

IMPACT OF RESPIRATORY GATING USING 4DCT ON THERAPEUTIC GAIN (TG) IN PATIENTS WITH THORACIC MALIGNANCIES

Introduction: Respiration can significantly affect thoracic tumor motion and, therefore the accuracy of tumor targeting with radiation. 4DCT respiratory gating allows us to quantify the excursion of tumor in three-dimensions over the course of the respiratory cycle and, therefore to customize tumor margins in individual patients. This may optimize target coverage and minimize normal tissue exposure to high radiation dose. This study was undertaken to evaluate the uncomplicated tumor control probability (UTCP) calculated from the Dosimetry of 4DCT gated treatment plans as compared to traditional non-gated treatment plans.

Materials and Methods: Lung tumors consist of malignant cells of various degrees of differentiation and, therefore, different degrees of radiation response. Tumor Control Probability (TCP) provides a quantitative biophysical measure of tumor dose and has been estimated using the numerically calculated equivalent uniform dose (EUD) obtained from the dose distributions in the target volume. The concept of EUD assumes that two different target dose distributions are equivalent if they cause the same radiobiological effect such that the corresponding number of expected surviving clonogens is equal. TCP mathematically models tumor response using the α/β ratio, the clonogen cell density (CCD) and the SF_2 . Using the linear quadratic expression for cell killing, we calculated TCP using the following formula:

$$TCP = e^{-N(SF_2)^{\frac{D}{D_{ref}} \frac{\alpha/\beta + D/n}{\alpha/\beta + D_{ref}}}}, \quad (1)$$

where N is the number of clonogenic cells in the tumor, calculated by multiplying CCD with tumor volume; $\alpha/\beta = 10$ Gy, where α and β are radiosensitivity parameters related to cell killing from single or multiple hit events respectively. D equals EUD, n equals the number of treatment fractions and SF_2 is the surviving fraction after irradiation at a reference dose (D_{ref}) of 2Gy. Since the population of clonogenic cells differs in their radioresistance, we assumed a probability distribution of cells surviving at 2 Gray ranging from 0.1 to 0.5 to generate a weighted SF_2 . Since CCD may vary from patient to patient and may also differ within the tumor volume of the same patient, we based our calculation of TCP on CCD of 10M/cc and 220M/cc.

Normal tissues receive radiation dose during the treatment of tumors, and the NTCP is the probability that a certain percentage of the patient population will incur unfavorable reactions in the contiguous tissue at a particular dose. We calculated the NTCP of an organ for a uniform dose D to a volume V using Lyman-Kutcher-Burman method, and is given by

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-t^2/2} \cdot dt \quad (2)$$

Where, $t = \frac{D - TD_{50}(V)}{m \cdot TD_{50}(V)}$

The $TD_{50}(V)$ is the tolerance dose for a 50% complication probability due to uniform irradiation to a partial volume V, and is related to the tolerance dose for whole organ $TD_{50}(1)$, by $TD_{50}(V) = TD_{50}(1) / (V)^n$. In the above equations, parameters m and n deal with slope of the dose response curve and the volume effect respectively. These parameters and $TD_{50}(1)$ were obtained from published data.

The therapeutic gain (TG) is obtained by calculating the uncomplicated tumor control probability (UTCP) which is the probability of tumor control while having no complications using the following formula:

$$UTCP = (TCP \times \prod_i(1-NTCP_i)), \quad (3)$$

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Where, $i = 1$ to 4, represents normal tissues of heart, spinal cord, uninvolved lung and esophagus. Higher value of UTCP indicates biologically a treatment plan with higher therapeutic gain.

Ten patients underwent treatment planning with gated and non-gated CT. Gated CT images were obtained at full inspiration, full expiration and at 25th, 50th and 75th percentile of respiration. For non-gated plans, the planning target volume (PTV) included an all around 1 cm margin for tumor motion and 0.5 cm for set-up error. For “gated plans”, tumor volumes of individual CT images were superimposed with a 0.5 cm margin for set-up error. The prescription dose was 60-70 Gy at 2 Gy per fraction. Dose Volume Histograms (DVH's) were generated for the PTV's, heart, spinal cord, esophagus, and total lung in each treatment plan. For each patient, rival treatment plans achieved with gated and non-gated CT planning were compared on the basis of TCP, NTCP and TG.

Results: The average gated PTV was 292.7 cc versus 575.2 cc for non gated PTV. TCP was higher for gated plans. Specifically, TCP was 95.42% and 90.38% for gated plans with CCD of 10M and 220 M, respectively. For non-gated plans and CCD of 10 M and 220M, TCP was 93.52% and 85.36%, respectively as shown in Table 1. The gain in terms of normal tissue sparing in the gated treatment plans was also confirmed by NTCP calculations. Specifically, NTCPs for lung, esophagus, heart and spinal cord were 7.96%, 5.23%, 1.66% and 0.38% with gating versus 26%, 8.25%, 9.36% and 0.52% without gating as shown in Table 2. The greatest absolute difference in NTCP of 18.04% was observed for lung. The differences in UTCPs between gated and non gated plans were 26.21% and 24.98% for CCDs of 10M and 220 M, respectively which indicates that the gated plans are clearly superior compared to non gated plans.

Conclusions: 4DCT respiratory gating allows for radiation field reduction, also decreasing doses to lung and other normal tissues. 4DCT in combination with image guided radiation therapy will improve radiation target dosing while maximizing normal tissue sparing and may limit the incidence of radiation induced late toxicity in long –term survivors.

Table 1. Values of TCP for gated and non gated plans

Clonogen Cell Density	Gating (%)	Non-gating (%)
CCD	SF2 weighted	SF2weighted
10 Million	95.42	93.52
220 Million	90.38	85.36

Table 2. Values of NTCP for gated and non gated plans

Organ	Gated (%)	Non-gated (%)
Lung	7.96	26.00
Esophagus	5.23	8.25
Heart	1.66	9.36
Spinal cord	0.38	0.52