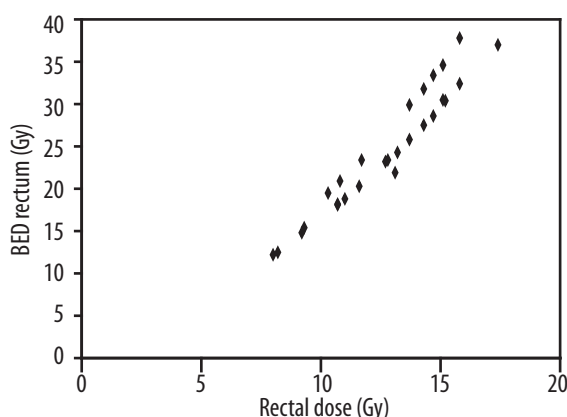

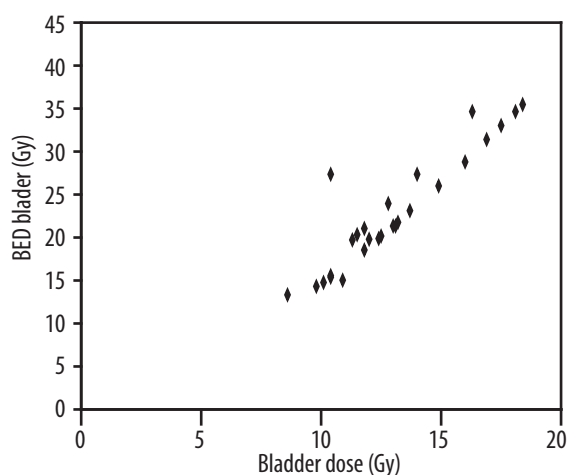**Figure 2.** Rectal dose vs. BED to rectum.

Figure 3. Bladder dose vs. BED to bladder.

[3–8]. There have been a few reports in the literature regarding the application of biological effect models to LDR interstitial brachytherapy for head and neck cancer [2,18]. Biological

Table 2. BED values at the prescription point, rectum and bladder and FOM values for the rectum and bladder.

BED Pre. point (new)	BED rectum (new)	BED bladder (new)	FOMR rectum	FOMB ladder
25.1	28.6	32.0	2.8	2.4
25.1	23.4	38.5	4.8	1.8
25.1	18.8	36.7	7.1	1.9
25.1	12.5	39.4	19.1	1.8
25.1	30.4	22.1	2.5	5.5
25.1	25.8	16.4	3.5	10.0
25.1	27.5	15.9	3.0	10.8
25.1	24.3	23.7	4.1	4.9
25.1	20.3	17.1	6.1	9.1
25.1	37.8	30.4	1.8	2.6
21.1	18.2	25.7	1.3	1.2
21.1	32.4	20.6	1.1	1.3
20.6	12.2	34.9	1.1	1.0
21.6	15.4	28.9	1.9	1.3
20.1	18.1	22.4	0.8	0.9
19.6	30.5	22.0	0.8	0.7
21.1	14.8	23.7	1.4	1.3
19.3	23.2	24.2	0.6	0.6
24.1	37.0	17.3	1.6	5.8
31.1	21.9	16.7	15.1	38.5
24.6	31.8	38.5	2.1	1.7
24.6	34.6	30.4	1.9	2.4
24.6	19.5	14.8	5.5	10.0
24.6	23.4	22.6	4.1	4.5
24.6	20.9	26.6	4.9	3.1
27.8	29.9	23.4	3.8	10.3
27.8	33.4	21.9	2.9	12.0

treatment planning has been suggested for HDR interstitial brachytherapy by a few authors [19,16]. However, these methodologies have not been utilised in interstitial brachytherapy for carcinoma of the cervix.

Ogino et al. [4] studied late rectal complications following high-dose-rate intracavitary brachytherapy for cancer of the cervix in 253 patients. The rectal point (RP) was defined according to the criteria recommended in the ICRU 38. The time-dose factor (TDF) and the biologically effective dose (BED) were calculated as components of the cumulative rectal reference dose using the rectal reference point dose in intracavitary brachytherapy combined with the external whole pelvis dose. Statistical comparison of factors affecting the incidence of late rectal complications was conducted using data from 161 patients. The incidence of late rectal complications among this group was 9 of the 161 patients (5.6%) for grade I, 51 patients (31.7%) for grade II, 11 patients (6.8%) for grade III, and 13 patients (8.1%) for grade IV. The TDF and BED values were significantly
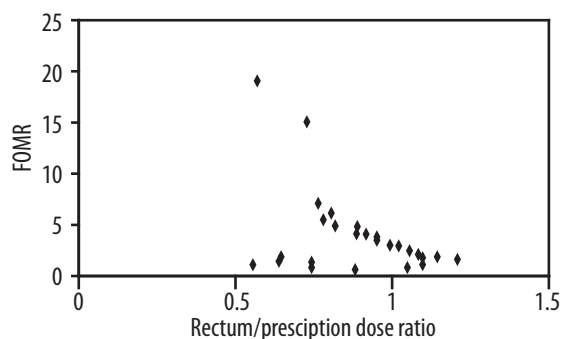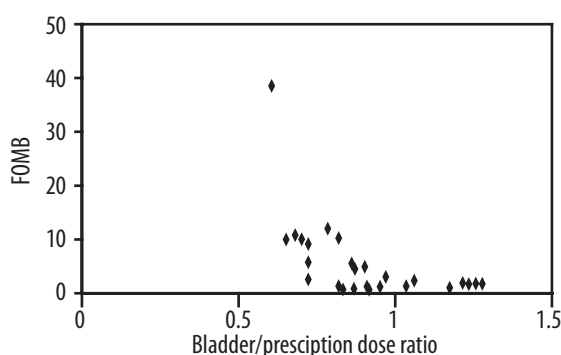
Figure 4. Rectum/presription dose ratio vs. FOMR.

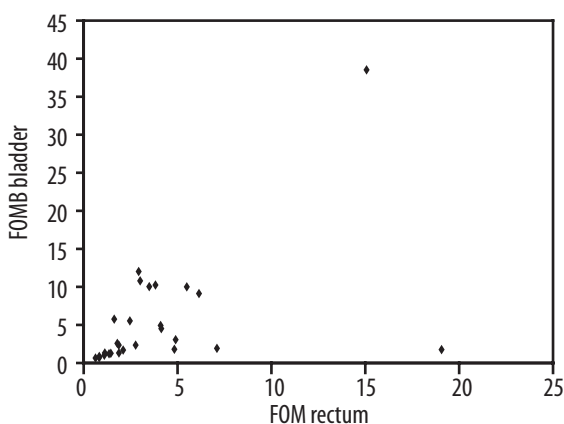**Figure 5.** Bladder/presription dose ratio vs. FOMB.

Figure 6. FOM Rectum vs. FOM bladder.

correlated with the incidence of late rectal complications, and also showed strong correlation (r=0.976) with each other. Grade IV rectal complications were not observed in any patients with TDF values below 130 or BED values below 147. The calculated incidence of complications ranged from 5 to 10% at TDF values from 104 to 124 and

at BED values from 119 to 146. The author concluded that, according to his data, studies into the incidence of rectal complications may be useful in reducing the incidence of such complications arising after HDR-ICR treatments for cancers of the uterine cervix. This could be done by adjusting the dose per fraction and number of fractions of HDR-ICR in individual patients, and by improving techniques for the insertion of the intracavitary radiation apparatus.

Roeske et al. [20] analysed late rectal complications, following definitive radiation therapy for carcinoma of the uterine cervix, in 183 patients. Treatments consisted of external beam pelvic radiotherapy (EBRT) (median dose: 45Gy, typically delivered in fractions of 1.6 to 2Gy) followed by intracavitary radiotherapy (ICRT) consisting of one or two insertions. The total prescribed point A dose ranged from 75 to 90Gy. Conventional total rectal doses were obtained by adding together the EBRT and ICRT rectal doses. To account for differences in dose rates between the ICRT and EBRT methods, and for variations in the EBRT fractionation schemes, biologically equivalent rectal doses (BED) were calculated using the linear quadratic model. The influence of varying the proportions of EBRT and ICRT rectal doses were evaluated. Twenty eight patients developed late rectal sequelae. Diabetes, point A, and conventional EBRT doses were the most significant factors in the multivariate analysis. Logistic regression analysis demonstrated a low risk (<10%) of late rectal sequelae below conventional and biological rectal doses of 75Gy and 135 BED respectively. The percentage of rectal dose delivered by EBRT significantly influenced the dose-response relationship. A definitive threshold percentage above which rectal sequelae were more common was identified over the range of doses evaluated. The threshold was 87% at a total rectal dose of 60Gy and decreased to 60% at 80Gy. The author concluded that the volume of rectum irradiated is an important and independent parameter in the development of late rectal sequelae.

Clark et al. [3] predicted late complications in patients treated by high-dose-rate brachytherapy for carcinoma of the cervix in 43 patients treated with concomitant irradiation and chemotherapy (Cisplatin 30 mg/m^2 given weekly throughout the duration of the irradiation). To date, the results have been compared with those from 119 patients treated with radiation alone, in order to assess the confounding effects of cisplatin. The biological effective dose received by each patient

at the rectal reference point, as defined by the ICRU 38, was calculated. Radiotherapy consisted of 46Gy external beam irradiation plus three high-dose-rate intracavitary treatments of 10Gy each, and delivered to point A. The relationship between the biologically effective dose delivered to the rectal reference point and the development of late complications showed a strong dose-response with a threshold for complications occurring at approximately 125Gy, corresponding to a brachytherapy dose of approximately 8Gy per fraction. This value is approximately the same biologically effective dose threshold as that found for external beam irradiation in the head and neck region. The data from the group of patients treated without cisplatin is comparable to that from the first group of patients in the lower dose ranges; higher doses were not used and thus are not available for comparison. Applying the linear quadratic model to clinical results, authors have established a threshold for late rectal complications for patients treated with external beam irradiation and with high-dose-rate brachytherapy for carcinoma of the cervix. The threshold is consistent with similar data for external beam irradiation in the head and neck region.

Ferrigno et al. [20] retrospectively analysed dose effectiveness and late complications in high-dose-rate brachytherapy among 138 patients treated for cancer of the uterine cervix. Median external beam radiotherapy to the whole pelvis was 45Gy in 25 fractions. Parametrial boost was performed in 93% of cases, with a median dose of 14.4Gy. Brachytherapy by HDR was performed during external beam radiotherapy, or following its completion, with a dose of 24Gy in four weekly fractions of 6Gy to point A. Median overall treatment time was 60 days. The cumulative biologic effective doses (BED) at the rectal and bladder reference points were correlated with late complications in these organs and the dose of external beam radiotherapy at the parametrium was found to correlate with small bowel complications. Overall survival, disease-free survival, and local control at 5 years were 53.7%, 52.7% and 62% respectively. By multivariate and univariate analysis, overall treatment time up to 50 days was the only statistically significant adverse variable for overall survival and actuarial local control. The 5-year actuarial incidence of rectal, bladder and small bowel late complications were 16%, 11% and 14% respectively. Patients treated by cumulative BED at rectum points above $110Gy_3$ and at bladder points above $125Gy_3$ had a higher, but not statistically significant, 5-year actuarial rate of

complications in these organs. Patients who received parametrial doses larger than 59Gy had a higher 5-year actuarial rate of complications in the small bowel; however, this was not statistically significant. The authors concluded that 45Gy to the whole pelvis, combined with four fractions of 6Gy to point A with HDR brachytherapy, is an effective and safe fractionation schedule in the treatment of stage II and III cancer of the cervix if realized within 50 days. To decrease small bowel complications, the authors suggested decreasing the superior border of the parametrial fields to the S2-S3 level and the total dose to 54Gy.

Sakata et al. [6] examined the incidence of radiation-induced late rectal complications by analysing measured rectal dose data in patients with cancer of the uterine cervix, treated with high-dose-rate intracavitary brachytherapy. Doses were measured in 105 patients with cancer of the cervix during high-dose-rate intracavitary brachytherapy, using a semiconductor dosimeter that can measure five points in the rectum simultaneously. On basis of these measurements, equivalent doses, to which the biologically equivalent doses were converted as if given as fractionated irradiation at a rate of 2Gy/fraction, were calculated as components of the cumulative dose at five rectal points in intracavitary brachytherapy combined with the external whole pelvic dose. The calculated values of equivalent doses for late effects at the rectum ranged from 15 to 100Gy (median 60Gy for patients who did not develop complications and 76Gy for patients who subsequently developed grade II and III complications). The data showed a very definite dose-response relationship, with a threshold for complications at approximately 50Gy and the curve starting to rise more steeply at approximately 60Gy. The steepest part of the curve had a slope equivalent to approximately 4% incidence for every 1Gy increase in equivalent doses. The radiation tolerance doses, 5% and 50% complication probability, were about 64 and 79Gy, respectively. The data almost agree with the prescribed dose for rectal radiation tolerance on the basis of recorded human and animal data. The probability of rectal complications increased drastically after reaching maximal rectal doses of >60Gy.

Sood et al. [7] studied the predictive value of the linear-quadratic model in the treatment of cervical cancer using high-dose-rate brachytherapy. The purpose of the study was to determine, retrospectively, whether a dose-response relationship existed between the biologic effective dose (BED) at

point A, the bladder, the rectum and the clinical outcomes. This was based on the authors' experiences with external beam radiotherapy (EBRT) and high-dose-rate-brachytherapy in the treatment of cervical cancer in 49 patients. Median EBRT dose was 45Gy (range: 41.4 to 50.4Gy) and the high-dose-rate-brachytherapy median dose was 18Gy (range: 18 to 19Gy) in two fractions. Twenty three patients received concomitant cisplatin-based chemotherapy. The cumulative BED_s were calculated at point A (BED_{10}) and at the bladder and rectal reference points (BED_3) using the linear-quadratic equation. In patients treated with RT alone, the local failure rate was 10%. The failure rates were 19% in patients receiving a BED_{10} >$89Gy_{10}$ or <$89Gy_{10}$ to point A, respectively. The corresponding local failure rates were 20% and 0% in patients treated with concomitant chemotherapy. In patients treated with RT alone, the local failure rate was 7.7% and 23% in patients with a BED_{10tf} (BED including time factor) >$64Gy_{10}$ or <$64Gy_{10}$, respectively. The median BED_3 values at the rectal and bladder points were $95.5Gy_3$ and $103.6Gy_3$, respectively. Only 1 case of grade II late rectal toxicity was recorded and no cases of late bladder toxicity occurred. In patients treated with RT alone, a BED_{10tf} > $89Gy_{10}$ and a BED_{10tf} > $64Gy_{10}$ indicated a trend towards a better local control rate. This difference was not observed in patients receiving chemotherapy. A BED_3 <$100Gy_3$ was associated with negligible late toxicity. Although the BED_{10} in this study was about $10–15Gy_{10}$ less than that in the published literature, the 4-year local control rates of 80% and 83% and disease-free survival rate of 75% and 70% with and without chemotherapy, respectively, compare well with the rates in other studies in the literature.

Toita et al. [8] determined the dose and fractionation schedule for a combination of external beam radiotherapy (EBRT) and high-dose-rate intracavitary brachytherapy (HDR-ICBT) for uterine cervical cancer in 88 patients. Twenty-five patients were classified as early disease (non-bulky stage I/II, less than 4-cm diameter) and 63 patients as advanced disease (greater than 4cm diameter or stage IIIB), according to the ABS definition. The median cumulative point A dose (the sum of the EBRT midline dose and the point A dose of ICBT) was 58Gy (range: 24–64Gy). Pelvic EBRT was delivered before application of ICBT. HDR-ICBT was performed once a week, with a fractional point A dose of 6Gy. No planned optimization was carried out. The median cumulative biologic effective dose (BED) at point A (EBRT + ICBT) was $64.8Gy_{10}$ (range: 48–$76.8Gy_{10}$) for early

disease, and $76.8Gy_{10}$ (range: 38.4–$86.4Gy_{10}$) for advanced disease. The median cumulative BED at ICRU 38 reference points (EBRT + ICBT) were $97.7Gy_3$ (range: 59.1–$134.4Gy_3$) at the rectum, $97.8Gy_3$ (range: 54.6–$130.4Gy_3$) at the bladder, and $324Gy_3$ (range: 185.5–$618Gy_3$) at the vagina. Actuarial pelvic control rates and late complication rates were analysed according to cumulative doses and calculated BEDs. The 3-year actuarial pelvic control rate was 82% for all 88 patients: 96% for those with early disease, and 76% for advanced disease. For pelvic control, no significant dose-response relationship was observed in the treatment schedules or cumulative BED at point A for either early or advanced disease. The 3-year actuarial late complication rates (grade ≥1) were 12% for proctitis, 11% for cystitis, and 14% for enterocolitis. The authors suggested that a cumulative BED of 70–$80Gy_{10}$ at point A is appropriate for uterine cervical cancer patients treated with a combination of EBRT and HDR-ICBT. The present study and other data in the literature suggest that the cumulative BED at the rectal point should be kept below 100–$120Gy_3$ in order to prevent late rectal complication.

Nag et al. [16] developed a simple program that can be easily used by clinicians to calculate the tumour and late tissue equivalent doses (as if given in 2Gy/day fractions) for different high-dose-rate (HDR) brachytherapy regimens. The program accounts for the normal tissue sparing effect of brachytherapy. Since doses given to normal tissues in HDR brachytherapy treatments are different from those delivered to the tumour, a normal tissue dose modifying factor (DMF) (depending on the anticipated dose to normal tissue) was applied in a spreadsheet to obtain more realistic equivalent normal tissue effects. The program requires the clinician to enter only the external beam total dose and dose/fraction, HDR dose, and the number of HDR fractions. It automatically calculates the equivalent doses for the tumour and normal tissue effects, respectively. Generally, the DMF applied is <1 since the doses to normal tissues are less than the doses to the tumour. However, in certain circumstances a DMF of >1 may need to be applied if the dose to normal critical tissues is higher than the dose to the tumour. Additionally α/β ratios for tumours and normal tissues can be changed from their default values of 10Gy and 3Gy, respectively. This program has been used to determine HDR doses needed for the treatment of cancers of the cervix, prostate, and other organs. It can also been used to predict late normal tissue effects, thus alerting the clinician to the possibility of undue morbidity

associated with a new HDR regimen. The novelty of this program is that the equivalent doses are expressed as if given at 2Gy per fraction rather than as BED values and a more realistic equivalent normal tissue effect is obtained by the application of a DMF. The author concluded that the use of his method should promote the use of LQ radiobiological modeling to determine doses to be used for HDR brachytherapy. The author also warned that the program should be used as a guide only and should be correlated with clinical outcome.

Manning et al. [19] studied the application of radiobiological principles to account for the potential biological impact of dose delivery at varying dose rates within an HDR implant. The model under study used a generalized version of the linear-quadratic (LQ) cell kill formula to calculate the surviving fraction of cells subjected to HDR irradiation. Using a planar interstitial HDR implant with the dwell times optimized, to produce a homogeneous dose distribution along a reference plane parallel to the implant plane, surviving fractions were compared at selected reference points subjected to the same total dose. The homogeneity of biological effects was compared to the homogeneity of dosage by plotting the effects at the reference points. The effects were examined with LQ parameters α, β, and sub-lethal repair time T_1, which was varied over a range typical of human cells. In regions in which the dose was relatively uniform, the surviving fraction for some values of the model parameters were found to vary by as much as an order of magnitude, owing to differences in the HDR irradiation profiles at different dose points. This effect was more pronounced for shorter times and smaller α/β rations, and increased with increasing total irradiation time. Conventional HDR treatment planning currently considers dose distribution to be the primary indicator of clinical effects. These results demonstrated that plans optimized to maximize homogeneity within a target volume may not reflect the effect of the sequential nature of HDR dose delivery on cell killing. The author concluded that biological effect modeling may improve our understanding of, and our ability to predict, the adverse effects of treatment, such as fat necrosis and fibrosis. The author also suggested that accounting for irradiation history and repair kinetics in the evaluation of HDR brachytherapy plans may add an important new dimension to planning capabilities.

Mazeron et al. [2] studied the effects of dose rate on local control and complications in the definitive irradiation of 279 T1-2 squamous cell carcinomas of the mobile tongue and the floor of the mouth with interstitial iridium-192 implants. The dose was not adjusted for dose rate. The reference dose was taken as 85% of the basal dose. The total dose delivered was between 60 and 70Gy. The results showed that local control is significantly related to dose and is independent of the dose rate; the local control dose-effect curve reached a plateau above approximately 62.5Gy while reducing the dose below 62.5Gy led to a rapid increase in local failures. Necrosis is significantly related to dose when the dose rate is less than 0.5Gy per hour. Local control is dose-rate dependent only below 62.5Gy. Necrosis is related to dose rate, but independent of dosage. Dose correction may lead to an increase in the local failure rate without causing a reduction in necrosis. Also, dose rate correction may reduce necrosis without reducing local control. A multivariate analysis revealed that dose, dose rate and tumour diameter significantly influenced local control while only tumour diameter and site influenced the risk of necrosis. A trend towards a significant relationship between the dose rate and necrosis was observed. To maximize local control whilst minimizing necrosis, the author recommended a dose of 65–70Gy at a dose rate of 0.3–0.5Gy/hr.

Local control and necrosis were correlated with ERD. Statistical calculations showed that local control and necrosis are related to ERD. ERD was also evaluated, along with other values for α/β (1–25Gy) and $T_{1/2}$ (0.5–1.5 hr). No significant influence of these modifications to the ERD were demonstrated on either the distribution of patients according to local control or necrosis.

Pernot et al. [18] studied the influence of tumour related, radiobiological and general factors on local control and survival in a series of 361 tumours of the velotonsillar area treated exclusively by irradiation. 18 patients received brachytherapy alone and 343 patients received a combination of external beam irradiation and brachytherapy. All the brachytherapy cases were treated using Ir-192 sources. The results after 5 and 10 years showed local control in 80% and 74%, loco-regional control in 75% and 70%, overall survival in 53% and 27%, specific survival in 63% and 52%, respectively. The radiobiological factors (ERD) showed less recurrences if the total duration of the treatment was <55 days and the number of days between external beam irradiation and brachytherapy was <20 days. The authors concluded that for a combination of external beam irradiation and brachytherapy, the stage and localization of the tumour and the total duration of treatment

are significant. For complications, classified into four grades, only the dose rate was found to be significant.

CONCLUSIONS

We evaluated FOM values for the rectum and bladder on the basis of formulae suggested by Dale and Sinclair. Two patients had a FOM rectum value greater than 10. A FOM value for bladder higher than 10 was observed in six patients. Only in one patient were FOM values for both the rectum and the bladder above 10. The FOM values maximized with decreases to the critical organ dose to prescription dose ratios for both the rectum and bladder.

Good physical optimization can lead to good radiobiological optimization. Radiobiology can not improve on a bad quality implant. HDR interstitial brachytherapy, which gives better geometrical sparing for critical normal organs such as the rectum and bladder, should be the treatment of choice for cervical cancer patients. In optimizing treatment for a patient, maximization of the FOM value should be supplemented by comparison with reference BED values and new treatments for the rectum and bladder.

REFERENCES:

1. Kumaraswamy, Viswanathan N, Mohan DS, Belliappa MS: Influence of Brachytherapy dose rate on complications in the treatment of carcinoma of the uterine cervix. Endocurie, Hypertherm Oncol, 1991; 7: 171–7

2. Mazeron JJ, Simon JM, Pechoux CL et al: Effect of dose rate on local control and complications in definitive irradiation of T_{1-2} squamous cell carcinoma of mobile tongue and floor of mouth with interstitial iridium-192. Radiother Oncol, 1991; 21: 39–47

3. Clark BG, Souhami L, Roman TN et al: The prediction of late rectal complications in patients treated with high dose rate brachytherapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys, 1997; 38: 989–93

4. Ogino I, Kitamura T, Okamoto N et al: Late rectal complication following high dose rate intracavitary brachytherapy in cancer of the cervix. Int J Radiol Oncol Biol Phys, 1995; 31: 725–34

5. Roeske JC, Mundt AJ, Halpern H et al: Late rectal sequelae following definitive radiation therapy for carcinoma of the uterine cervix: A dosimetric analysis. Int J Radiol Oncol Biol Phys, 1997; 37: 351–8

6. Sakata K, Nagakura H, Oouchi A et al: High-dose-rate intracavitary brachytherapy: Results of analyses of late rectal complications. Int J Radiol Oncol Biol Phys, 2002; 54: 1369–76

7. Sood B, Garg M, Avadhani J et al: Predictive value of linear-quadratic model in the treatment of cervical cancer using high-dose-rate brachytherapy. Int J Radiol Oncol Biol Phys, 2002; 54: 1377–87

8. Toita T, Kakinohana Y, Ogawa K et al: Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer: Analysis of dose and fractionation schedule. Int J Radiol Oncol Biol Phys, 2003; 56: 1344–53

9. Supe SS: Application of linear quadratic model of dose effect relationship to radiotherapy. Ph.D Thesis, Marathwada University, 1993

10. Dale RG: The application of the linear quadratic dose effect equation to fractionated and protracted radiotherapy. Br J Radiol, 1985; 58: 515–28

11. Dale RG, Sinclair JA: A proposed figure of merit for the assessment of unscheduled treatment interruptions. B J Radiol, 1994; 67: 1001–7

12. Fowler JF: The linear quadratic formula and progress in fractionated radiotherapy. Br J. Radiol, 1985; 62: 679–94

13. Orton CG, Cohen L: A Unified approach to dose effect relationships in radiotherapy I: Modified TDF and linear quadratic equations. Int J Radiat Oncol Biol Phys, 1988; 14: 549–56

14. Orton CG: Recent developments in time dose modelling. Aus Phys Eng Sci Med, 1991; 14: 57–64

15. Deore SM, Srivastava SK, Supe SJ et al: α/β value and importance of dose per fraction for the late rectal and recto-sigmoid complications. Strahlenther Onkol, 1997; 169: 521–6

16. Nag S, Gupta N: A simple method for obtaining equivalent doses for use in HDR brachytherapy. Int Jr Radiat Oncol Biol Phys, 2000; 46: 507–13

17. Supe SS, Ganesh KM, Vaithianathan H, Sankar BN: Evaluation of radiobiological quality index of interstitial brachytherapy treatments of the cervix. J Clin Radiother Oncol, (Submitted for publication)

18. Pernot M, Malissard L, Hoffstetter S et al: Influence of tumoral, radiobiological, and general factors on local control and survival of a series of 361 tumors of the velotonsillar area treated by exclusive irradiation (External beam irradiation + brachytherapy or brachytherapy alone). Int Jr Radiat Oncol Biol Phys, 1994; 30: 1051–7

19. Manning MA, Zwicker RD, Arthur DW, Arnfield M: Biologic treatment planning for high-dose-rate brachytherapy. Int J Radiol Oncol Biol Phys, 2001; 49: 839–45

20. Ferrigno R, Novaes PERDS, Pellizzon ACA et al: High-dose-rate brachytherapy in the treatment of uterine cervix cancer. Analysis of dose effectiveness and late complications. Int J Radiol Oncol Biol Phys, 2001; 50: 1123–35