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Evaluation of Tumor Control and Normal Tissue Complication Probability in Head and Neck Cancers with Different Sources of Radiation: A Comparative Study

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ABSTRACT

Introduction: The ultimate goal of radiation treatment planning is to yield a high tumor control probability (TCP) with a low normal tissue complication probability (NTCP). Historically dose volume histogram (DVH) with only volumetric dose distribution was utilized as a popular tool for plan evaluation hence present study aimed to compare the radiobiological effectiveness of the cobalt-60 (Co-60) gamma photon and 6MV X-rays of linear accelerators (Linac) in the radiotherapy of head and neck tumors.

Materials and Methods: TCP and NTCP were calculated using DVH through the BIOPLAN software developed by Sanchez-Nieto and Nahum . The treatment planning was performed for all the patients using both treatment modalities (i.e., Co-60 and 6 MV Linac). The TCP was also manually calculated using a mathematical formula proposed by Brenner's et al.

Results: The average TCP calculated by the BIOPLAN for Co-60 and 6 MV X-rays were 44.6% and 60.8%, respectively. Furthermore, the average NTCPs obtained for the organ at risk, namely optic nerve, for Co-60 and 6 MV X-ray were 0.24 % and 0.03 %, respectively. Regarding the spinal cord, the average NTCPs for Co-60 gamma photon and 6 MV X-ray of Linac were 0.05 % and 0.002%, respectively.

Conclusion: As the findings of the present study indicated, Co-60 unit could provide comparable TCP along with minimal NTCP, compared to the high-cost technologies of Linac. The design of treatment plans based on the radiobiological parameters facilitated the judicious choice of physical parameters for the achievement of high TCP and low NTCP.

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Introduction

Radiotherapy began as an empirical radiobiological approach with emphasis on physical dose homogeneity in the target volume. The focus of radiotherapy has gradually shifted towards consequential biological dose underscoring the improvement of the treatment outcomes and reduction of complications by utilizing the radiobiological parameters of plan evaluation. The close interaction between radiobiological response models and clinical practice has yielded improved evaluation tools, such as tumor control probability (TCP) and normal tissue complication probability (NTCP), which are very close to the clinically observed treatment outcomes and complications [4].

The physical dose distribution displayed on the computed tomography (CT) slices may not be adequate to judge the quality of treatment plan. The treatment outcome and toxicities in radiotherapy are largely dependent on the radiosensitivity of tumor types and tolerance of the surrounding normal tissues. The treatment planning system (TPS) provides a dose volume histogram (DVH). The DVH only presents the graphical representation of dose distribution on the planning target volume (PTV) and organ at risks (OAR). However, DVH fails to provide any information about the sub-volume doses of the target volume and OAR, which may be critically important for overall biological responses.

Brenner [3] predicted the relationship between dose, volume, and sub-volume doses in the TCP for a course of radiotherapy. He concluded that the tumor volume and clonogen density had a profound influence on the radiation dose required for various types of tumors. The classical plan evaluations, which were based on DVH, were restricted to volumetric distribution of the physical dose and did not quantify the probable treatment response. In a given plan, DVH may represent the dose to 98% of the target volume. This may be conventionally considered as a perfect plan; however, it does not predict about tumor treatment and normal tissue toxicities.

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Niemierko et al. [5] emphasized that the endpoint of any radiotherapy treatment plan should correlate with the biological outcome for a given physical dose delivered. Sanchez-Nieto et al., [6] proposed a model termed as delta TCP and suggested that TCP is affected by the minimum dose, even if it is delivered to a very small volume (i.e., 20% dose deficit to 5% of the volume makes the TCP decrease by 18%). Withers [7] suggested that the TCP does not linearly increase with radiation dose.

The clonogenic density and rate of tumor proliferation also affect the end responses. The final outcome may depend on killing the last surviving clonogen. Tumor control is not possible even if one clonogen survives; therefore, the total delivered physical dose may be wasted. Niemierko and Goitein [8] proposed a model for the evaluation and optimization of the three-dimensional (3D) dose distributions when the tumor is non-uniformly irradiated.

With this background in mind, the present study aimed to compare the treatment plans using cobalt-60 (Co-60) gamma photon and 6MV X-rays of linear accelerators (Linac) in terms of such radiobiological parameters as TCP and NTCP.

Materials and Methods

The radiotherapy plans analyzed in this study were obtained from the routine clinical practice performed for the diagnosis and treatment of the patients with head and neck cancers. All the patients were simulated in treatment posture using thermoplastic immobilization cast on CT simulator (Somatom ensation Open 16 Slice CT, Siemens Health Care, Germany). The CT slices of 3 mm thickness were obtained from the regions of interest. Subsequently, the CT data were transferred using the DICOM 3.0 protocol. The radiotherapy plans were generated in Xio version 5.0 using Monaco IMRT Optimizer 5.0 (Elekta Medical Systems).

The target volume, OAR, and planning volume at risk were delineated slice by slice for the regions of interest. A total of 20 patients with head and neck cancers were planned using the conventional 3D conformal radiotherapy (CRT) and the intensity modulated radiation therapy (IMRT) with 6 MV X-rays from Linac. The patients were also planned for Co-60 teletherapy (average energy of 1.25 MeV). Multiple plans were generated for the patients for both radiation energies, and the optimal plan was selected by the visual inspection of the slices on the basis of the suitability of isodose distribution on PTV, OAR, and planning organ at risk volume.

The DVH provided by the treatment planning system for the target and OARs were analyzed. Further radiobiological evaluations of these treatment plans were performed using the BIOPLAN software developed by Sanchez-Nieto et al. [2]. The TCP was also calculated manually using the Brenner's formulae [3]. This manual calculation was accomplished by transferring the DVH data of the selected plans to excel sheets. Subsequently, the TCP values obtained by the BIOPLAN and Brenner's formulae were compared (Table 1, Figure 1).

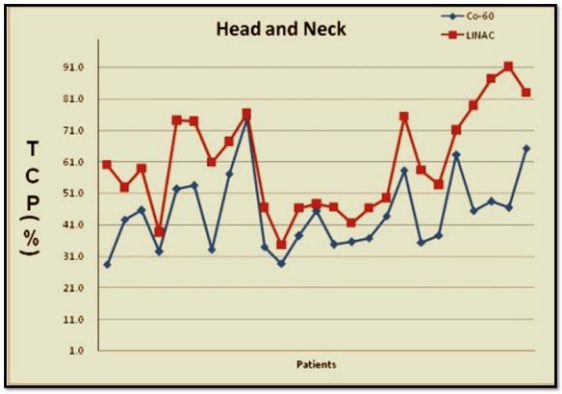

Figure 1. Comparison of Tumor Control Probability (TCP) for Head and Neck

Evaluation of tumor control probability and normal tissue complication probability using BIOPLAN

BIOPLAN [8] is a user-friendly software, which facilitates the biological evaluation of the treatment plans. The input data for the BIOPLAN are the differential DVH data [i.e., volume (%) and dose (%)], obtained from the treatment planning system. The BIOPLAN utilizes the dose prescribed to the target volume, irradiated volume, normalization percentage for TCP and NTCP calculation, as well as minimum, maximum, and average dose to the PTV. The biological parameters of the tumor (i.e., α and α/β) and clonogen density (i.e., number of clonogen cells/cubic centimeter) were also included for the calculation of TCP through the BIOPLAN.

The basic equation of TCP utilizes the Poisson statistical model according to which the probability of occurrence of N number of a particular event is defined as:

$$P(n) = [\exp(-a) * (a)^n]/n! \quad (1)$$

Where "a" is a positive real number, equal to the expected number of occurrences happening during the given interval.

From the radiobiological point of view, the above equation is modified as follows:

Tumor control probability

$$(n)=[\exp(-N_S) * (N_S)^n]/n! \quad (2)$$

Where N_S is the expected number of cells survived during the given interval after an exposure to dose D (Gy) and n is the actual number of the survived cells. For complete tumour treatment (i.e., n=0), the final equation of TCP could be obtained:

$$TCP\ (n=0)=\exp(-N_S) \quad (3)$$

The BIOPLAN uses the differential DVH data of TPS; in other words, it counts for each and every dose bin, which depends on the physical and dosimetric properties of the treatment unit.

Table 1. Tumor Control Probability (TCP) %- Head &Neck

Gamma Photon (Co-60)	6 MV X-Ray photon (Linear Accelerator)	Variation(%) wrt Co-60	(Brenner's et al)
28.3	59.9	111.7	98.4
42.7	52.8	23.7	95.3
45.6	58.8	28.9	92.2
32.4	38.6	19.1	55.7
52.3	74.1	41.7	94.3
53.4	73.8	38.2	72.8
33.1	60.7	83.4	81.3
57.2	67.4	17.8	89.9
74.8	76.3	2.0	99.9
34.0	46.4	36.5	96.1
28.6	34.6	21.0	37.3
37.5	46.2	23.2	90.5
45.5	47.5	4.4	91.6
34.7	46.5	34.0	79.1
35.5	41.5	16.8	78.3
36.8	46.2	25.5	90.0
43.8	49.5	13.0	86.6
58.2	75.3	29.4	81.0
35.4	58.3	64.7	80.7
37.6	53.7	42.8	80.4
63.3	71.0	12.2	80.0
45.4	78.8	73.6	79.7
48.4	87.3	80.3	79.4
46.4	91.1	96.4	79.0
65.3	82.8	26.8	78.7
Average	Average	Average	Average
44.6	60.8	38.7	82.7

The BIOPLAN software calculates the NTCP for the spinal cord and optic nerve using the relative seriality model. This model uses the binomial statistics to obtain the probability of the damage of normal tissue or NTCP. It accounts for the serial and parallel architecture of the functional subunits. The expression for NTCP is :

$$NTCP = \left[1 - \prod_{j=1}^{k} \left(1 - NTCP(D_j)^s\right)^{v_j}\right]^{1/s} \quad (4)$$

This formula describes the response of the whole organ to an arbitrary dose distribution (Dj, vj) as a function of the response of the whole organ to a homogeneous dose distribution. The number of functional subunits has been made to coincide with the k bins in the DVH, where "s" is the relative seriality factor. NTCP (Dj) can therefore be expressed as:

$$NTCP(D_j) = 2^{-e^{e \cdot \gamma \cdot \left(1 - \frac{D_j}{D_{50}}\right)}} \quad (5)$$

Where γ parameter is the maximum relative slope of the dose-response curve, and D50 is the whole organ uniform dose that would produce a 50% complication probability.

The BIOPLAN has a library of s, γ, and D50 values for some critical organs and clinical end. The NTCP values for optic nerve and spinal cord are illustrated in Table 2.

Evaluation of tumor cancer probability using Brenner's model

Brenner's model facilitates the manual estimation of the TCP value. This model incorporates the dependence of TCP on the size of the irradiated volume, density of clonogenic cells, and received dose together with the α and β parameters of the linear-quadratic model of cell kill [3]. In a study conducted by Webb and Nahum [9], it was revealed that a large reduction in the clonogenic cell density at the edges of a tumor would permit only a very modest decrease in dose if the TCP is not to be reduced.

The effect on TCP is a complicated function of the variation in both dose and clonogenic cell density. This model can be used to describe situations in which both dose and clonogenic cell densities are inhomogeneously distributed. Based on this model, if a volume V of clonogenic tumor cells with uniform density ρ is irradiated to a uniform dose D, the number of the clonogenic cells surviving the irradiation can be calculated as [3]:

$$N_s = \rho V \exp\{-(\alpha D + G\beta D^2)\} \quad (6)$$

Where G is a quantity of ≤ 1, which depends on the fractionation schemes and allows for incomplete repair and half time for sub-lethal damage repair. The equation for TCP could be written as:

$$TCP(V, D) = \exp(-N_s) \quad (7)$$

A constant value of 10 Gy was assumed for the ratio α/β. Therefore, the equation of TCP for the above mentioned head and neck tumor can be given as:

TCP $(V, D)=\exp\{-\rho V \exp(-1.2\ \alpha D)\}$ (8)

In this study, we utilized equation VIII. An excel program was generated for the easy execution of the formulae. The values of constants ρ and α were taken as 10^7 cell/cc and 0.297, respectively. Table 1 presents the TCP values calculated for Co-60 gamma photon and 6 MV X-rays of Linac.

Results

Based on the BIOPLAN software, the minimum and maximum TCP values for Co-60 gamma photon were 28.3% and 74.8%, respectively. These values in the Brenner's formulae were revealed to be 98.4% and 99.9 %, respectively. Furthermore, the average TCP values for 6MV X-rays of Linac were 60.8% and 82.7% based on the BIOPLAN and Brenner's formulae, respectively (Table 1 and Figure 1).

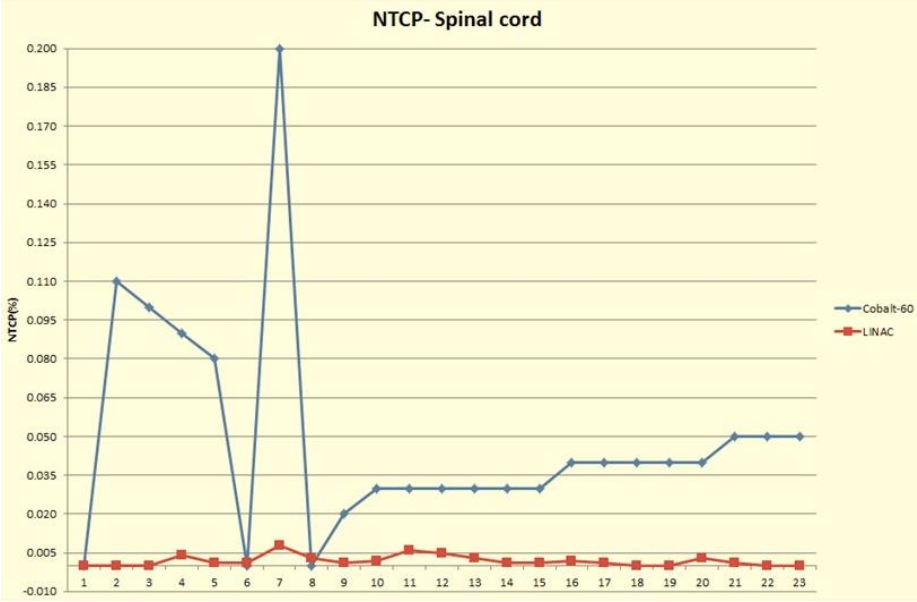

Figure 2. Comparison of Normal Tissue Complication Probability (NTCP) for Spinal Cord

Table 2. Normal tissue Complication Probability (%)- Head & Neck

Optic Nerve			Spinal cord		
Gamma Photon Co-60	X-Ray photon LINAC	Variation(%) wrt Co-60	Gamma Photon Co-60	X-Ray photon LINAC	Variation (%) wrt Co-60
0.00	0.00	0.00	0.00	0.000	0.00
0.00	0.00	0.00	0.11	0.000	100.00
3.00	0.00	100.00	0.10	0.000	100.00
0.29	0.20	31.00	0.09	0.004	100.00
0.28	0.00	100.00	0.08	0.001	100.00
0.27	0.00	100.00	0.00	0.001	0.00
0.20	0.20	0.00	0.20	0.008	100.00
0.31	0.00	100.00	0.00	0.003	0.00
0.00	0.03	0.00	0.02	0.001	100.00
0.23	0.03	87.39	0.03	0.002	100.00
0.19	0.03	85.69	0.03	0.006	100.00
0.19	0.03	86.54	0.03	0.005	100.00
0.06	0.02	60.20	0.03	0.003	100.00
0.06	0.02	62.28	0.03	0.001	100.00
0.06	0.02	64.46	0.03	0.001	100.00
0.05	0.02	66.77	0.04	0.002	100.00
0.05	0.02	69.22	0.04	0.001	100.00
0.05	0.01	71.81	0.04	0.000	100.00
0.05	0.01	74.57	0.04	0.000	100.00
0.05	0.01	77.50	0.04	0.003	100.00
0.05	0.01	80.63	0.05	0.001	100.00
0.05	0.01	83.97	0.05	0.00	100.00
0.04	0.01	87.55	0.05	0.00	100.00
Average 0.24	Average 0.03	Average 87.83	Average 0.05	Average 0.00	Average 100.00

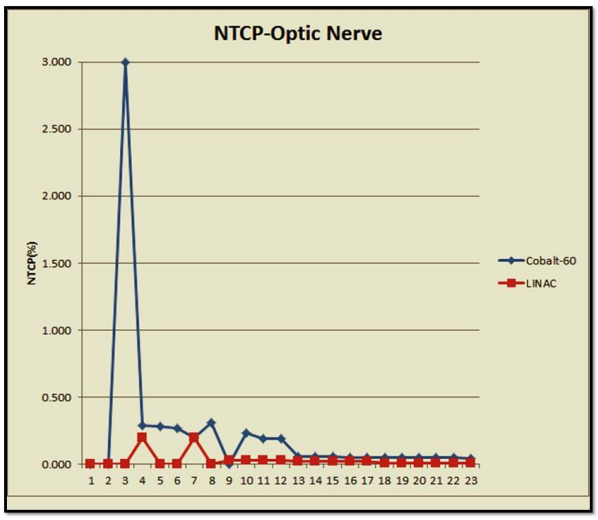

Figure 3. Comparison of Normal Tissue Complication Probability (NTCP) for Optic Nerve

The NTCP for optic nerve and spinal cord is detailed in Table 2. The average NTCPs for spinal cord were 0.05% and 0.002% for Co-60 gamma photon and 6MV X-ray photon of Linac (Figure 2). For optic nerve, the average NTCP with Co-60 and 6MV X-rays were 0.24% and 0.03%, respectively (Figure 3).

Discussion

The TCP calculated by the Brenner's formulae suggested that with careful plan optimization, Co-60 gamma photon could also provide a TCP of approximately 90%. It is evident that for head and neck cancers, except for the advanced stage, the TCP may be around 80-90% on an average, which is attainable without exceeding the tolerance of the normal structures. In 1992, Fowler [10] proposed the concept of consequential dose or radiobiological effective dose in fractionated radiotherapy planning for computing the biological effective dose and extrapolated response dose as well as their utilization in the radiotherapy plan optimization.

In the present study, the concept of biological effective dose for converting the physical dose plan to radiobiological indices of TCP and NTCP was utilized for the tumors of head and neck. The BIOPLAN mostly rendered the NTCPs of < 0.1% and 0.03-0.03% for the spinal cord and optic nerve, respectively. These values suggested that the dose-volume constraints have typically higher uncertainty with respect to their impact on the outcome [1]. Dose-volume response of tumors and normal tissues was also studied by Kallman et al. [11] in terms of parallelity and seriality. The mentioned study revealed that the biological toxicity of the serial and parallel organs would be best evaluated through the biological plan.

Injury to normal tissue is a much more complex and gradual process; therefore, NTCP is of higher importance in toxicity prediction. Kallman et al. described the volume dependence of the dose-response of normal tissues by a new parameter (i.e., relative seriality) of the infrastructure of the organ. For example, the spinal cord has a high seriality, which is in accordance with its tolerance. As suggested by Webb and Nahum [9], in the majority of the calculations of the biological effect of radiation on tumors, it is assumed that the clonogenic cell density is uniform, even if non-uniform dose distribution is also taken into account.

In practice, tumors would almost certainly have a non-uniform clonogenic cell density. This study extended a model of TCP to incorporate a variable clonogenic cell density, while simultaneously assuming a constant 2 Gy fraction size and a uniform radiosensitivity throughout the course of the treatment. One clear conclusion was that a large reduction in the clonogenic cell density at the edges of a tumor (i.e., DVH curve, which was sloppy at shoulder, Figure 4) would permit only a very modest decrease in dose if the TCP is not to be reduced.

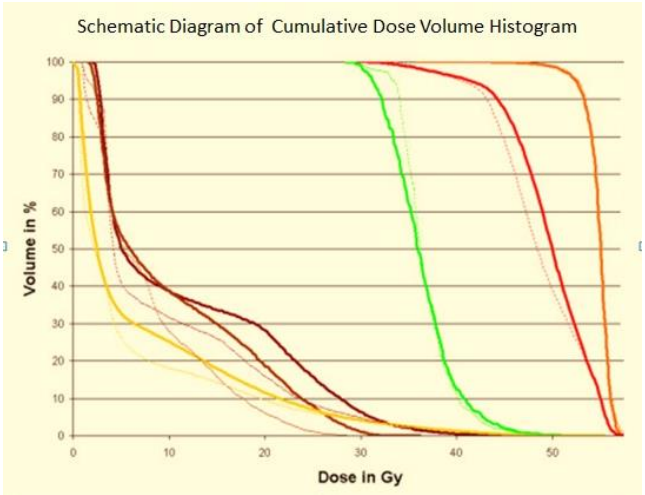

Figure 4. Schematic diagram of DVH

Anders Brahme [12] concluded that once the accurate genetically and/or cell survival-based predictive assays become available, the radiation therapy will become an exact science. Under this circumstance, the radiation therapy facilitates truly individual optimization considering the panorama of side-effects that the patient is willing to accept.

The present study was an attempt to provide a working model for routine application in radiation therapy plan evaluation, which is in conformity with Anders Brahme [12] proposal. The evaluation of TCP and NTCP provides beforehand prediction about the probable treatment and toxicities for a given course of radiotherapy. On the contrary, the DVH is totally silent on response prediction and provides only the graphical representation of the target volumes and OARs.

Conclusion

As the findings of the present study indicated, Co-60 unit could provide comparable TCP along with minimal NTCP, compared to the high-cost technologies of Linac. The design of treatment plans based on the radiobiological parameters facilitated the judicious choice of physical parameters for the achievement of high TCP and low NTCP.

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References

1. Deasy JO, Mayo CS, Orton CG.. Treatment planning evaluation and optimization should be biologicaly and not dose /volume based. Med. Phys. 2015; 42(6):2753-6. DOI: 10.1118/1.4916670.
2. Sanchez-Nieto B, Nahum AE.. Bioplan software for the biological evaluation of radiotherapy treatment plans. Medical Dosimetry. 2000; 25(2),:71-6. DOI: 10.1016/S0958-3947(00)00031-5.
3. Brenner DJ. Dose, volume, and tumor-control predictions in radiotherapy. Int. J. Radiat Oncol Biol. Phys. 1993; 26, (1): 171-9. DOI: 10.1016/0360-3016(93)90189-3.
4. Fletcher GH. Keynote address: the scientific basis of the present and future practice of clinical radiotherapy. Int J Radiat. Oncol. Biol. Phys 1983; 9:1073-82. DOI: 10.1016/0360-3016(83)90399-1.
5. Niemierko A, Urie M, Goitein M. Optimization of 3D radiation therapy with both physical and biological end points and constraints. Int. J. Radiat. Oncol. Biol. Phys. 1992; 23:99-108. DOI: 10.1016/0360-3016(92)90548-V.
6. Sanchez-Nieto B, Nahum AE. The delta-TCP concept: a clinically useful measure of tumor control probability. Int. J. Radiat. Oncol. Biol. Phys. 1999; 44(2), : 369-80. DOI: 10.1016/S0360-3016(99)00029-2.
7. Withers HR. Biological basis of radiation therapy.; The Lancet. 1992 Jan 18;339(8786):156-9. DOI: 10.1016/0140-6736(92)90218-R.
8. Niemierko A, Goitein M. Implementation of a model for estimating tumor control probability for an inhomogeneously irradiated tumor. Radiother. Oncol. 1993; 29:140-7. DOI: 10.1016/0167-8140(93)90239-5.
9. Webb S, Nahum A.E. A model for calculating tumor control probability in radiotherapy including the effects of inhomogeneous distributions of dose and clonogenic cell density. Phys. Med. Biol. 1993; 38: 653-66. DOI: 10.1088/0031-9155/38/6/001.
10. Fowler JF. Brief summary of radiobiological principles in fractionated radiotherapy. Semin. Radiat. Onco. 1992; 2:16–21. DOI: 10.1016/S1053-4296(05)80045-1
11. Källman P, Ågren A, Brahme A. Tumour and normal tissue responses to fractionated non-uniform dose delivery. Int. J. Radiat. Biol. 1992; 62(2):249-62. PMID: 1355519.
12. Brahme A. Individualizing cancer treatment: biological optimization models in treatment planning and delivery. International Journal of Radiation Oncology* Biology* Physics. 2001 Feb 1;49(2):327-37. DOI: 10.1016/S0360-3016(00)01501-7.