INTRODUCTION

In the first part of the last century, radiation therapy was considered an empirical, clinical discipline. This situation has changed considerably during the past 40 years. this change from an empirical and clinical discipline to a precise clinical science has been accompanied by innovations in physics and technology **(*Schlegel et al., 2006*).**

Within the last 2 decades, a number of new challenging radiation therapy modalities has come into the practice of radiation oncology. This includes:

1. Particle beam therapy.
2. Intraoperative radiotherapy.
3. 3DCRT.
4. Stereotactic radiotherapy and radiosurgery.
5. IMRT.
6. IGRT
7. Radioimmunoglobulins.

1- Particle Beam Therapy:

Charged-particle radiotherapy is an exciting contemporary area of radiotherapy clinical research. The majority of this work is being done with proton beams having essentially the same radiobiologic properties as conventional photon/electron radiation but allowing a much more precise control of the radiation dose distribution ***(Laramore et al., 2007).***

The advantages of proton therapy in terms of normal tissue effects should follow the reduction of tissue volumes exposed to low/ moderate dose: significant reductions in acute tissue effects are expected and experienced. For late reacting tissues, the predicted benefits are in the reduction of chronic low-grade symptoms and so improving the quality of life. For tumor control, dose escalation beyond what is achievable with X-ray therapy is possible. Also, some tumors not presently treated by X-rays can be treated by proton beam therapy instead of radical surgery ***(Jones, 2008).***

2- Intraoperative Radiotherapy (IORT):

IORT is now accepted as a locoregional treatment modality that produces local effects and contributes to treatment success by increasing local control without major treatment morbidity ***(Calvo et al., 2007)***

3- 3d Conformal Radiotherapy (3dCRT):

The rationale for conformal radiotherapy (CFRT) is straightforward to state. The goal is to achieve a tumoricidal high-dose volume which conforms to (i.e. wraps closely around) the planning target volume (PTV) whilst simultaneously the organs-at-risk (OARs) (which might lie tightly adjacent to the PTV) receive a dose sufficiently low as not to cause any complications ***(Webb et al., 2007)***

4- Streotactic Radiosurgery (SRS) and Radiotherapy:

Stereotactic radiotherapy and radiosurgery techniques are increasingly being used where improved accuracy is required for treating well-defined targets inside the head. Their improved methods of patient fixation, multimodality imaging, fiducial marker-based treatment planning, treatment setup, verification and delivery represent a significant step forward in the evolution of high-precision radiotherapy ***(Warrington et al., 2007).***

5- Intensity Modulated Radiation Therapy (IMRT):

IMRT is a powerful technique that provides new degrees of freedom in customizing the dose distribution for photon radiotherapy. With the development of computer-controlled treatment machines equipped with multileaf collimators, it is now possible to deliver these treatments reliably ***(Ping et al., 2004).***

6- Image Guided Radiotharapy (IGRT):

IGRT as presently used implies that a 3D imaging system is provided on the treatment machine, allowing accurate assessment of the beam setup in relation to the tumor before each individual fraction ***(Nabhum et al., 2007)***.

7- Radioimmunotherapy (RIT):

Antibody-based therapeutics are designed to counteract various evasion strategies. They release their antineoplastic potential in different ways: Some deliver the lethal hit directly to the tumor cell; others work indirectly through the initiation of secondary mechanisms, largely depending on the type of antibody employed ***(Reiner et al., 2007).***

8- **Many Other Modalities:** e.g. Image-based brachytherapy planning.

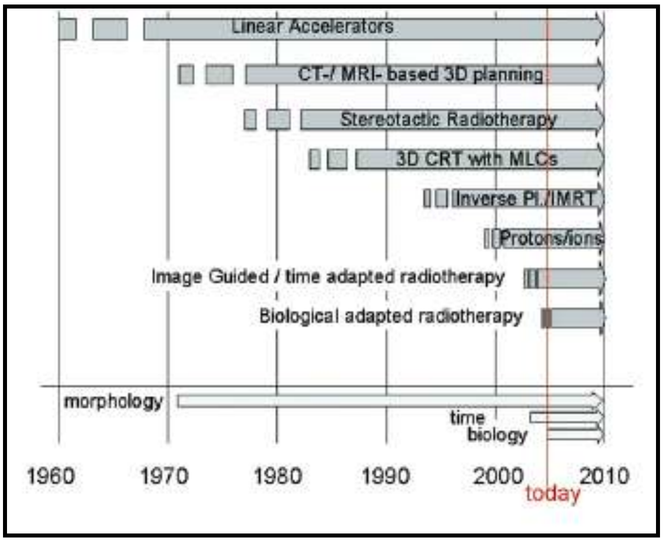

Fig. (1): Development of radiation therapy ***(Schlegel et al., 2006).***

AIM OF THE WORK

This work aims at studying the revolutionary impact of the new radiotherapy modalities on treatment outcome including the prognosis, survival and quality of life (QOL) of cancer patients taking into consideration the cost effectiveness of these modalities and their applicability in managing cancer patients in developing countries.

Chapter (1)

PARTICLE BEAM THERAPY

Particles currently used in radiation oncology are neutrons, which are uncharged and have high linear energy transfer (LET) characteristics; protons and alpha-particles, which are charged but have the same low LET radiobiologic properties as x-rays; and heavy charged particles such as carbon and neon ions, which have high LET properties, (although the electron is certainly a "particle" it is used routinely in clinical practice, has no extraordinary radiobiologic properties, and will not be considered here) ***(Laramore et al., 2007).***

Basic radiobiology related to particle therapy:

Radiobiologic properties of particle beam therapy:

1. Radiobiological effectiveness(RBE):

"It is the ratio of absorbed doses of 2 radiations required to produce the same biologic effect". This concept has arisen from observations that ionizing particulate radiations can be several times more effective per unit dose in producing biologic effects than X-rays or gamma rays ***(Castro et al., 2004).***

2. Oxygen enhancement ratio (OER):

"It is the ratio of the radiation dose required to produce a specific biologic effect under anoxic conditions to the dose required to produce the same effect under well-oxygenated conditions". The oxygen effect is important in the case of sparsely ionizing radiation such as X-rays (OER=2.5); is absent for densely ionizing radiation such as alpha particles (OER=1); and has an intermediate value for fast neutrons (OER=1.6) ***(Hall et al., 2006).***

3. Linaer energy transfer (LET):

"It is the rate of energy transferred by ionizing radiation along its path". Notably, the biologic effect of radiation is highly dependent on its LET and compared to standard forms of radiotherapy, protons and alpha-particles also are considered to be low LET particles. Fast neutrons are high LET particles. Heavy charged particles are also high LET particles. Therefore, the radiobiology of protons and alpha-particles is considered to be essentially the same as that of standard radiotherapy except at the very end of the Bragg peak, where the LET increases ***(Laramore et al., 2007).***

Radiobiologic advantages of high LET radiotherapy:

1. Decreased repair of radiation injury with High LET radiation which is evidenced by the absence of a shoulder on the cell survival dose response curve (see Fig.2)

2- For several cell types tested in vitro, the late S phase has been shown to be most resistant to low LET radiation. On the other hand, High LET radiation can overcome cell cycle –dependent resistance and is advantageous in fast growing tumors with a large proportion of cells in the S phase ***(Castro et al., 2004).***

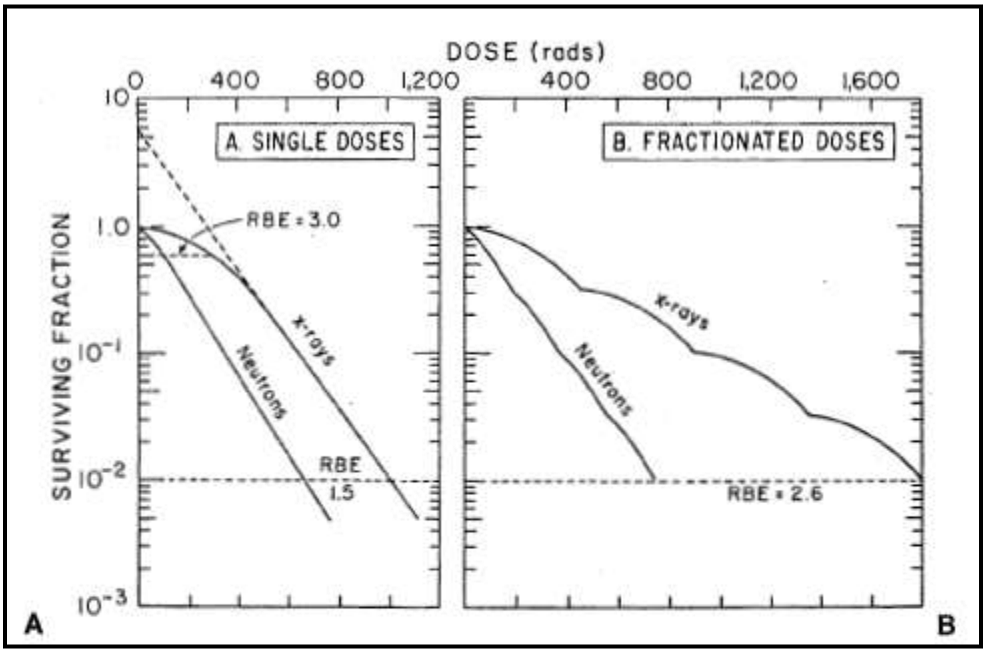

Fig. (2): Typical survival curves for mammalian cells exposed to x-rays and fast neutrons. **A:** single doses. **B:** fractionated doses ***(Hall et al., 2006).***

I- Proton therapy:

- ***Physical rationale of proton therapy:***

Protons have different dosimetric characteristics than photons used in conventional radiation therapy.

- *Depth dose characteristics of proton beam:*

After a short build up region, conventional radiation shows an exponentially decreasing energy deposition with increasing depth in tissue. In contrast, protons show an increasing energy deposition with penetration distance leading to a maximum (the Bragg peak effect) near the end of the range of the proton beam.

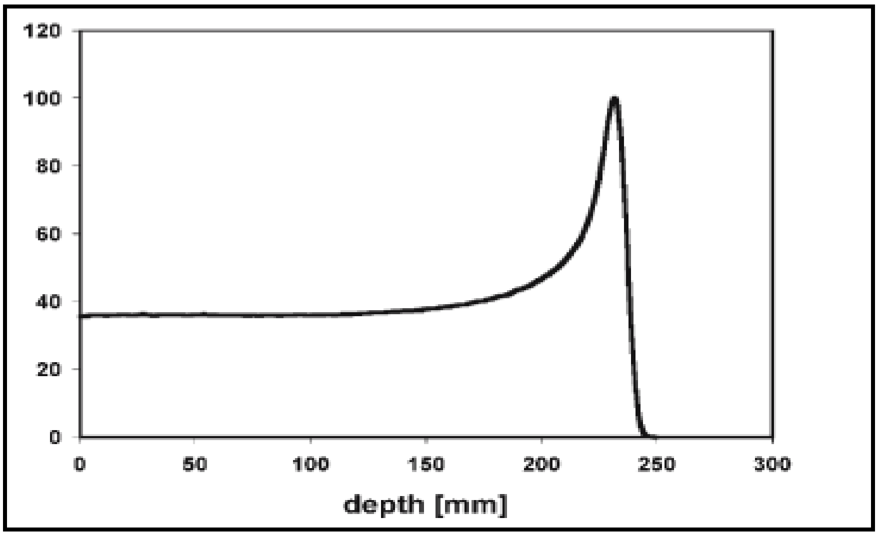

Fig. (3): Typical dose deposition of a proton beam ***(Bortfeld et al., 2006).***

This physical characteristic of protons causes an advantage of proton treatment over conventional radiation because the region of maximum energy deposition can be positioned within the target for each beam direction. This creates a highly conformal high dose region e.g. created by a spread out Bragg peak (SOBP), with the possibility of covering the tumor volume with high accuracy. At the same time this technique delivers lower doses to healthy tissue than conventional photon or electron techniques ***(Bortfeld et al., 2006***).

- *Penumbral characteristics of proton beam:*

In addition to the difference in the depth-dose characteristics, there is a slight difference when considering the lateral penumbra. For large depths the penumbra for proton beams is slightly wider than the one for photon beams by typically a few millimeters ***(Bortfeld et al., 2006***).

- ***Technical aspects of proton therapy:***

Proton beams for therapeutic application range in energy from 150 to 250 Mev. These beams can be produced by a cyclotron or a linear accelerator ***(Khan, 2003).***

Fig. (4): Isochronous cyclotron ***(Bortfeld et al., 2006).***

Doses are typically specified in terms of “cobalt gray equivalent” (CGE) where CGE equals the physical dose multiplied by RBE ***(Laramore et al., 2007).***

Large synchrotrons or cyclotrons are needed to accelerate protons and heavier ions to energy levels high enough for the treatment of deep-seated tumors. Patient -reproducible immobilization and positioning with high accuracy needs to be ensured. Precision head and body immobilization systems, stereotactic target localization, and image guidance with pretreatment correction of even small interfractional set-up deviations are commonly used at modern particle therapy centers. Adding a safety margin around the clinical target volume is not sufficient because movements of the target during the scanning process will also lead to dose inhomogeneities in the center of the tumor volume (***Tsujii et al., 2008).***

- ***Treatment outcome with proton therapy:***

1- Uveal Melanomas:

Uveal melanoma is the most common primary ocular malignancy and its management is controversial. Both prospective and retrospective studies have demonstrated no difference in survival rates comparing enucleation with irradiation. Moreover, selecting the optimal method of radiation treatment whether episcleral plaque or charged particle techniques is dependent on tumor and patient parameters as well as accessibility to specialized treatment facilities***(Char et al., 2004).***

Proton therapy was investigated at several proton facilities. After proton RT, 5-year local control rates in the range of 96% and eye retention rates between 75% and 92% could be observed .A target dose of 60 CGE in four fractions was delivered in most of the patients. Secondary enucleations due to radiation-induced complications such as glaucomas were reported in about 6% of the patients (***Tsujii et al., 2008).***

2- Optic Pathway Gliomas:

At Loma Linda University (LLU), seven children with optic pathway gliomas were treated with proton radiation therapy. At a median follow-up of 37 months, all patients were locally controlled. A reduction in tumor volume was seen in three patients and was stable in the other four. Visual acuity was stable in those who presented with useful vision. Proton plans were compared to photon plans for individual patients. With proton therapy radiation, there was a 47% reduction in the dose to the contralateral optic nerve. There was an 11% reduction in the dose to the chiasm and a 13% reduction in the dose to the pituitary gland. There was also a reduction in the dose to the temporal lobes and frontal lobes ***(Laramore et al., 2007).***

3- Skull base tumors:

A- Skull base chordomas and chondrosarcomas:

Chordomas and chondrosarcomas of the skull base are rare, indolent tumors with a natural history of locally invading their surroundings. Safe, maximal resection is the mainstay of treatment, followed by adjuvant radiation therapy. Even with multimodality therapy, local recurrence remains the most common failure pattern, translating to an adverse overall survival. Compared with other forms of radiation therapy, proton beam therapy has been used to increase the dose delivered to the tumor while elegantly sparing the dose to adjacent critical normal structures ***(Chang et al., 2008).***

As an example, ***Colli et al. (2001)*** published a retrospective analysis of nonrandomized treatment groups treated with protons or photons and found that chordoma patients treated with protons had a significantly higher local control probability. High local control rates in chordomas and chondrosarcomas of the skull base after proton RT have also been reported by others.

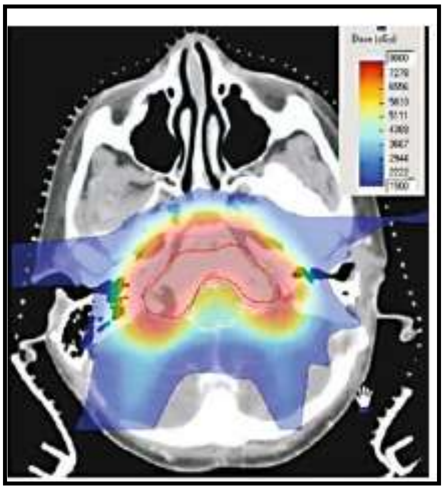

Fig. (5): Proton dose distribution for skull base chordomas ***(Bortfeld et al., 2006).***

B- Skull base meningioma:

Benign and malignant meningiomas of the skull base are also of interest for proton beam radiotherapy. Benign meningiomas constitute approximately 20% of all intracranial neoplasms. Although histologically benign, they may cause significant morbidity as a result of their frequent proximity to the optic structures. At the Massachusset general hospital (MGH) a series of 46 patients with recurrent and/or partially resected/biopsied tumors was treated with a combination of protons and photons to a median dose of 59.8 CGE with a recurrence-free survival at 10 years of 88%. However, in this patient group there were eight patients who developed a significant long-term morbidity as a result of the treatment and one patient died of a brainstem necrosis ***(Wenkel et al., 2000).***

4- Pediatric tumors:

Investigators at (PSI, Paul Scherrer Institute) looked at the potential influence of improved dose distribution with proton beams compared to conventional or IMRT x-ray beams on the incidence of treatment-induced secondary cancers in children. Two children, one with parameningeal rhabdomyosarcoma (RMS) and another with medulloblastoma, were used as models for this study. After defining the target and critical structures, treatment plans were calculated and optimized, four for the RMS case (conventional x-ray, IMRT, protons, and intensity modulated proton therapy) and three for the irradiation of the spinal axis in medulloblastoma (conventional x-ray, IMRT, protons). The secondary cancer incidence was estimated using a model by the International Commission on Radiologic Protection. This model allowed estimation of absolute risks of secondary cancer for each treatment plan based on dose-volume distributions for nontarget organs. Proton beams reduced the expected incidence of radiation-