Chapter 1

Radiobiology of Radiotherapy

Cancer is a non-communicable disease. In simple words cancer occurs due to uncontrolled growth of cells. The cancer cells can spread to different organs of the body via blood vessels and arteries and refereed as metastasis. According to world health organization (WHO) nearly 10 million people died in 2020. Breast in female and lung in male are the most common cancer found. The other common cancers are cancers are colon, cervix, rectum and prostate. There are multiple risk factors responsible for cancer, but around one third of death happen from tobacco chewing. High body mass index, alcohol consumption, unhealthy diet and carcinogens. There are number of categories and types of cancers, mainly divided on the basis of histopathology of cancer cells. Examples are carcinoma, sarcoma, leukemia, lymphoma and multiple myelomas etc. depending upon cancer staging, site and histopathology different types of treatment modalities are available. These treatment modalities are surgery, chemotherapy and radiotherapy. Treatment of cancer can be possible by all these three modalities or combination of any two depends on type of cancer. Surgery is a standard treatment modality in many solid tumors in which tumor is surgically removed from cancer site. Chemotherapy is a kind of systemic treatment where cytotoxic drugs are administered through intravenously. The third treatment modality is a radiation therapy which we will discuss in this chapter in detail.

1.1 Background

After the discovery of X-ray in 1895 by W. C. Roentgen, application of X-rays did not take long time to treat cancer patients. In 1897, radioactivity discovered by Henri Becquerel which further studied by Marie and Pierre Curie. They discovered two radioactive elements named as polonium and radium. Till that time through knowledge of biological effects of radiation were unknown but radioactive sources were used for various applications. In beginning of nineteenth century number of studies reported the use of X –rays and radium in medicine. By orthovoltage technique, skin cancers were most commonly treated. In 1910, Coolidge invented a device to treat cancers of deeper depth. In 1928, R. Wideroe presented an idea of accelerating the electrons in a tube through the application of radiofrequency. This unique idea was adopted for construction of linear accelerators, which clinically available in 1950. Period from 1930 to 1950 known as era of super-voltage X-ray tubes, able to deliver energy from 50 kV to 200 kV. After 1950, high energy X-rays used for the treatment of cancers ranging from surface to deep seated tumors.

1.2 External Beam Radiation Therapy (EBRT)

EBRT is a non-invasive treatment in which radiation enters in the body from an external source. In EBRT, dose delivered by different particle radiations such a photon, proton, electron, neutron and heavy ions. However, most commonly used particles for treatment are photons and electrons. High energy photons (6, 10, & 15 MV, C0-60) are used to treat deep seated tumors because of high penetrating power. Electrons are short range particles and deposit dose towards the surface therefore suitable for treatment of superficial tumors or surface treatment. The integrated dose and exit dose in high energy photons also significant. With advancement new modalities for treatment available like Proton therapy. Protons are positively charged particles with a spectrum of large Bragg peak. Because of Bragg peak there is a biological advantage of protons against photons. Bragg peak refers to the maximum dose deposition at the exit beam which directly affect total integral dose. Protons have superior dose

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distribution when compared to photons and electrons. Although proton therapy can be more suitable for solid tumors, its application is more advantageous in pediatric malignancies. The radiotherapy departmental workflow shown in fig. 1 below.

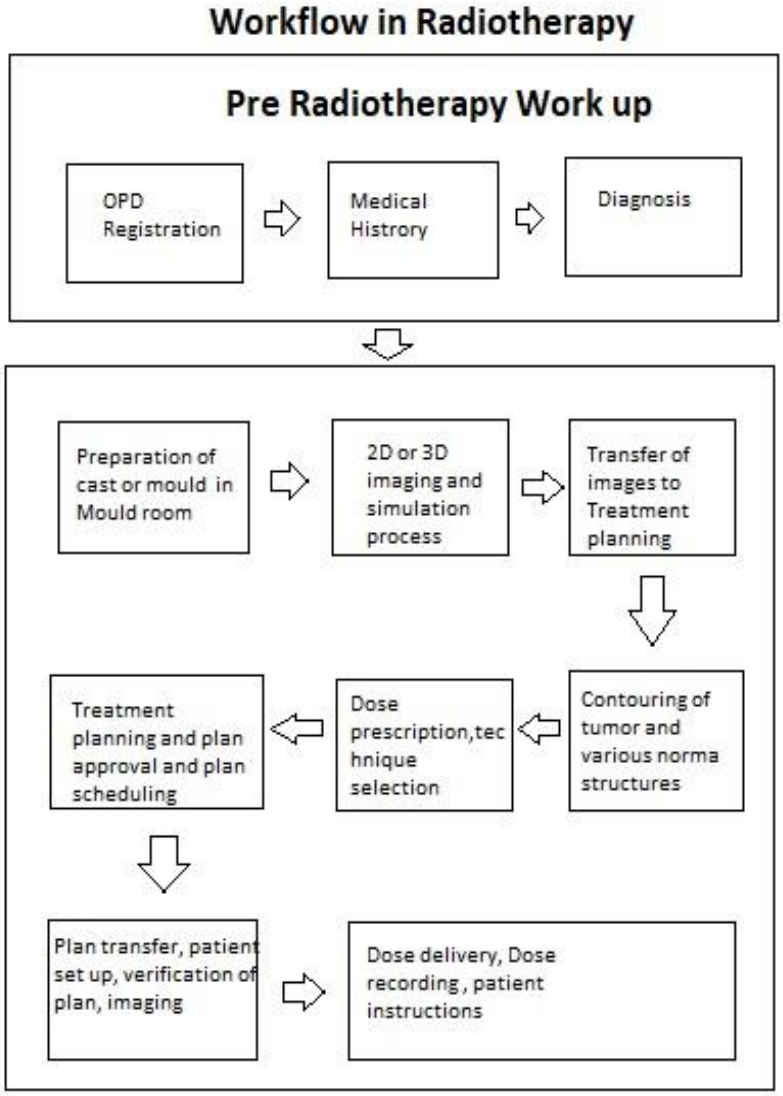

Figure 1: *Diagram explaining workflow in radiotherapy department.*

1.3 Definition of contouring volumes before planning

There are different volumes has to be contoured on computed tomography (CT) 3D images before planning as shown in figure 1.1.

Gross Tumor Volume (GTV): It is a gross palpable or visible malignant growth according to ICRU 50 report.

Clinical Target Volume (CTV): It is the volume that contains the GTV plus margin that takes into account subclinical microscopic disease.

Internal Target Volume (ITV): The ITV contains CTV plus internal margin. The ITV is to consider variation in size and position of the CTV due to organ motion such as breathing.

Planning Target Volume (PTV): It is the volume containing the GTV, CTV and a margin around the CTV that accounts for setup variation or errors.

Treated volume: It is the volume of tissue that is planned to receive a prescribed dose. It is the volume enclosed by the isodose surface/line corresponding to that dose level, for example 95% isodose line covering the target.

Irradiated volume: It is the volume of tissue that is irradiated to a dose considered significant in terms of normal tissue tolerance, and is dependent on the treatment technique used.

Conformity index: It is the ratio of planning target volume to the treated volume, and shows how well target volume **is** covered by the prescribed dose while minimizing dose to normal tissues.

Organs at Risk (OAR): It is normal tissues/organ surrounding or adjacent to tumor volume that has a possibility of receiving high dose (prescribed dose to tumor). OAR classified in two types depending on their functional and structural organization in body as shown in figure 1.2.

Serial: It is understood that each organ consist functional subunits. But in case of the chain receives a radiation dose above the tolerance organ functionality is lost (e.g. spinal cord). The functional subunits (FSUs) of serial organs are structured serially. It means if critical damage due to radiation occurs in any functional subunit, complications are observed in the whole organ. Examples include esophagus and rectum.

Parallel: The functional sub-units (FSUs) FSUs are parallel in structure. If critical damage due to radiation occurs in any functional subunit, complications are only observed in that subunit, and the organ continues its function. Examples include parotid glands, lungs and liver.

Serial Parallel (Mixed): tissues that have functional sub-units with both behaviours (serial and parallel).

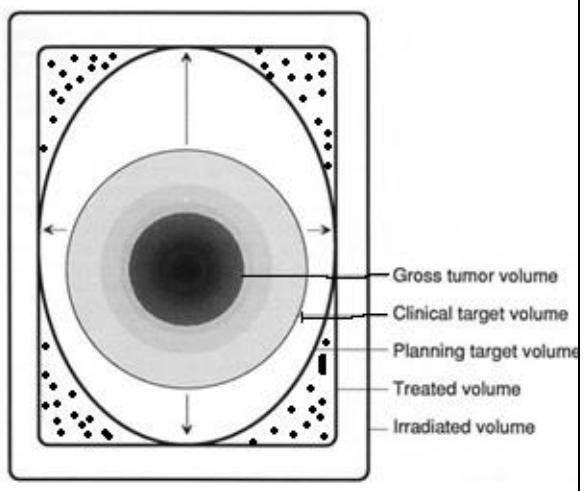

Figure 1.1: *Different contouring volumes*

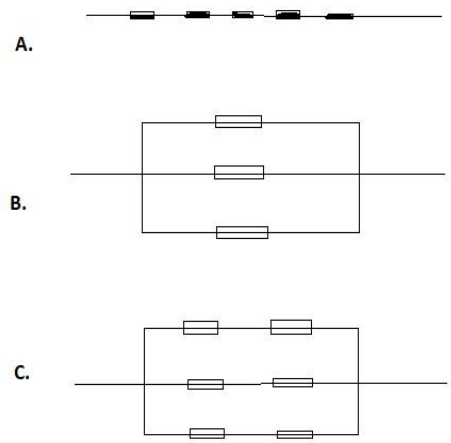

Figure 1.2: *A is a serial organ, is a parallel organ and C is mixed organ*

1.4 Types of treatment techniques in EBRT

Conventional technique: This technique also refers two dimensional (2D planning). It is the oldest technique in which dose is delivered by rectangular and square fields. The field size defined on the patient surface by orthogonal images (Anterior and lateral port images). There is high normal tissue toxicity associated with conventional technique. But the conventional technique do not required multimodality imaging like CT and MRI because planning is based on manual dose calculation. Conventional technique takes less time for planning and delivery of dose against modern techniques

(IMRT/VMAT). This technique is cheaper than modern techniques.

3D CRT: Abbreviated as three dimensional conformal radiotherapy. With the invention of revolutionary device multileaf collimator (MLC) there is high probability to save normal health tissue and organ at risk surrounding the tumor. It is a CT based planning technique and required treatment planning system. 3D CRT planned by number of fields depends upon the planning objectives. The role of number of fields to conform target volume by MLC from different direction to minimize dose to normal healthy tissue as well as to bring down OAR dose within tolerance limit.

IMRT: Abbreviated as Intensity Modulated Radiotherapy, it is a CT based planning technique required treatment planning system. In IMRT, non-uniform fluence map can be produce to confirm target and increase target coverage and to minimize dose to normal tissue and OAR by the way of intensity modulation of incident beam. The dose distribution. Homogeneity and conformity of IMRT technique is superior to conventional and 3D CRT. There is two types of IMRT, first is step and shoot IMRT (At a define gantry angle MLC takes shape of segment and then beam ON) and second is dynamic IMRT (At a define gantry angle MLC keeps on changing shape of segments while beam is in ON state)

VMAT: Abbreviated as Volumetric Modulated Arc Therapy, it is a CT based planning technique. This technique also achieves dose distribution by intensity modulation. The special feature of this technique is that Gantry moves in Arc while changing gantry speed, MLC speed and movement, dose rate which results in superior dose distribution compared to IMRT technique. The radiation is delivered in cone beam geometry. As radiation is delivered continuously during arc motion of gantry, it significantly reduces treatment time. VMAT produces better conformity, homogeneity and less number of MU against IMRT technique.

1.5 Plan Evaluation

Practically, for each patient a number of treatment plans can be generated which differs from each other in terms of dose distribution. A best plan is selected and approved for treatment on the basis of merits of the plan. Plan evaluation is a process in which evaluation of set objectives for the treatment is verified. Generally plan evaluation performed through slice by slice visual verification of prescription isodose line conforming to planning target volume (PTV) in addition with dose volume histogram (DVH) analysis.

1.6 Dose Volume Histogram (DVH)

It is a plan evaluation tool and represents the 3D dose distribution of target volume and various organ at risk volume on 2D plot. It is the graph plotted dose versus volume. The ideal way of evaluating the plan is the 3D dose distribution slice by slice by various ways like dose colourwash and isodose lines. All other methods of analyzing the dose distribution is surrogate and involve loss of information. The problem with 3D dose distribution is to assess large information and it is cumbersome task to quantify each information visually. It is difficult to understand the relationship between dose and anatomy. In order to create DVH of any 3D organ, one look at dose value of each voxel in the organ and forms a histogram. Because the volume of each voxel is known, the volume of the organ receiving each dose level is known. DVH can displayed in both absolute and relative form. DVH broadly divided two types cumulative and differential.

Differential DVH: It is the generic form of any organ, displaying the volume of the organ that receives dose within each dose bin. (Typical dose bin width in TPS is 0.1 cGy to 1Gy) It is useful to display the dose to target volume because we can easily visualize minimum dose, maximum dose and the dose

most representative of the entire target volume as shown in figure 1.3.

Cumulative DVH: In this volume receiving at least at a given dose values are plotted. The CDVH integrates the direct histogram, so it always begins at 100% (e.g 100% volume of the organ at least receives 0 dose) and end at the maximum dose. In this DVH there is bin by bin integration of dose versus volume as shown in figure 1.3.

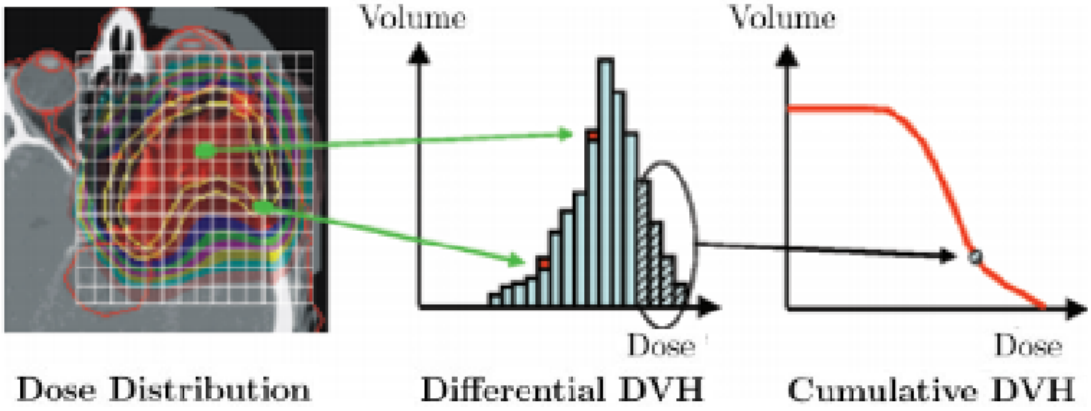

Figure 1.3: *Showing dose distribution, cumulative DVH and differential DVH.*

Problems with DVH: It is insensitive to small volume hot spots and cold spots, the shape of DVH alone is misleading, DVH can be calculated for defined or contoured volume of interest and DVH missed spatial dose information (each voxel information).

Recommendation regarding DVH: DVH should always use in addition with visual 3D slice by slice dose distribution verification. DVH should always use in addition with dose volume statistics to know volume of hot spots and cold spots.

1.7 Basic Radiobiology

Direct and Indirect Action

Ionizing radiation effect have broadly classified in two types.

Direct effect: It is the effect shown in figure 1.4(a) there is ionization of atoms in DNA molecules because of energy absorption via photoelectric effect and Compton interaction. The free electron can break single or double DNA strand. A single strand break usually repairable whereas double strand break result in cell death.

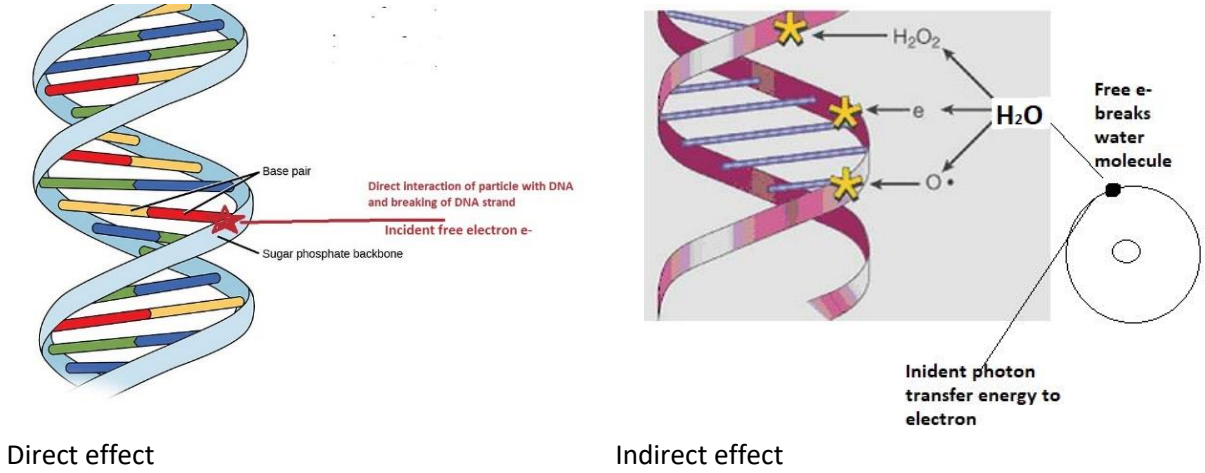

Figure 1.4: *Mechanism of action a) Direct effect b) Indirect effect*

Indirect Effect: It is the effect shown in figure 1.4(b) of ionizing radiation there is a formation of free radicals by transfer of energy. The free radicals formed due to interaction of radiation with water molecules since the human body mostly made of 70 % water.

When water is ionized, positively charged water molecule is formed.

$H_2O \longrightarrow H_2O^+ + e^-$

The free electron interacts with surrounding water molecule and formed negatively charged water molecule

$e^- + H_2O^+ \longrightarrow H_2O^-$

These charged molecules undergo the following reaction

$H_2O^+ \longrightarrow H^+ + OH$

$H_2O^- \longrightarrow H + OH^-$

These free radicals (H or OH) have very short life of 10^{-10} s, within this time they travel from cytoplasm to nucleus and damages DNA.

When H combines with O_2, it forms more lethal free radicals with longer life called hydrogen oxide (HO_2) even H2O2 (hydrogen peroxide) of life 10^{-5} s and caused lethal DNA damage.

Linear Energy Transfer (LET)

LET is defined as energy deposited along the tract of particle traversing in a medium shown in figure 1.5. It is a quantity which measure the interaction between particle and medium. The unit of LET is keV/µm. LET has two types low LET and high LET.

High-LET radiation transfers more energy per unit length of medium, therefore probability of causing DNA damage in a short period of time is high.

Examples of high LET radiation are protons, neutrons, Alpha particle, Carbon ions and all types' heavy charged particles.

Low-LET radiation transfers comparatively less energy along the tract of particle traversing in a medium. Therefore dose of low-LET radiation is not more destructive than the same dose of high-LET radiation. Examples of low LET radiation are photons, gamma rays, electrons and beta particles.

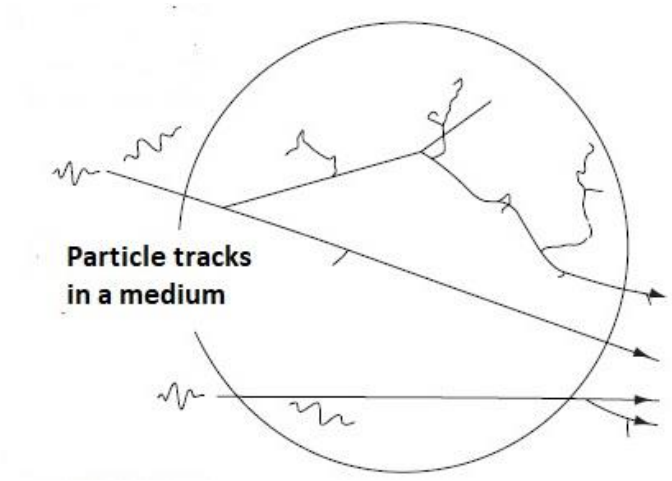

Figure 1.5: *Indicating track of particle traversing in a medium with energy deposition.*

Properties of LET

1. LET is directly proportional to square of particle charge.
2. LET decreases with particle velocity.
3. LET increases with mediums density.
4. LET decreases with mediums atomic number.
5. Lethal effect increases as LET increases.

Relative Biological Effectiveness (RBE)

Biological effect of all type of radiation is not same means 1 Gy dose of X –ray cannot be same as 1 Gy dose of proton particle. To distinguish this behaviour of radiation quantity named as RBE proposed.
It is the ratio of doses from standard radiation to the dose from test radiation to produce same biological effects.

$$RBE = \frac{Dose\ of\ standard\ radiation\ to\ cause\ an\ effect}{Dose\ of\ test\ radiation\ to\ produce\ same\ effect}$$

Where, Standard radiation either 250 KVp X-ray or Co-60 gamma rays.

Oxygen Enhancement Ratio (OER)

It is the ratio of doses in hypoxic condition to the dose of radiation in normoxic condition to achieve same biological endpoint.

$$OER = \frac{Dose\ of\ radiation\ in\ absence\ of\ oxygen\ to\ cause\ an\ effect}{Dose\ of\ radiation\ in\ presence\ of\ oxygen\ to\ produce\ same\ effect}$$

A clinically relevant OER is in the range of 2.5 to 3.5.

Types of Radiation Damage

Lethal damage (LD): It is an irreversible and irreparable damage. In this damage there is double strand breakage in DNA causing cell death. This damage happens because of direct effect of radiation.
Sub Lethal Damage (SLD): It is a repairable damage. Generally repairing starts within hours under normal conditions, unless extra radiation dose is not delivered to boost sub lethal damage. In this damage there is a single strand breakage in DNA. This damage happens because of indirect effect of radiation. This is commonly observed in low LET radiation like photons and electrons.
Potentially lethal damage (PLD): It is a repairable damage, depends upon the changes occurring in the cell environment after exposure to radiation.

Biological Effects of Radiation

The radiation effects on tissues and organs divided into three types as follows.
Acute effects: In this effect changes observed in the first 6 months after radiation exposure.
Subacute effects: In this effect changes observed between 6 and 12 months after radiation exposure.
Chronic effects: In this effect changes observed after 12 months of radiation exposure. For example, carcinogenesis, genetic mutations etc.

Stochastic Effects: It is the chronic effects of radiation called as stochastic effects or probabilistic effect. There is no defined threshold dose for stochastic effects. There is no relation exist between the individual effect and the dose.

Deterministic Effect: It is the acute and sub-acute effects of radiation called as deterministic effects or non-stochastic effects. There is a direct relation between the individual effect and the amount of dose. In this effect there is predefined threshold dose.

For example, skin erythema, cataract, myelitis, sterility, and fibrosis etc.

Therapeutic Index (TI)

The therapeutic index is the ratio of tumor control probability (TCP) and normal tissue complication probability (NTCP) for different doses.

TI = normal tissue tolerance dose/tumor control dose OR (NTCP/TCP)

To achieve good TI, need to maintain optimal balance between TCP and NTCP.

TCP and NTCP or also called dose response curves are sigmoid in shape. The aim of treatment is to keep the TCP curve to the left and the NTCP curve to the right (Fig.1.6).

The therapeutic window as shown below increases if the region between the two curves is wide, which means the benefit from treatment increases.

Tumor Control Probability (TCP)

The efficacy of radiotherapy treatment is evaluated by TCP. It increases with increase of dose and gets saturated at a certain dose. The TCP depends on dose per fraction, the total prescribed dose, volume of irradiation and accuracy of dose delivery or treatment reproducibility. The relationship between TCP & NTCP is shown in figure 1.6.

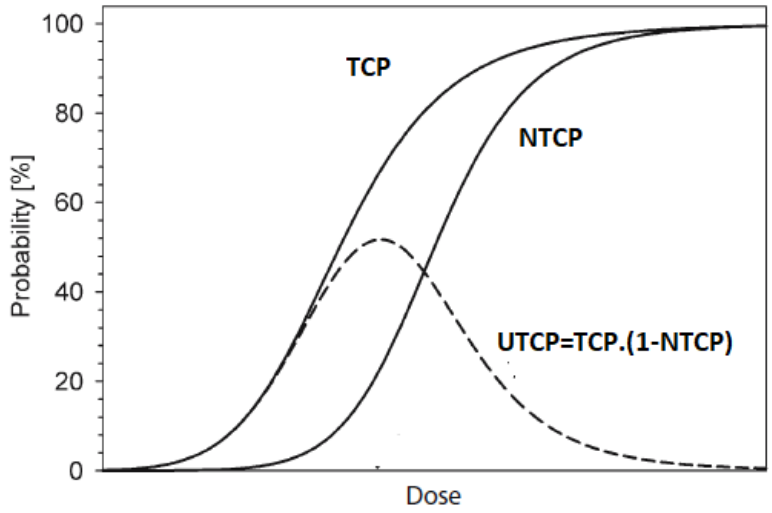

Figure 1.6: *Graphical representation showing dependence of TCP, NTCP and UTCP on dose.*

TCP affected by many factors some are tissue specific factors mentioned below.

1. Intrinsic radiosensitivity of tumor cells
2. Size and location of tumor
3. Oxygenation effect (OER)
4. Cellular type of tumor

Some are treatment-related factors such as:

5. Dose fractionation schedule
6. Type of radiation (high LET or Low LET)
7. Dose rate
8. Use of radiosensitizers and radiprotectors
9. Combination therapy like surgery and chemotherapy
10. Type of Technique (e.g. 3D, IMRT, VMAT)

Normal Tissue Complication Probability (NTCP)

The NTCP depends on dose per fraction, the total prescribed dose, the volume of tissue exposed to the radiation. NTCP measures the amount of damage received by the organ at risk and normal healthy tissue. It is increases with increase of radiation dose.

There are following tissue specific factors affecting NTCP

1. Tissue specific radiosensitivity
2. Amount of volume of organ tissue exposed to radiation
3. Type of organ like serial or parallel

Some are treatment-related factors such as:

1. Dose fractionation schedule
2. Type of radiation (high LET or Low LET)
3. Dose rate
4. Use of radiosensitizers and radiprotectors
5. Combination therapy like surgery and chemotherapy
6. Type of Technique (e.g. 3D, IMRT, VMAT)

5Rs of Fractionated Radiotherapy

Repair

The dose delivery in fractionation allows normal healthy tissues time to repair and recover. Half time is a parameter which means time required for cell repair after radiation damage ($t_{1/2}$), and the value can be ranged from minutes to hours.

It is recommended to have at least 6 hour of interval between two fractions to provide sufficient time for repair of sub lethal damage. Normal tissue have better repair mechanism than tumor when there is a fractionation gap of 12 to 24 hours.

Some organs have slower rate of recovery such as spinal cord therefore there should be at least 8 hour time interval.

Repopulation

It is the intrinsic nature of tumor and healthy normal cells to keep on proliferate even after exposer of radiation. The time required to double the number of tumor cell is known as the “tumor doubling time,” denoted by Tp. This doubling time is less than two days for most of tumors and also known as repopulation time. Repopulation time varies during treatment such as in beginning it is slow, but it rapidly increases after the first fractional dose of treatment. This increase in repopulation rate is called “accelerated repopulation,” and the time taken for it to begin is termed the “kick-off time” denoted by T_k. Accelerated repopulation becomes even faster if the treatment is interrupted after the tumor doubling time for any reason. Accelerated repopulation starts after 28 days of treatment (some references says 21 days) for head and neck tumors.

Re-assortment or Redistribution

The radio-sensitivities of cells vary with the phase of the cell cycle. The most sensitive phases are M and G2, while the most resistant is the S phase. Cells in resistant phases of the cell cycle may progress into a sensitive phase during the next dose fraction. Therefore, the probability that tumor cells will be exposed to radiation during a sensitive phase increases, and this probability will continue to increase over the course of the treatment, and so the benefit of the radiation will also increase.
The durations of cell cycle phases: G1 = 1.5–14 h, S = 6–9 h, G2 = 1–5 h, M = 0.5–1 h
The most sensitive: M and G2
The most resistant: S

Reoxygenation

As the tumor volume increases through the proliferation of tumor cells, the vascularity of the tumor tissue becomes insufficient to meet its requirements, and hypoxic–necrotic regions begin to occur within the tumor tissue. Hypoxic cell are 2 to 3 times more radio-resistant than radiosensitive cells to radiation. During fractionation both normal tissue and tumor tissue gets oxygenated. Because of oxygenation tumor tissue becomes radiosensitive and die over a full course of radiotherapy where as normal tissue keeps on repairing from damage.

Intrinsic Radiosensitivity

Radiosensitivity (the fifth R of radiotherapy) is a concept that involves multiple components. Radiosensitivity may be affected by environmental conditions. The term “radiosensitivity” was first defined by Bergonie and Tribendau in 1907; they suggested that radiosensitivity was directly proportional to mitosis and inversely proportional to differentiation. Since radiosensitivity may be affected by external conditions, the term SF2 was introduced by Fertil in 1981.

Biological effective dose (BED)

It is the term introduced to assess and compare the biological effect of different fractionation schedules against conventional fractionation. It is represented by the following equation.(Fowler 2010)

$$BED = nd\,(1+d/(\alpha/\beta)) \quad \text{---------- (1)}$$

Where, n and d are the number of fractions and dose per fraction of fractionation schedule
α/β is a ratio of linear to quadratic component

The time corrected BED (TC BED) formula which is a modified form of BED formula with an overall time factor included is as given by

$$BED = nd\left(1+\frac{d}{\alpha/\beta}\right)-\frac{log_e 2}{\alpha Tp}(T-Tk) \quad \text{---------- (2)}$$

Where,
T is overall treatment time in days (with first day = Day 0, not Day 1)
Tk is onset time of kick-off time of repopulation in the tissue of interest
α is a radiosensitivity coefficient of non-repairable damage
Tp is a doubling time of head and neck cancer repopulating cells after Tk

The equivalent dose (EQD_2) at 2 Gy/fraction is the dose conversion formula when fractionation schedule varies from the conventional fractionation schedule. It can be defined by two different formulas as mentioned below.

$$EQD2 = Di\left(\frac{\frac{\alpha}{\beta}+di}{\frac{\alpha}{\beta}+2}\right) \quad \text{---------- (3)}$$

$$EQD2 = \frac{BED}{\left(1+\frac{2}{\alpha/\beta}\right)} \quad \text{---------- (4)}$$

Where, Di is the total dose and di is the dose per fraction of the reference fractionation schedule.

1.8 Radiobiological Models

Biological models started to appear in between 1980s and early 1990s when modern techniques began to evolve. During that period, the concept of dose volume histogram (DVH) introduced in RT treatment planning system. The DVH presented simplify form of 3D dose distributions in target and normal-tissue volumes. The potential use of DVHs to predict tumor control probability (TCP) and normal tissue complication probability (NTCP) was soon recognized, and biological models for TCP and NTCP began to appear in the literature.

A different types of dose-response or biological models for tumor and normal tissue are available in literature and can be categorized as mechanistic and phenomenological. The mechanistic models describe the underlying complex biological processes, whereas the phenomenological also called statistical models simply intend to fit the available data empirically. Mechanistic models are often considered preferable, as they may be more rigorous and scientifically sound. However, the underlying biological processes for most tumor and normal tissue responses are fairly complex and often are not fully understood, and it may not be feasible to accurately or completely describe these phenomena mathematically. It is not recommended to extrapolate model predictions from models beyond the realm within which the model and parameter values were evaluated and validated. Recently phenomenological models were introduced in the currently available Biological based TPS e.g. Monaco, Eclipse, Pinnacle and Raystation due to their simplicity in implementation.

Strandqvist model was developed by Magnus Strandqvist in the year 1944. In this model relationship of skin tolerance to radiation dose for a particular skin cancer treatment time is plotted using a logarithmic curve. The slope of this curve is constant and equal to 0.22. It was found that this slope value was valid for skin cancer, but Strandqvist observed that the slope was 0.33 for skin erythema. In short, this model assumed that the tolerable fraction dose related to the treatment time T as $T^{0.33}$.

Ellis model was developed by Ellis in the year 1966. Strandqvist model focused only total dose whereas Ellis model considered the dependence of the tolerable dose on the number of fractions and the overall treatment time. The dose obtained using Ellis model known as the nominal standard dose (NSD). Therefore, it is also known by alternative name as NSD model. The NSD is the dose required to damage maximum to tumor tissue and minimum tolerable dose to healthy normal tissues. It is presented by the following equation.

$D = \text{NSD} * N^{0.24} * \text{T}^{0.11}$

$\text{NSD} = \text{D} * N^{-0..24} * \text{T}^{-0.11}$

Where, D is total dose to skin surface, N is fractional dose & T is overall treatment time.

Orton–Ellis model is an upgraded form of the Ellis model. This model also called as the TDF (Time Dose Factor) model. It is presented by following equation.

$TDF = d^{1.538} * X^{-0.169} * 10^{-3}$

Where, d is number of fractions and X is a treatment time.

Linear–Quadratic Model (LQ Model)

In this model, developed by Douglas and Fowler in 1972 by in vitro observation, it is found that DNA damage follows linear quadratic relationship with radiation dose. According to LQ model cell killing have two components linear component (direct killing) and quadratic component (Indirect killing).

$$S = e^{-(\alpha D + \beta D^2)}$$

Single hit (α killing) is unrepairable damage and independent of dose rate.
Two hit kill (β killing) is a repairable damage and depends upon fractionation and dose rate.

α/β is the ratio of dose for which the death of acutely responding tissue is equal to the number of late responding tissue or the dose for which the linear and quadratic components.

In general for tumor or acutely responding tissue the α/β value is 10 Gy and for normal or late responding tissues the α/β value is 3 Gy.

There are the following applications of LQ model in Radiotherapy.

To formulate and compare equivalent fractionation regimens.
To calculate additional doses or perform gap correction when there is treatment gaps during radiotherapy.
To get information on acute and late responses of normal tissue and tumour tissue.
To design altered fractionation schedules.

EUD based TCP and NTCP models (Gay and Niemierko model)

Equivalent uniform dose (EUD) is the dose which represents that, if the dose is distributed uniformly throughout the organ or tissue can produce the same biological effect as of the dose distributed non-uniformly in the same organ or tissue.(Gay and Niemierko 2007; McGary, Grant, and Woo 2000)

$$EUD = \left\{\sum_{i=1}(v_i D_i^a)\right\}^{\frac{1}{a}}$$

Where, **a** is a tissue specific parameter and different for normal tissue and tumor tissue, and $\mathbf{V_i}$ is the volume representing the i^{th} fractional volume receiving dose **Di**.

Normal tissue complication probability can be calculated by the below formula.

$$\mathrm{NTCP} = \frac{1}{\left[1-\left(\frac{\mathrm{TD}_{50}}{\mathrm{EUD}}\right)^{4\Upsilon 50}\right]}$$

Where, TD_{50} is the dose representing 50% complication risk if uniformly distributed throughout the organ volume. Υ_{50} is a parameter represents the slope of the dose-response sigmoid curve and it has no unit.

Similarly, tumor control probability (TCP) can be calculated by the below formula.

$$\mathrm{TCP} = \frac{1}{\left[1-\left(\frac{\mathrm{TCD}_{50}}{\mathrm{EUD}}\right)^{4\Upsilon 50}\right]}$$

Where, TCD_{50} is the dose required to control 50% of the tumors when delivered homogeneously throughout the tumor of interest.

Zaider Minerbo TCP model

It is a TCP model based on the concept that birth and death is a stochastic process. According to this model TCP defined as "no clonogenic cells remain present within the tumor tissue at the time t after the beginning of radiotherapy treatment. It is presented by equation as below.(Zaider et al. n.d.)

$$TCP(t) = \left[1 - \frac{\left(S(t)e^{(b-d)t}\right)}{\left(1 + bS(t)e^{(b-d)t}\int_0^t \frac{dt'}{S(t')e^{(b-d)t\prime}}\right)}\right]n$$

Where,

S(t) is the survival probability when 'n' clonogenic cells present initially (at time t=0)

b is the birth rate and d is the death rate

$b=0.693/T_{pot}$

d/b represents cell loss factor and 't' refers to any time during or after the treatment.

The linear quadratic Poisson TCP model

The radiobiological model that most extensively used for describing dose response relation for tumor tissue is based on Poisson statistics.(Adamus-Górka et al. 2011; Karger 2006; Mavroidis 2002) The tumor control probability expressed as

$\mathrm{TCP} = \exp(-N\, p(D))$ ---------- (5)

Where, N is the number of clonogens or cells present initially before irradiation, and p(D) is the probability of cell survival fraction after receiving the dose D.

$p(D) = \exp(-\alpha D)$,

The equation (5) can be reformulated by including two parameters Υ_{50} and D_{50} describing normalized slope and dose at the point of 50% probability of control.

$$\boldsymbol{TCP = \left(\frac{1}{2}\right) e^{\left[2\gamma 50\left(1-\frac{D}{TCD50}\right)\right]} / ln2}$$

The Lyman-Kutcher-Burman (LKB) model

Lyman model describes uniformly irradiated partial volumes of organs with respect to complication probability. Therefore, it is required to reduce the non-uniform dose distribution to uniform dose distribution. This can be achieved by various mathematical averaging methods, e.g. to develop an effective volume (Veff) irradiated to a reference dose or an effective dose uniformly applied to the whole volume. The second method of applying an effective uniform dose to the entire volume in known as equivalent uniform dose (EUD). According to Lyman-Kutcher-Burman model, normal tissue complication probability can be calculated by the following mathematical formula (Adamus-Górka et al. 2011; Karger 2006; Moiseenko, Battista, and Van Dyk 2000).

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} exp\left[\frac{-t^2}{2}\right] . dt$$

$$Where, t = \frac{[D - TD50/5(v)]}{m.TD50/5(v)}$$

The model parameters are n, m, and TD_{50};
Where, n determines the magnitude of the volume effect and accounts for differences in tissue architecture; m measures the slope of the sigmoid curve represented by the integral of the normal distribution; and TD50 representing the uniform dose throughout the volume of organ that results in 50% complication risk.

Relative Seriality (RS) Model

In this model volume effect expressed as combination of serial and parallel organ functional subunits. The RS model derive partial organ volume irradiation responses from the response function of the whole organ volume. It is expressed by following equation (Mavroidis 2002).

$$P_I(D,V) = \left(1 - \prod_{i=1}^{M} \left(1 - P(D_i, V_{ref}\right)\right)^{\frac{1}{s}}$$

Where,

V/Vref is the fractional irradiated volume of an organ for which values of D50 and γ were calculated representing internal organization of organ.

S is the relative seriality parameter

Serial organs have small volume dependence whereas parallel organs have large volume dependence.

When s=1, it corresponds to serial structure with minimum volume dependence like spinal cord and esophagus.

When s=0, it corresponds to parallel structure with strong volume dependence like lung, liver and parotid glands.

The k Model

This model applied Poisson survival function and expressed by the equation.(Mavroidis 2002)

$$P(D,V) = exp\left\{-e^{e\gamma+kln\left(\frac{V}{V_{ref}}\right)-\left(\frac{D}{D_{50}}\right)(e\gamma-\ln ln2)}\right\}$$

This models decreased risk of causing injury when a smaller volume of tissue irradiated. The parameter k corresponds to volume effect for an organ and it is considered to be equal to one for uniformly irradiated tumors and considered negative for normal tissues.

Critical Element (CE) Model

Critical element model most suitable for serial type of normal tissues. When in the formulation of relative seriality model, setting the value of s equal to one. The equation transformed into the critical element model.(Karger 2006; Mavroidis 2002)

$$P(D,V) = 1 - \left(1 - P(D,V_{ref})\right)^{\frac{V}{Vref}}$$

The CE model based on the assumption that each element of an organ is equal and every element of an organ is critical. The responses of different elements cannot be correlated exactly. This means that if any element of an organ damages complication will be raise in whole organ.

Critical Volume Model

The critical volume model was developed by Niemierko in 1997. This model is used empirically for 3D treatment plans that involve calculating the equivalent uniform dose (EUD). This model is based on the hypothesis that clonogenic cells that have the same survival curves can be irradiated with same uniform dose. The α/β ratios, clonogenic cell number, dose, number of fractions, type of tissue and type of tumor, as well as the SF2 are fed into this formulation. It is expressed by the equation.(Adamus-Górka et al. 2011; Mavroidis 2002)

$$P = \sum_{t=M+1}^{N} \binom{N}{t} P_{FSU}^{t}(1 - P_{FSU})^{N-t}$$

Where,
N is the total number of functional subunits (FSU) in the organ.
M is the minimum number of FSU that can bring down failure when irradiated.
P_{FSU} is the effective complication probability for one FSU.

Parallel Architecture Model

This model descries the probability of damaging a subunit at a given biological equivalent dose. It is most suitable for organs that shows a large volume effect. It is expressed by logit expression as given below.(Adamus-Górka et al. 2011; Mavroidis 2002)

$$\boldsymbol{p(D) = \frac{1}{1+(D_{50}|D)^{k}}}$$

Where,

D_{50} represents the dose at which 50% of subunits of an organ gets damaged.

k is the slope parameter which determines the rate at which probability of damaging a subunit increase with dose.

p(D) is the increasing function of the number of functional subunits gets inactivated by radiation exposure.

2 Review of Literature

Ivo Beetz et al reported that when RB models applied in a specific treatment technique like 3D CRT, the outcome cannot be generalized or extrapolated to patient population treated with another technique such as IMRT or VMAT. Author investigated that the prediction powers of RB models for patient rated xerostomia and sticky saliva after 6 months completion of radiotherapy (RT). He concluded that the 3D CRT based model prediction is less valid for patients treated with modern technique IMRT or VMAT.(Beetz, Schilstra, Burlage, et al. 2012; Beetz, Schilstra, Van Luijk, et al. 2012).

Tsair Fwu Lee et al did a prospective study of 236 patients based on patient quality of life (QoL) HN 35 questionnaire form from EORTC guideline to predict incidence of moderate to severe patient reported xerostomia. The study included head and neck squamous cell carcinoma (HNSCC) 152 patients and 84 patients of nasopharyngeal carcinoma (NSC) treated with IMRT technique. Author exercised validation of QUANTEC dose constrained guidelines against QoL questionnaire datasets and found that QoL dataset validated the QUANTEC dose constrained criteria for parotid gland. According to author QUANTEC 20/20 Gy dose constraint suitable for clinical application in HNSCC and QUANTEC 25 Gy dose constraint justified for NPC patients.(Lee et al. 2014; Lee and Fang 2013)

Feng Ming et al discussed the toxicity prediction probability by physical models and various dosimetric dose descriptors for late radiation induced toxicity in late responding tissues for example parotid gland, heart, bladder, rectum and spinal cord. In his review article author draw attention towards LKB model, relative seriality model and critical element model that how prediction power analyses in different late responding organs. According to author NTCP correlates with simple dose volume parameter such as mean dose and V20, V30, V50 etc. Author suggested that application of biological models should be limited when treatment technique, fractionation endpoints are different from the original data (i.e. any type of extrapolation of an existing model to a different clinical scenario).(Kong et al. 2007)

V A Semeneko et al estimated model parameters of LKB model for radiation induced xerostomia and pneumonitis late toxicity. This study is based on measurement of saliva flow below 25% within six months after radiotherapy. The derived parameters for LKB models are m=0.41, TD_{50}=29.9 Gy when lung considered as a paired organ. In case of ipsilateral lung: m=0.35, TD_{50}=37.6 Gy assuming n=1.

For combined parotid gland, m=0.53, TD_{50}=31.4 Gy assuming n=1. The above mentioned parameters for both lung and parotid were estimated by maximum likelihood method for LKB model.(Semenenko and Li 2008)

Magdalena Adamas-Gorka et al compared seven different biological models critical volume model, relative seriality model, critical element model, parallel architecture model, weibull distribution model, inverse tumours and LKB model. The maximum likelihood statistical analysis tool used to fit the model to experimental data. Author reported that for white matter necrosis, the weibull and LKB model superior to other models. In case of vascular damage, RS model have better prediction power than critical volume, critical element, inverse tumour, parallel architecture models but all these four models presented similar results. Author suggested that biological model should predict the shape of dose response curve and it should consider the volume and fractionation effects (Adamus-Górka et al. 2011).

Gary Luxton et al claims to introduce a new formula for NTCP as a function of equivalent uniform dose(EUD). In this formula a single parameter (exponential function) used to calculate NTCP within accuracy 3% of LKB model. In this study author developed Lyman Probit model with Kutcher-Burman reduction algorithm for considering the case of inhomogeneous dose distribution (Luxton, Keall, and King 2008).

Megan E Daly et al tested LKB model prediction power to analyses the risk of myelopathy from stereotactic radiosurgery plans. This study included 24 patients of spinal hemoglioblastomas. The LKB model has shown good prediction complication probability for organs like rectum, liver and parotid and lung from non-uniform partial volume irradiation. Author used LKB parameters m=0.175, TD_{50}=66.5Gy and n=0.05 to calculate NTCP. LKB predicted thirteen complications out of 24 patients which overestimated the actual number of complication observed (observed=1) (Daly *et al.* 2012).

Molly M Mc Lulloch et al investigated LKB model for prediction of toxicity of duodenal organ in liver stereotactic body radiotherapy (SBRT) patients. Author analyses the differences between planned and accumulated dose based on NTCP models by comparing the LKB model based NTCP. The planned dose based NTCP overestimates the toxicity risks for duodenal at dosed below 20Gy and underestimates the toxicity risks for doses above 20Gy. Author recommended that NTCP model based prediction based on accumulated dose changes up to 16% than planned dose for total patient data of 30 patients (McCulloch *et al.* 2018).

Minna Wedenberg et al author perform validation of QUANTEC dose constraints for two biological models, Poisson model and LKB model. The data set from QUANTEC used to fit dose response curve of both models by bootstrap statistical analysis and maximum likelihood method. The study presented the value of biological model parameters indicated correlation non Gaussian distribution. For both data set LKB model preferred over the Poisson model (Wedenberg 2013).

G Narayansamy et al did dual institutional study to evaluate radiobiologically IMRT treatment of head and neck patient's clinical efficacy. The author employed LKB model for normal tissue and OAR and Poisson model for tumour tissue to calculate NTCP and TCP. The NTCP is predicted for parotid glands, larynx and esophagus by using histogram analysis research tool (HAIT) for the output the biological parameters used in the study are (For bilateral parotid m=0.18, TD_{50}=28.4 Gy assuming n=1, for esophagus m=0.36, TD_{50}=47 Gy assuming n=0.69, For larynx m=0.17, TD_{50}=70 Gy assuming n=0.08). As per Emami et al author found the correlation between severity of xerostomia and NTCP values were

significant as well as for dysphagia correlation was significant with respect to calculated NTCP (Narayanasamy *et al.* 2015).

I EI Naqa at al developed in 2006 DREES dose response explorer system. It is the open source software tool based on MATLAB coding to explore radiotherapy outcomes and calculate TCP and NTCP. DREES software provided applications of fitting analytical data of NTCP and TCP models, to estimate uncertainty in model parameters, performance assessment of univariate and multivariate analysis and graphical presentation to visualize TCP or NTCP prediction versus various models (El Naqa *et al.* 2006).

Ioannis Tsougos et al developed software named as dose response models in clinical radiotherapy (DORES). The software is developed in visual basic programming language and included 3 biological models LKB, RS and Parallel architecture model. The software required information of dose volume histogram, total prescribed dose and dose per fraction. There is no TCP model included in the software (Tsougos *et al.* 2009).

J UZAN et al. developed in house program written in C++ language and it accepts DVH file in excel format. The program included Poisson TCP model, LKB model and RS model for estimation of TCP and NTCP. Author validated his program outcome for various organs at institutional level (Uzan and Nahum 2012).

B Sanchez-Nieto is the first researcher who developed a tool or software to evaluate treatment plans based on radiobiological models. This software named as BIOPLAN developed in Microsoft visual basic version 3 and visual basic version 5 professional addition. This software provided Poisson model, LKB model and RS model for TCP and NTCP estimation. The software also provides plan comparison features. The BIOPLAN requires inputs of DVH files per structure in a simple ASCII format (Sanchez-Nieto and Nahum 2000).

Emami et al (1991) compiled tolerance dose values for uniform irradiation of 28 clinical structures based on literature data and personnel experience. Lyman *et al.* (1985) model is defined for uniform irradiation, as normal tissues are not uniformly irradiated in clinical practice therefore an effective volume method for DVH reduction proposed by Kutcher & Burman in 1989, which is now most commonly used. The combined formalism is now referred as the Lyman-Kutcher-Burman (LKB) model in literature. Burman *et al.* (1991) fit the tolerance dose data into a phenomenological NTCP model proposed by Lyman in 1985 (Emami *et al.* 1991).

Arun S oinam et al *(2011)* compared LKB model versus Niemerko model for NTCP and Niemerko versus poisons based model for TCP calculation. This comparison was mainly focused in view of ranking treatment plans. In his study it was found that Niemerko model failed to predict the same NTPC data of Emami et al. whereas LKB model predicted the same complication data. It was also found that LKB taking into account fractionation effect produced less NTCP as compared to LKB model without fractionation correction. Both poisson based & nierko model based for TCP calculation equally produced the same TCP of Okuneff et al data (Oinam *et al.* 2011).

Oscar Acosta (2013) ; The majority of RB models predicting toxicity based on DVH which lacks spatial accuracy, since they consider the organs as a homogeneous volume & therefore ignore intra-organ radiosensitivity. Author proposed the concept of 3D voxel base dose mapping which can reveal

relationships between local dose & toxicity, at least to some extent. RB models are not able to correlate the treatment outcome with the spatial dose distribution (Acosta *et al.* 2013).

Brad Warkentine et al developed in-house software module for TCP and NTCP estimation. Author compared various models based on software output (TCP & NTCP). The compared models were sigmoidal dose response (or LKB), critical volume (individual), critical volume (population) NTCP models and Poisson TCP and Zaider Minerbo LQ model. The author focused that plan evaluation based on physical parameters need additional support to quantify the output of competing plans therefore biological model based plan evaluation can provide aid in plan evaluation (Warkentin *et al.* 2007).

Hiram A Gay and Andrzej Niemierko provided a free MATLAB program in their research article for calculating TCP and NTCP. The program included EUD based TCP model and NTCP model. Authors provided step by step information how to use the program and recommended to validate model prior implementing in the clinical setting. The authors also provided model parameter dataset based on Emami et al data (Gay and Niemierko 2007).

Joe H Chang et al developed radiobiological tool called as RADBIOMOD for radiotherapy plan evaluation. This program is different from all previous program reported in literature because it is developed in Microsoft excel environment which is most commonly available with readers. The author included multiple TCP models such as modified Poisson and Zaider and Minerbo TCP models. NTCP models included LKB model and EUD model. This program can accept both cumulative and differential DVH input file in excel format. The author supplied with comprehensive dataset for TCP and NTCP model biological parameters. Author cross validated his program output with some other software available in literature (Chang *et al.* 2016).

3 Aims & Objectives

Aim of the study:

1 To develop a tool for plan evaluation based on radiobiological models.
2 To evaluate the clinical application of radiobiological (RB) models for the estimation of the incidence of radiation induced complications in a relatively large group of cancer patients.
3 To do validation of RB models outcome based on patient rated quality of life (QoL) instruments specifically designed for organ specific toxicity. These QoL instrument consist of set of disease specific questionnaire forms.

General Objectives:

1) To incorporate radiobiological (RB) models in general clinical practice for plan evaluation. Prepare a departmental protocol of plan evaluation based on RB model and physical dose volume parameters.
2) To compare the results of various RB models in terms of their prediction power as well as to test the accuracy of prediction power in terms of biological endpoints of organ of interest.
3) For the purpose of research, e.g while designing altered fractionation schedules (accelerated and hypofractionation). If Radiobiological models are tested and validated, it can support clinicians during designing different fractionation schedule in terms of toxicity assessment.

Specific objectives

1. To examine whether these models are reliable enough to be taken into account in the current clinical practice with the use of the modern radiotherapy techniques.
2. To evaluate the predictive strength of the Gay & Niemierko EUD, Poisson model and Lyman-Kutchar-Burman (LKB) models regarding the incidence of radiation induced toxicities in early and late responding tissues.
3. Furthermore, to illustrate statistical methods for examining whether certain published radiobiological parameters are compatible with a clinical treatment methodology and patient group characteristics.

4 Conclusion

The development of Radiobiological response models will be of great importance for the future improvements in radiotherapy treatment. As better and more accurate Radiobiological data for tumor and normal tissue is continuously being collected which can help for biological based plan evaluation and biological based optimization will become more trustworthy in order to implement clinically. So, tools that will use radiobiological data of different organs and that will judge how good a certain treatment plan qualitatively and quantitatively. On the other hand, these develop tools will be incorporated into system (TPS), which will be easy to be use by providing friendly interface. From the above analysis it is important to realize that treatment plan evaluation using both physical and biological criteria/indices can help medical physicist and radiation oncologist to overcome difficult clinical.

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