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Biological Effective Dose and Overall Treatment Time in the High Dose Rate Brachytherapy of Nasopharyngeal Carcinoma

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Abstract: The aim of this study is to evaluate the decrease of biological effective dose (BED) and its correlation with local control of tumour in the treatment of nasopharyngeal carcinoma (NPC) when the overall treatment time is prolonged. A retrospective study was carried out on 39 NPC with stage II and III treated with fractionated High Dose Rate–Brachytherapy (HDR-BT)boost, following external beam radiation therapy (EBRT) treated in the period from 2009 to 2015. All patients were irradiated by HDR –Intra Luminal Radiotherapy (ILRT) following EBRT using a telecobalt unit and a technique that employed two lateral opposed fields with a dose of 66 ± 4 Gy. The total biological equivalent dose prescribed was 106.50 ± 9 Gy (range 92 - 123 Gy). The probabilities of disease recurrence within a median follow-up of 25 months (range 13 – 72 months) are expected as 0.03, 0.26, 0.58 and 0.90 (p=0.05) for the overall treatment time of 75, 150, 250 and 350 days respectively. It was observed that the local recurrence of disease increases with increased treatment time and it is significant (p=0.05) when the overall treatment time is above 100 days where BED lost becomes more than 0.10 Gy/day. The relative risk of local recurrence of stage III is about 2.59 times higher than that of stage II patients.

Keywords: HDR-ILRT, Nasopharyngeal Cancer, BED, Treatment Time

1. Introduction

Head and neck malignancies is relatively quite common in the north eastern part of India [1-2]. Among the head and neck cases, nasopharyngeal carcinoma (NPC) is observed frequently occupying top position in our hospital. NPCs are relatively radiosensitive tumours. The ideal treatment for primary NPC is normally radical radiotherapy with or without chemotherapy, as surgery is generally not feasible due to the peculiar location of the nasopharynx [3-8]. This anatomical site is surrounded by critical organs such as optic apparatus, pituitary gland, hypothalamus, spinal cord and the temporal lobes which could lead to significant morbidity. High Dose Rate brachytherapy (HDR-BT) is commonly used with External Beam Radiation Therapy (EBRT) to locally increase the dose to an area at greatest risk for tumour recurrence, such as the original distribution of gross tumour or to the tumour at a surgical resection site [9]. In our institute, HDR-BT following to EBRT is routinely used to boost the dose delivered to the primary NPC site in all loco-regionally confined disease treated with intent to cure.

The growth of unirradiated cancer cells have been observed showing the relatively long doubling times (median 30 days) of tumour volumes. Studies showed that the prolongation of the overall treatment time resulted in worse results of radiotherapy [10-11] and doubling time of tumour cells might be reduced during RT to 5 days [12]. Clinical studies on advanced NPC [13] and other head and neck cancers irradiation have shown the importance of treatment time for local control of disease [12, 14-16]. Physical dose distributions in routine radiotherapy planning do not

necessarily reflect on the biological effects under various irradiation schemes. The Biological Effective Dose (BED) method has been used as a means to assess the biological effectiveness following irradiation of tissues. The linear-quadratic (LQ) model is used by radiologists as a convenient tool to quantify biological effects of radiotherapy [17-19]. Inadequate BED delivery to the treated volume is frequently identified as a possible cause of failure in the radiotherapy of cancers [12-16, 20, 21]. In this study we evaluated BED of the prescribed dose at the reference points of treatment of NPC with the overall treatment time. It is also further discussed critically the need to maintain BED for local control of the NPC.

2. Material and Methods

2.1. Patient Selection

Forty one consecutive patients of NPC stage II and III (stages II – 20 patients and III -21 patients) who attended the department of Radiotherapy, Regional Cancer Centre, Regional Institute of Medical Sciences, Imphal, India and were treated during the period from June, 2009 to July, 2015 is the subject of study. All patients were subjected to the routine diagnostic and metastatic work-up. Two patients for stage III were found developed distant metastasis (1 each in lungs and bone) after the treatment was over in the median time of 18 months (range 15 – 21 months) and were excluded from the study.

2.2. EBRT

All patients (except 6, due to simulator machine problem) were simulated and planned in a customized thermoplastic mask in the supine position. All patients were irradiated using a cobalt unit with bilateral parallel-opposed portals with appropriate shielding. Treatment was performed once a day, 5 times a week. The dose was calculated in the mid-plane on the axis of the beam. The total EBRT dose delivered was in the range of 60-70 Gy/30-35 #/6-7 weeks (median dose= 66 Gy).

2.3. ILRT Applicator Placement and Brachytherapy Treatment Planning

Inflatable balloon nasopharyngeal applicator (Elekta) was used. The applicator was inserted through the ipsilateral nostril depending on the location of the gross disease in the nasopharynx with patient in the seated position. About 6 cc of air was pumped inside the hollow plastic tube which lead to the nasopharyngeal balloon covering the source transfer tube toward the end expanding to about 3cm length with 2cm diameter. Nasal packing was done to avoid any displacement or changes in the geometry of the applicator placement. The position of the applicator was confirmed and simulation done using Simulix Simulator (Elekta). Brachytherapy treatment planning was done using Plato Sunrise Treatment Planning System (Elekta). Dose prescription was done at points1 cm away from the source for the total treatment length in the range of 3-5 cm (median= 4 cm) using standard source loading pattern. The median dose delivered with HDR-ILRT was 15 Gy (range: 3- 7.5 Gy in 5 -2 fractions). The strength of the source (Ir-192) was in the range from 4.081 to 0.347 cGy x m^2 x h^{-1}.

2.4. Overall Treatment Time

ILRT is normally given following EBRT after a gap of about one week. However continuous radiotherapy was not possible in many NPC patients. The first day of the radiotherapy till the last day including all gaps is taken as overall treatment time. The relation between the overall treatment times with BED is discussed critically in this study.

2.5. Clinical Details

Out of 39 patients, 38 patients (Stage II – 20 patients, Stage III- 18 patients) were found to be having complete response; one patient of stage III was found to be partial responders at the completion of the treatment. The follow up at 6 - 12 months post treatment showed five patients of stage II and two patients of stage III had local disease seen and detected by imaging modalities. The median follow up of patients was 25 months (13-72 months).

2.6. Biological Effective Dose Evaluation

Biological effects (E) following to irradiation of tissues is determined by the surviving fraction of target cells [22-23] as

$$E = -\log(\text{surviving fraction})$$

$$= -\log[\exp\{-(\alpha d + \beta d^2)\}] = \alpha d + \beta d^2 \text{ - - -} \quad (1)$$

where α, β are the constants for linear and quadratic component of the surviving equation (α and β are normally expressed in the units of Gy^{-1} and Gy^{-2} respectively) and 'd' is the radiation dose delivered to the tissue.

Eqn. (1) may be rewritten as:

$$E/\alpha = d[1+d/(\alpha/\beta)] \text{ - - -} \quad (2)$$

This E/α is term as Biological Effective Dose (BED).

The assumption of α/β=10 Gy for rapidly proliferating tumours (e.g. Squamous cell cancer) [24-26] was used in this study. This value of α/β=10 Gy is in agreement with GEC-ESTRO recommendation [27]. The cumulative BED (CBED) for the combined EBRT (BED_{EBRT}) and HDR ILRT (BED_{ILRT}) may be written as

$$CBED = BED_{EBRT} + BED_{ILRT} + PCF \text{ ---} \quad (3)$$

Where $PCF = -[\{0.693/(\alpha T_p)\}(T+G-T_k)]$ = proliferation correction factor, T_p = the potential doubling time of proliferating tumour cells, T_k= kicking off time in proliferation after starting irradiation, T = treatment time in days and G = gap in days between two treatment modalities of radiotherapy or between any one therapy respectively [28]. The value of $\alpha=0.35Gy^{-1}$[26], T_p=13 days[28-31], T_k= 28 days [19, 26] is considered in this study.

GEC-ESTRO [27] also suggested that, for the whole treatment, total dose values should be reported as physical dose, indicating the fractionation and dose rate and in addition as biologically weighted dose, EQD_2(biologically equivalent dose in 2 Gy fraction). EQD_2 is logistically and conceptually equivalent to BED, but has numerical values which can be related directly to clinical experience as the method converts all treatments and partial treatments into isoeffective schedules of 2Gy fractions [31].

2.7. Statistics

Disease control was measured from the date of the initiation of radiation therapy to the last follow-up examination. The survival analysis was determined using the Kaplan – Meier survival method. The statistical significance of observed data was calculated using the Student's t-test and Chi-square test and $P < 0.05$ was considered as significant difference.

3. Results

The reduction factor of BED with overall treatment time and their respective percentage of fall are given in Table 1. The graph between BED and overall treatment time is shown in Figure 1. It is well fitted to a linear equation ($Y = -0.152X + 110.7$) with co-efficient of determination R^2 equal to 1. There is a sharp decline of BED with the increase of overall treatment time. The percentage of reduction of BED w. r. t. the prescribed BED (i.e. 106.50 Gy) are 3.14, 6.01, 6.72, 10.30, 17.46, 31.76 and 46.06 for the overall treatment time of 50, 70, 75, 100, 150, 250 and 350 days respectively. The extra BED required for maintaining the prescribed BED is 3.35, 6.40, 7.16, 10.97, 18.59, 33.82 and 49.05 for the above overall treatment times. The recurrence of disease for the patients both for stage II and III (P=0.05) treated with HDR-ILRT (following to EBRT) within classes of overall treatment time is given in Table 2. The ratio of the outcome of event (i.e. recurrence of disease) and total number of events for respective classes of overall treatment time provides the probability of the event corresponding to the class of overall treatment time. Uncertainties (error) involved in obtaining the observed data (e.g. during the treatment procedure, small sample size etc.) may be minimized by fitting a mathematical model using least square technique to the observed data. The degree of goodness of fit is normally evaluated by co-efficient of determination R^2. The best fit mathematical model (i.e. expected data) of this observed data is a linear equation ($Y = 0.003x - 0.214$) with R^2 value equal to 0.90 (Figure 2). The expected probabilities of recurrence of disease within a median follow-up of 25 months (range 13 – 72 months) are 0.03, 0.26, 0.58 and 0.90 for the overall treatment time 75, 150, 250 and 350 days respectively. This expected probability is not significantly different from the observed data at 5 percent level of probability (as per χ^2 distribution). Figure 3 shows the Kaplan-Meier Graph of Disease free survival Probabilities (%) with the overall treatment time for stage II and III patients. The expected median value of overall treatment time at which disease free survival probability drops to 50 percent is observed as 271 days for stage II and 175 days for stage III NPC patients in this study. The extra physical doses required to maintain the same biological effect are estimated at 2.65, 5.10, 5.97, 8.96, 15.26, 27.95 and 40.80 Grays for the overall treatment time of 50, 70, 75, 100, 150, 250 and 350 days respectively.

Table 1. *Variation of BED with various overall treatment times for a prescribed Biological dose of 106.50 Gy.*

Overall treatment time (days)	Biological equivalent dose (Gy) (without PCF in eqn-3)	BED (Gy) With PCF Eqn(3)	BED change w. r. t. prescribed BED (%)	BED lost per day (Gy)	Extra BED require to maintain prescribed BED (Gy)
50*	106.50	103.15	3.14	0.07	3.35
70	106.50	100.10	6.01	0.09	6.40
75	106.50	99.34	6.72	0.09	7.16
100	106.50	95.53	10.30	0.10	10.97
150	106.50	87.91	17.46	0.12	18.59
250	106.50	72.68	31.76	0.13	33.82
350	106.50	57.45	46.06	0.13	49.05

*A few cases ILRT duration is either shorten to a week with 1 or 2 days gap after EBRT or ILRT started during EBRT resulting overall treatment time less than two months.

Table 2. *Recurrence of disease in different overall treatment time of nasopharyngeal cancer.*

Stage of nasopharyngeal cancer		Disease recurrence (total number of radiotherapy patients) for different treatment duration			
		<100 days	100-200 days	200-300 days	>300days
II		0(9)	2(6)	2(4)	1(1)
III		1(15)	1(3)	0(1)	0(0)
Observed total		1(24)	3(9)	2(5)	1(1)
Recurrence	Probability from data	0.04	0.33	0.40	1.00
	Expected probability	0.03	0.26	0.58	0.90
Expected total		1(24)	2(9)	3(5)	1(1)

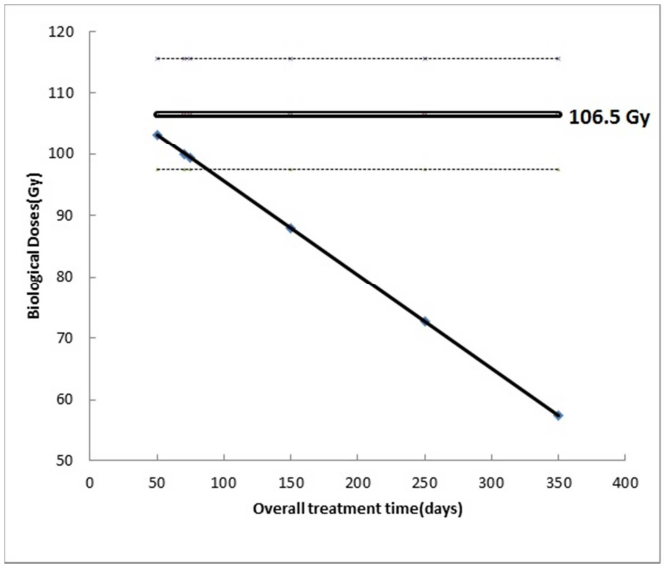

Figure 1. *Graph between BED (Gy) vs overall treatment time (days), Hollow line- is the prescribed biological equivalent dose, dash lines are the standard deviations Solid line- is the biological effective dose.*

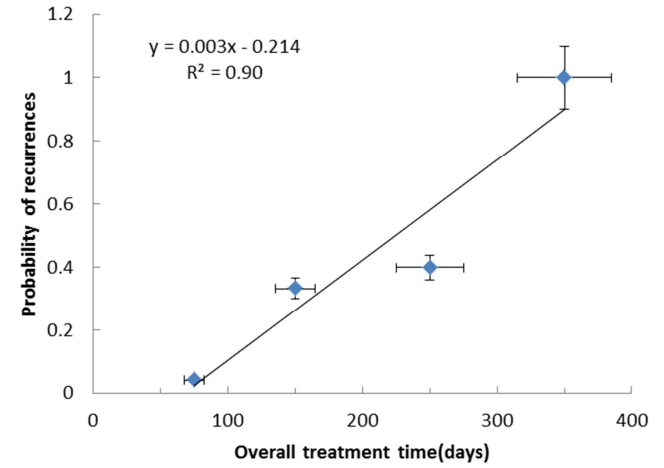

Figure 2. *Graph showing the probabilities of local recurrence with overall treatment time (days). Solid line is a simple mathematical model giving the probabilities of local recurrence with overall treatment time (days).*

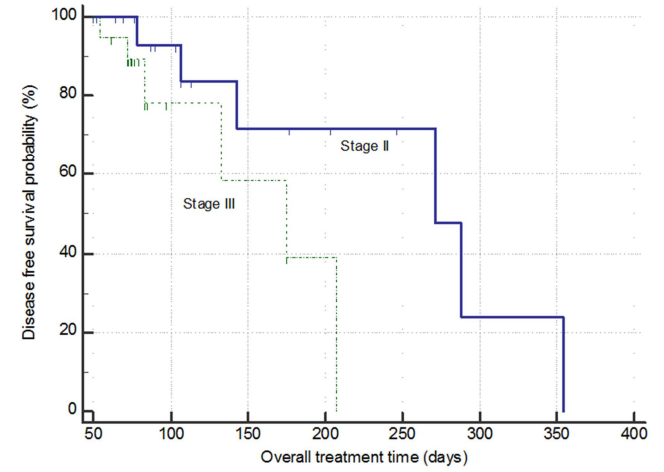

Figure 3. *Kaplan-Meier Graph of Disease free survival Probabilities (%) with the overall treatment time for stage II and III patients.*

4. Discussion

The HDR – ILRT following to EBRT are widely used for effective management of NPC [7, 9, 13, 33]. There is also a routine gap of about a week in between EBRT and ILRT. However continuous radiotherapy was not possible in many NPC patients. Some patients had treatment interruption related to the machine break down, holidays and problems with the transportation of patients. Gaps of treatment for some patients were related to severe mucosal reaction after EBRT or other intercurrent illness.

The gaps between EBRT and HDR brachytherapy were of different origin. In this resource crunch area using one Ir-192 HDR source, there is variation of gap in scheduling HDR-BT, break down of HDR-BT machine and patient without report in time. Sometimes there is a gap in receiving new Ir-192 source whereas the existing one had already exhausted its strength. A small group of patients was treated with a planned gap in between two treatment modalities. There was no intention to increase the overall treatment time of patient but unavoidable situation leads the increase in the overall treatment time.

The purpose of this study is to share our experience of the use of brachytherapy boost NPC which is most cost effective in our present setting. The predictive quality of linear quadratic model in the radiotherapy of patients with NPC has been discussed in literatures [12-16]. Jones et al. [34] suggested that the concept of biological effective dose is useful for quantifying the treatment expectations; however, a careful interpretation of results is required before clinical decision. Jones et al.[35] evaluated the rate of loss of tumour control with extension of treatment time to assess the relative contributions of radiobiological parameters (radiosensitivity, clonogen doubling time, clonogen numbers and fractionation schedule) to such loss. Pitfalls in estimating the influence of overall treatment time on local control have been discussed by Tucker [36]. Randomised clinical studies have shown the importance of treatment time for local control of disease [12-16]. Tarnawskiet al. [12] observed that when the treatment time is prolonged without treatment interruptions 0.36 Gy/day is lost due to the repopulation of tumour cells. During the treatment gap proliferation is faster and 0.67 Gy/day is lost. In this study the variation of BED with different overall treatment times for a median prescribed biological dose of 106.50Gy (i.e. BED_{EBRT} + BED_{ILRT}) is shown in Table 1. There was a standard deviation of 9 Gy in the prescribed dose (range: 92 to 123 Gy). A few cases, either ILRT duration is shortened and completed in a week or ILRT started during the later part of EBRT resulting the overall treatment time lesser than two months which otherwise is more than two months. Figure 1 shows a sharp decline of BED with the increase of overall treatment time for the prescribed dose 106.50 Gy. This is in agreement with the earlier works on BED with overall treatment time [12-14, 21, 37]. The BED lost per day (i.e. total BED lost per overall treatment time in days) in this study was found in the range

of 0.07 to 0.13 Gy. The change in BED w. r. t. the prescribed BED is more than 10 percent from 100 days onwards of the overall treatment times. The recurrence of disease within classes of treatment time for delivering the prescribed dose is given in Table 2. The expected total number of patients having recurrence of disease for respective classes are evaluated by multiplying corresponding expected probabilities with total number of patients within the classes of treatment times. Figure 2 shows graph between probabilities of recurrence of disease (stage II and III) with mid value of overall treatment time within classes of treatment time. This graph shows that NPC treated with ILRT following EBRT without any correction of biological dose at different overall treatment time indicates decline in disease free survival due to the possible repopulation of the disease [12] with increasing overall treatment time, especially from 100 days treatment time onwards. Thus, from Figures 1&2 reduction in BED may be correlated with the increasing disease recurrence. This is in agreement with earlier works on local control of Head and neck carcinoma with overall treatment time [12-14]. Moreover, prolonged radiation treatment time is associated with worse overall survival in patients receiving radiation therapy for head and neck cancer even in the setting of chemoradiation [10-11]. However, there is no such association between overall survival outcomes of NPC patients and treatment time duration in the range of 36 -63 days [38]. The sample size of this retrospective study is small; however it may be fitted to a simple linear equation ($Y = 0.003X – 0.214$) with R^2 equal to 0.90 for any statistical conclusion. The expected probabilities of disease free survival of this study of six years are estimated by subtraction of expected probability of recurrence from total probability (i.e. 1.00) as 0.97, 0.74, 0.42 and 0.10 for the overall treatment time of 75, 150, 250 and 350 days respectively. The disease free survival probabilities for stage II and III of nasopharyngeal patients treated with radiation using the Kaplan – Meier survival method for the overall treatment time is shown in Figure 3. The estimated relative risk of local recurrence occurring in stage III is observed as 2.59 times higher than stage II NPC patients at 95% confidence level of probability. If it is required to maintain a relatively constant BED, the study suggests a need to deliver an extra dose to compensate the BED lost to either EBRT or ILRT. There is also a suggestion that 1% change in BED may produce 1% change in tumour control probability [19]. This suggestion is in agreement with our finding of recurrence of disease with lowering BED.

5. Conclusion

This retrospective study of nasopharyngeal carcinoma patients of stage II and III treated with ILRT (following to EBRT) with various overall treatment time shows: 1. Linear Quadratic model based analysis of biological effective dose reveals fall of BED with increase of overall treatment time. The possible reason could be the increase of sub lethal damage repairing and repopulation of disease in the long overall treatment time; 2. The reduction in disease free survival with increase in overall treatment time may be associated with the decrease of biological effective dose at the target; 3. Clinical end point of this study is more significant from 100 days of overall treatment time where BED lost become more than 0.10 Gy/day; 4. The relative risk of local recurrence of stage III is higher (about 2.5 times) than that of stage II nasopharyngeal patients.

References

[1] National cancer registry programme, North East population based cancer registries, incidence & distribution of cancer, 2nd report: 2005-2006, NCRP, Bangalore, India: *Indian Council of Medical Research* Sept, 2008.

[2] Sharma AB, Singh TT, Singh KN, Gartia RK. Survey of patient dosimetry for head & neck cancer patients undergoing external radiotherapy: a study from NE hospitals of India. *J cancer Res Ther* 2009; 5 (4): 263-6.

[3] Chang JT, See LC, Tang SG, Lee SP, Wang CC, Hong JH. The role of brachytherapy in early stage nasopharyngeal carcinoma. *Int J RadiatOncolBiolPhys* 1996; 36: 1019-24.

[4] Hunt MA, Zelefsky MJ, Wolden S, Chui CS, LoSasso T, Rosenzweiq K, et al. Ttreatment planning and delivery of IMRT for primary nasopharynx cancer. *Int J RadiatOncolBiolPhys* 2001; 49: 623-32.

[5] Marsiglia H, Haie-Meder C, Sasso G, Mamelle G, Gerbaulet A. Brachytherapy for T1-T2 floor of the mouth cancers: The Gustave-Roussy Institute experience. *Int J RadiatOncolBiolPhys* 2002; 52: 1257-63.

[6] Leborgne F, Leborgne JH, Zubizarreta E, Mezzera J. Cesium-137 needle brachytherapy boost after external beam irradiation for locally advanced carcinoma of the tongue and floor of the mouth. *Brachytherapy* 2002; 1: 126-30.

[7] Malde R, Agarwal JP, Gupta T, Dinshaw K. High dose rate brachytherapy boost for primary nasopharyngeal carcinoma: preliminary results of an ongoing prospective study. *Bull Cancer* 2005; 92 (7-8): 45-50.

[8] Bing-Qing X, Zi-Wei T, Ya-Lan T, Zhi-Gang L, Xian-Hui L, Wei Y, et al. Forty-six cases of NPC treated with 50 Gy radiotherapy plus hematoporphyrin derivative: 20 years of follow-up and outcomes from the Sun Yat-sen University Cancer Center. Chin J Cancer 2016; 35: 37.

[9] Nag S, Dobelbower R, Glassgow G, Gustafson G, Syed N, Thomadsen B, Williamoon JF. Inter-society standards for the performance of brachytherapy: a joint report from ABS, ACMP and ACRO. *Critical Reviews in Oncology/Hematology* 2003; 48: 1-17.

[10] Shaikh T, Handorf EA, Murphy CT, Mehra R, Ridge JA, Galloway TJ. The Impact of Radiation Treatment Time on Survival in Patients With Head and Neck Cancer. *Int J Radiat Oncol Biol Phys*. 2016; 96 (5): 967-975.

[11] Silke T, Johanna D, Henning P, Adrian M, Alexander G, Cprdula P et al. Survival and overall treatment time after postoperative radio(chemo)therapy in patients with head and neck cancer. *Head and Neck. 2016;* 38 (7): 1058–1065.

[12] Tarnawski R, Skladowski K, Swierniak A, Wygoda A, Mucha A. Repopulation of tumour cells during radiotherapy is doubled during treatment gaps. *Journal of Theoretical Medicine* 2000; 2: 297-305.

[13] Sharma BA, Singh LJ, JayshreePh, Goswami G, Singh YI, Singh TT. EQD2 and Overall Treatment Time in the HDR Brachytherapy of the Advanced NPC. J Nasopharyngeal Carcinoma, 2016, 3 (5), e33. doi: 10.15383/jnpc.33.

[14] Maciejewski B, Preuss-Bayer G,Trott KR. The influence of three numbers of fractions and of overall time on local control and late complications rate in squamous cell carcinoma of the larynx. *Int J RadiatOncolBiolPhys* 1983; 9: 321-8.

[15] Horiot JC, Bontemps P, Van den Bogaert W, Le Fur R, van den Weijnqaert D, Bolla M, et al. Accelerated fractionation compared to conventional fractionation improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. *RadiotherOncol* 1997; 44 (2): 111-21.

[16] Dische S, Saunders M, Barret A, Harvey A, Gibson D, Parmar M. A randomised multicentre trial of CHART vs conventional radiotherapy in head and neck cancer. *RadiotherOncol* 1997; 44 (2): 123-36.

[17] Dale RG. The application of linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol* 1985; 58: 515-28.

[18] Ledorgne F, Fowler JF, Leborgne JF, Zubizerreta E, Chappell R. Biologically effective doses in medium dose rate brachytherapy of cancer of the cervix. *RadiatOncolInvestig* 1997; 5: 289-99.

[19] Stewart AJ, Jones B. Radiobiologic concepts for brachytherapy. In: Brachytherapy applications and techniques. Devlin PM(ed). *Lippincott Williams &Wilkins*, Philadelphia 2007.

[20] Dimopoulos JCA. Dose volume histogram parameters and local tumour control in MRI guided cervical cancer brachytherapy. Int J RadiatOncolBiolPhys 2009; 75: 56-63.

[21] Sharma AB, Singh TT, Singh JL, Singh IY, Devi SY. Biological effective doses in the intracavitary high dose rate brachytherapy of cervical cancer. *Journal of Contemporary Brachytherapy* 2011; 3 (4): 188-92.

[22] Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue response. *Int J RadiatOncolBiolPhys*1982; 8: 1981-97.

[23] Thames HD, Withers HR, Peters LJ, Fletcher GH. Changes in early and late radiation responses with altered dose fractionation: implications for dose survival relationships. *Int J RadiatOncolBiolPhys*1982; 8: 219-26.

[24] Sood B, Garg M, Avadhani J, Gorla G, Malhotra H, Guha C et al. Predictive value of linear-quadratic model in the treatment of cervical cancer using HDR brachytherapy. *Int J RadiatOncolBiolPhys*2002; 54: 1377-87.

[25] Dala RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol* 1985; 58: 515-28.

[26] Fowler J. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989; 62: 679-94.

[27] Potter R, Haie-Meder C, Van Limbergen E, Barillat I, De Brabandere M, Dimopoulos J, *et al*. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters aspects of 3D image-based anatomy, radiation physics, radiobiology. *RadiotherOncol* 2006; 78: 67-77.

[28] Passi K, Kehwar TS, Vashistha R, Singh B, Jain V, Gupta ST. High dose rate brachytherapy with EBRT in the treatment of carcinoma of cervix: dosimetic and radiobiologic analysis. *Journal of Radiotherapy in practice* 2009; 8: 215-27.

[29] Stanton PD, Cooke TG, Foster G, Smith D, Going JJ. Cell Kinetics in vivo of human breast cancer. *Br J Surg* 1996; 83 (1): 98-102.

[30] Keisch M, Vicini F, Kuske RR, Hebert M, White j, Quiet C et al. Initial clinical experience with the MammoSite breast brachytherapy application in woman with early-stage breast cancer treated with conserving therapy. *Int J RadiatOncolBiolPhys* 2003; 55 (2): 289-93.

[31] Kim Y,Werts ED, Trombetta MG, Miften M. Evaluation of the interfractional biological effective dose(BED) variation in MammoSite HDR brachytherapy. *Journal of applied clinical medical physics* 2010; 11 (3): 124-34.

[32] Michael C Joiner. A simple α/β – independent method to derive fully isoeffective schedules following changes in dose per fraction. *Int J RadiatOncolBiolPhys*2004; 58: 871-5.

[33] Levendaq PC, Nijdam WM, Van Aqthoven M, Uyl-de Groot CA. Chemotherapy and HDR brachytherapy in the management of advanced cancers of the nasopharynx: clinical impact of high technology – is it worth the cost? *Brachytherapy* 2002; 1: 11-20.

[34] Jones B, Dale RG, Deehan C, Hopkins KI, Morgan DA. The role of biologically effective dose (BED) in clinical oncology. *ClinOncol (R CollRadiol)* 2001; 13: 71-81.

[35] Jones B, Dale RG. The reduction of tumour control with increasing overall time: Mathematical considerations. *Br J Radiol*. 1996; 69: 830-8.

[36] Tucker SL. Pitfalls in estimating the influence of overall treatment time on local tumour control. *ActaOncol*. 1999; 38: 171-178.

[37] Mandal A, Anupam KA, Lalit MA. Clinical significance of cumulative BED and overall treatment time in the treatment of carcinoma cervix. *J Med Phys*. 2007; 32 (2): 68-72.

[38] Li P-J, Jin T, Luo D-H, Shen T, Mai DM, Hu WH et al. Effect of Prolonged Radiotherapy Treatment Time on Survival Outcomes after Intensity-Modulated Radiation Therapy in Nasopharyngeal Carcinoma. *PLoS ONE*. 2015; 10(10):e0141332. doi:10.1371/journal.pone.0141332.