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CURENT ADVANCES AND STRETEGIES FOR REDUCING THE SIDE EFFECTS OF RADIATION THERAPIES USED FOR VARIOUS TYPES OF CANCERS

Jagtar Singh[1]*and Manvi Kaur[1]

[1]Department of Biotechnology, Panjab University, Chandigarh, India
Telephone: +91-172-2534065; Fax No: +91-172-2541407;

E-mail: jagtar@rediffmail.com

ABSTRACT: Cancer originates from the abnormal expression or activation of positive regulators and functional suppression of negative regulators. The World Health Organization (WHO) estimates that 84 million people will die of cancer between 2005 and 2015 without intervention. Research suggests that one-third of cancer deaths can be avoided through prevention. Major cancer treatment modalities are surgery, radiation therapy and chemotherapy. Radiation therapy is an important cancer treatment method and is used for approximately 50% of all cancer patients with varying success. Therapy uses high-energy waves or particles to destroy cancer cells. It can be used basically for three main reasons: to achieve high radiation dose into tumors; minimizing dose into surrounding normal tissues; to avoid complications as far as possible. The recent advances in this treatment method have led to the improvement in cancer death statistics. It can also be combined with surgery or chemotherapy for better results. This review covers general applications, various side effects/agents and factors affecting to get rid of these effects and strategies to improve radiation therapy.

Keywords: Boron neutron capture therapy, computational tools, intensity modulated radiation therapy (IMRT), positron emission tomography (PET), proton beam radiation therapy, radiosensitivity

INTRODUCTION

Cancer is a leading cause of death worldwide and each year globally, 12.7 million people discover cancer in which 7.6 million people die from the disease. Up to 20% of cancer deaths in low- and middle-income countries and 9% of cancer deaths in high-income countries have been recorded. The World Health Organization (WHO) estimates that 84 million people will die of cancer between 2005 and 2015 without intervention and it will increase by nearly 80% by 2030 (www.cdc.gov, 2011). More than 30% of cancer deaths can be prevented by Radiation therapy (or radiotherapy) which is an important technique for decreasing tumor size. High energy waves are targeted at the cancerous growth. These waves cause damage within the cells, disrupt cellular processes, prevent accurate cell division, and ultimately cause the cells to die (NCI., 2002). Radiation therapy is one of the most technologically advanced fields in modern medicine. It is often given as the first line therapy to patients with many types of cancers, especially those with unresectable tumors. In comparison to other treatment modalities, radiotherapy provides many advantages including spatio-temporal flexibility in tumor-targeting, non-invasiveness and organ-preservation (Ahn and Brown, et. al., 2010). Radiation therapy research and outcome studies have recently become a focus of much attention because many sophisticated technologies are widely used in this treatment (Jani, et. al., 2007, McGivney and Perkel, 1998; Unpublished). Basic principle behind this therapy is that ionizing radiations can cause cell death or genetic change either directly or indirectly. The direct effect causes a alteration in the molecular structure of biologically important molecules, most likely DNA. The indirect action of radiation is that when it interacts with water molecules in the cells, resulting in the production of highly reactive and unstable free radicals or reactive oxygen species, which then immediately react with any biomolecules in the surrounding area, producing cellular damage (Fang, et. al., 2002) .

Origin and Progression of Radiation Therapy

Radiation therapy has been in use as a cancer treatment for more than 100 years, with its earliest roots traced from the discovery of x-rays in 1895 by Wilhelm Rontgen (www.web.archieve.org. 2008). It began to grow in the early 1900s mainly due to the work of Nobel Prize-winning scientist Marie Curie, who discovered the radioactive elements polonium and radium. This began a new era in medical treatment and research (www.web.archieve.org. 2008). Earlier medical linear accelerators have been used as sources of radiation. Godfrey Hounsfield's invention of computed tomography (CT) in 1971, three-dimensional planning has created a shift from 2-D to 3-D radiation delivery that allows physicians to more accurately determine the dose distribution using axial tomographic images of the patient's anatomy. Orthovoltage and cobalt units have largely been replaced by megavoltage linear accelerators which are useful for their penetrating energies and lack of physical radiation source. New imaging technologies, including magnetic resonance imaging (MRI) in the 1970s and positron emission tomography (PET) in the 1980s, has moved radiation therapy from 3-D conformal to intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT). These technologies allowed radiation oncologists to target tumors precisely, which have resulted in better treatment outcomes, more organ preservation and fewer side effects (www.rtanswers.com).

Reactions of Normal and Cancerous Tissue to Therapy

The response of tumors and normal tissues to radiation depends on their patterns of growth before and during therapy (Wang, 2000). Cell death is not sudden, but occurs when the cells try to divide but fail, this process is termed as abortive mitosis. Because of this, radiation damage manifest more quickly in tissues containing cells that are dividing rapidly (Cohen-Jonathan, et. al., 1999). Normal tissue compensates for the cells lost during radiation treatment by speeding up the division of remaining cells. Whereas tumor cells divide more slowly after radiation treatment, and the tumor may decrease in size. This depends on the balance between cell production and cell death. Carcinomas are an example of a type of cancer that often has high division rates. These types of cancer respond well to radiation therapy. Sometimes tumor may start to grow again after cessation of therapy, often slower than before.

Types of Cancer Treated by Radiation Therapy

Cancers that are treated with this therapy are prostate, skin, head and neck, throat, larynx, breast, brain, colo-rectal, lung, bone, leukemia, ovarian, and uterine. Cancers that are more responsive to radiation therapy alone are skin and lip, head and neck, breast , cervical and endometrium, prostate, Hodgkin's disease and local extranodal lymphoma, seminoma of testis and dysgerminoma of ovary, medulloblastoma, pineal germinoma, and ependymoma (Wang, 2000), retinoblastoma, choroidal melanoma. On the other hand tumors with limited response to radiation therapy and can be treated with combined therapies are Wilms tumor, Rhabdomyosarcoma, colorectal cancer, soft tissue carcinoma, embryonal carcinoma of testis. Many other malignant cancers are not curable with radiation because they are difficult to detect early enough and/or they have a much higher growth rate (Wang, 2000).

Applications of Radiation Therapy

Radiation therapy has many applications which are discussed below **(Table 1)**.

Types of radiation therapy

Traditional Radiation Therapy

In traditional radiation therapy, treatment planning is based on planar radiography with the help of a simulator. A conventional simulator is a diagnostic machine having some components of a radiation therapy linear accelerator. Treatment location is judged from physical examination, imaging and surgical reports. Radiation beam direction and shapes are then selected with the help of bony landmarks. These are usually based on established beam arrangement techniques for the specific cancer type. There are limitations with this planning system. There is very little available anatomy other than bony anatomy on the radiograph to design treatment portals. The lack of three dimensional information of target and real volume of normal tissue may result in incomplete tumour volume coverage or excessive irradiation of normal tissue. Furthermore, assessment of dosimetry is usually based on a single plane, conventionally the mid-plane. The failure of dose computation throughout the target volume may lead to inability to identify the accurate dose in homogeneities in target volume due to differing body contour and organ composition (Ching, 2002).

Table1. Applications of radiation therapy.

Applications	Role	Examples
Patients medically unfit for surgery	In comparison with surgery radiation offers improved or equivalent tumor control with less morbidity Both require an individualized assessment and discussion of the patient's condition and preferences. Radiation and surgery are often combined during treatment for larger tumors(Wang, 2000) Cardiac, pulmonary, or other chronic disease are not suitable for surgery, but can be treated with radiation therapy	Anal cancer, head and neck cancer (e.g., (laryngeal, Oropharyngeal (Gerber and Chan, 2008) Cervical and prostate cancers, acoustic neuroma, meningioma) Endometrial and lung cancers
Anatomically challenging cancers	Close proximity of tumor growth to critical structures like blood vessels precludes surgery, but not radiation therapy (Gerber and Chan, 2008)	Bladder, pancreatic, and skin cancers
Palliative RT (Alleviate or reduce symptoms	Relieves bony pain (Gerber and Chan, 2008) Stops or limits bleeding Relieves luminal (airway, biliary, gastrointestinal) obstruction	Breast, lung, prostate, renal, other cancers that are metastatic to bone Gastrointestinal, genitourinary, and lung cancers Lung and colon cancers

Modern radiation therapy

It has moved towards specialized planning that involves three-dimensional reconstructions of images and computer optimization algorithms. Types of external beam radiation therapy are discussed below **(Table 2)** (Gerber and Chan, 2008).

Internal radiation therapy/ Brachytherapy

The radiation source is permanently or temporarily placed within the patient or near the target tumor and it is therefore of following two types (Gerber and Chan, 2008):

Temporary brachytherapy implant

In this type a radiation source is placed within or near the tumor target and is subsequently removed. Catheters (smaller) or applicators (larger) are placed in body cavities or tissues and the radiation source is placed within these devices. The patient may be hospitalized in a private room during treatment or the patient may undergo outpatient treatment for up to several weeks; radiation source is removed between treatments. Examples are cervical cancer, sarcoma, vaginal cancer, oral cavity cancers.

Permanent brachytherapy implant

It involves a low-dose rate (i.e., long half-life) radiation source which is placed within or near the tumor target. Radioactive seed implants are placed into target tissue through a catheter under local or general anesthesia. Initially, the patient should limit social contacts after placement for up to one month. Implants are permanent, but radiation dissipates within six months. Example is prostate cancer.

Radioimmunotherapy/Systemic radiation therapy

It is a targeted cancer treatment having role to increase the efficacy of monoclonal antibodies. Radioisotope is coupled to a monoclonal antibody resulting in tumor-specific target agent (Sharkey, et. al., 2005). Radioisotope is administered intravenously or orally; inpatient or outpatient, depending on the specific treatment. Radiation precautions are required for one week after treatment (Gerber and Chan, 2008).

Table 2. External beam radiation therapy.

Types	Description	Uses	Administration
Three-dimensional conformal radiation therapy	Either CT or MRI is used to target tumors while minimizing radiation exposure to healthy tissues	Most solid tumors	Daily treatment of as short as one to two minutes each are administered Monday through Friday for two to seven weeks. Area may be marked with freckle-size tattoos or colored ink marks to guide the radiation beam. A mesh face mask or body mold may be used to immobilize the patient.
Four-dimensional radiation therapy (Image guided radiation therapy)	Computer-assisted tracking or gating of CT images of moving targets	Tumors susceptible to movement, most commonly in the lung, liver, pancreas, or breast	Similar to three-dimensional conformal therapy and for gating patients may be asked to hold their breath while the radiation beam is activated
Intensity-modulated radiation therapy	The radiation beam is divided into components ("beamlets"), which permits sparing of normal tissues	Tumors surrounding or adjacent to normal critical structures, most commonly head and neck or prostate cancers	Similar to three-dimensional conformal therapy, although individual treatments may last more than thirty minutes
Stereotactic radiosurgery (e.g., Gamma Knife)	Multiple radiation beams converge on target tumor, delivering high-dose radiation to the tumor, but little to surrounding tissues	Intracranial lesions, such as brain metastases, meningiomas, acoustic neuromas, arteriovenous malformations, and trigeminal neuralgia	Single treatment is given. A positioning frame is used to ensure proper patient positioning and immobility. Treatment lasts forty five to sixty minutes
Stereotactic body radiation therapy (e.g., Cyberknife)	High-dose radiation delivered using robotic guidance	Treatment of spine tumors, localized lung cancer, and other tumors in patients who are not candidates for surgery.	Most commonly delivered as three to five fractions. A robotic arm containing the radiation source rotates around the patient to deliver radiation from multiple positions and each treatment lasts up to two hours. For positioning fiducial markers or rigid bony frame may be placed before hand
Proton beam radiation therapy	Deliver higher doses of shaped beams of radiation directly into the tumor while minimizing the dose to normal tissues which leads to reduced side-effects and improved survival rates (Suit, 2003). Creates a highly conformal high dose region, e.g., created by a spread-out Bragg peak (SOBP), than conventional photon or electron technique (Paganetti and Bortfeld, 2005)	Tumors close to the skull base, spinal cord and in pediatric patient (Laramore, 2009)	Newer technologies, such as laser-accelerated proton therapy, could replace the cyclotron facilities for proton therapy, which will be a compact, cost-effective way to deliver energy-and intensity-modulated proton therapy (EIMPT) (Ma and Maughan, 2006)

Trastuzumab (Herceptin) is a humanized IgG1 monoclonal antibody against HER2 and is approved by the US Food and Drug Administration for the treatment of metastatic breast cancer (Metro, et. al., 2008). The cell surface protein human epidermal growth factor receptor 2 (HER2) is a target antigen that have important function in cell proliferation and is usually known to be overexpressed in cancers of the breast (20–30%) especially (Albanell, et. al., 2003; Natali, et. al., 1990; Metro, et. al., 2008), 177Lu-DOTA.

Herceptin, a new radiopharmaceutical in the radioimmunotherapy of breast cancer is very important finding for patients who cannot tolerate the therapeutic dosage of Herceptin or who have heart problems and could be further evaluated (Rasaneh, et. al., 2010). Some of the more US Food and Drug Administration (FDA) approved monoclonal antibodies for cancer radioimmunotherapy are rituximab, gemtuzumab ozogamicin, alemtuzumab, and ibritumomab tiuxetan. Rituximab is a genetically engineered chimeric anti-CD20 mAb, having mouse variable and human constant regions (Mclaughlin, et. al., 1998). Beta-emitting 90Y ibritumomab tiuxetan (*Zevalin*) and I-131 tositumomab (*Bexxar*) have shown clinical efficacy in relapsed B-cell non-Hodgkin's lymphomas with acceptable toxicities (Krasner and Joyce, 2001; Spies, 2004; Tobinai, 2002; Verel, et. al., 2005; Wiseman, et. al., 2003; Kaminski, et. al., 2000). 3p-C-NETA instantly formed a very stable complex with (90)Y or (177)Lu. 3p-C-NETA is an excellent bifunctional ligand for RIT (Chong, et. al., 2011). PR81 is a monoclonal antibody that has high affinity to MUC1, which is over expressed on breast and other tumors. Study shows that this new radiopharmaceutical may be considered as a promising candidate as a radioimmunotherapeutical agent for breast cancer (Mohammadnejad, et. al., 2010). The mAb 3/F11 was (177) Lu labelled using 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) as chelating agent [(177)Lu-DOTA-3/F11] may be a suitable radioimmunotherapeutic agent for the treatment of prostate cancer (Behe, et. al., 2011). Alpha particle and Auger electron emitters show promise as future radioimmunotherapy agents but are mostly still in pre-clinical stages (Lin and Iagaru, 2010).

Boron neutron capture therapy (BNCT)

BNCT is a highly selective treatment modality that can target the tumor without causing excessive radiation damage to the normal tissues (Barth and Joensuu, 2007). BNCT is based on the principle that non-radioactive isotope 10B atoms that have absorbed low energy (<0.5 eV) neutrons (thermal neutrons) splits into alpha (4He) particles and recoiled lithium nuclei (7Li), [10B(neutron, alpha) 7Li] (Coderre and Morris, 1999). These particles deposit large amounts of energy along their very short paths (<10 lm). Patients are irradiated with thermal neutrons after administration of 10B-containing agents, which have the characteristics of accumulating selectively in tumors. If a reasonable number of 10B atoms accumulate in tumor cells with a large gradient of 10B concentration between the tumor cells and normal tissue cells, subsequent thermal neutron irradiation exhibits selective killing of tumor cells without harming normal tissue cells. Therefore, BNCT has the chance to deliver a curative dose to tumors diffusely spreading in radiosensitive organs, such as lung or liver, without causing harmful side effects (Suzuki, et. al., 2006; Suzuki, et. al., 2007).

Factors affecting radiation therapy

Radiation Dose

The radiation dose is a measure of the energy absorbed in a material, e.g. in tissue. However, the biological effect of radiation is not just dependent on how much energy is deposited in the cells, but also on the way in which it is deposited (Paul Scherrer Institute).The energy dose is measured in Gray (Gy). It is the basic unit of radiation. Absorbed dose is the amount of energy (joules) absorbed per unit mass (kg). This unit, gray (Gy), has replaced the unit of rad used in the past i.e. 100 rads = 1 Gy; 1 rad = 1 cGy. A typical therapy dose would be about 60 to 70 Gy to destroy a tumor. Usually it is delivered in individual fractional doses on several consecutive days of radiotherapy (about 30-40 fractional doses in total) (Gazda and Coia, 2004).

Timings of Radiation therapy

For most types of external-beam radiation therapy usually patients have to travel to the hospital or an outpatient facility up to 5 days a week for several weeks. One dose (a single fraction) of the total planned dose of radiation is given each day. Occasionally, two treatments per day are given. Most types of external-beam radiation therapy are given in once-daily fractions to minimize the damage to normal tissue. Also to increase the chances that cancer cells are exposed to radiation at the points in the cell cycle when they are most vulnerable to DNA damage (Lawrence, et. al., 2008; Connell and Hellman, 2009) .Other fractionation schedules that are helpful in radiation therapy (Lawrence, et. al., 2008) , includes:

- Accelerated fractionation—treatment given in larger daily or weekly doses to reduce the number of weeks of treatment.
- Hyperfractionation—smaller doses of radiation given more than once a day.
- Hypofractionation—larger doses given once a day or less often to reduce the number of treatments.

The timing of radiation therapy depends on the type of cancer being treated and the goal of treatment (cure or palliation). A patient may receive radiation therapy before, during, or after surgery in the following ways:

Neoadjuvant radiation therapy

Radiation therapy given before surgery is called pre-operative or neoadjuvant radiation. Neoadjuvant radiation may be given to shrink a tumor so it can be removed by surgery and less likely to return after surgery (Lawrence, et. al., 2008). Neoadjuvant chemotherapy has advantages over adjuvant chemotherapy, including improved patient compliance, a smaller primary tumor, and pathologic evaluation of treatment efficacy. Examples are esophageal and rectal cancers (Gerber and Chan, 2008).

Intraoperative radiation therapy

Radiation therapy given during surgery is called intraoperative radiation therapy (IORT). IORT can be external-beam radiation therapy (with photons or electrons) or brachytherapy. IORT is sometimes used when normal structures are too close to a tumor to allow the use of external-beam radiation therapy.

Adjuvant radiation therapy

Radiation therapy given after surgery is called post-operative or adjuvant radiation therapy. Radiation therapy given after some types of complicated surgery (especially in the abdomen or pelvis) may produce too many side effects; therefore, it may be safer if given before surgery in these cases (Lawrence, et. al., 2008). Examples are breast, endometrial, gastric, pancreatic, rectal cancers, malignant glioma, sarcoma, seminoma (Gerber and Chan, 2008).

The combination of chemotherapy and radiation therapy given at the same time is sometimes called chemoradiation or radiochemotherapy. For some types of cancer, this combination may kill more cancer cells (increasing the likelihood of a cure), but it can also cause more side effects (Lawrence, et. al., 2008; Connell and Hellman, 2009).

Radiosensitivity

Radiosensitivity i.e. cancer's sensitivity to radiation therapy has been considered one of the most important radiobiological factors in determining how tumors respond to radiotherapy. Radiation therapy can damage DNA and also lead to accumulation of damage in cancer cells, causing them to die or reproduce more slowly. Therefore, measuring cell proliferation ability is an important indication of radiosensitivity (Vermund and Gollin, 1968). Recently, Real-Time Cell Electronic Sensor (RT-CES) assay can replace the clonogenic assay and has been reported to have role in measurement of the impact of radiation on cancer cell proliferation (Wang, et. al., 2009), methodological details, assay validity, and interpretation of data. The RT-CES assay also fulfilled the requirements of the radiotherapy sensitivity assay. Principle behind RT-CES system is to monitor the changes in electrode impedance induced by the interactions between test cells and electrodes (Xing, 2006; Xing, 2005). The more cells attached to the sensor, the higher the impedance that could be picked up by RT-CES. So, dynamic data generated by the RT-CES can truly is the true reflection of cell proliferation (Roa, et. al., 2011). Followings are the examples of radiosensitizers:

1. 5-Iododeoxyuridine (IUdR) and caffeine are important radiosensitizers with different mechanisms of interaction with ionizing radiation (IR). IUdR is a thymidine analogue sequentially phosphorylated to 5-iodo-dUTP and is inserted into DNA in competition with TTP. IUdR-DNA insertion subsequently alters cellular radiosensitivity by enhancing IR induced DNA damage (Kinsella, 1996).
2. In vitro investigation confirmed that nedaplatin with irradiation is highly effective for cervical cancer (Tanaka, et. al, 2007).

3. The radiosensitizing nature of betulinic acid on sequential irradiation has been demonstrated in HNSCC cell lines (Eder-Czembirek, et. al, 2010).
4. UROD (Uroporphyrinogen Decarboxylase) is a useful tumor-selective sensitizer for both radiation and chemotherapy, with potential importance to many human malignancies (Ito, et. al., 2011).

Treatment machines

Linear accelerators

By means of a linear accelerator, high-energy radiation is delivered to tumors. A beam of electrons is generated and accelerated through a waveguide that increases their energy to the keV to MeV range. These electrons strike a tungsten target and produce x-rays. X-rays generated in the 10–30 keV range are known as grenz rays, whereas the energy range for superficial units is about 30–125 keV (Dong, et. al., 2006).

Orthovoltage units

Orthovoltage units generate x-rays from 125–500 keV and continue to be used today to treat superficial lesions. They were practically the only machines treating skin lesions before the recent emergence of electron therapy (Dong, et. al., 2006). The maximum dose from any of these low-energy units is found on the surface of patients; thus, skin becomes the dose-limiting structure when treating patients at these energies. The depth at which the dose is 50% of the maximum is about 7 cm.

Megavoltage units

The megavoltage linear accelerator has been the standard radiotherapy equipment for the past 20-30 years. Its production of x-rays is identical to that of lower-energy machines. However, the energy range of megavoltage units is quite broad (4-20 MeV) (Dong, et. al., 2006). The depth of the maximum dose in this energy range is 1.5-3.5 cm. The dose to the skin is about 30-40% of the maximum dose. Most megavoltage units today also have electron-beam capabilities, usually in the energy range of about 5-20 MeV. In order to produce an electron beam, the tungsten target is moved away from the path of the beam. Unlike that of photons, the electron skin dose is quite high, about 80-95% of the maximum dose. Optimal treatment planning is obtained with a relatively constant intensity across the width of the beam. This process is accomplished by placing a flattening filter below the target. In order for the radiation beam to conform to a certain size, high atomic number collimators are installed in the machine. They can vary the field size from 4 × 4 cm to 40 × 40 cm at a distance of 100 cm from the target, which is the distance at which most treatments are performed.

Imaging techniques

Computed Tomography (CT)

It gives three-dimensional anatomic image of the internals of an object (Dong, et. al., 2006; Kistler, et. al., 2006; Noller, et. al., 2006; Dong, et. al., 2006). The CT image set is transferred to the RTP system for treatment planning. Firstly, tumor lesion can be clearly detected in the image and it is called gross target volume (GTV). Tumor cells are often dispersed around GTV and these are not visible in the image. Based on physiologic information and clinical experience, a clinical margin is added to GTV to make so called clinical target volume (CTV). Lastly addition of planning margin is made for uncertainties that can occur through the whole process of radiotherapy. This is called planning target volume (PTV) and it is the volume supposed to be irradiated to prescribed dose (ICRU 1993; ICRU 1999). Cone-beam CT (CBCT) is another novel form of 3D in-room imaging that can minimize patient positioning inaccuracies. CBCT is a scaled-down version of a CT scanner that is built into the treatment machine. Images taken from a CBCT at the time of treatment can be overlaid on the original planning CT, and specialized software can be used to detect positioning errors with millimeter accuracy (Kim and Suh, 2006).

Magnetic Resonant Image (MRI)

MRI also provides three-dimensional image of the internals of an object. It is based on the principles of nuclear magnetic resonance (NMR). Strong magnetic fields and non-ionizing radiation in the radio frequency (RF) range are applied in MRI (Bushberg, et. al., 2002).

Thus considered to be harmless to the patient while CT involves radiation dose that may increase the chance of cancer incidence. But sometimes patients may feel the symptoms of vomiting and nausea when magnetic field is too strong. However, MRI is inferior to CT in spatial resolution that is the ability to distinguish two structures in small distance from each other. Therefore, MRI image set is not directly used in radiation therapy. Instead, it is combined with CT image set and useful information (i.e., high contrast tumor lesion that is clearly seen in MRI image set but not in CT image set) is transferred to CT image set (Kessler, et. al., 1991; Pelizzari, et. al., 1989).

Positron emission tomography (PET)

The most commonly used material in PET imaging is 18F-Fluordeoxyglucose (FDG). It is not an easy task to use PET-only image set for radiation treatment planning due to the lack of detail information on patient anatomy that is necessary for accurate treatments. Also there is no simple method to fuse PET data with a radiation treatment planning CT. Recent development of PET-CT overcomes these limitations (Heron, et. al., 2006). This integrated system gets over the limitations of manual or software fusion of independent PET and CT images, resulting in a more robust set of images (Kim, et. al., 2006).

Dynamic Imaging - Four Dimensional (4-D) Imaging

The management of patient motion; especially the respiration motion has been an important issue in radiation therapy. In dynamic imaging, also called 4-D imaging, respiration signal, which is assumed to have a strong correlation with internal anatomy motion, is continuously obtained while the patient is imaged. Then the acquired image data are sorted based on phase of respiration cycle and a complete set of image is reconstructed for any given phase. Phased image sets show more clear quality of image because the effect of motion is eliminated (Kim, et. al., 2006).

Computational tools

Many computational tools have been designed and developed for radiotherapy research and outcome analysis for example.

CERR (Computational environment for radiotherapy research)

It has four important needs in treatment planning research: (a) offers a convenient and powerful software environment to develop and prototype treatment planning concepts, (b) work as a software integration environment to combine treatment planning software written in multiple languages (MATLAB, FORTRAN, C/C++, JAVA, etc.), together with treatment plan information (c) come up with the ability to extract treatment plans from disparate planning systems using the widely available AAPM/RTOG archiving mechanism, and (d) offers a convenient and powerful tool for sharing and reproducing treatment planning research results (Deasy, et. al., 2003).

DICOM (Digital Imaging and Communication in Medicine based toolbox)

It is developed for the evaluation and verification of radiotherapy treatment plans (Spezi, et. al., 2002).

MMCTP (McGill Monte Carlo treatment planning)

This software package is designed for the research development of Monte Carlo (MC) and patient-specific treatment planning (Alexander, et. al. 2007).

EUCLID (An outcome analysis tool)

This tool builds a mathematical model to predict an outcome probability of radiotherapy based on a large number of clinical, biological, physiological and dosimetric factors (Gayou, et. al., 2007).

BIOPLAN (BiOlogical evaluation of PLANs)

It has been developed as PC-based user-friendly software that allows the user to evaluate a treatment plan from the (more objective) point of view of the biological response of the irradiated tissues, and at the same time, provides flexibility in the use of models and parameters (Sanchez- Nieto, et. al., 2000).

TCP-NTCP CALC (Tumor control probability and normal tissue complication probability Calculation)

Convenient computational module has been developed for estimating the TCP and the NTCP arising from a dose distribution calculated by a treatment planning system, and characterized by differential (frequency) dose-volume histograms (DDVHs) (Warkentin, et. al., 2004).

SABER (A new software tool)

This software system provides biological plan evaluation with a novel combination of features. It incorporates hyper-radiosensitivity using the induced-repair model and applies the new concept of dose convolution filter (DCF) to simulate dose wash-out effects due to cell migration, bystander effect, and/or tissue motion during treatment. It incorporates both spatial and biological information into the treatment planning process (Zhoa, et. al., 2010).

Side effects of radiation therapy

One drawback of radiotherapy is that radiation is not specific to cancerous cells and may damage healthy cells as well. Radiation therapy can cause both early (acute) and late (chronic) side effects (**Table 3**). Acute side effects occur during treatment, and chronic side effects occur months or even years after treatment ends (Lawrence, et. al., 2008). These side effects depend on the area of the body being treated, the dose given per day, the total dose given, the patient's general medical condition, and other treatments given at the same time.

Table 3. Tissue specific side effects of radiation therapy.

Tissues	Side effects	References
Skin	Erythema, Alopecia, Dry or moist Desquamation, Fibrosis, Contraction, Non-healing ulcer, Leukotrichia	(Farrelly and Margarel, 2003)
Oral cavity	Mucositis, Salivation, Halitosis, Bone necrosis, Periodontal disease, Xerostomia	
Nasal cavity	Rhinitis, Nasal discharge, Chronic discharge	
Eye	Keratitis/corneal ulcer, Conjunctivitis, Blepharitis, Uveitis, Cataract, Keratoconjuntivitis, sicca	
Cervical region	Pharyngitis, Esophagitis, Tracheitis, Hypothyroidism, Esophageal Stricture	
Intestinal tract	Colitis, Enteritis, Stricture	
Foot	Pad slough, Lost or deformed nails, Lost or deformed nails	
Spinal cord	Inflammation, Edema, Myelopathy, Infarction	
Brain	Inflammation, Edema, Encephalopathy, Infarction, Hemorrhage	
Kidney	Nephritis, Fibrosis, Decreased function	
Bladder	Cystitis, Fibrosis	
Hair	Alopecia	(Gunderson and Tepper, 2007; www.cancer.gov. 2008; Hensley, et. al., 1999; Keefe, et. al., 2007)
Lungs	Pneumonitis, Loss of lung capacity, Fibrosis	
Heart	Pericarditis, Coronary artery disease	
Stomach	Nausea, Vomiting, Ulceration	
Vagina	Vaginal dryness and irritation,Vaginal stenosis or stricture	
Ovaries, Testis	Infertility	
Prostrate	Urinary Obstruction, Impotence	
Bone marrow	Myelosuppression	
Joints	Scar tissue accumulation, loss of motion	
Lymph node	Lymphedema	

Emergence of second cancer after radiation exposure depends on the body part that was treated. For example, girls treated with radiation to the chest for Hodgkin lymphoma have an increased risk of developing breast cancer later in life. The lifetime risk of a second cancer is highest in children or adolescents (Travis, et. al., 2008). Chemotherapy drugs, genetic risk factors, and lifestyle factors can also enhance the risk of late side effects. Agents to get rid of side-effects of radiation therapy are given below **(Table 4).**

Table 4. List of agents reducing the side-effects of radiation therapy.

Agents reducing side-effects of radiation therapy	
Biafine®	Water-based emulsion, generally prescribed at the onset of radiation dermatitis or at the beginning of radiotherapy (Bostrom, et. al., 2001; Schmuth, et. al., 2002).
Calendula	Found significantly better than Biafine® in preventing mild-to-severe acute radiation dermatitis in breast cancer patients, as well as in providing pain relief (Pommier, et. al., 2004). Patients are prescribed to use it at least twice a day at the onset of radiation therapy and continued this until completion of treatment.
Aloe vera	Gel added to soap has a protective effect for patients who received higher cumulative radiation doses as it prolongs the time to detectable skin damage from three to five weeks (Olsen, et. al. 2001).
N-acetylcysteine	The application of gauze soaked in 10 percent N-acetylcysteine for 15 minutes before radiation therapy was associated with more rapid healing of skin reactions and less use of pain relievers compared to an untreated control group (Kim, et. al., 1983).
Unsaturated essential fatty acids (EFAs)	EFAs containing both gamma-linolenic acid (GLA) and eicosapentaenoic acid (EPA) to modify radiation-induced skin reactions were studied in pigs (Hopewell, et. al., 1994).
Pentoxifylline	Safe and effective in preventing radiation necrosis, particularly in the prevention of radiation-induced lung toxicity (Ozturk, et. al., 2004).
Antibiotics	These are beneficial in preventing mucositis (Donnelly, et. al., 2003; Okuno, et. al., 1997).
Honey	Reduces the symptoms of mucositis (Biswal, et. al., 2003).
Flower *Matrichariachamomile*	Beneficial in reducing mucositis during radiotherapy (Henriksson, et. al., 1999), due to its antibacterial properties (Carl, et. al., 1991). One study showed that if Kamillosan® (a camomile preparation) oral rinse was given to patients receiving radiation therapy and chemotherapy, mucositis was less severe than expected (Carl, et. al., 1991).
Hydrolytic enzymes	They have anti-inflammatory properties and are effective in reducing normal tissue reactions such as oral (Kaul et al., 1999) and gastrointestinal mucositis (Dale, e.t al., 2001).
Antioxidants	Dietary antioxidants (including vitamin E, vitamin C, and selenium) as well as antioxidant enzymes found within cells (e.g., superoxide dismutase and glutathione peroxidase) maintain an appropriate equilibrium between the desirable and undesirable effects of reactive oxygen species formed by radiation therapy (Seifried, et. al., 2003).
Vitamin A	Radiation therapy effectiveness is increased when combined with vitamin A and it is due to an increased immune response against the tumor (Tannock, et. al., 1972).
Vitamin C	Experimental studies show that radiation treatment reduces the level of vitamin C in the body (Beliaev, 1991). Conversely, studies of mice have shown that supplementing vitamin C at high doses preferentially radiosensitizes tumors while offering some protection to normal tissues (Tewfik, et. al., 1982).
Vitamin E	Vitamin E has been recognized as one of the most important antioxidants. Tocopheryl succinate (dry powder vitamin E) enhanced radiation damage to ovarian and cervical cancer cells in culture, while protecting healthy cells (Kumar, et. al., 2002).
Selenium	Selenium is a very efficient scavenger of reactive oxygen species and a radiosensitizer, with a very low toxicity profile (Schueller, et. al., 2004).
Melatonin	Melatonin functions as a radioprotector (Karbownik, et. al., 2000). It has been suggested that supplementing with an adjuvant therapy of melatonin may benefit cancer patients who are suffering from toxic therapeutic regimens such as radiotherapy and/or chemotherapy, and may alleviate symptoms caused by radiation-induced organ injuries (Karslioglu, et. al., 2005).
Amifostine (Ethyol®)	This drug protects the salivary glands from radiation damage if it is given during treatment. Amifostine is the only drug approved by the FDA to protect normal tissues from radiation during cancer treatment and it is also called a radioprotector (NCI Fact Sheet, 2010).

Strategies to Optimize Radiotherapy Response

Protein biomarker called Ki-67

Results of the largest known biomarker study of prostate cancer patients treated with radiation therapy indicate that the presence of a protein biomarker (Ki-67) is a significant predictor of outcome in men treated with both radiation and hormones (Li, et. al., 2004). When a tumor cell tests positive for Ki-67, the tumor is actively growing, and the greater the proportion of prostate tumor cells with Ki-67, the more aggressive the cancer (Wilson, et. al., 1996).

Guarding against anemia and measurement of tumor oxygen levels

Anemia is one of the most common blood abnormalities of cancer. Cancer patients with low hemoglobin levels do not respond as well to radiotherapy as non-anemic patients (Ludwig, et. al., 2001); due to problem in oxygen transport to tumor cells (Dunst, 2004). Low tumor oxygen levels (hypoxia) is a problem for radiotherapy because radiation's ability to kill cancer cells (i.e., radiosensitivity) rapidly decreases in areas of oxygen depletion, as free radicals cannot be produced because of limited oxygen supply (Fridovich, 1999). After the identification of hypoxia, effort can be made to solve this problem through the use of hyperbaric oxygen. Hyperbaric oxygen is a type of therapy in which the patient breathes pure, 100-percent oxygen at pressures two to three times greater than normal atmospheric pressure (Feldmeier, 2004).

CONCLUSIONS

Cancer is a disease of abnormal and uncontrolled cell proliferation. Radiation therapy is one of the current approaches for cancer treatment and containment, where cancerous tissue is exposed to high energy radiations and/or particles. All the radiation therapy approaches exploit the inherent growth dissimilarities between normal and cancer cells and try to specifically harm the cancer cells only. There are a range of radiation therapy approaches that are suitable for a particular cancer type and tissue location. Radiation therapy techniques have evolved from traditional approaches where the site of radiation application is decided by physical examination and the machines are relatively simple that do not give three dimensional purview of the tissue, the modern radiation therapy approaches include the three dimensional image reconstructions and usage of computer algorithms. There are however, shortcomings to these modern techniques also where they have non-targeted action on healthy cells in vicinity of cancerous tissue. The recent advances like stereotactic body radiation therapy, proton beam radiation therapy and boron neutron capture therapy are aimed at targeted action of radiations on cancer cells. Future research aimed at making radiation therapy more target oriented will make this technique even more attractive for cancer treatment and hence such research is most anticipated in this field.

REFERENCES

A. Alexander, F. Deblois, G. Stroian, K. Al-Yahya, E. Heath and J. Seuntjens (2007). MMCTP: A radiotherapy research environment for Monte Carlo and patient specific treatment planning. Physics in Medicine & Biology**:** Vol. 52 (13) N297-308.

A.B. Jani, L.W. Davis and T.H. Fox (2007). Integration of database for radiotherapy outcomes analysis. Journal of the American College of Cardiology: Vol. 4 (11) 825-31.

A. Bostrom, H. Lindman, C. Swartling, B. Berne and J. Bergh (2001). Potent corticosteroid cream (mometasone furoate) significantly reduces acute radiation dermatitis: results from a double-blind, randomized study. Radiotherapy and Oncology: Vol. 59 (3) 257-65.

B. Kumar, M.N. Jha, J.S. Bedford and K.N. Prasad (2002). D-alpha-tocopheryl succinate (vitamin E) enhances radiation-induced chromosomal damage levels in human cancer cells, but reduces it in normal cells. Journal of the American College of Nutrition: Vol. 21 (4) 339-343.

B. Ozturk, I. Egehan, S. Atavci and M. Kitapci (2004). Pentoxifylline in prevention of radiation-induced lung toxicity in patients with breast and lung cancer: a double-blind randomized trial. International Journal of Radiatherpy. Oncolology. Biology. Physics: Vol. 58 (1) 213-219.

B. Sanchez-Nieto and A.E. Nahum (2000). BIOPLAN: Software for the biological evaluation of radiotherapy treatment plans. Medical Dosimetry: Vol. 25 (2) 71-76.
B. Zhoa, M.C. Joiner, C.G. Orton and J. Burmeister (2010). SABER: A new software tool for radiotherapy treatment plan evaluation. Medical Physics: Vol.7(11) 5586-92
B.J. Warkentin, N. Stavreva, C. Field and B.G. Fallone (2004). A TCP-NTCP estimation module using DVHs and known radiobiological models and parameter sets. The Journal of Applied Clinical Medical Physics: Vol. 5 (1) 50-63.
B.M. Biswal, A. Zakaria and N.M. Ahmad (2003). Topical application of honey in the management of radiation mucositis: a preliminary study. Support. European Journal of Cancer Care: Vol. 11 (4) 242-8.
C. Eder-Czembirek, B.M. Erovic, C. Czembirek, M. Brunner, E. Selzer, R. Potter and D. Thurnher (2010). Betulinic acid a radiosensitizer in head and neck squamous cell carcinoma cell lines. Strahlenther. Onkol journal: Vol. 186 (3) 143-8.
C. Krasner and R.M. Joyce (2001). Zevalin: 90yttrium labeled anti-CD20 (ibritumomab tiuxetan), a new treatment for non-Hodgkin's lymphoma. Current Pharmaceutical Biotechnology: Vol. 2 341-9.
C. Noller, R.M. Hirschberg, D.H.W. Gronemeyer, W. Henninger and K.D. Budras (2006). Computed tomography anatomy of the normal feline nasolacrimal drainage system. Veterinary Radiology & Ultrasound: Vol. 47 (1) 53-60.
C. Wang (2000). Basic concepts of clinical radiation oncology, In: Wang, C., (Eds.), Clinical Radiation Oncology: Indications, Techniques, and Results, second ed. Wiley-Liss., University of Michigan. 1-14.
C.A. Pelizzari, G.T. Chen, D.R. Spelbring, R.R. Weichselbaum and C.T. Chen (1989). Accurate 3-dimensional registration of Ct, Pet, and or Mr images of the brain. Journal of Computer Assisted Tomography: Vol. 3 20-26.
C.M. Ma and R.L. Maughan (2006). Within the next decade conventional cyclotrons for proton radiotherapy will become obsolete and replaced by far less expensive machines using compact laser systems for the acceleration of the protons. Medcal Physics: Vol. 33 (3) 571-3.
Cancer Facts: Radiotherapy: (2002). National Cancer Institute.
D.E. Gerber and T.A. Chan (2008). Recent Advances in Radiation Therapy. American Family Physician: Vol. 78 (11) 1254-62.
D.E. Heron, R.P. Smith and R.S. Andrade (2006). Advances in image-guided radiation therapy - The role of PET-CT. Medical Dosimetry: Vol. 31 (1) 3-11.
D.M. Keefe, M.M. Schubert, L.S. Elting, S.T. Sonis, J.B. Epstein and J. E. Raber-Durlacher (2007). Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer: Vol. 109 (5) 820-31.
E. Cohen-Jonathan, E.J. Bernhard and W.G. McKenna (1999). How does radiation kill cells? Current Opinion in Chemical Biology: Vol. 3 (1) 77-83.
E. Ito, S. Yue, E.H. Moriyama, A.B. Hui, I. Kim, W. Shi, N.M. Alajez, N. Bhogal, G.H. Li, A. Datti, A.D. Schimmer, B.C. Wilson, P.P. Liu, D. Durocher, B.G. Neel, B, O'Sullivan, B. Cummings, R. Bristow, J. Wrana and F.F. Liu (2011). Uroporphyrinogen decarboxylase is a radiosensitizing target for head and neck cancer. Science Translational Medicine: Vol. 3 (67) 67ra7.
E. Spezi, D.G. Lewis and C.W. Smith (2002). A DICOM-RT based toolbox for the evaluation and verification of radiotherapy plan. Physics in Medicine & Biology: Vol. 47 (23) 4223-4232.
F.A. Tewfik, H.H. Tewfik and E.F. Riley (1982). The influence of ascorbic acid on the growth of solid tumors in mice and on tumor control by X-irradiation. International Journal for Vitamin and Nutrition Research: Vol. 23 257-63.
F.I. Lin and A. Iagaru (2010). Current concepts and future directions in radioimmunotherapy. Current Drug Discovery Technology: Vol. 7 (4) 253-62.
F.Y. Ching (2002). Modern advances in radiotherapy. Available from: http://www.eimjm.com/Vol1-No2/vo1-No2%20A3.html.

G. Metro, M. Mottolese and A. Fabi (2008). HER-2-positive metastatic breast cancer: trastuzumab and beyond. Expert Opinion on Pharmacotherapy: Vol. 9 (15) 2583-601.
G.A. Wiseman, E. Kornmehl, B.J. Leigh, W.D. Erwin, D.A. Podoloff, S. Spies, R.B. Sparks, M.G. Stavin, T. Witzig and C.A. White (2003). Radiation dosimetry results and safety correlations from 90Y-ibritumomab tiuxetan radioimmunotherapy for relapsed or refractory non-Hodgkin's lymphoma: combined data from 4 clinical trials. Nuclear Medicine: Vol. 44 465-474.
G.D. Wilson, M.I. Saunders, S. Dische, F.M. Daley, B.M. Robinson, C.A. Martindale, B. Joiner and P.I. Richman (1996). Direct comparison of bromodeoxyuridine and Ki-67 labelling indices in human tumours. Cell Proliferation: Vol. 29 (3) 141-152.
G.E. Laramore (2009). Role of particle radiotherapy in the management of head and neck cancer. Current Opinion on Oncology: Vol. 21 (3) 224-31.
G.O. Ahn and J.M. Brown (2009). Influence of bone marrow-derived hematopoietic cells on the tumor response to radiotherapy: Experimental models and clinical perspectives. Cell Cycle: vol.8 (7) 970-976.
H. Ludwig and K. Strasser (2001). Symptomatology of anemia. Seminar on Oncology: Vol. 28 7-14.
H. Paganetti and T. Bortfeld (2005). Proton beam radiotherapy - The state of the art. New Technologies in Radiation Oncology. pp. 1-36.
H. Vermund and F.F. Gollin (1968). Mechanisms of action of radiotherapy and chemotherapeutic adjuvants: A review. Cancer: Chapter 21 58-76.
H.D. Suit (2003). Protons to replace photons in external beam radiation therapy. Clinical Oncology: Vol. 15 (1) S29-31.
H.E. Seifried, S.S. McDonald, D.E. Anderson, P. Greenwald and J.A. Milner (2003). The antioxidant conundrum in cancer. Cancer Research: Vol. 63 (15) 4295-8.
H.S. Chong, H.A. Song, C.S. Kang, T. Le, X. Sun, M. Dadwal, X. Lan, Y. Chen and A. Dai (2011). A highly effective bifunctional ligand for radioimmunotherapy applications. Chemical communications (Cambridge, United Kingdom: Vol. 47 (19) 5584-6.
I. Fridovich (1999). Fundamental aspects of reactive oxygen species, or what's the matter with oxygen. Annals of the New York Academy of Sciences: Vol. 893 13-18.
I. Karslioglu, M.V. Ertekin, S. Taysi, I. Kocer, O. Sezen, A. Gepdiremen, M. Koç and N. Bakan (2005). Radioprotective effects of melatonin on radiation-induced cataract. Journal of Radiation Research: Vol. 46 (2) 277-82.
I. Verel, G.W. Visser and G.A. van Dongen (2005). The promise of immuno-PET in radioimmunotherapy. Journal of Nuclear Medicine: Vol. 46 (1) 164S-171S.
I.F. Tannock, H.D. Suit and N. Marshall (1972). Vitamin A and the radiation response of experimental tumors: an immune-mediated effect. Journal of the National Cancer Institute: Vol. 48 (3) 731-41.
I.K. Beliaev (1991). Evaluation and correction of the vitamin C status in relation to the problem of the experimental modification of long-term radiation effects. Radiobiologiia: Vol. 31 (6) 819-23.
ICRU. 1993. Prescribing, recoding and reporting photon beam therapy. ICRU Report 50. International Commission on Radiation Units and Measurements. Bethesda. Maryland. pp. 3-16.
ICRU. 1999. Prescribing, recoding and reporting photon beam therapy (supplement to ICRU Report 50). ICRU Report 62, International Commission of Radiation Units and Measurement. Bethesda. Maryland.: pp.3-20.
J. Albanell, J. Codony, A.Rovira, B. Mellado and P. Gascon (2003). Mechanism of action of anti-HER2 monoclonal antibodies: scientific update on trastuzumab and 2C4. Advances in Experimental Medicine and Biology: Vol. 32 253-68.
J. Dong, H. Calkins, S.B. Solomon, S.H. Lai, D. Dalal and A. Lardo (2006). Integrated electroanatomic mapping with three dimensional computed tomographic images for real-time guided ablations. Circulation: Vol. 113 186-194.
J. Dong, T. Dickfeld, D. Dalal, A. Cheema, J.E. Marine, C.R. Vasamreddy, C.A. Henrikson, H.R. Halperin, R.D. Berger, J.A.C. Lima, D.A. Bluemke and H. Calkins (2006). Initial experience in the use of integrated electroanatomic mapping with three-dimensional MR/CT images to guide catheter ablation of atrial fibrillation. Journal on Cardiac, Vascular and Thoracic Surgery: Vol. 17 459-66.

J. Dunst (2004). Management of anemia in patients undergoing curative radiotherapy erythropoietin, transfusions, or better nothing. Strahlenther. Onkol journal: Vol. 180 (11) 671-681.

J. Farrelly and M.C. McEntee (2003). Principles and applications of radiation therapy. Clinical Techniques in Small Animal Practice: Vol. 18 (2) 82-87.

J. Mohammadnejad, M.J. Rasaee, M.H. Babaei, M. Paknejad, M.H. Zahir, M. Salouti, R.A. Bitarafan and M. Mazidi (2010). A new radiopharmaceutical compound (131I-PR81) for radioimmunotherapy of breast cancer: Labeling of antibody and its quality control. Human Antibodies: Vol. 19 79-88.

J.A. Coderre and G.M. Morris (1999). The radiation biology of boron neutron capture therapy. Journal of Radiation Research: Vol. 151 1-18.

J.A. Kim, D.G. Baker, S.S. Hahn, N.T. Goodchild and W.C. Constable (1983). Topical use of N-acetylcysteine for reduction of skin reaction to radiation therapy. Seminar on Oncology: Vol. 10 (1) 86-88.

J.J. Feldmeier 2004. Hyperbaric oxygen for delayed radiation injuries. Undersea and Hyperbaric Medicine Journal: Vol. 31 (1) 133-45.

J.O. Deasy, A.I. Blanco and V.H. Clark (2003). CERR: a computational environment for radiotherapy research. Medical Physics: Vol. 30 (5) 979-985.

J.P. Donnelly, L.A. Bellm, J.B. Epstein, S.T. Sonis and R.P. Symonds (2003). Antimicrobial therapy to prevent or treat oral mucositis. The Lancet Infectious Diseases: Vol. 3 (7) 405-412.

J.T. Bushberg, J.A. Seibert, E.M. Leidholdt and J.M. Boone (2002). Magnetic Resonance Imaging, in: The Essential Physics of Medical Imaging, second ed. Lippincott Williams & Wilkins, Philadelphia, PA, pp. 415-468.

J.W. Hopewell, G.J. van den Aardweg, G.M. Morris, M. Rezvani, M.E. Robbins and G.A. Ross (1994). Amelioration of both early and late radiation-induced damage to pig skin by essential fatty acids. International Journal of Radiation Oncology • Biology • Physics: Vol. 30 (5) 1119-25.

J.Z. Xing, J. Zhu, J.A. Jackson, S. Gabos, X.J. Sun, Wang, W. Roa, X. Yang, L. Guo, B. Huang, S. Khatibisepehr, S. Gabos, J. Chen and J. Xing (2011). Real-time cell-impedance sensing assay as an alternative to clonogenic assay in evaluating cancer radiotherapy. Analytical and Bioanalytical Chemistry: Vol. 400 (7) 2003-11.

J.Z. Xing, J. Zhu, S. Gabos and L. Xie (2006). Microelectronic cell sensor assay for detection of cytotoxicity and prediction of acute toxicity. Toxicology in Vitro: Vol. 20 995-1004.

K. Tobinai (2002). Rituximab and other emerging monoclonal antibody therapies for lymphoma. Expert Opinion on Emerging Drugs: Vol. 7 289-302.

L.B. Travis, D. Hodgson, J.M. Allan and F.E. Van Leeuwen (2008). Second Cancers, in: DeVita, V.T. Jr., Lawrence, T.S., Rosenberg, S.A. (Eds.), Cancer: Principles and Practice of Oncology, eighth ed. Lippincott Williams and Wilkins, Philadelphia.

L.L. Gunderson and J.E. Tepper (2007). Clinical Radiation Oncology, second ed. Elsevier, Philadelphia, PA.

M. Behe, K. Alt, F. Deininger, P. Bühler, U. Wetterauer, W.A. Weber, U. Elsässer-Beile and P. Wolf, (2011). In vivo testing of 177Lu-labelled anti-PSMA antibody as a new radioimmunotherapeutic agent against prostate cancer. In Vivo: Vol. 25 (1) 55-9.

M. Karbownik and R.J. Reiter (2000). Antioxidative effects of melatonin in protection against cellular damage caused by ionizing radiation. Proceedings of the Society for Experimental Biology and Medicine: Vol. 225 (1) 9-22.

M. Schmuth, M.A. Wimmer, S. Hofer, A. Sztankay, G. Weinlich, D.M. Linder, P.M. Elias, P.O. Fritsch and E. Fritsch (2002). Topical corticosteroid therapy for acute radiation dermatitis: a prospective, randomized, double-blind study. British Journal of Dermatology: Vol. 146 (6) 983-91.

M. Suzuki, Y. Sakurai, S. Hagiwara, S. Masunaga, Y. Kinashi, K. Nagata, A. Maruhashi, M. Kudo and K. Ono (2007). First attempt of boron neutron capture therapy (BNCT) for hepatocellular carcinoma. Japanese Journal of Clinical Oncology: Vol. 37 376-381.

M. Suzuki, Y. Sakurai, S. Masunaga, Y. Kinashi, K. Nagata, A. Maruhashi and K. Ono (2006). Feasibility of boron neutron capture therapy (BNCT) for malignant pleural mesothelioma from a viewpoint of dose distribution analysis. International Journal of Radiation Oncology • Biology • Physics: Vol. 66 1584-1589.

M.J. Gazda and L.R. Coia (2004). Principles of radiation therapy, in: Cancer Management: A multidisciplinary approach, eighth ed. CMP, University of Michigan, pp. 9-21.

M.L. Hensley, L.M. Schuchter, C. Lindley. N.J. Meropol, G.I. Cohen, G. and Broder (1999). American Society of Clinical Oncology clinical practice guidelines for the use of chemotherapy and radiotherapy protectants. Journal of Clinical Oncology: Vol. 17 (10) 3333-55.

M.L. Kessler, S. Pitluck, P. Petti and J.R. Castro (1991). Integration of multimodality imaging data for radiotherapy treatment planning. International Journal of Radiation Oncology • Biology • Physics: Vol. 21 1653-1667.

M.S. Kaminski, J. Estes, K.R. Zasadny, I.R. Francis, C.W. Ross, M. Tuck, D. Regan, S. Fisher, J. Gutierrez, S. Kroll, R. Stagg, G. Tidmarsh and R.L. Wahl (2000). Radioimmunotherapy with iodine (131)I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood: Vol. 96 (4) 1259-66.

National Cancer Institute Fact Sheet. (2010). Available from: http://www.cancer.gov/ cancertopics/ factsheet/ Therapy/radiation.

National Cancer Institute. Radiation therapy and you. http://www.cancer.gov/cancertopics/radiation-therapy-and-you. Accessed August 13, 2008.

O. Gayou, D.S. Parda and M. Miften (2007). EUCLID: an outcome analysis tool for high dimensional clinical studies. Physics in Medicine & Biology: Vol. 52 (6) 1705-19.

O. Olsen and P.C. Gotzsche (2001). Cochrane review on screening for breast cancer with mammography. Lancet: Vol. 358 (9290) 1340-1342.

P. McLaughlin, A.J. Grillo-Lopez and B.K. Link (1998). Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. Journal of Clinical Oncology: Vol. 16 2825-2833.

P. Pommier, F. Gomez, M. P. Sunyach, A. D'Hombres, C. Carrie and X. Montbarbon (2004). Phase III randomized trial of *Calendula officinalis* compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer. Journal of Clinical Oncology: Vol. 22 (8) 1447-1453.

P. Schueller, S. Puettmann, O. Micke, V. Senner, U. Schaefer and N. Willich (2004). Selenium influences the radiation sensitivity of C6 rat glioma cells. Anticancer Research: Vol. 24 (5A) 2913-7.

P.G. Natali, M.R. Nicotra, A. Bigotti, I. Venturo, D.J. Slamon, B.M. Fendly and A. Ullrich (1990). Expression of the p185 encoded by HER2 oncogene in normal and transformed human tissues. International Journal of Cancer: Vol. 45 (3) 457-61.

P.M. Kistler, M.J. Earley, S. Harris, D. Abrams, S. Ellis, S.C. Sporton, R.J. Schilling (2006). Validation of three dimensional cardiac image integration: Use of integrated CT image into electroanatomic mapping system to perform catheter ablation of atrial fibrillation. Journal of Cardiovascular and Electrophysiology: Vol. 17 341-348.

P.P. Connell and S. Hellman (2009). Advances in radiotherapy and implications for the next century: A historical perspective. Cancer Resarch: Vol. 69 (2) 383-392.

P.S. Dale, C.P. Tamhankar and G.V. Daftary (2001). Co-medication with hydrolytic enzymes in radiation therapy of uterine cervix: evidence of the reduction of acute side effects. Cancer Chemotherapy and Pharmacology: Vol. 47 S29-34.

Proton therapy at the Paul Scherrer Institute. (2008). Available from: http://www.psi.ch/info/ MediaBoard/Protonentherapie_08_e.pdf.

R. Henriksson, P. Bergstrom, L. Franzen, F. Lewin and G. Wagemus (1999). Aspects on reducing gastrointestinal adverse effects associated with radiotherapy. Acta Oncologica: Vol. 38 (2) 159-64.

R. Kaul, B.K. Mishra, P. Sutradar, V. Choudhary and M.S. Gujral (1999). The role of Wobe-Mugos in reducing acute sequele of radiation in head and neck cancers-a clinical phase-III randomized trial. Indian Journal of Cancer: Vol. 36 (2-4) 141-8.

R. Li, K. Heydon, M.E. Hammond, D.J. Grignon, M. Roach, H.B. Wolkov, H.M. Sandler, W.U. Shipley and A. Pollack (2004). Ki-67 staining index predicts distant metastasis and survival in locally advanced prostate cancer treated with radiotherapy: an analysis of patients in radiation therapy oncology group protocol 86-10. Clinical Cancer Research: Vol. 10 (12 Pt 1) 4118-24.

R.F. Barth and H. Joensuu (2007). Boron neutron capture therapy for the treatment of glioblastomas and extracranial tumours: as effective, more effective or less effective than photon irradiation. Radiotherapy and Oncology: Vol. 82 (2) 119-22.

R.F. Robison, History of Radiation Therapy. Available from: http://www.rtanswers.com/ aboutus/history.aspx.

R.M. Sharkey and D.M. Goldenberg (2005). Perspectives on cancer therapy with radiolabeled monoclonal antibodies. Journal of Nuclear Medicine: Vol. 46 (1) 115S-27S.

S. Kim and T.S. Suh (2006). Imaging in radiation therapy. Nuclear Engineering and Technology: Vol. 38 (4) 327-342.

S. Rasaneh. H. Rajabi, M.H. Babaei and F.J. Daha (2010). 177Lu labeling of Herceptin and preclinical validation as a new radiopharmaceutical for radioimmunotherapy of breast cancer. Nuclear Medicine Biology: Vol. 37 949-955.

S.H. Okuno, R.L. Foote, C.L. Loprinzi, S. Gulavita, J.A. Sloan and J. Earle (1997). A randomized trial of a nonabsorbable antibiotic lozenge given to alleviate radiation-induced mucositis. Cancer: Vol.79 (11) 2193-9.

S.M. Spies (2004). Imaging and dosing in radioimmunotherapy with yttrium 90 ibritumomab tiuxetan (Zevalin). Seminars in Nuclear Medicine: Vol. 34 (1) 10-13.

T. Tanaka, K. Yukawa and N. Umesaki (2007). Radiation reduces carboplatin sensitivity and enhances nedaplatin sensitivity in cervical squamous cell carcinoma in vitro. European journal of gynaecological oncology: Vol. 28 (5) 352 EP-355 DO.

T.J. Kinsella (1996). An approach to the radiosensitization of human tumors. The cancer journal from Scientific American: Vol. 2 184-193.

T.S. Lawrence, R.K. Ten Haken and A. Giaccia (2008). Principles of Radiation Oncology, in: DeVita, V.T. Jr., T.S. Lawrence, Rosenberg, S.A. (Eds.), Cancer: Principles and Practice of Oncology, eighth ed. Lippincott Williams and Wilkins, Philadelphia.

University of Alabama at Birmingham Comprehensive Cancer Center, History of Radiation Oncology" (from the Wayback Machine). Archived from the original on 2008-01-05. Available from: http://web.archive.org/web/20080105043216/http://www3.ccc.uab. edu/show.asp?durki=68504.

W.Carl and L.S. Emrich (1991). Management of oral mucositis during local radiation and systemic chemotherapy: a study of 98 patients. Journal of Prosthetic Dentistry: Vol. 66 (3), 361-369.

World Cancer Day 2011. Cancer Prevention and Control. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/cancer/dcpc/resources /world_cancer_day.htm. Accessed February 4, 2011

X.B. Xu (2005). Dynamic monitoring of cytotoxicity on microelectronic sensors. Chemical Research in Toxicology: Vol.18 154-161.

Y.L. Wang, Z. Hong, L. Ning, X.H. Wang, J.F. Hao and W.P. Zhao (2009). Potential mechanisms involved in resistant phenotype of MCF-7 breast carcinoma cells to ionizing radiation induced apoptosis. Section B of Nuclear Instruments and Methods in Physics Research: Vol. 267 1001-1006.

Y.Z. Fang, S. Yang and G. Wu (2002). Free radicals, antioxidants, and nutrition. Nutrition: Vol. 18 872-879.