From the Editor

Prof KP Mishra, Ph.D.

Editor-in-Chief, Journal of Nehru Gram Bharati University (JNGBU)

The pursuit of research is a continual search for truth using scientific methods and aims creation of new knowledge for the benefit of mankind. It is commonly accepted that developing new approaches and technologies to solve the unsolved problems of life pose a challenge requiring greater efforts and rigorous investigations to overcome the situation. Advancement of knowledge requires proper documentation of what has been known and established. Therefore, it is considered utmost important that apart from gaining new knowledge and testing its veracity, its preservation and dissemination among peers and public contributes rather significantly in further exploration process. In modern times documentation of research outputs and technology development have witnessed dramatic progress and access to information has enhanced our capacity to read, understand, interpret and utilize available knowledge on a particular subject.

University has decided to launch a new journal covering diverse range of subjects and topics serving the goal of communication of research results to spectrum of readers and scholars. The major objective of **Journal of Nehru Gram Bharati University (JNGBU)** is to publish original research papers, review articles, hypothesis, short communications and other eye-catching and trend setting new ideas/research results. The journal will publish papers after peer review and rigorous refereeing process. The Journal is guided and advised by an Editorial Board and Advisory Committee to maintain a high quality of publication material. At this stage, Editorial Board is incomplete but it will be completed by inviting to serve on the board reputed scientists/professionals from the world over in time to come.

The scope of the journal is to publish papers from humanities to science and technology including social and management research. Papers of multi disciplinary nature with wide reader interest will be considered for publication. Efforts will be made to publish submitted papers within shortest possible time after receiving the recommendation of esteemed referees.

I take this opportunity to invite review articles from experts and established researchers and wish to encourage young researchers/beginners to submit their findings for publication in JNGBU. There is no barrier to subject domain but emphasis will be given to new knowledge and topical reviews to keep a check on focus of reader interests and propagation of new knowledge and technology. To begin with, there is no restriction of language in which article is prepared but overall framework of the guidelines for manuscript has to be adhered to and maintained regardless of other factors.

Let me acknowledge the support and encouragements that have been generously received from our colleagues in particular and scientists, educationists and professionals in general from various fields. I wish to especially acknowledge the wholehearted support and commitment from the Board of Management of our University, especially the total trust in my academic capabilities by our Chancellor, Shri JN Mishra in realizing the vision of launching this Journal.

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Conference Report

ICREH- 2010 :

An **International Conference on "Radiation, Environment & Health" (ICREH-2010)** was organized by Nehru Gram Bharati University during **November, 19-21, 2010** in which approximately 400 scientists from India & abroad participated and presented their research work.

Announcements

Upcoming Conferences:

ICRCS- 2012:

International Conference on Radiation, Cancer and Society (ICRCS- 2012) is going to be organized by Nehru Gram Bharati University, Allahabad on **26-28, November 2012.**

An **International Conference on "Atoms for Peace"** of WONUC (World Organization of Nuclear Workers) is to be organized by Nehru Gram Bharati University, Allahabad in 2013.

DIFFERENTIAL EFFECTS OF LOW AND HIGH DOSE OF RADIATION IN DIRECTLY IRRADIATED AND BYSTANDER CELLS WITH RELEVANCE TO RADIATION RISK ASSESSMENT

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Low dose radiation biology has been area of active research to understand the cellular and biological effects after low dose radiation with relevance to environmental and health consequences of radiation. Determination of radiation dose limits by regulatory agencies is based on linear no-threshold (LNT) model of radiation risk assessment, which is conceptualized as linearity of risk irrespective of radiation dose. However, LNT model has been challenged by many radiation biologists based on emerging scientific facts. Observations in many experimental systems support either threshold ('J' shaped) or hermetic effects of radiation. Accumulated evidences show that effect of low and high dose radiation is non-linear depending on dose/dose rate applied. The differential response of low and high radiation is not only observed in directly irradiated cells but also in bystanders (cells did not receive direct radiation), which makes the research area further exciting. The present paper provides highlights of such finding and their relevance in low dose radiation biology especially in radiation risk assessment.

Keywords: *Radiation, LNT model*

INTRODUCTION

Like other genotoxicants, radiation is also known to induce cancer above certain doses. Human population undergoes exposure to chronic or acute low doses of radiation in various conditions such as in high natural background areas, nuclear workers working in different activities of nuclear power production, passengers and crew members while long flight durations, astronauts during space travel and during diagnostic radiology etc. Effect of low doses under such exposure conditions needs to be studied for radiation risk assessment for environmental, diagnostic and occupational low dose radiation biology. Moreover, during cancer radiotherapy, extra-tumor regions/organs of the patients also receive undesired low dose exposure, which needs to be investigated to address the issue of long term health effects of cancer radiotherapy [1, 2].

It may be pertinent to mention that low dose from different conditions varies in terms of dose rates and whether the dose is purely of one type or mixed with low and high LET radiation. Hence, the situations for low dose radiation exposure may be categorized: (i) low dose radiation exposure from natural sources, which are beyond our control and relatively very protracted; (ii) exposure from various man made radiation sources to public / nuclear workers and diagnostic / therapeutic radiology. Moreover, there are situations of radiation exposure conditions during accidental radiation exposure, where the dose and dose rate are many folds higher than low dose

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radiation exposures. The public perception about health effects of radiation exposure has been markedly impacted by the devastating atomic bombing in Hiroshima and Nagasaki in 1945 during World War II, catastrophic nuclear accident at Chernobyl in 1986 [1] and more recently Fukushima nuclear accident in 2011. Hence, determination of dose limits for nuclear workers and public have been greatly influenced by the negative socio-psychological feelings. The regulatory authorities use a more conservative linear no-threshold (LNT) model of radiation risk assessment, which states that risk of radiation is linear irrespective to dose and any dose (no matter how small) of radiation is harmful to cause cancer. In other words according to the LNT model, the probability of cancer from small dose of radiation can be calculated by linear extrapolation of observed risk at high radiation dose. The LNT theory is based on three assumptions: (i) cancer may result from a single ionizing event in a critical cell, hence any radiation dose no matter how small is potentially harmful; (ii) the probability of adverse health effects of radiation is linearly related to absorbed dose, (iii) radiation damage is non-repairable.

Employment of such model in radiation risk assessment has resulted in severe fear in public about radiation and an indiscriminatory phobia against application of radiation and radiation technologies, neglecting many of their positive aspects [3-5]. The annual dose limits for workers are an effective dose of 20 mSv per year averaged over five year with not more than 50 mSv in any single year. These dose limits are many folds lower than doses at which observable health effects of radiation could be seen. Still, regulating agencies believe that there is no safe dose of radiation and regulations should be established for exposure limits as low as possible, if not zero. Hence, the permissible dose limits in case of manmade radiation sources are regulated very strictly by national/international agencies keeping in mind the concept of As Low As Reasonably Achievable [6]. Such understanding results in tremendous economic pressure on nuclear industry while operation, generation, maintenance of nuclear power plants, applications of radiation technologies for various applications including in diagnosis and therapy. Risk of cancer risk after low dose of X-rays especially during computed tomography (CT) scans has been discussed and a matter of debate in literature. In this context, it may be important to remember that in diagnostic radiology, a typical dose to the lung from a conventional chest X-ray could range from about 0.01 to 0.15 mGy, while the doses to an organ examined with a conventional CT may vary from 10 mGy to 20 mGy, or even may be as high as 80 mGy for CT of coronary angiography. According to one school of thought, the radiation exposure during CT scans is high [7, 8], which may be responsible for increased cancer risk in certain population. However, another school of radiation biologists contradicts-CT scans may in fact decrease the cancer risk [9, 10]. The former thought is based LNT model of radiation risk, where the low dose risk calculation is mainly based on extrapolation on results available from atomic bomb survivors, who received high doses. Based on scientific facts, a group of radiation biologists believe that LNT model is not valid for risk associated with low doses, and instead of linearity, a 'J' shaped curve persists for low dose effects (Fig. 1). It has been shown in many laboratories including ours that in the low dose range of radiation, biological processes like repair and adaptive response govern the cellular response of radiation, which do not support LNT model.

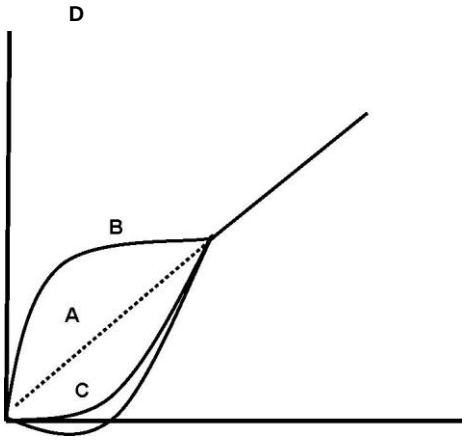

Fig. 1. Linear No-Threshold (LNT) Model for dose and risk of radiation and deviations from LNT model.

The well considered LNT model (A: dotted) is being challenged by either (B) supra-linear i.e. the risk are more predominant with increase in per unit dose of radiation; (C) up to certain dose range there is no risk ('J' shape curve), which follow linearity at subsequent doses of radiation; (D) the protective or advantageous effects by low dose / dose rate of radiation (also called 'radiation hormesis'), which may reduce in rate of mutations and neoplastic transformation below the spontaneous frequency.

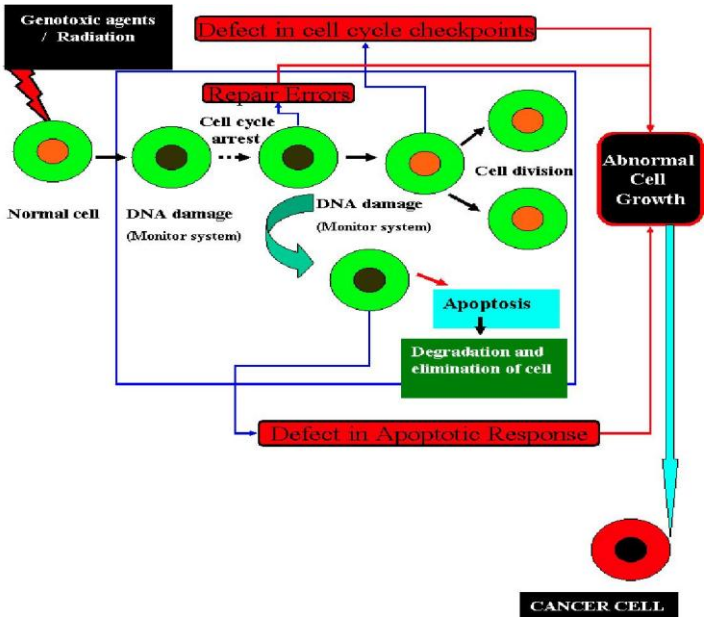

Fig. 2. Schematic of role of various cellular processes and checkpoints in transformation of normal cells after exposure to various genotoxic agents including radiation.

The fundamental assumptions of LNT model have been challenged based on certain radiobiological facts. After radiation exposure transformation of a normal cell to tumor cell is being controlled and governed by many cellular processes (like apoptosis) and DNA damage repair checkpoints (Fig. 2). Moreover, it is difficult to establish a linear relationship with magnitude of radiation induced DNA damage with cancer incidence, which is a multi-step process regulated/prevented at each tier. Moreover, immune cells / tissue microenvironment play a critical role in elimination cancer cells and in prevention of cancer incidence. Even if, a normal cell gets transformed to cancer cells, out of benign and malignant only malignant cancer are of pathological importance and pose health consequences. According to one calculation, the magnitude of average spontaneous DNA double stand breaks (DSB) is about 1000 times more than radiogenic DSB from background radiation. A dose of 1 mGy of low dose radiation (100 kVp X-ray) in average 1 nanogram mass generates, on average 1 particle track; ~150 reactive oxygen species; 2 DNA alterations of any kind; 10^{-2} DSB; 10^{-4} chromosomal aberrations; and the probability of an oncogenic transformation of the hit cell with lethal outcome is about 10^{-13} to 10^{-14}. The ratio of the probabilities for radiation induced lethal cancer and the corresponding DSB is about 10^{-11} to 10^{-12} [11, 12]. At every step of radiation induced cancer incidence, there is possibility of reversal and negating the radiation effects, which further do not fall in line of LNT model of radiation risk assessment. Based on radiobiological knowledge, it may be stated that it is not the damage but rate of damage and net damage would decide the fate of a cell.

In the perspective of LNT debate, it may be important to mention that low and high dose of radiation exert differential cellular response and such observations pose one of the major challenge against LNT model. The present paper provides highlights of such finding and their relevance in low dose radiation biology.

DIFFERENTIAL RADIATION RESPONSE OF LOW AND HIGH DOSE OF RADIATION:

By virtue, cells repair the damage exerted after radiation exposure and eventually cells takes normal course in case of successful repair of lesions. In case of incomplete or erroneous repair of damage, cell undergoes either transformation or apoptosis or necrosis or senescence. The fate of cell would be governed by many cellular factors as well as magnitude/type of radiation exposure. The lower severity of damage in case of low dose of radiation not only get repair easily but also induces machinery responsible for reducing the magnitude of damage during subsequent radiation doses, referred as 'radiation induced adaptive response'. However, after low and high dose of radiation exposure, a different but opposite effects have been shown.

In one of our recent study, it was observed that after chronic low dose of radiation (10 cGy; 0.2 cGy/h) translationally controlled tumor protein (TCTP) was significantly (two folds) upregulated than an acute dose of 4 Gy in normal human fibroblasts. The expression and regulation of TCTP was found to be associated with decrease in micronucleus formation. The DNA damage repair by TCTP after low dose of radiation involves ATM and DNA-PK [13]. In another study, we have compared effect of chronic low dose with an acute high dose in terms of alterations in mitochondrial membrane polarization and import of frataxin protein. Our results showed that the mitochondrial membrane potential was significantly higher in case of chronic low dose than acute dose of radiation. Moreover, in contrary to decrease in import of protein in case of acute toxic

dose of radiation, low dose radiation showed increase in import of mitochondrial protein [14].

Differential response of low and high dose of radiation has been not only seen in case of normal cells, but also in bystander tumor cells. Our results showed that irradiated conditioned medium (ICM), obtained from human promyelocytic leukemic cells (HL-60) γ-irradiated from low-dose (5 cGy; ICM-L) and high-dose radiation (1 Gy; ICM-H) showed differential response to bystander (unirradiated) HL-60 and normal human blood lymphocytes. Apoptosis in normal lymphocytes cultured in ICM-H was significantly higher than when cells were cultured in unirradiated conditioned medium or ICM-L. Moreover, sensitivity of bystander HL-60 cells was found to be higher after ICM-L. ICM-H was found to induce the apoptotic death in both bystander HL-60 and normal lymphocytes [15]. These results suggest that differential bystander response from irradiated cancer cells toward cancer and normal cells depend on the applied dose and/or dose rate of radiation. Such observations may be associated with fact that the nature and magnitude of factors secreted from tumor cells after low and high dose are different, hence, exert different effects to bystander cells.

In our recent study, we have analyzed the level of cytokines from human tumor cell lines after acute (2, 6Gy) and fractionated doses (3×2Gy) of gamma-irradiation [16]. Our results showed that after irradiation, the levels of most of the cytokines increased markedly in a dose dependent manner. However, it was interesting to observe that the fold change in cytokine levels was lower in irradiated conditioned medium of tumor cells collected after fractionated than respective acute dose in most of the tumor cell lines, except in MCF-7 cells. These results suggest the differential response of tumor cells to secrete cytokines after low and high dose of radiation, which may have significant implication in tumor radio-sensitivity.

CONCLUSIONS

Based on the observations from many laboratories including ours, it has been established that nature and magnitude of cellular response after low doses are either threshold or hormetic effects, in contrary to linear response at high doses. Hence, the ultimate health effects under two exposure regiments could not be linear. It may also not be judicious to extrapolate the radiation risk associated with high doses to low dose regimen. Based on these evidences, time has ripened to review the validity of LNT model for radiation risk assessment.

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EMERGING GLIMPSES OF BIOART (BIOLOGICALLY ADOPTIVE RADIOTHERAPY)

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Both intensity-modulated and Image guided radiation therapy have great potential to further increase tumor control rates and decrease morbidity. A homogeneous escalation of 'biological' dose within a tumor has better potential to increase the likelihood of local cure, especially within the mid-range (e.g. 15% to 80%) of tumor control rates. However, when the dose to critical normal tissues is tightly constrained, the dose distributions within the treatment volume may necessarily be heterogeneous, and the effect on tumor control probability will depend upon the magnitude of over- or under dosage, and on the proportions of the tumor clonogen population receiving higher or lower than the nominal dose. Dose-volume histograms provide a measure of heterogeneity of dose within the planned treatment volume, but tumor control probability is also influenced by other variables, e.g. inherent tumor clonogen radiosensitivity and growth rates during a course of treatment, oxygenation and clonogen density throughout the target volume. Heterogeneity in these factors introduces heterogeneity in tumor responses and a less steep change in tumor control probability with change in dose, reducing the gains or losses that would be predicted to result from heterogeneity of dose. The magnitude of a dose reduction is the major determinant of decline in tumor control probability. A large dose reduction to even a small volume of tumor can profoundly decrease tumor control probability. Conversely, the most rapid improvement in tumor control probability occurs the closer to 100% the amount of tumor exposed to an increased dose. Escalation of dose is of little value unless it is distributed through most of the tumor: even very large increases in dose to small volumes are of little benefit. **Keywords :** *BIOART, Radio Sensitivity.*

Introduction

A concept of EUD (equivalent uniform dose) was proposed by Martin A. Ebert (2000) to find out the level of tumor radiosensitivity in case of dose variations within the tumor volume. An approach called EUBED (equivalent uniform biologically effective dose) has been suggested by Jones L.C. et al (2000) to replace EUD. EUBED considers dose and dose per fraction as the modifying parameters for comparing treatment plans. Many authors have proposed different empirical TCP (Tumor Control Probability) models, popular amongst them are of Brahme et al, Goiten et al, Bernner et al and Gibbs et al. These models facilitate the choice of the treatment plan with its clinical end result.

During external beam radiotherapy, normal tissues are irradiated along with the tumor. Attempt is made to minimize dose to the normal tissues while delivering a high dose to the target volume. Biological equivalent dose concept using Linear Quadratic (LQ) Model of cell kill was introduced by Zaider et al by introducing biological response parameters **a** and |**3**.

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Radiobiological Basis of Radiotherapy Planning: New Paradigm

Linear Quadratic Model (LQ Model)

The size of the dose per fraction rather than the number of fraction, is the basic parameter to determine the induction of cell reproductive death as well as other cellular damage, i.e., effectiveness per unit dose of the given treatment. The frequency of observed effects a function of dose can, therefore be presented as;

$$F(D) = aD+PD$$

Where, **a** and |**3** are tissue specific constants with the units of Gy- and Gy- respectively. In broad terms, **a** and |**3** are measures of the relative importance of each of the two processes, and thus the ratio (a/p) is of prime significance. The ionizing radiations produce two types of lesions in the cells. The part which cause effective lesions with a frequency increasing linearly with absorbed dose D, while others called sub-effective lesions cause the same cellular effects through the mutual interaction which increase with the square of the dose D. Barendsen has defined this function for unit dose and called as Relative Effectiveness (RE) i.e. $RE = 1+ D(p/a)$

Biologically Effective Dose (BED can be written as:

$$BED = Nd[1+d(p/a)]$$

i.e., BED = Nd x RE= Total Dose x RE = $(TD)_N$ x RE) Where, $(TD)_N$ is the total dose in N fraction.

Tumor Control Probability (TCP)

All tumor control probability models assume that a tumor is destroyed if all viable clonogenic cells within it are killed. Brahme in 1984 and Goiten in 1987 have derived TCP from the product of probabilities that individual clonogens are killed. The simplest form of these models assumes that clonogens in the tumor have identical radiosensitivities and are uniformly distributed. If the dose to each clonogen is homogeneous and each clonogen respond independently, Poisson statistics show that the TCP for each clonogen, TCP(v,D), can be obtained from the TCP for uniform irradiation of the whole tumor, TCP(1,D) as follows:

$$TCP(v,D) = [TCP(1,D)]$$

The product of all clonogens TCPs determines the TCP for the inhomogeneous irradiation and given as:

$$TCP = i=1n \quad [TCP(vi, Di)]$$

Where, TCP(vi, Di) is the tumor control probability for the i^{th} clonogen receiving dose Di and N is the number of clonogens. The probability of controlling a tumor is dominated by any clonogen with low probability of being killed, and TCP is very sensitive to cold spots in the dose distribution of tumor. Due to difference in radiosensitivity of tumor cells and variation in tumor size, a discrepancy is found in the calculated value and the response seen in clinical studies.

NTCP (Normal Tissue Complication Probability)

This radiobiological quantity predicts the probability of a complication as a function of the dose or biologically equivalent dose and volume. In some models partial volume tolerance doses are related to each other through a power law in volume. This implies that there is always a partial-volume dose for which a given probability of complication occurs, no matter how shall be the partial volume.

Zaider et al, have interpolated the normal tissue complication data given by Emami et al for any irradiation pattern and defined a

procedure to find an effective volume. On the basis of interpolation of NTCP data of Emami et al, Zaider et al, have proposed following three parameter empirical formula for normal tissue complication probability:

$$P(D,v) = \exp[-(N0 /v). e \quad]$$

Here, N_o, k, and **a** are tissue-specific, non-negative adjustable parameters. The expression in the exponent e^{-aD} is reminiscent of the linear quadratic model for the cellular survival equation. The quadratic term |**3**D is not included for simplicity in using the data.

Zaider has applied Kutcher and Burman's method to obtain NTCP for a non-homogeneous dose distribution. a final equation for NTCP(v_{eff}) can be written as:

$$NTCP(ve_{ff}) = \exp[-N0/\{ iZvi\ e \quad \}]$$

This formula can also be used to estimate NTCP of OR using mean dose and whole OR volume using DVH curve for comparison of various treatment plans.

Equivalent Uniform Dose (EUD) and Equivalent Uniform Biologically Effective Dose (EUBED)

Equivalent Uniform Dose (EUD) concept is not adequate for assessing normal tissues complication, however, it can be used to adjust the dose prescription ensuring that all plan deliver the same EUD to tumor. L.C.Jones and P.W. Hoban, introduced the concept of Equivalent Uniform Biologically Effective Dose (EUBED)[95]. This value incorporates the distribution of dose and dose per fraction while comparing treatment plans. Reduced dose per fraction at the edge of the target volume will exacerbate the effect of reduced dose on cell kill. An equation similar to the equation proposed by Niemerko can be written as, using linear (a) component of LQ survival curve.

$$e^{-a.EUD} = \sum_{i} vi\, e^{-aDi}$$

Where, vi is the fractional volume receiving a dose Di (from DVH data). by the solution of EUBED = n.eud. {1 + eud/(a/|3)}

This implies that;

$$EUD = n.\ eud$$

This provides a mean for comparing dose distributions, accounting both for possible differences in dose per fraction at the prescription level and the variation in dose per fraction as relative dose varies across the tumor.

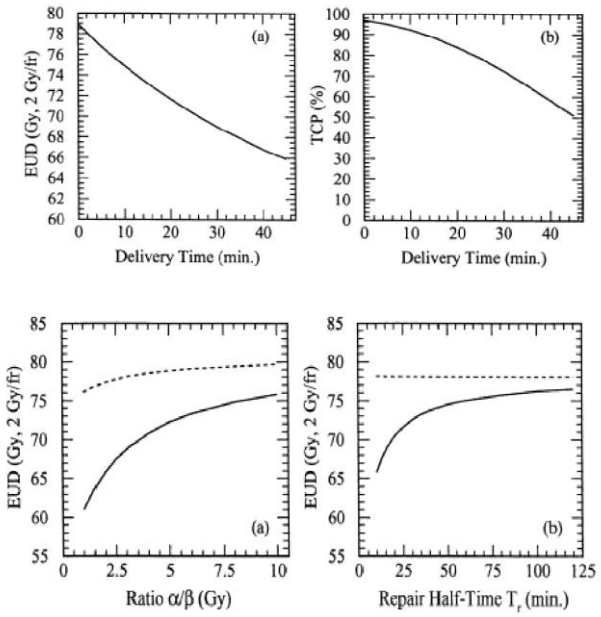
Heterogeneity in Biological Dose Per Fraction

Planned heterogeneity of physical dose distribution is a characteristic capability of conformal radiation therapy, especially when combined with intensity modulation. The associated heterogeneity in 'biological' dose always exceeds that in physical dose because the response of both normal and malignant tissues is a non-linear function of dose; that is, the change in biological effect is always amplified by the curved shape of the cellular dose-survival response regardless of whether the actual physical dose is greater or less than the reference dose. The extent of the discrepancy between physical and 'biological' doses is greater in slowly proliferating tissues, and probably also slowly proliferating tumors, than in the more proliferative, earlier-responding normal and malignant tissues because the dose-response curve is curvier for late, than early-responding tissues (10-26), as discussed later. Thus, not only does the change in biological effect of dose not precisely match the change in physical dose, but there is no universal modification factor which can be applied to all tissues to convert physical dose distributions into biological dose distributions. However, if the relative curvature of the dose-response

curve for the tissue in question were known, the changed biological effectiveness of a heterogeneous dose per fraction, or of a new fractionation regimen, could be quantified in terms of a linear quadratic description of the survival curve.

Overall Duration of Therapy

The adverse effect on local control from regrowth of surviving tumor clonogens during the latter part of a course of treatment has been quantified for many human tumors. This potential for regenerative 'escape' by surviving tumor clonogens can be reduced by increasing the intensity of treatment, i.e. by accelerating the rate of dose accumulation or by adding other cytotoxic agents, e.g. chemotherapy. If a steep gradient in dose distribution permits a higher tumor dose per fraction than is possible with standard therapy (through exclusion of



critical normal tissues from the high dose treatment volume), then the dose intensity to the tumor can be selectively increased. For example, if a complex beam arrangement, with or without intensity modulation, produces steep dose gradients, it may be possible to include the tumor within, say, the 80% isodose line, in which case the dose per fraction within the tumor is increased by a factor ranging up to 1.25 (100:80). If a dose of 70 Gy in 7 weeks were prescribed to encompass all the tumor at the 80% isodose, the total dose within the tumor would range between 70 Gy and 87.5 Gy, in an overall time of only 7 weeks, an acceleration of up to 25% in dose intensity. Obviously, this heterogeneity can be further increased by prescribing to the 50% isodose line, depending upon the steepness of the dose-gradient and clinical judgement regarding tumor control and complication probabilities. (Note also that the biological dose

intensity within the treatment volume would be further increased by the 'double trouble' of both higher total dose and larger dose per fraction, the extent of the gain being greater the lower the a:b ratio for the tumor). The potential gain from this type of dose escalation depends upon the dose-volume distribution.

CONCLUSIONS

In homogeneities in dose within a tumor affect the probability of cure to an extent that is influenced by many factors:

1. Steepness of the TCP curve, which is a function of the effective slope of the dose survival curve for clonogenic tumor cells, which in turn is affected by the intrinsic radiosensitivity of the tumor cell population, and their fractionation response (a:b ratio), the extent of hypoxia, and growth rate of surviving clonogens during treatment, and other less-defined factors.

2. Magnitude of variation of dose within the tumor volume: a large degree of under dose to even a small volume can have grave consequences. In terms of dose volume histograms, 'notches' in the shoulder may be associated with a rapid rate of decline in TCP values relative to those predicted from

homogenous irradiation, especially if the TCP from homogeneous irradiation is high.

3. The density of clonogenic cells in areas of over- or under dosage.

4. Volume of tumor under dosed.

5. Volume of tumor overdosed. The effectiveness of over dosage in controlling tumors increases more rapidly the closer the percentage of tumor overdosed approaches 100%. High doses limited to small percentages (e.g. B50% of the tumor) are essentially worthless in improving TCP.

6. The rate of change in TCP as a function of volume under- or overdosed varies with the TCP which would result from a homogeneous dose. Although we can model these effects in a general way, imprecision in biological and radiobiological parameters limits potential clinical application.

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REDOX IMBALANCE AMELIORATES TUMORIGENESIS: PROMISING INDIGENOUS MEDICINAL PLANTS AND THEIR BIOACTIVE COMPOUNDS AS CHEMOPREVENTIVE AND THERAPEUTIC AGENTS

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Cancer is a major cause of death, and globally studies are being conducted to prevent cancer or to develop effective nontoxic therapeutic agents. As of jeopardy behind the carcinogenesis, oxidative stress is closely related to all aspects of cancer, from carcinogenesis to the tumor-bearing state, from treatment to prevention. Despite the advancement in chemotherapy; the incidence of various forms of cancer is rapidly rising all over the world. Furthermore, continuous population growth, exorbitant cost, severe side effects along with multi drug resistance of conventional medicines have emphasised the use of medicinal plants, since they exhibits pluripotent activity and safe in long term use. This article reviews the therapeutic potential of medicinal plants and their potent bioactive compounds as a source of therapeutic drug candidate for the prevention and treatment of cancer.

Keywords: *Cancer, medicinal plants, oxidative stress, prevention, bioactive compounds*

Introduction

Cancer is a complex, debilitating disease; intricately associated with redox imbalance in various biochemical and molecular cascades of the cell. It is the second leading cause of death after cardiovascular disease, worldwide. Moreover, it is reported that deaths from cancer are continuously increasing with an estimated 13.1 million deaths in 2030; globally [1].In India, around 5,55,000 people died of cancer in the year of 2010[2]. Till date, cancer treatment strategies usually consist of various combinations of surgery, radiation therapy and chemotherapy; despite these therapeutic strategies cancer mortality rate is unaltered. Although, conventional therapeutic strategies have significantly prolonged the life expectancy with symptomatic relief of the average cancer patients, but still mortality rate is increasing alarmingly. Moreover, the major disadvantage of the modern therapeutic interventions is to exert severe side effects on the cost of high expenditure. Pertaining to it, the phrase is well sound in the cancer research "Prevention is always better than cure", since, in the case of cancer where a cure, if at all possible, is associated with high cytotoxic loads and/or other invasive procedures. With advanced understanding of molecular etiology of cancer, it has become apparent that strategies which prevent DNA damage and/or increase the probability of DNA repair by inhibiting aberrant proliferation; may prevent membrane depolarization and/or permeability through inhibiting the lipid oxidation may be useful strategy for the chemoprevention and treatment.

In recent years, increasing experimental and clinical data has provided compelling evidences for the involvement of oxidative stress in large number of pathological states including carcinogenesis (3, 4, 5). As it is evident that in the normal cells, there is an equilibrium between free radicals (FR)/ reactive oxygen species (ROS) and/or reactive nitrogen species (RNS)generation and endogenous antioxidant activity to

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counteract over their deleterious effect through various defence mechanisms; however, if this balance is disturbed may causes oxidative stress, which further triggers injury to micro and macro molecules like proteins, DNA and membrane lipids culminating to tumorigenesis and subsequent cell death. In spite of it, several research findings suggest that oxidative stress is not always detrimental and sometimes can be utilized therapeutically like chloroquin, quinine, mefloquine, primaquin, artemisinin (6) and ciprofloxacin (7) are known to act by the mechanism of oxidative stress. Recently, new therapeutic strategies have been emerged and take advantage of increased reactive oxygen species or inhibition of endogenous antioxidant defence, hence producing a state of oxidative stress selectively in cancer cells have gained importance. Moreover, several studies have suggested that oxidized proteins or attenuated endogenous enzymes can be selectively used as biomarkers as preliminary screening tools in the cancer research.

Natural products derived from plants have received considerable attention as potential cancer chemopreventive and chemotherapeutic agents over few decades. On the basis of epidemiological and animal studies, it has been reported that diets rich in fruits and vegetables are associated with a reduced rate of cancer mortality. Dietary phytochemicals consist of a wide variety of biologically active compounds which are known to exert their anticancer activity on the three stages of carcinogenesis, which include initiation, promotion and progression. Natural products rich in polyphenols, such as green tea and red wine, have been shown to have strong chemopreventive and chemotherapeutic properties in different types of cancer cells. Moreover, the polyphenol-induced cytotoxic effect appears to target specifically cancer cells [8, 9].

Taken together it is evident that multiple factors are associated with cancer progression; henceforth, it is apparent that the treatment strategy requires therapeutic candidates with multi-targeted pharmacological action. In this context, despite major therapeutic advancements, existing conventional drugs only provide symptomatic relief with severe side effect in long term use. Pertaining to it, medicinal plants and their bioactive compounds have immense potential as therapeutic candidates, since they possess potent pharmacological activities, low toxicity and economic viability. A number of Indian medicinal plants have been used for thousands of years in the Indian System of Medicine (Ayurveda) for the management of various disorders including cancer. Several plant-derived bioactive compounds are currently successfully employed in cancer treatment. There are many classes of plant-derived cytotoxic natural products studied for further improvement and development of drug. Interest has revived recently in the investigation of medicinal plants to identify novel active phytochemicals that might lead to drug development. The activities of various bioactive components of plant origin as polyphenols, saponins, alkaloids and flavonoids, which have shown synergistic action with other drugs make them ideal drug candidate in alternative cancer therapies.

Etiology of Cancer:

The etiology and pathogenesis of cancer is suggested to be multi-factorial in nature with intricate combination of genetic and environmental components. Although, carcinogenesis majorly attributed through environmental factors(90–95%) that mutate

genes encoding critical cell-regulatory proteins; only 5–10% of allcancer cases can be caused through genetic defects. The significant risk factors for carcinogenesis are

Environmental and occupational exposure such as UV radiation, exposure to carcinogenic chemicals such as vinyl chloride, benzene, asbestos and aflatoxin contamination in food.

Genetic factors including inherited mutations, activation of pro-oncogenes, defective tumor suppressor genes.

Viral infections such as *Epstein-Barr-Virus* (EBV), *Hepatitis-B-Virus* (HBV), *Human Papilloma Virus* (HPV).

Sedentary life style includes physical inactivity and obesity, cigarette smoking, diet (fried foods, red meat), alcohol, UV exposure, environmental pollutants, infections and stress.

Medication such as alkylating agents and immunosuppressant's.

Oxidative stress and carcinogenesis:

Oxidative stress is closely related to all aspects of cancer, from carcinogenesis to the tumor-bearing state, from treatment to prevention. The human body is constantly under oxidative stress arising from exogenous origins (e.g., ultraviolet rays) and endogenous origins (at the cellular level where mitochondria are involved). When such oxidative stress exceeds the capacity of the oxidation-reduction system of the body, gene mutations may result or intracellular signal transduction and transcription factors may be affected directly or via antioxidants, leading to carcinogenesis. The tumor-bearing state is also said to be under oxidative stress associated with active oxygen production by tumor cells and abnormal oxidation-reduction control. One of the mechanisms by which anticancer agents and radiation therapy exert their effects is through apoptosis of cancer cells. Oxidative stress is also involved in the problem of resistance to these treatments. The efficacy of antioxidants in the prevention of carcinogenesis is currently under investigation. Issues to be addressed in the future include the establishment of easy, accurate methods of measurement and evaluation of the extent of oxidative stress in the body as well as the clinical application of experimentally obtained knowledge to the prevention and treatment of cancer [10, 11].

Since, cancer is a multistage process comprised of three major stages: initiation, promotion, and progression. Cumulative research findings suggested that oxidative stress interacts with all three stages of carcinogenesis. During the initiation stage, ROS triggers DNA damage by introducing gene mutations and structural alterations of the targeted DNA. In the promotion stage, ROS can contribute to abnormal gene expression, blockage of cell-to cell communication, and modification of second messenger systems, thus resulting in an increase of cell proliferation or a decrease in apoptosis of the initiated cell population. Finally, oxidative stress may also participate in the progression stage of the cancer process by adding further DNA alterations to the initiated cell population [12].Active oxygen may be involved in carcinogenesis through two possible mechanisms: the induction of gene mutations that result from cell injury and (13) the effects on signal transduction and transcription factors. Which mechanism it follows depends on factors such as the type of active oxygen species involved and the intensity of stress.(14) Cellular targets affected by oxidative stress include DNA, phospholipids, proteins, and carbohydrates

on the cell membrane. Oxidized and injured DNA has the potential to induce genetic mutation. That some telomere genes are highly susceptible to mutation in the presence of free radicals is now apparent and it is known that tumor suppressor genes such asp53 and cell cycle-related genes may suffer DNA damage. In addition, oxidized lipids reactwith metals to produce active substances (e.g.epoxides and aldehydes) or synthesize malondialdehyde, which has the potential to inducemutation. Active oxygen species act directly or indirectly via DNA damage on gene expression(DNA binding of transcription factors) and signalling at the cellular level. Some antioxidantsplay a role in such signal transduction, e.g., glutathione and thioredoxin, workingin the mechanisms of redox regulation.(15,16)The aspect common to these substances isthat thiol works as the major subject of redoxcontrol, implementing regulation of the activityof transcription factors and taking part ingene expression. It is also known that thioredoxinin the extracellular setting exerts a growthpromotingaction and a cytokine-like action oncertain cells. This contributes to the activationof protein kinase, the oncogenes Fos and Jun,and the transcription factor NF-βB (17,18).

Preventive and therapeutic efficacy of antioxidants

As of now it is evident that there is strong relation between oxidative stress and cancer, it has been assumed that ingestion of antioxidants such as vitamins E and C and β-carotene is useful in preventing carcinogenesis, and various related investigations have been implemented.(19) Inhibition of inflammation using antioxidants has also been studied in relation to the risk of carcinogenesis, as in the nonspecific inflammatory disease.(20) This approach is expected to become useful for the prevention of cancer in the long run. However, it is possible that antioxidants may play a role as pro-oxidants, as has been suggested for vitamin C.(21)

Summary of etiological factors, mechanisms and protective strategies used for Chemotherapy

Factors	Carcinogenesis
Etiology	Genetic Environmental Genetic susceptibility to environmental factors
Mechanism in tumorigenesis	Oxidative and nitrosative stress Inflammation Mitochondrial dysfunction Excitotoxicity
Mechanisms of apoptotic cell death	Loss of mitochondrial membrane potential Mitochondrial permeability transition Loss of cytochrome-c from mitochondria Accumulation of cytosolic calcium Activation of apoptotic pathways
Therapeutic approaches and potential targets	Anti-inflammatory Mitochondrial (coenzyme Q10, Carnitine, uncoupling protein 2 expression) Excitotoxicity (antiglutamate) Calcium overload (calcium channel blockers) Protein accumulation (heat shock proteins, proteasomal enhancers) Antiapoptotic stabilizers

Promising indigenous medicinal plants and their bioactive compounds as chemopreventive and therapeutic agents:

A huge reservoir of bioactive compounds exists in many species of plants of Earth, only a small percentage of which have been examined and continued to be an important source of anticancer agents. Worldwide pharmaceutical industries and researchers are trying to identify new anticancer compounds from medicinal plants. With the current decline in the number of new molecular entities from the pharmaceutical industry, novel anticancer agents are being sought from traditional medicines. The search for anti-cancer agents from plant sources started in earnest in the 1950s with the discovery and development of the vinca alkaloids, vinblastine and vincristine, and the isolation of the cytotoxic podophyllotoxins.Epidemiological studies have consistently shown that regular consumption of fruits and vegetables strongly associated with reduced risk of developing chronic diseases such as cancer as the phytochemical extracts from it exhibit strong antioxidant activity.(22)

A well-known Ayurvedic formulation Triphala (TPL) is composed of the three indigenous medicinal fruits Phyllanthus emblica (L.), Terminalia chebula (Retz.) and Terminalia belerica (Retz). It is a widely prescribed Ayurvedic drug and is used as a colon cleanser, digestive, diuretic, and laxative. Experimental studies from our laboratory and others in the past decade have shown that Triphala is useful in the prevention of cancer, since it possesses antineoplastic, radioprotective and chemoprotective effects. Gallic acid is the major bioactive compound of this herbal formulationwhich exhibits novel anti-tumor and anticancer properties (23). Our research group has reported that Triphala exhibited differential behaviourbetween tumor and normal cells through ROS mediated pathway. Findings further supported thatsusceptibility of TPL treated cancer cells were dose dependent irrespective to the normal cells (24). Furthermore, due to differential behaviour, TPL act asan efficient radioprotector; may be in-part by modulating the activities of radiation-sensitive enzymes and protecting DNA from radiation induced damage(25).

Andrographis paniculata and its major bioactive compoundAndrographolide is used in traditional Siddha and Ayurvedic systems of medicine. Andrographolide treatment inhibited the *in vitro* proliferation of different tumor cell lines. The compound exerts direct anticancer activity on cancer cells by cell cycle arrest at G0/G1 phase through induction of cell cycle inhibitory protein p27 and decreased expression of cyclin dependent kinase 4 (CDK4). (26,27). The leaf extract of *Withania somnifera*selectively targets tumor cells and its bioactive compound withaferin-A,is a potent anti-metastatic agent against breast cancer. Recent research findings suggest that Withaferin-A at least in part, mediated through its effects on vimentin and vimentin ser56 phosphorylation (28,29)*Both clinical and pre-clinical studies have suggested that Morinda citrifolia* exhibits cancer preventive effect (30). An alcoholic extract of *Biorhythms sensitivum* exerts antitumor activity and inhibit the solid tumor development on mice induced with Dalton's lymphoma ascites (DLA) cells (31). Research findings have suggested that *Tinospora cordifolia* (guduchi)exhibits anti-neoplastic activity on Ehrlich ascities carcinoma (32). Nimbolide, a triterpenoid extract from the flowers of the neem tree was found to have antiproliferative activity against various cancer cell lines (33).*Allium sativum* seems to be active against

erythroleukemia as well as breast and prostate cancer cells [34]. Cumulative research findings suggest that extract of *Camellia sinensis* prevents prostate, colon, and gastric cancers may be in part by preventing blood vessel growth in tumors *[35]*.***Catharanthus roseus****:* It is one of the very few medicinal plants, which has a long history of uses in the treatment of various disorders including cancer. The alkaloids vinblastine and vincristine present in the leaves are recognized as anti-cancerous drugs. Vinblastine is used in combination with other anticancer agents for the treatment of lymphocytic lymphoma, [36]. Vinblastine and vincristine are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers, including leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma [37]. ***Standard extract and bioactive compounds of Coleus forskholii*** is useful in the treatment of cancer, congestive heart failure. Reports are available that active principle of *Coleus forskohlii*, forskolin, increase of cyclic AMP levels in the culture medium of human prostatic cancer cells thereby cellular growth of the cancer found inhibited. This will be a possible new, safe approach to prostatic carcinoma therapy *[38]*.***Combretum caffrum.****The* bark of the *Combretum caffrum* is combined with a number of other herbs; together they form a formidable anti-cancer treatment. Varieties of anti-cancer compounds called combretastatins are found within the tree bark of *Combretum caffrum* the most potent of which is combretastatin CA-4. It bind to the protein tubulin, which is essential to cytoskeletal architecture, intercellular transport, cell migration, wound healing, and mitotic spindle development for chromosome segregation and cell division. A member of the mitotic inhibitor class of anti-cancer drugs, combretastatin disrupts tumor blood vessel networks by constricting blood supply to tumours. Combretastatin A-4 is active against colon, lung and leukemia cancers and it is expected that this molecule is the most cytotoxic phytomolecule isolated so far [39].Dysoxylum binectariferum: Ayurvedic plant commonly used for the treatment of rheumatoid arthritis. Rohitukine was isolated as the constituent responsible for anti-inflammatory and immuno-modulatory activity Flavopridol, was found to possess tyrosine kinase activity and potent growth inhibitory activity against a series of breast and lung carcinoma cell lines. It also showed broad spectrum in vivo activity against human tumor xenografts in mice, either alone or in combination with other anti-cancer agents, against a broad range of tumors, including leukemias, lymphomas and solid tumors (40).

Some of the important medicinal plants of anticancer activities are enlisted in Table 01

Medicinal Plant	Extract/compound	Cell Line/Model	Pharmacological effect and targets	Reference s
Acanthopana x senticosus (Harms)	Aqueous extract	tert-butyl hydroperoxide (t-BHP)	Potent antioxidantImmunomodulato r	[41]
Allium sativum (L.)	S-allylcysteineaqueous garlic extract	PC-3HeLa	cell cycle arrest at the G0/G1 phasesjBcl-2 ; **f** Bax and caspase 8Immunomodulator, antioxidant	[42] [43] 34

Medicinal Plant	**Extract/compound**	**Cell Line/Model**	**Pharmacological effect and targets**	**Reference s**
Bacopa monnieri (L.)	methanol extract of the whole plant/dammarane triterpene saponins	MDA-MB-231	Antioxidant, antitumor activity	[43]
Bauhinia variegate (L)	Methanolic extract	skin papilloma model	anticarcinogenicand antimutagenic activity	[58]
Berberis vulgaris (L.)	berberine	SCC-4 cells ; murine xenograft animal modelCCl_4-intoxicated miceMCF-7 and MDA-MB-231	Inhibits tumor growthInhibited TNF-ct, COX-2, and iNOS expressioncell cycle arrest at G0/G1	[53][52] [54]
Cassia fistula (L.)	Ethyl acetate extract/ Rhein	COLO 320 DM	Cytotoxic to cancer cells	[57]
Centella asiatica (L.)	Ethanol extract	MCF-7	Induction of mitochondrial and DNA damage	[44]
Curcuma longa (L.)	CurcuminCurcuminoid s	MDA-MB-231,BT474 Cells(GBM) 8401	Anti-apoptosis, p53Antioxidant, NF-KBDownregulation of Skp2 Proteinmitochondrial protection	[60]62,61
Catharanthus roseus (L.)	Vinca alkaloids	Lung adenocarcinom a cells	ROS-mediated JNK activation, Mcl-1 downregulation, DNA damage, mitochondrial dysfunctionblocks G_2-M cell cycle(binds to tubulin in the mitotic spindle)	[51][50] 36}
Eclipta alba (L.)	Hydroalcoholic extract	HepG2, C6 glioma , A498 cell	inhibited the cell proliferation,DNA damage, NF-kB was down-regulated	[45]
Morus alba (L.)	Ethanol extractPolyphenol extractOxyresveratrol	HepG2p53-negative (Hep3B) and p53-positive (Hep3B with transfected p53)	apoptosisAMPK/PI3K/Akt and Bcl-2 family pathways	[56][55]
Ocimum sanctum (L.)	Alcoholic extract (leaves)	lung carcinoma (NSCLC) A549	induces apoptosis and potent Antioxidant	[65][64]

Medicinal Plant	Extract/compound	Cell Line/Model	Pharmacological effect and targets	References
Plumbagozeylanica (L.)	Plumbaginethanolic extract- leaves	leukemia cells, NB4Ehrlich Ascites Carcinoma EAC	ROS mediated apoptosisAnticancer; antioxidant	[59][48]47
Syzygium Cumini (L.)	aq. extract of dry Seed	Swiss albino mice	anti-tumor and anti-oxidative	[59]
Tinospora cordifolia (L.)	Ethanolic extract	LNCaP	Antioxidant	[66]
Withania somnifera (L.) Dunal.	Withaferin A (WFA)	Lu1205,M14, Mel501 and SK28	ROS production, Bcl-2 down-regulation	[67,65]
Zingiber officinale Rose.	Rhizome extract	HCT 116 and HT 29 colon	triggers apoptosis	[63, 67]

Standard Antioxidants, Bioactive compounds and their supposed mode of action.

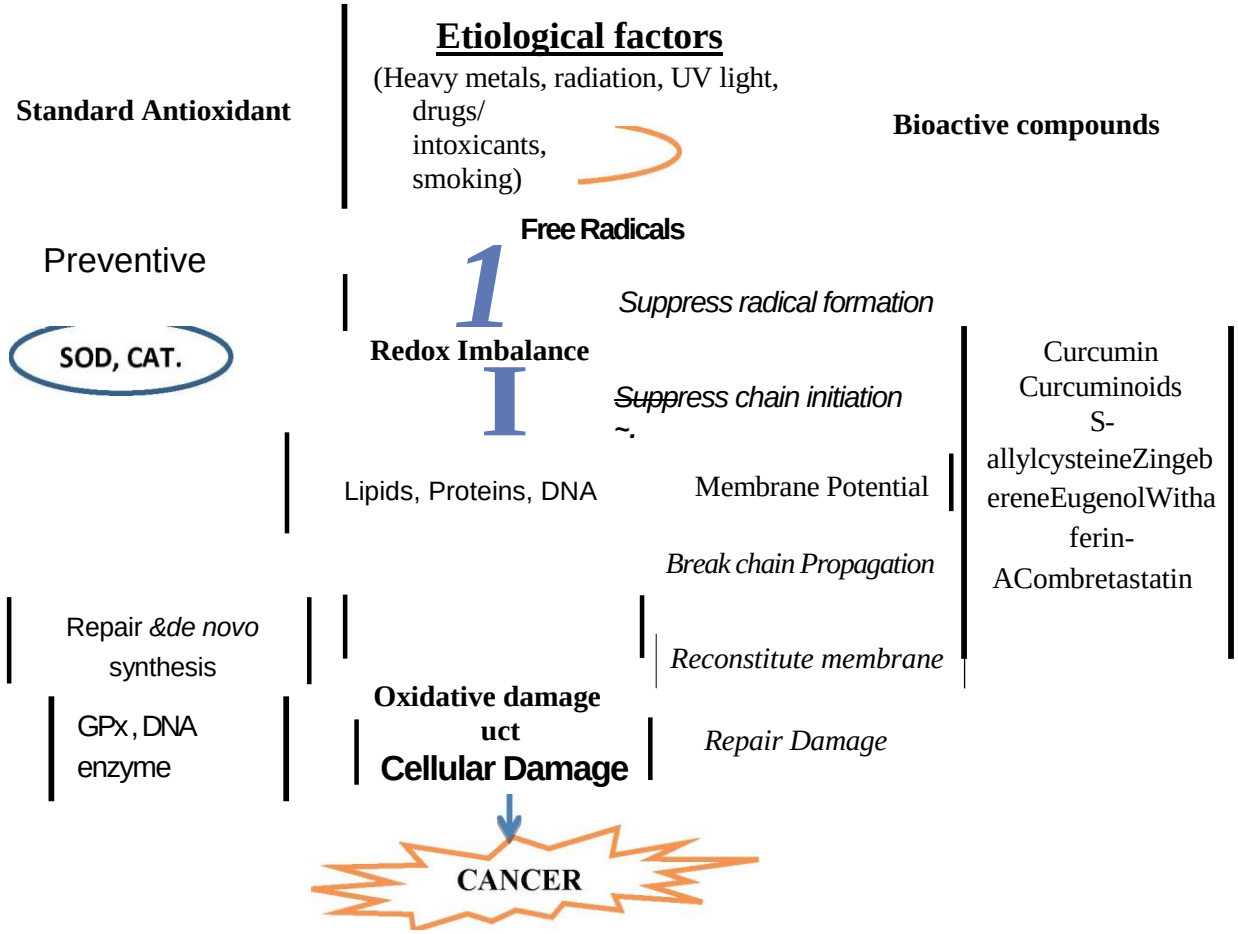

Figure 1: Probable Mode of Action of Bioactive compounds as chemopreventive agents

Conclusion

This article reveals a detailed review of potent indigenous medicinal plantsand their bioactive compounds useful to treat various types of cancer. From the present review, it can be concluded that since, cancer is a multifactor disease; it may require treatment with compounds able to target multiple intracellular components. The isolation, identification of active principles and pharmacological studies of the active phytoconstituents may be considered and studied elaborately to treat effectively for various types of cancer. It will be helpful to explore the medicinal value of the plants and for the new drug discovery from them for the researchers and scientists around the globe. Furthermore, it is of urgent need to develop the compounds which can act synergistically, may prevent malignancies, safe in long term use as well as cost effective is the fascinating challenge for the cancer researchers. Moreover, the benefit of antioxidant ingestion after cancer has also yet to be demonstrated.

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TREATMENT OF RADIATION-INDUCED NORMAL TISSUE DAMAGE

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Normal tissue toxicity is a common side effect of radiotherapy treatment of cancer patients. It is also a major concern in populations subjected to accidental exposure to ionising radiation. At present, there is not a standard protocol for the treatment of radiation-induced normal tissue lesions. Recently, a number of modalities have been identified and used, mainly experimentally and few clinically, to alleviate radiation damage. These include essential fatty acids, vasoactive drugs, enzyme inhibitors, antioxidants, growth factors and stem cells. Our approach to the treatment of radiation lesions was through the application of antioxidants and transplantation of adult stem cells; obtained from bone marrow or adipose tissue. These modalities were tested on a number of radiation-induced normal tissue lesions including skin, oral mucosa, neural tissues, lung and gut and it concluded that both modalities were effective in amelioration of radiation-induced normal tissue lesions. In the course of stem cell transplantation experiments it was observed that the improvements did not tally with the number of transplanted cells. This suggested that probably the transplanted exogenous cells initiated a process of recovery/regrowth of the endogenous stem cells that led to an improved functional response.

Keywords: *radiation, antioxidant,*

Introduction

Radiotherapy, besides surgery and chemotherapy, is one of the principal modalities in the treatment of cancer. At present over 50% of all cancer patients in Western world receive radiotherapy at one stage in their course of treatment. Theoretically, localized tumours can be eradicate by radiotherapy provided that a large enough dose of radiation could be delivered. However, this is not practical because radiation does not discriminate between tumours and normal tissues and there is always the danger of damaging normal tissues adjacent to the tumour. The larger the dose of radiation the greater the probability of local tumour eradiacation and equally the risk of normal tissue damage. This implies that the dose of radiation delivered to the tumour will always be limited by the risk of damaging normal tissues within the treatment field and those surrounding the tumour. Besides the dose of radiation there are other factors such as the total radiation dose, overall treatment time , dose per fraction , dose rate and radion quality that can influence the outcome of radiation therapy. These factors have been studied in great detail in the past and factors such as dose fractionation have been optimized through a number of protocols. The therapeutic ratio has been further improved by using multiple field treatment (MFT) and intensity-modulated radiation therapy (IMRT). In practice, even with the most-optimal treatment planning, normal tissues surrounding the tumour and those within the path of radiation will be affected by radiation. Therefore, normal tissue damage still remains the most important limiting factor in optimizing radiotherapy. During the recent years a large number of pharmacological modalities have been tried and tested in the treatment of radiation-induced lesions with limited success. These have been reviewed elsewhere (Rezvani, 2008). This paper reports some of our

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unpublished work and reviews the published material on the treatment of normal tissue lesions by stem cell transplantation.

Stem cell approach to the treatment of radiation-induced lesions:

According to the 'target cell' hypothesis it is assumed that radiation injury develops as a result of sterilization of the target cells. Although it is now accepted that the process of the development of radiation lesion is much more complex and the expression of damage starts before target cell depletion, the fact that the ultimate lesions manifest as a result of denudation of functional cells remains unchallenged. For example in epidermis of skin, oral mucosa or the lining of gut the loss of functional cells, due to radiation-induced sterilization of colonogenic stem cells, results in the erosion of the epithelial layer. During the healing phase subsequent repopulation of the epithelium is predominantly by the proliferation of surviving colonogenic basal cells from within the irradiated area or those migrating from outside the radiation field.

In late responding tissues such as central nervous system also, contrary to the classical beliefs, the involvement of stem cells is now well accepted. A similar pattern of events, albeit in a more complex way, also occurs in late responding tissues where injury to cell initiates a cascade of events starting by expression of stress signals from damaged cells followed by depletion of stem cells and development of fibrosis or scaring that results in loss of functional cells and ultimate lesion development. Stem cell approach to the treatment of radiation-induced lesions is based on the assumption that the donor stem cells replace the damaged host stem cells, possibly before establishment of the lesion, and this prevents the development or shortens the duration/severity of the lesions in both early and late responding tissues. In this article it will be argued that the beneficial effects of stem cell transplantation is not necessarily due to the replacement of damaged cells by transplanted cells but most probably due to a paracrine effect. Transplanted cells secrete some bioactive factors that initiate the stimulation of the host stem cells to regenerate the damaged tissues.

Types of Stem Cells

Stem cell is undifferentiated cell that can divide through mitosis, self-renew other factors such as the total radiation dose, overall treatment time, dose per fraction, dose-rate and radiation quality that can influence the outcome of radiation therapy. These factors have been studied in great detail in the past and factors such as dose fractionation have been optimized through a number of protocols. The therapeutic ratio has been further improved by using multiple field treatment (MFT) and intensity-modulated radiation therapy (IMRT). In practice, even with the most-optimal treatment planning, normal tissues surrounding the tumour and those within the path of radiation will be affected by radiation. Therefore, normal tissue damage still remains the most important limiting factor in optimizing radiotherapy. During the recent years a large number of pharmacological modalities have been tried and tested in the treatment of radiation-induced lesions with limited success. These have been reviewed elsewhere (Rezvani, 2008). This paper reports some of our unpublished work and reviews the published material on the treatment of normal tissue lesions by stem cell transplantation.

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of MSCs for autologous stem cell therapy. Expansion rate, differentiation and immunomodulatory potencies of BM-MSCs and adipose tissue derived mesenchymal stem cells (ADSCs) are comparable (Ra et al, 2011).

Stem cell treatment:
Bone marrow transplantation:

Application of stem cells in medical practice is not new and in fact stem cells are used for decades in the treatment of both malignant and non-malignant diseases e.g. leukaemia, lymphoma and certain types of anaemia in allogenic bone marrow transplantation procedures (Friedrichs et al, 2010) where whole marrow or stem cells extracted from marrow are transplanted to reconstruct the haemopoietic tissues of the patient after radiation

Chemotherapy induced myeloabalation. Bone marrow transplantation was initiated by the work of Lorenz et al (1951) followed by Barnes et al (1956) who demonstrated that irradiated mice could be protected by transplantation of bone marrow cells. Bertho eta al (2002) studied the effects of bone marrow derived mononuclear cells in the treatment of radiation-induced pancytopenia in a non-human primate model. The animals were irradiated with 8 Gy total body dose and the cells were transplanted 24 hours after irradiation. Results showed that stem cell transplantation shortened the period and the severity of pancytopenia and improved hematopoietic recovery. A historical review of the development of bone marrow transplantation is given by Thomas (1999).

Studies on spinal cord:

With regard to the application of stem cells on non-haemopoietic tissues Groves et al (1993) and Franklin et al (1995) demonstrated that transplantation of oligodendrocyte progenitor cells resulted in extensive re-myelination of areas of persistent demyelination in the adult rat's spinal cord. Later a 12-mm section of the cervical spinal cord of 5-week-old rats was irradiated with a single dose of 22 Gy of Co-60 .-rays (Rezvani et al 2001). This dose is known to produce myelopathy in rats within 6 months of irradiation. These authors tested the effect of two different types of adult stem cells. The cells were transplanted intradurally, 90 days after spinal cord irradiation and it was shown that the paralysis-free survival rates of rats that received stem cell transplantation were a third higher than historical controls at 183 days after irradiation. It was concluded that transplantation of neural stem cells 90 days after irradiation significantly ameliorated the expression of radiation-induced myelopathy in rats.

Studies on gut:

Semont et al (2010) transplanted human bone marrow derived mesenchymal cells (hBM-MSC) into gut irradiated NOD/SCID mice by infusion. In this study mice were subjected to a total body irradiation (TBI) at a dose of 3.5 Gy immediately followed by the delivery of local irradiation to the abdomen at a dose of 5 Gy resulting a total dose of 8.5 Gy to the abdominal region. Animals were killed at 3-120 days after irradiation and small intestine (jejunum) was collected for functional, structural and cellular homeostasis analysis. It was concluded that hBM-MSC transplantation improved the recovery of the small intestine, both structurally and functionally and extended the life of mice. This was attributed to the improvements in the renewal capability of small intestinal epithelium. hBM-MSC infusion also assisted in reestablishment of cellular homeostasis through increasing endogenous proliferation processes and inhibition of

radiation-induced apoptosis of small intestinal epithelial cells. In our lab (unpublished work) the effect of hADSC transplantation after gut irradiation was studied on six-week-old female Lister hooded rats. A 4 cm length of the colon of rat was irradiated, under isoflourane aneshesia, with a 11 Gy single dose of 250 kVX-rays, at a dose-rate of ~1.1 Gy/min. For irradiation, preanesthetised rats (2-3% isoflourane in oxygen) were restrained in the jig and 4 cm length of abdomen from anal margin that included 4 cm of the colon was marked as irradiation field. The rest of the animal was shielded by a 4mm thick lead. During irradiation anaesthesia was maintained by continuous flushing of the irradiation jig with oxygen and 2 % isoflourane at a rate of ~3 l/min. Four animals were irradiated at a time. After irradiation, animals were randomly allocated to one of the five test groups as follows: R+PBS: Radiation only (11 Gy) that received 1mL of PBSinjected ip; R+hMSC: 11 Gy radiation+2million human ADSC injected ip, 24 hrs after irradiation; R+hMSC lys: 11 Gy radiation+2 million human ADSC lysate injected ip, 24 hrs after irradiation; R+CMhMSC: 11 Gy radiation+conditioned medium made from 2 million human ADSC injected ip, 24 hrs after irradiation; R+CMx3hMSC: 11 Gy radiation+three applications of conditioned medium made from 2 million human ADSC injected ip, 24 hrs, 72 hrs and 120 hrs after irradiation. Three other animals were sham irradiated and allocated to un-irradiated control group. A total of 18 animals (3 per group) were used. Animals in test groups received either 2 million human adipose tissue derived MSCs in 1 mL PBS by ip injection, conditioned medium made from 2M hADSCs or the same number of cells lysated by 10 times freezing and thawing prior to injection.

Nine days after irradiation the animals were killed and 4 cm of colon, measured from anal margin, was excised and fixed in 4% paraformaldehyde. After fixation, the colon was cut transversally into four equal parts. These samples were dehydrated and embedded in paraffin wax. Sections, 5 mm thick, were cut from each of these tissue samples and stained with hematoxylin and eosin. These sections were scanned by light microscopy and the number of crypts per circumference was counted on each section. The mean number of crypts from four sections of three animals' colons in each group was obtained and mean values calculated. The results showed a significant reduction in the number of crypts per circumference nine days after irradiation (80±9) compared to that of unirradiated controls (178±8). However, transplantation of hADSCs or injection of CM increased the number of surviving crypts per circumference to 110±10. Injection of the hADSC cell lysate resulted in similar level of improvement (126±18). The best improvement was achieved after three injections of conditioned medium (163±9).

Studies on liver:

Mouiseddine et al (2012) studied the effects of stem cell transplantation on radiation induced liver damage. In this study NOD–SCID mice were subjected to a 10.5 Gy abdominal dose from a Co-60 source and the effects of hBM-MSC on biological and histological markers of liver injury were assessed. It was shown that irradiation induced significant apoptosis in the endothelial layer of vessels and elevated the transaminases ALT (353.9 ± 37.5 vs. 108.6 ± 18.9 U/I) and AST (40.3 ± 4.9 vs. 20.3 ± 0.8 U/I) levels after 5 days ($p < 0.001$). However, transplantation of hBM-MSCs by infusion almost completely removed the apoptosis from 29± 7 in radiation alone group to 3±2 in stem cell transplanted

animals. Transaminases values at 5 days after irradiation were also significantly ($p < 0.05$) decreased in stem cell transplanted animals; AST (198.8 ± 43.1 U/I) and ALT (14.9 ± 4.7 U/I).

Studies on skin:

hBM-MSCs, intravenously transplanted into NOD/SCID mouse, showed significant improvement in the development and healing of radiation-induced skin damage (François et al, 2007). The hind leg skin of mice was irradiated with 30 Gy single dose of Co-60 gamma rays and stem cell transplantation was carried out 24 hours after irradiation. It was demonstrated that the skin of mice transplanted with stem cells was partially healed at 6 weeks. This was followed by a complete healing of the epidermis at 8 weeks after irradiation. Only a partial healing of skin lesion was observed in radiation only group of animals at 8 weeks.

Agay et al (2010) irradiated the skin of minipigs with 50 and 60 Gy Co-60 gamma rays and followed up for over 30 weeks. These authors demonstrated that intradermal injection of autologus BM-MSCs, 2-3 times a week from 4-14 weeks after irradiation, lead to improved vascularisation.

Studies Salivary Gland:

Lombaert et al (2006) assessed the effects of autologus BM-MSC mobilized by administration of granulocyte stimulating factor (G-CSF) in regeneration of irradiated salivary glands and reported a significant improvement in the gland weight, number of ancinar cells and salivary flow rate.

Clinical studies:

Bertho et al (2008) reported a case of a 27 year old Chilean radiation accident victim who received a major gamma dose to his buttock. This patient was treated by excision of the irradiated buttock and wound closure by a skin allograft that did not last very long and got infected immediately. Later at day 90 after irradiation the patient received a skin autograft together with 168 million autologus BM-MSC followed by 226 million BM-MSCs nine days later. A complete healing 75 days after stem cell transplantation was reported.

There are a number of studies that report the treatment of radiation-induced normal tissue lesions by autologus fat grafting. Rigotti et al (2007) reported the results of twenty patients suffering from severe side effects of radiotherapy. These patients were treated with autologus fat grafting that resulted in a systematic improvement or remission of symptoms in all evaluated patients. Phulpin et al (2009) treated aesthetic defects caused by radiotherapy in head and neck cancer patients by fat grafting. The treatment resulted in improved quality of life and amelioration of radiation-induced lesions. Kim et al (2010) treated six patients by serial autologous fat grafting after irradiation to the orbit and enucleation. Four of the six patients were successfully fitted for orbital prostheses and the authors concluded that autologous fat grafting could be used for improved ocular implantation to the irradiated enucleated orbit. Serra-Renom et al (2010) and Salgarello et al (2012) also reported a favourable outcome and formation of new subcutaneous tissue after post mastectomy fat grafting in breast-irradiated patients. Breast irradiated patients do not respond favourably to allopathic breast reconstruction and the procedure is usually associated with complications (Cordeiro et al, 2004). The favorable results obtained by fat grafting can be attributed to MSC component of the transplanted fat. Fat contains much more MSCs than bone marrow (about 100,000 MSCs per gram of fat).

Homing of the transplanted cells:

There are a number of studies that have shown the distribution of transplanted stem cells in irradiated animals. Almost all studies demonstrate that transplanted MSCs migrate specifically to the radiation-damaged tissues. Migration, and homing kinetics of human BM-MSCs injected into NOD/SCID mic were studied (Chapell, 2003; François et al, 2006) after total body or abdominal irradiation. These authors demonstrated that systemic delivery of BM-MSCs migrated to liver, bone, bone marrow, gut, hearth, kidney, brain, lung, stomach and were found up to 3 months post irradiation in gut, lung, bone marrow, and heart in total body irradiated animals. The transplanted cells were scarcely detectable in other body areas and in the blood. After abdominal radiation exposure these cells engrafted preferentially in the abdomen: liver, spleen, stomach, kidney and gut. These observations support the hypothesis that MSC can home to sites of radiation injury. Homing of transplanted stem cells to damaged tissue is not specific to radiation-damaged tissue. Many other studies have shown that the transplanted cells mainly home to damaged tissues and bone marrow. Kraitchman et al (2005), with the use of a combined single-photon emission CT (SPECT)/CT scanner and a radiotracer, studied the in vivo trafficking of allogeneic BM-MSCs in experimental acute myocardial infarction in dogs. BM-MSCs were intravenously injected 72 hours after induction of acute non-transmural myocardial infarct created by a 90-minute closed-chest left anterior descending coronary artery balloon occlusion with the use of x-ray cardiac catheterization techniques, followed by reperfusion. It was demonstrated that BM-MSCs after intravenous injection were distributed to non-target organs such as the liver, kidney, and spleen within 24 to 48 hours. Focal and diffuse uptake of MSCs in the infarcted myocardium was detected in the first 24 hours after injection and persisted until 7 days after injection.

Discussion:

Cell loss and regeneration is a natural process that happens in almost all tissues. Cells lost due to ageing or other insults are continually replaced by proliferation of stem cells and differentiation tissue specific progenitor cells. The function of normal tissues is as a result of the balance between cell loss and cell production. The target cell theory of radiation injury, that was developed on the basis of earlier studies by Puck & Marcus (1956), considers radiation-induced cell loss as the cardinal cause of normal tissue damage or tumor ablation by radiation. Although it is now accepted that the process of the development of radiation lesion is much more complex and the expression of damage starts before target cell depletion and is mediated by the secretion of many biologically active factors by the damaged cells, the fact that the ultimate lesions manifest as a result of denudation of functional cells remains unchallenged. After irradiation, while the cell loss continues the cells killed or damaged by irradiation fail to produce replacements for the lost cells. The number of cells lost exceeds the number of cells produced and the balance tips over the cell loss. This results in a deficit in the number of differentiated cells. When the cell number reduce below a critical level, a lesion or a functional insufficiency manifests. The latency period of the lesions caused by irradiation corresponds to the turnover time of the functional cells of each individual tissue. On the basis of target cell hypothesis, the early normal tissue response and tumour response were adequately explained by the

reproductive sterilization of parenchyma cells. However, this hypothesis could not adequately describe the development of late damage. Vascular damage, that in turn develops as a result of endothelial cell loss, was seen responsible for the development of late damage. For example the acute cutaneous or mucosal erosions are considered as a consequence of sterilization of epithelia and the latency period of these lesions correspond to the turnover time of the target cells. However, the late dermal or submucosal reactions are considered vascular mediated and attributed to the impairment of circulation due to the loss of blood vessels. The same is true of radiation damage to the central nervous system where the glial hypothesis (Zeman & Samorajski 1971; Burns et al, 1972) suggests that white matter necrosis is related to the reproductive sterilization of glial cells (oligodendrocytes and/or their progenitors) and that demyelination and necrosis develop as a consequence of the gradual loss of these cells with time after irradiation. The vascular hypothesis (Delattre et al, 1988; Powers et al, 1992) considers damage to the vasculature as the key step in the development of white matter necrosis. Whatever the initiating mechanisms, both the glial and vascular hypotheses agreed upon the fact that the end result of radiation damage to the CNS was demyelination of axons and necrosis that develops due to reproductive sterilization of glial cells or vasculature. It was on the basis of these hypotheses that researchers attempted the modification of radiation-damaged tissue by stem cells. The evidence reviewed above and those quoted by the others (Herodin et al, 2005; Caplan, 2009, Coppes & Stokman, 2011) effectively support the idea that radiation damage can be ameliorated by transplantation of stem cells. However, almost all published papers either were not able to trace the transplanted cells in the damaged tissues or reported a very low level of engraftment that could not justify the functional improvement observed after stem cell transplantation. Transplantation of stem cells 90 days after induction of radiation-induced myelopathy reduced the paralysis by third but no transplanted cells were found in the spinal cord (Rezvani et al, 2001). Lombaert et al (2006) showed a significant improvement in the gland weight, number of ancinar cells and salivary flow rate of salivary gland irradiated male-eGFP+ bone marrow chimeric female C57BL/6 mice after mobilization of oautologus BM-MSCs by administration of G-CSF but did not observe the GFP/Y chromosome donor cell lables and neither the expression of G-CSF receptor in ancinar cells. The authors concluded that the repair process did not include transdifferentiation of BM-MSCs to salivary gland cells. Mouiseddine et al (2012) observed improvements in liver irradiated animals after stem cell transplant but did not find any MSCs in the liver. All these findings point to the fact that transplanted stem cells exert their action in a paracrine fashion. Reduction in radiation-induced complication and iprovement in formation of subcutaneous tissue after post mastectomy fat grafting in breast irradiated patients (Serra-Renom et al, 2010; Salgarello et al, 2012) can well be attributed to the stem cell component of the fat graft that acted also in a paracrine fashion. This implies that the beneficial effects of stem cell transplantation is not necessarily due to the replacement of damged cells by exogenously transplanted cells. Most probably the repopulation of damaged tissue by transplanted cells is due to a paracrine effect. Transplanted cells secrete some bioactive factors that initiate the stimulation

of the host stem cells to regenerate the damaged tissues. This supports the suggestion by Mouiseddine et al (2012) that cytokines and growth factors produced by the transplanted MSCs stimulate the regeneration of damaged orgas by an indirect effect. MSCs Secret angiogenic and antiapoptotic factors (Rehman et al, 2004) and express numerous genes of neurotrophins and extracellular matrix proteins required for the nerve growth and myelination. Induction of neural differentiation of ADSCs enhances production of brain-derived neurotrophic factor (BDNF) as well as ability of these cells to induce nerve fiber growth via BDNF production (Lopatina et al, 2011). Bioactive factors secreted by MSCs are both immunomodulatory and trophic. In damaged tissues the trophic component of secretions inhibits ischaemia-induced apoptosis and scarring, stimulates angiogenesis and the mitosis of tissue intrinsic progenitor cells. The immunomodulation component inhibits lymphocyte surveillance of the injured tissue (Caplan, 2009). MSCs also release bioactive factors such as VEGF, IGF-1, EGF, keratinocyte growth factor, angiopoietin-1, stromal derived factor-1, macrophage inflammatory protein-1a and ß and erythropoietin (Chen et al, 2008). Chiellini et al (2008) identified a total of 73 proteins released in the secretome of human ADMSCs. This included proteases, protease inhibitors, extracellular matrix components, cyclosklethan components, anti-inflammatory/antioxidant proteins, heat shock proteins and metabolic enzymes. Paracrine effect of stem cells is exerted through the intercellular communication by the exchange of protein and RNA-containing microparticles and exosomes. Microparticles are a hetrogeous population of small vesicles with a diameter of 1001000 nanometer. These are membrane-coated particles released during the activation of cells or apoptosis (Distler et al, 2005; 2006). Exosomes are smaller microparticles (40–100 nm) that have a bilipid membrane with the same orientation as plasma membrane and a cargo that includes both proteins and RNA. MSCs are known for secreting therapeutic paracrine factors and RNA-containing microparticles. Chen et al (2010) demonstrated that MSC conditioned medium contained small RNAs encapsulated in cholesterol-rich phospholipid vesicles and concluded that MSCs could facilitate miRNA-mediated intercellular communication by secreting microparticles enriched for pre-miRNA. Gatti et al (2011) showed that microparticles released from MSCs protected against ischaemia-reperfusioninduced acute and chronic kidney injury. They also demonstrated that pretreatment of microparticles with RNase, to inactivate the RNA cargo, abrogated their protective effects. Janowska-Wieczorek et al (2001) demonstrated that mouse bone marrow cells covered with platelet derived microparticles engrafted lethally irradiated mice significantly faster than those not covered, indicating that platelet derived microparticles play an important role in the homing of the transplanted cells. Microparticles released by stem cells can be found in the conditioned media produced by the activated cells. Beneficiary effects of microparticle containing conditioned medium from MSCs have been demonstrated by many authors in the treatment of various number of lesions (Poll et al, 2008; Bruno et al, 2009; Li et al, 2012; Zhang et al, 2012) and inhibition of the progression of established tumour growth (Bruno et al, 2012). Many of these authors have suggested microparticles as a potential new therapeutic approach. The results of gut

studies summarized above (Rezvani, unpublished data) support the feasibility of cell free approach and effectiveness of stem cell microparticles. However, the potentials of mciroparticles secreted from activated MSCs and cell free approach should be further investigated in the treatment of radiation-induced injuries.

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BRACHYTHERAPY IN GYNAECOLOGICAL CANCERS – AN OVERVIEW

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The history of radiation therapy began in Paris in 1896 with discovery of Radioactivity by Henry Becquerel .The first recorded successful Brachytherapy of Basal Cell Carcinoma of the face was conducted at St. Petersburg in 1903 - within 5 years of isolation of Radium by Marie & Pierre Curie.

The use of Radium therapy in the treatment of Cancer Cervix was first presented at the Congress of Halle in 1913. Intra-cavitary Brachytherapy commenced in a planned way at Stockholm in 1914 by Forssel followed by Regaurd at Peris (1921) Manchester system developed by Paterson Parker first described doses as function of time & defined anatomical points - point "A" &"B" - which would form the basis for development of "basic dosimetry in Radiotherapy ".

All these systems were Low Dose Rate manual Applications using Radium 226. A brief of the following systems:

- **A-Stockholm System (1914)**
- **B-Paris system (1921)**
- **C-Manchester system (1934)**

A- STOCKHOLM SYSTEM: (rod shaped applicators were used) Applications details were empirical and mostly followed the rigid rules of radium distributions.

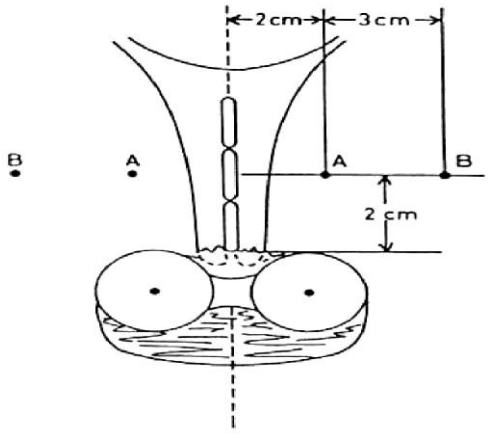
i- 53-88 mg of radium in uterine cavity

ii- flat box vaginal packing 60-80 mg of ^{226}Ra

iii- 2 to3 application in three weeks

iv- 27-30 hrs each application aim is the local **control** of the disease

v- mg- hrs as treatment prescription (not practicable)



1914-1928 - 1537 cases; 5 years survival 21.3%

B-PARIS SYSTEM

3- Uterine source, 3-vaginal source, 10 to 15 mg radium each 5-8 days of treatment 1:1 packing in uterine; vaginal **1919-1926** - 678 cases; 5 years survival 26% **Paris System :**

^ Single Application

^ 5 days to deliver 7200-8000 mg-hrs.

>• Almost equal amounts of Radium were used in uterus and vagina.

>• The intrauterine tube contained three sources in the ratio of 1:1:0.5.

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Two cork intravaginal cylinders (colpostats) had one source each of each of almost the same strength as the top of intrauterine source.

C- MANCHESTER SYSTEM

I- Point A&B was defined, 20-35 mg radium in uterine tandom 15-25 mg in vaginal ovoids for 8000R at **point A**

II- In place of mg hrs, 140hrs of time was used for dose prescription

- ***Concept of Point A and B were based on physical as well as anatomical consideration. Point A coincided with Crossing point of Uterine artery and Ureter and point B represented pelvic wall.***
- ***Dose rate was 57.2 R/Hr.***
- ***It provided the pear shaped distribution of one dimensions irrespective of tumour***
- ***Concept of Tumour as a volume& not a point***

All the three classical systems used Radium226 as sources of Brachytherapy & delivered the radiation in typical Low Dose Rate Systems.

Radium as a source of Radiation therapy got gradually abandoned due to its potential hazards. However because of vast clinical experience & radiobiological data accumulated by usage of Ra226 it is considered as a standard isotope in low dose brachytherapy with which all other substitutes of brachytherapy sources are compared.

Commonly used Brachytherapy sources are :

Radionuclide	Half-life	Photon Energy (MeV)	Half-value Layer (mm lead)
226 Ra	1600 years	0.047 - 2.45 (0.83 ave)	8.0
222 Rn	3.83 days	0.047 - 2.45 (0.83 ave)	8.0
^{60}Co	5.26 years	1.17, 1.33	11.0
137 Cs	30.0 years	0.662	5.5
192 Ir	74.2 days	0.136 - 1.06 (0.38 ave)	2.5
198 Au	2.7 days	0.412	2.5
^{125}I	60.2 days	0.028 ave	0.025
103 Pd	17.0 days	0.021 ave	0.008

Popular source for HDR : 192-Ir

- Many different forms available
- "Iridium 192", E= 0.38 Mev
- Most important source for HDR applications

Medium half life (74.2 days) - decay correction necessary for each treatment

Needs to be replaced every 3 to 4 months to maintain effective activity and therefore an acceptable treatment time.

With better understanding of Radiobiology the dose delivery system of Brachytherapy also got modified over the years .

The Radiobiological rationale for LDR Brachytherapy in brief :

- Low dose rate increases Therapeutic Ratio - limited only by tumor cell repopulation
- Relative efficacy of LDR will depend on cell repopulation rate.
- Alternative schemes involving small number of fractions or high dose rate should be designed on equi -effect consideration for late complication , not tumor control.

The different Dose Rate Systems practiced are:

Delivery modes of Brachytherapy -

Dose rate definitions after Corbett (1990)

- Low Dose Rate 0.4- 2 Gy/hour around 0.5Gy/hour
- Medium Dose Rate 2-12 Gy/hour (not often used)
- High Dose Rate >12Gy/hour but usually in the region of 150 Gy /hr
- Pulsed Dose Rate pulses of around 1Gy/hour

Advantage HDR	**Disadvantage HDR**
1) Greater accuracy	Expensive installation
2) Short treatment time	Sources expensive
3) OPD procedure	Extra room protection
4) More no. of pt can be treated	More no of fractions
5) Complete staff protection	Poor pt compliance

HDR brachytherapy is gradually becoming more popular because of its added advantages. Considering the Radiobiological aspect, the late effects (complications) may be expected to increase for a given level of tumor control. Brachytherapy in gynecological cancers prove to be an exception to this, as pointed out by Dale(1990) & Brenner & Hall(1991), due to the following reasons :

- The radiation dose causing unwanted late effects is much less than the actual treatment dose.
- The limiting organs at risk Bladder & Rectum are some distance away from the Brachytherapy sources
- Packing & retraction of sensitive organs result in 20% decreased dose to bladder & rectum.- this physical advantage cancels out the radiobiological disadvantage.

Principles of Brachytherapy

- Improved local control
- Optimize the therapeutic ratio
- Maximum dose escalation
- Minimize normal tissue irradiation
- Organ and function preservation
- Improved quality of life
- Marked gains in survival

Additional benefits of HDR Brachytherapy

No source preparation No source inventory Optimization of dose distribution • Single rate source to be replaced

All Brachytherapy modalities feasible

Intracavitory
Interstitial
Intra operative/ intra luminal/ intravascular
Intra luminal

Triumph of Intracavitary Radiation Therapy in treatment of Cancer Cervix or other Gynecological Cancers is attributed to the following facts:

- Cervix is an accessible organ
- Cx & vagina can accommodate applicators
- Cx & vagina can tolerate very high doses of radiation :
  - ♦ Tolerance of Cervix - 200Gy
  - ♦ Tolerance of Vagina - 250 Gy
  - ♦ Tolerance of Endometrium - 250-300 Gy
  - ♦ Tolerance of Bladder - 60 Gy

  Tolerance of Rectum - 55gy

  Dose limiting organs
- I/C RT allows high dose to target volume, rapid fall off of dose-less dose to surrounding structures.

Management of patients with Gynecological Cancers

- History ,in details with special emphasis on menstrual, obstetrics & sexual history of both wife & husband
- General physical examination
- Local examination -including per vaginal & per rectal examination
- Routine Investigations
  - > Hemogram
  - ^ Blood Biochemistry including KFT, LFT
  - ^ X-ray chest PA view ^ USG abdomen & pelvis Investigation to confirm Diagnosis
  - > EUA & biopsy in cancer Cervix
  - > Endometrial biopsy in cancer Body Uterus

    Punch / Excisional biopsy in Cancer Vulva / Vagina
- Investigations to stage the disease / metastatic work up
  - ^ USG abdomen & pelvis
  - ^ CT Scan abdomen & Pelvis - specially in Ca.Endometrium
  - >• MRI -specially in Cancer Vulva
  - > PET Scan
  - ^ Cystoscopy - routinely in Cancer Cervix stage II onwards
  - > Ba- enema
  - ^ Procto-sigmoidoscopy - where indicated
  - >• Bone- Scan - where indicated
- Special investigations

  ^ Tumor markers/ biomarkers SCC-Ag ,CA 125- ,CEA, CA 19.9

<u>Pre Requisites for starting patients on Brachytherapy</u>

- Anemia to be corrected
- Infection to be controlled Supportive treatment
- Tumor should not be too bulky

Indications of Brachytherapy in Gynecological Cancers :
Cancer Cervix:

Stage IA
IB1 ^.only Intra-cavitary Brachytherapy
Treatment Protocol: LDR
ICRT---------- 1wk----------ICRT
HDR ICRT---1wk---ICRT---1wk---ICRT----
1wk----ICRT Dose - LDR - 35-40 Gy to pt. A x 2 sittings with a gap of 1wk
- HDR 8-9 Gy x 4 sittings with a gap of one wk between each

Stage IB2 - ICRT + External Beam Radiotherapy with Central shield
IIA - Treatment Protocols: LDR
IIB (Tumor
Size<4cms) ICRT—lwk------ ICRT--------- EBRT with CS
ICRT—lwk—EBRT with CS---------ICRT
HDR:
ICRT—ICRT-------ICRT ----ICRT--------EBRT with CS
ICRT—ICRT ------EBRT with CS ----- ICRT—ICRT

Dose - EBRT with CS -35 Gy/3wks/15frs.
LDR 35-40 Gy to pt. A x 2 sittings with a gap of lwk -
HDR 8-9 Gy x 4 sitting with 1 wk gap between each

Stage IIB EBRT + ICRT +/- Perineal Implant
IIIB Dose - EBRT- 50Gy/5wks/25 frs.
ICRT -LDR- 30 Gy to pt A HDR 7-
8 Gy to pt A in 2 sittings

Perineal implant 8-10 Gy in 2 sittings
♦♦♦ Dose to pt. A not to exceed 80 Gy

Cancer of Body Uterus :(Post Operative)

Stage la G3 I LDR -35- 40 Gy surface dose in 2 sittings
Stage lb G1+G2 r~ Vaginal Sorbo Dose : HDR - 7-8 Gy surface dose in 4 sittings

Stage Ic +IIa+ lib - Post Op. EBRT + Vaginal Sorbo
Dose - EBRT-50 Gy/ 5wks/ 25frs
Vaginal Sorbo -LDR – 20 Gy surface dose
-HDR – 7-8 Gy surface dose in 2 sittings

Cancer of Vagina

Stage I
Stage II \~ selected cases - ICRT alone
Dose - LDR- 35-40Gy surface dose in 2 sittings - HDR- 7-8 Gy surface dose in 4 sittings In all other stages - EBRT + ICRT +/- Perineal Implant Dose - EBRT - 50Gy/5wks/25 frs.
ICRT - LDR- 20 Gy surface dose
-HDR- 7-8 Gy surface dose in 2 sittings
Perineal Implant- 8-10 Gy surface dose in 2 sittings

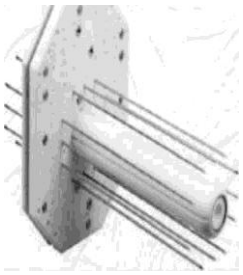
Cancer Of Vulva:

In Selected Cases : Mould Therapy / Interstitial Implant

Parametrial Implants in Gynecological cancers

Indications: Indications for interstitial brachytherapy in gynaecological malignancies are

- In patients with locally advanced cervical cancer, the parametrial extent of the tumor cannot be encompassed by standard intracavitary brachytherapy.
- Narrow Vagina use of appropriate vaginal applicators to arrive at a sufficient dose distribution due to poor geometric conditions.
- Prior hysterectomy with the impossibility of a tandem placement.
- Recurrence inside an area previously irradiated restricting the use of further external irradiation.
- Primary vaginal tumours,- interstitial brachytherapy has been reported when para-vaginal extension is not correctly encompassed with standard intracavitary brachytherapy).
- Vaginal recurrences specially from endometrial cancer have been recognized as good candidates for interstitial brachytherapy techniques with potential sparing of bladder and rectum. These techniques have been shown to improve dose distribution particularly for deeply infiltrating tumours.



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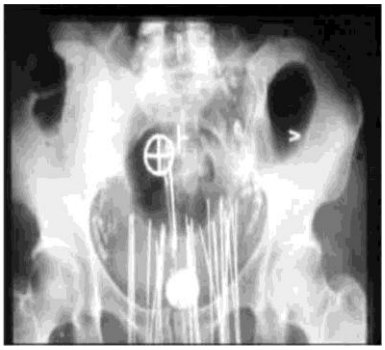


Syed Neblett Applicator

Principles of treatment:

Tumor Localization is done by:

- Clinical examination
- Ultrasound +/ - with rectal probe
- CT Scan / MRI

Select Treatment Protocol : to suit individual patient requirement. Homogenous Dose distribution to target volume keeping the dose to normal / critical structures within their tolerance dose.

Brachytherapy procedure in brief:

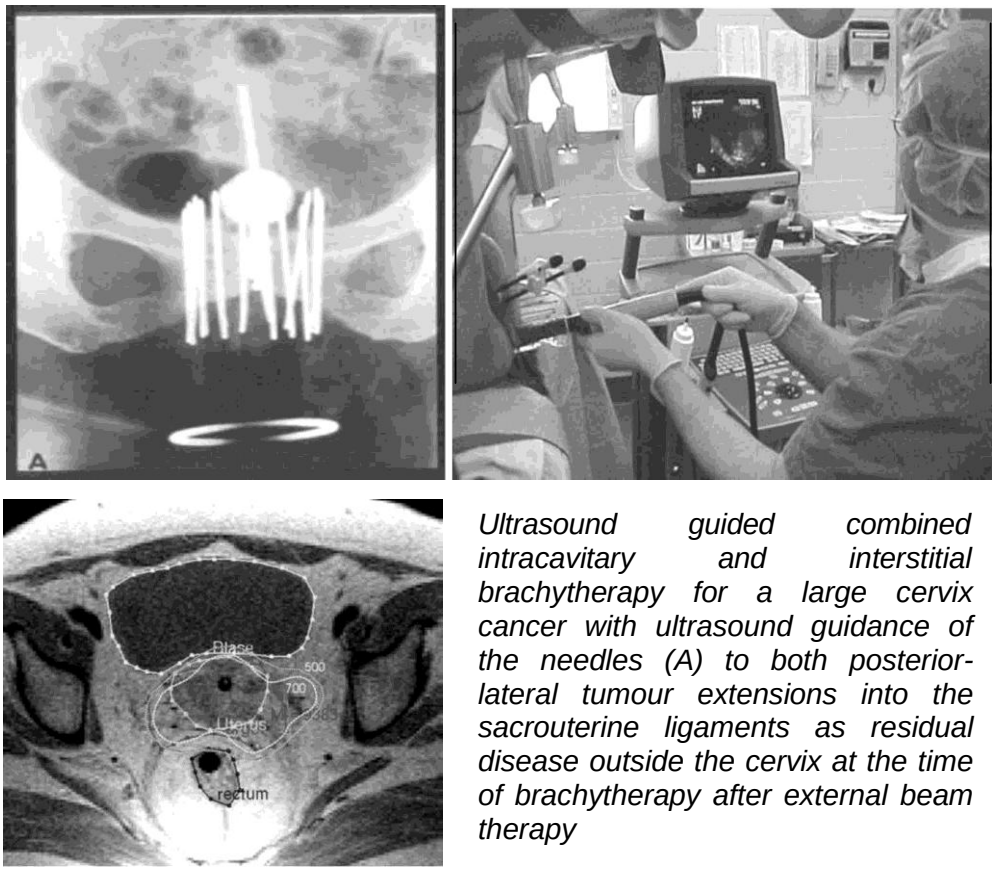
The Brachytherapy procedure is usually performed under spinal or general anaesthesia. Patient is catheterised with a Foley's catheter & about 7 cc. of radio-opaque dye is injected into the balloon of the catheter. The uterine catheter is inserted after cervical dilation in cases of

Intracavitary Brachytherapy. This is followed by the two vaginal ovoids.

A tight vaginal pack insures that the dose limiting organs that is Bladder & Rectum are kept as away from the radiation sources. As possible. A Rectal catheter placed helps delineate the rectal points.

In case of Perineal Implants the uterine catheter is inserted after cervical dilatation. There, after two markers are inserted into the anterior and posterior lip of the cervix, the initial needle is inserted into one of the cervical lips to a depth of 2-3 cm beyond the cervical os. This first needle is very important, as it will regulate the depth of all the other needles secondarily inserted through the template. The vaginal cylinder is then inserted over the uterine catheter which is fixed to each other by tightening screws. The template is then fixed to the vaginal cylinder. Generally, 20 to 30 needles are inserted transperineally through the holes of the template. Perineal sutures allow the fixation of the template. At the end of the procedure, gauze is placed between the skin and the template. These templates have allowed the development of interstitial implants. Some problems faced during procedure are the needle positioning represents one of the limits in the use of such techniques. Despite the design of the templates, the parallelism of the needles is not systematically respected. The needle tips converge or diverge within the pelvic tissues. Several technical modifications have been investigated.

Intracavitary Brachytherapy can also be combined with Perineal Implants



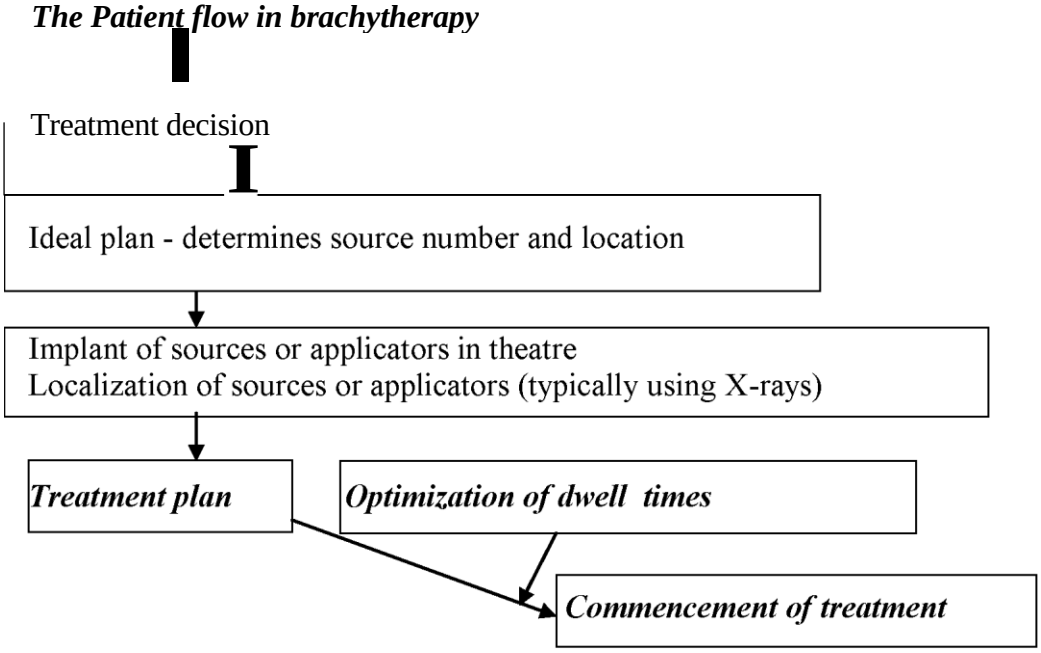
Ultrasound guided combined intracavitary and interstitial brachytherapy for a large cervix cancer with ultrasound guidance of the needles (A) to both posterior-lateral tumour extensions into the sacrouterine ligaments as residual disease outside the cervix at the time of brachytherapy after external beam therapy

After the procedure is over orthogonal X-rays / CT Scan helps delineate the position of the catheters / needles , Rectal, Bladder & other critical points . Dose to various points are calculated within the target volume

- Manually by Severt' s Integral
- Computerised planning System

The idea is to achieve a homogenous dose distribution within the target volume & to keep the dose to critical organs within their tolerance levels. Modifications/ Optimisation if required, are done. Dose is prescribed & treatemen commenced. Reporting of the treatment has to be done as per proper guide lines.

The Patient flow in brachytherapy



Specification and Reporting Guidelines… Why?

Brachytherapy prescription is difficult

- because the treatment volume may have significant dose in homogeneities
- is genuinely 3 dimensional
- depends on implant geometry
- the implant is prone to movement over long treatment time In short dose prescription may vary depending on patient disease, experience of individual clinicians and accepted protocols, the reporting must be uniform - any suitable educated person must be able to understand what happened to the patient in case of:

• re-treatment of the patient
• clinical trials
• any potential litigation

A uniform dose prescription guide line is essential

- to harmonize the method of reporting
- to have a valid exchange of information
- to compare treatment outcomes between various protocols
- Various survival end points
- Treatment related morbidity and mortality

Specification and Reporting Guidelines should be practically feasible & adoptable by most centers.

There are several historic systems of prescribing brachytherapy

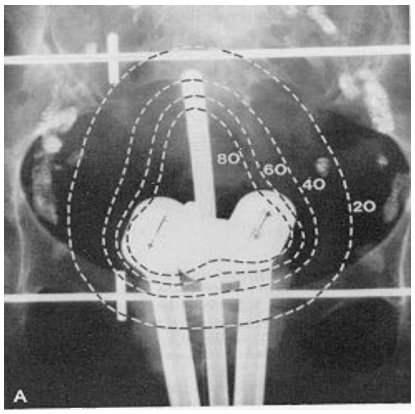
- Manchester
- Paris system, Stockholm

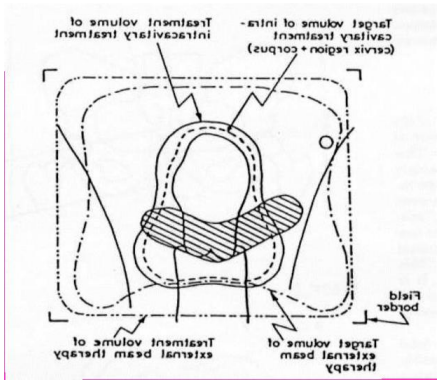
Nowadays most relevant reports of the ICRU are-Report 38 (Gynaecological brachy-therapy) 1985, Report 58 (Dose and volume specification for reporting interstitial brachytherapy) 1998.

ICRU 38:for Intra-Cavitary Brachytherapy

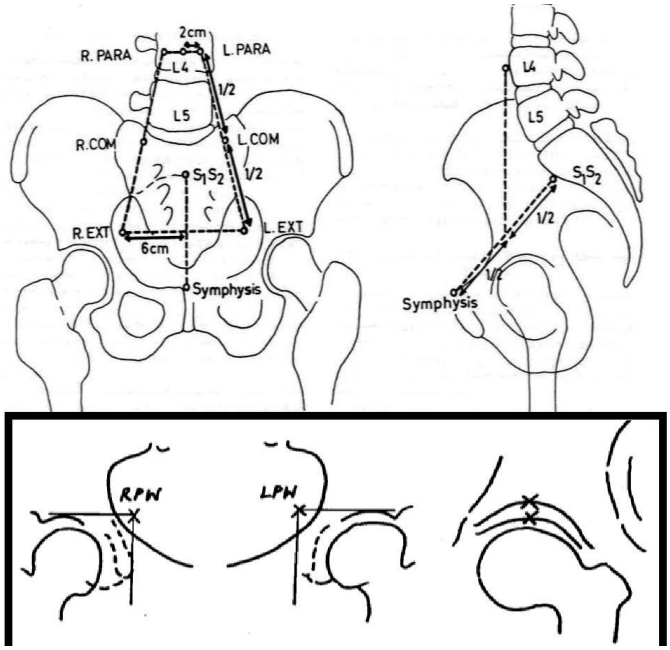
ICRU-38 Summery: Committee of: Gynaecological. , Radiation Oncologists and Radiation Physicists (1985)

- Description of the technique used
- Total reference air karma (cGy at 1 meter)
- Description of the reference volume
- Dose level if not 60Gy (dimensions of the ref. Volume (height, width, thickness)
- Absorbed dose at reference point
- Bladder ref. Point, rectal ref. Point, lymphatic trapezoid, pelvic wall ref point
- Time dose pattern



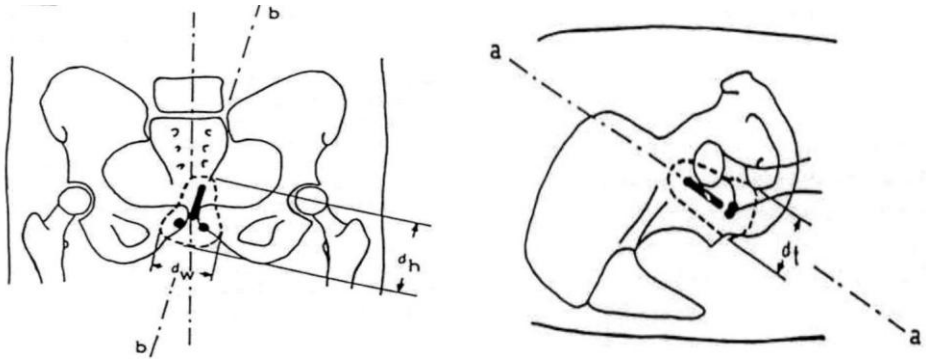


Treatment volume: target volume with in the treatment volume enclosed by a relevant isodose surface and encompasses at least the target volume

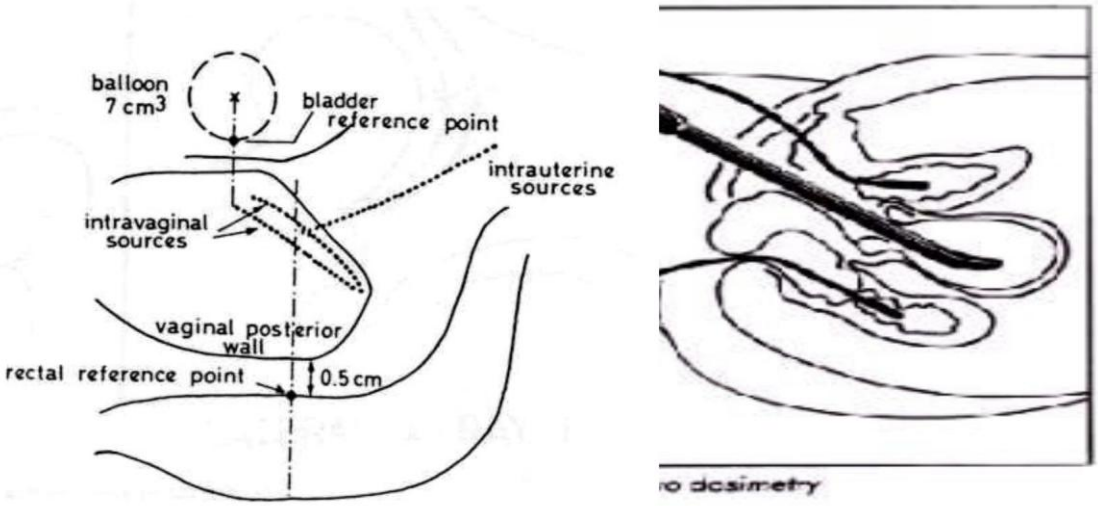


Reference volume : volume enclosed by the reference isodose surface dimensions to be defined

Lymphatic trapezoid: Its base is defined on AP and LAT radiograph by joining the top of the pubic symphysis with s_1-s_2 junction and from the center of resulting line a base of 12 cm is drawn (6 cm each side.) The top of the trapezoid is obtained by drawing a line perpendicular to the centre of the body of L_4 (2cm each side). The line joining the left and right side of the upper and lower points are drawn. The center of this line on the both sides are marked. The base represents external iliac (Rt & Lt) , center common iliac (Rt & Lt) and top lower paraortic points (Rt & Lt). The left right obturators and pelvic wall points are obtained by cross sections of the tangents drawn at the astabulam.



- **Bladder Point -** The most posterior point within the Foley catheter bulb along a direct AP line through the bulb's center**.**
- **Rectal point :** One half of a centimeter posterior to the vaginal mucosa in the patient's midline at the level of the posterior aspect of the ovoid.



ICRU-50/58 Recommendations

ICRU-50/58 recommended that the prescription reporting recording of the radiation therapy should be clearly specified and individualized in three dimensions with following informations:

- **Gross tumour volume (GTV**): This should include gross palpable or visible, demonstrable, extent and location of the malignant growth using CT, MRI, USG, NM or any other diagnostic modality.

Clinical Tumour Volume (CTV): There is generally a subclinical involvement around the GTV (microscopic about 1 cm and the CTV should be able to incorporate).

Planning target volume (PTV): This should include both GTV and CTV

Treatment volume : Defined clearly in 3 dimensions

Irradiated Volume : With distribution of dose profile in 3D

Results of treatment & survival:

Cancer Cervix

Perez et al from Mallinckdrot Institute of Radiology(1969-1986)-5 yr acturial Disease Free Survival

Stage	5yrDFS
IB	90%
IIA	78%
IIB	74%
III	55%
IV	10%

Stage for stage there is decrease in survival rate as disease advances

National Survey of 1984-1990 Patterns of Care Study USA

Stage	DFS
IA	93.7%
IB	80%
IIA	67.2%
IIB	64.7%
III	37.9%
IV	11%

IRCH, AIIMS – 5yr. acturial survival rate

Stage I	5yr. DFS 65%
II	63%
III	50%

Sequele of Brachytherapy treatment in GynecologicalCancers:

E arly Complications

- Nausea
- Vomiting
- Skin Reactiions (Mould / Implants)
- Vault necrosis
- Proctitis
- Colitis
- Vaginitis

Late Complications: 10-15%
Related to Dose
Previous treatment

- Proctitis
- Cystitis
- Vaginal Stenosis
- Rectal stenosis
- Urethral stricture

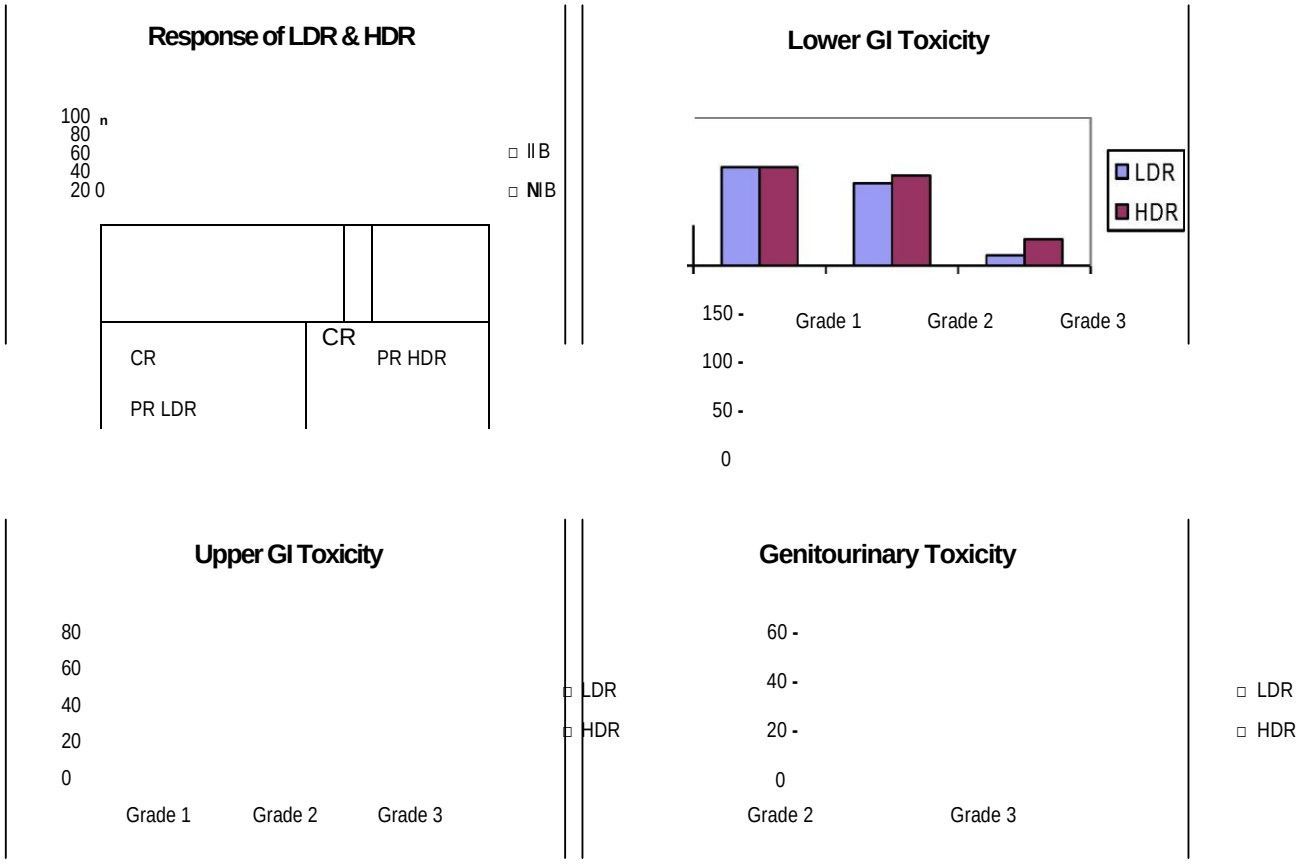
Management of Radiation Sequele:

Usually Symptomatic . In severe cases
Proctitis –Steroid retention enema
Cystitis- Instillation of sclerosing agents
Vaginal stenosis – Vaginal dialatation

Follow Up Schedule:

Follow Up is important to detect any residual, recurrence or radiation sequele
First 2 yrs. – 2 monthly
2-5 yrs. – 3 monthly
>5 yrs. 6 monthly

Comparison of response between HDR & LDR Intracavitary Brachytherapy for Cancer Cervix R.C.C. KNMH- Result



In a randomized study conducted at the RCC Kamala Neheru Memorial Hospital from 2006-2008 comparing the efficacy of LDR & HDR Intracavitary Brachytherapy in the treatment of Cancer Cervix. The results were comparable as regards to tumour control & toxicity.

Conclusion :

Role of Brachytherapy in Gynecological Cancers has been well established since the concept of Radiation therapy for malignant diseases. Use of CT Scan/MRI has completely changed the concept of point dose to volume dose and from single plane to multiple plane dosimetry, leading to complete indivdualisation of treatment matching to the need of tumor topology. ICRU –38 and ICRU-50/58 have given new meaning to whole lot of parameter viz. gross tumour volume, clinical target volume, planned target volume, treatment volume and irradiation volume for improvement of cure rate. Brachytherapy is at the threshold of being recognized as a major contributor in overalshare of radiotherapy. The

paradigm shift has taken place in the practices with advent of image guided brachytherapy

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DISTRIBUTION OF NON-RADIOACTIVE HEAVY ELEMENTS IN WATER OF RIVER GANGES FORM RISHIKESH TO ALLAHABAD: A STUDY ON POSSIBLE HEALTH EFFECTS

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Non-radioactive elemental distribution in Ganges river was investigated at selected locations from Rishikesh to Allahabad. Five sampling locations were selected along the river and water samples were collected for the measurement. Non-radioactive heavy element such as Zinc (Zn), Cadmium (Cd), Copper (Cu), Lead (Pb) were measured in water samples using Differential Pulse Anodic Striping Voltametric (DPASV) technique. Concentration of measured elements was found in the range of acceptable limit of Bureau of Indian Standard (BIS) and World Health Organisation (WHO) guideline values except at a few locations. The investigation showed that at some locations concentrations of measured elements were exceeding the standard limit which correspond to more anthropogenic activities. It is suggested that use of river water with maximum acceptable level of toxic heavy metals may cause deleterious health effects of people.

Keywords*: River Ganges, Non-radioactive elements, DPASV, health effect*

INTRODUCTION:

Characteristics and properties of all the known metallic elements have been extensively investigated. They can be categorized as radioactive heavy metal and Non-radioactive heavy metals. These elements may pose harmful effects on living system when their intake increases over acceptable limit through food and water. Radioactive elements possess both radiological hazard by ionization of the vital biological compounds and also by reacting chemically with them but, on the other hand, non-radioactive elements possess mainly chemical risks and their accumulation in body may cause diseases. The River Ganga rises in the Gangotri glacier at an elevation of 7138 m above mean sea level. It enters the plains at

Hardwar and covers over a distance of above 2290 km approx across UP, Bihar and West Bengal, [9].

In recent years, worrying anthropogenic activities were found responsible for the heavy metal contamination to the natural water resources and thus making it unhealthy for drinking and bathing. Among many sources metal mining operations often have to be considered with high metals concentration contributory to water resources [2] but in reference to river Ganges it was found that urbanization and industrialization at the river basin may be the major reasons for increasing contamination . Earlier studies have found that urban sewage and industrial effluents discharge was responsible for deteriorating the Ganga water quality [7]. Present study mainly focuses on distribution of non-radioactive concentration of heavy metals such as Cd, Cu, Pb, and Zn Concentration in river Ganges from Rishikesh to Allahabad and to evaluate the possible health effects which may be caused

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due to these non radioactive pollutants.

It is known that heavy metals produce serious health implications including carcinogenesis mediated tumor promotion [14].

Many investigations have shown the toxicity of the heavy metals like Metal uptake by plants have been shown to cause adverse effects on the growth of plant and also may pose cause serious health hazards to man [10]. Pollutants may induce changes in the mobility, growth inhibition, decreased reproductive ability, and higher mortality among population [19]. Irrigation by this contaminated river water may contaminate agricultural field soil and vegetables causing a serious risk to human health when humans and animals consumed it [11, 12, 18]. Intake of heavy metals through direct drinking of river water and through food chain may double the intake [6].

In the scenario of significant pollution from the anthropogenic activities, effective methods for decontamination be must be strategically adopted to save people from harmful effects by heavy metal pollutants. [4]

Materials Methods:

Study area:

The stations for the sampling and analysis were selected along the river Ganges, namely Allahabad, Kanpur, Narora, Haridwar and Rishikesh (Fig. 1). At each station different sites were selected for the sampling and further investigation. (see Table-1). Water samples were collected post monsoon in the month of November 2011 for the analysis.

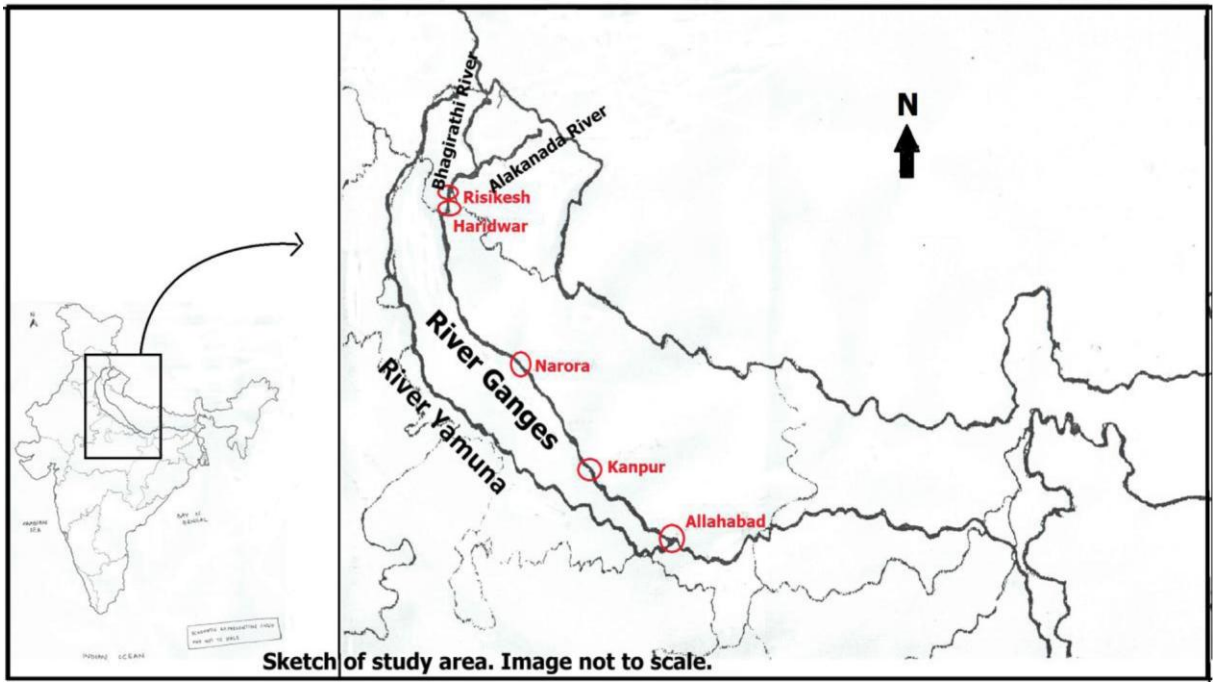

Fig-1: Sketch of the sampling location in River Ganges.

Station Code	Site Description	Latitudes	Longitudes	Altitudes
A	Rishikesh	29^0 57.19' N	78 10. 17 E	305
B	Haridwar	29^0 55.86' N	78 08. 34 E	277
C-1	Narora Colony Ghat	2812.61' N	78^0 23.08' E	166
C-2	Narora Barrage	28^0 11.37' N	78 23. 79 E	162
C-3	Narora Lower Canal	280 08.77' N	78 25. 77 E	168
D-1	Bithoor, Kanpur	26^0 36.83' N	80 16.49 E	81
D-2	Jajmau, Kanpur	26^0 26.09' N	80^0 24.53' E	100
E	River Ganges, Allahabad	$25^0$25.55' N	$081^0$52.97' E	64

Table1: Details of sample collection site

Methods:

Water samples were collected from the mid stream of river in polyethylene bottles which were previously soaked in 15% (v/v) HNO_3 for 24 hr and rinsed with double distilled water. All samples were filtered through 0.2 micron filter paper and measured for the elements using standard addition method protocol of Differential Pulse Anodic Striping Volta metric (DPASV) technique. Samples in triplicate were collected and measured.

Results and discussion:

The concentration values of all the measured elements from all the stations are given in the Table-3. In preliminary investigations, concentration of Cd in water of Ganges showed a variable pattern. Cadmium concentration was found within the limit of BIS and WHO (Table 1) except at station C-2, D-1 and D-2 and the measured values were 13 µg/L, 4.5 µg/L, 7.1 µg/L respectively. This indicates at locations D-1 and D-2, there may be large Cd discharge from the neighbouring industries. Major sources of Cd to the river water may be the effluent discharged from steel industries, dyes and plastics manufacturing units, phosphate fertilisers and rechargeable nickel-cadmium batteries. It is also used in welding and soldering, which may increase its concentration at the C-2 location where a Barrage has been built on the river. Post monsoon sample may also be the typical causal features. Long term ingestion of Cd causes the kidney failure and is reported to be a potential carcinogen [20]. Large amount of metal may also damage liver, and nervous system, and may lead to death. [13] Distribution of lead at the investigated points was almost linear except at the location C-2 and D-2 with a measured value of 26µg/L and 24µg/L respectively. Lead is one of the potential occupational toxins and is non biodegradable in nature [5] and among the organ systems, lead toxicity is mostly found in the nervous system [3].

Measurement of zinc was not found to be significant from Rishikesh to Allahabad except C-2 and D-2, and the concentration of Zinc was below the acceptable limit of BIS [1] and WHO [20].

Copper was not detected in water of Ganges from Rishikesh to Allahabad, except very low concentration at station C-2 and D-2 which is fairly below the acceptable limits. Copper was both an essential nutrient and a drinking-water contaminant. The primary source of copper in the river water seems to

be mostly from the corrosion of interior copper plumbing. [20].

It can be said that susceptibility to toxicants dose not only seem dependent on the toxic properties of any compound or its type but it also varies in relation to population growth rates [19].

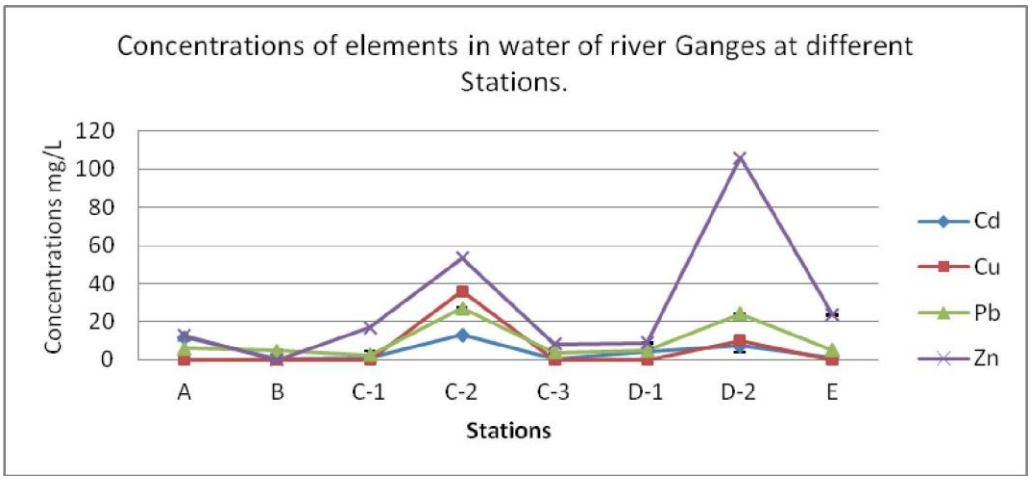

Figure 2: Concentration of elements in river Ganges

Parameters	BIS Limits Gig/L)	WHO Limits Gig/L)
Zn	5000	3000
Cd	10	3
Cu	50	2000
Pb	50	10

Table 2: Bureau of Indian Standards (BIS) 2009 and World Health Organisation (WHO) 2011 guideline values for the drinking water.

Station Code	Cd0ig/L) ±SD	Cu Qig/L) ±SD	Pb(jig/L) ±SD	Zn (jig/L) ±SD
A	11.6± 0.4	ND	5.9±0.1	12.8±0.1
B	0.6±0.5	ND	4.7±0.2	ND
C-l	1.3=1=0.5	ND	2.4±2.1	16.7±0.2
C-2	13.1±0.1	36.00±1.00	26.9±0.5	53.5±0.1
C-3	0.7±0.4	ND	3.6±0.6	8.3±0.1
D-l	4.5±0.4	ND	4.6±0.09	8.8±0.2
D-2	7.1±3.2	10.00±1.00	24.0±0.4	106.3±0.1
E	1.2±0.4	ND	5.00±0.1	023.5±0.4

Cd= cadmium, Cu= Copper, Pb= Lead, Zn= Zinc, ND= Not Detected

Table 3: Measured concentrations of some non-radioactive heavy metals in water sample of different stations (|ig/L)

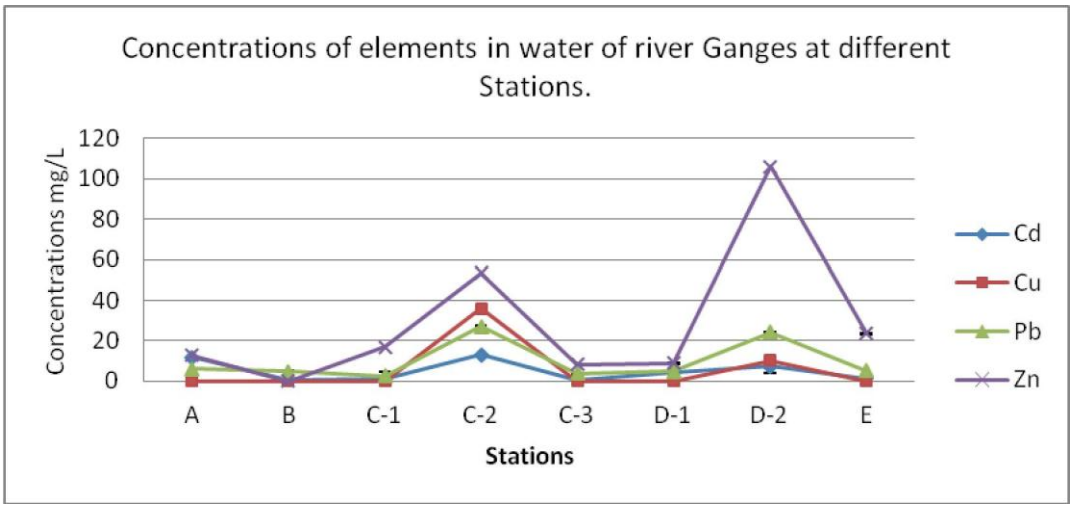

Figure 2: Concentration of elements in river Ganges

Parameters	BIS Limits (HS/L)	WHO Limits (HS/L)
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Cu	50	2000
Pb	50	10

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C-l	1.3=1=0.5	ND	2.4±2.1	16.7±0.2
C-2	13.1±0.1	36.00±1.00	26.9±0.5	53.5±0.1
C-3	0.7±0.4	ND	3.6±0.6	8.3±0.1
D-l	4.5±0.4	ND	4.6±0.09	8.8±0.2
D-2	7.1±3.2	10.00±1.00	24.0±0.4	106.3±0.1
E	1.2±0.4	ND	5.00±0.1	023.5±0.4

Cd= cadmium, Cu= Copper, Pb= Lead, Zn= Zinc, ND= Not Detected

Table 3: Measured concentrations of some non-radioactive heavy metals in water sample of different stations (|ig/L)

Conclusion:

In this study, it was found that concentration of non- radioactive heavy metals in river ganges did not follow any trend but the concentration was higher only at those places where Industrial load is higher and greater human involvement occurred in the form of barrage, pumps and other factors. To avoid the deleterious effects of non radioactive heavy metals preventive measures are to be adapted.

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STUDY ON THE OPINION OF PARENTS AND TEACHERS TOWARDS THE FACILITIES AVAILABLE IN "ASHA" SPECIAL SCHOOLS

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The present study is primarily a survey; an attempt has been made to examine the facilities available at ASHA special schools and the opinion of the parents and teachers towards these facilities. In the light of the objectives of the study infrastructure, building, health and safety, hygiene and recreational facilities available at school are the main features of attraction. Besides that the nature of the staff, their involvement in the overall development of the student are the another key factors that are to be investigated in the present study. The study of the opinions of parents, of children with disabilities and the teachers working in the schools are basically confined to their opinion towards the facilities available as physical, psychological and administrative.

Keywords: *ASHA special schools, children, staff, teachers*

Introduction

Over time, various professionals and organizations have experimented, in their own respective areas of interest and specializations, on a variety of methodologies in a quest in find the optimal strategy of working with children to enhance their quality of life. There are presently many schools/ organizations and governmental and non-governmental clinics/ hospitals and various other systems that are providing undoubted quality of rehabilitation services. We are also witnessing a rapid growth in the number of institutions and organizations dedicated to the advocacy of the cause. In spite of all the goodwill, hard work and dedication of the people involved, we still seem to be inadequately equipped to support this surge.

In the specific reference of the special education we are trying to cop up with the child's specific need. Special school is the component of education which employs specials instructional methodology or remedial instruction, instructional material, teaching learning aids and equipment to meet educational needs of the children with specials needs. The majority of special education teachers are using the general education curriculum or its modification to meet the child's individual needs. Special educators provide programs for specific learning disabilities, speech and language impairments, mental retardation and hearing impairment etc. Although, there are numbers of special, integrated schools and inclusive schools, but they fail to support the students with special needs in such a way that, they become a valuable and productive citizen to the country. In many of the schools there is no infrastructure at all. In our country most of the population is residing in rural areas where the school facilities are in poor condition. Building, sanitation, electricity and the availability of teaching staff is also a problem.

Teaching staff in special schools are mainly supported with the parents. It is a well established fact that the parent's involvement is the key of student's success. In 1991 the first "ASHA" school for children with special needs was established.

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From the time of its inception, up till now, the school has preceded step by cautious step to contribute and improve the quality of life for these children and their parents. Today, there are 132 students at "ASHA" school. "ASHA" School has been established at various army stations under the aegis of local formation headquarters or the local AWWA. Presently there are a total of 29 "ASHA" Schools in the country. "ASHA" schools getting grants from the Ministry of Social Justice and Empowerment (MOSJE), Government of India. Besides that the sale of "ASHA" greeting cards, fees from students and donations from other agencies are also contributing to run the schools. "ASHA" schools deals with nearly all the disabilities like: Mental Retardation; Cerebral palsy; Hearing Impairment; Muscular Dystrophy; Learning Disabilities; Speech and Languages Disorders; Multiple Disabilities; Autism; Attention Deficit Disorder's neurological Disease etc. Here questions arise that is there\ any difference in the functioning of "ASHA" schools of different places? Are there any facilities shortcomings in "ASHA" schools as compare to the other non army special schools? Parents involvement and the teachers satisfaction is the important factor of the school functioning. Here some other basic questions arise that-

- Are the teacher of "ASHA" schools, trained in special education
- Are parents satisfied with the facilities available in the "ASHA" special school? On considering the above questions in terms of school administration, facilities and resources available in 'ASHA' schools the researcher took up the present study entitled "A study of the opinion of parents and teachers towards the facilities available in "ASHA" special schools"

While playing their roles, teachers as well as parents should have provided some psychological and emotional support to overcome the learning difficulties among students especially for the students with special needs. Rimm has constructed a model of psychological assistance to overcome learning difficulties which consists of evaluation, communication, changes of expectations, identification of roles model, correction of shortcomings and changes of reinforcement (1). Steipek suggests that students' desire to learn and their progress depend on how teachers themselves imagine students' learning and what stressed by (6). He stated that the mechanism of organized support does not function if the mechanism of parents and school cooperation does not work. So parental involvement and voluntary participation in organizational process of social- pedagogical assistance is one of the main criteria for assistance effectiveness.

There had been a steady growth of educational facilities at primary stage in India (3). There are inadequate equipments/ aids; unsatisfactory seating arrangements and need of drinking water (4). Near about 18% of parents are daily bread earners and they didn't bothered about the education of their wards. They haved no time to watch and attend their wards (4) Nayak (2008) examined that attitude of both parents and teachers in an inclusive education. Results of the study reported that teachers look forward to teaching in an inclusive environment and are ready to face the challenges. Result of the study also showed significant difference in the opinion of teachers of normal school. Hence, on the basis of the above cited studies, many of the schools under the management of the defense ministry or Army were taken into consideration. Since, ASHA schools were meant for the wards of

Army personnel's only. But later on it was decided that the civilian staff and their wards are too seeks the facilitation with the ASHA schools. These schools were given independent management, and facilities to educate and rehabilitate the children with special needs.

Objectives of the study

On the basis of the nature of the study, the objectives of the study are:

1. To study the facilities available in 'ASHA' special schools.
2. To study the opinion of the parents having the children with special needs towards facilities available in 'ASHA' schools.
3. To study the opinion of the teachers working in the 'ASHA' schools towards the facilities available in 'ASHA' special schools.

Materials & Methods

The study of the opinions of parents of children with disabilities and the teachers working in the schools are basically confined to their opinion towards the facilities available as physical, psychological and administrative. The selected study is primarily a survey type of evaluative research involving systematic observations of variables by the use of standardized tools and systematic procedure. The study aims to evaluate the opinion of the parents and the teachers working in the ASHA schools towards the facilities available in the school. Considering the evaluative nature of the study and systematic observations of the opinions of teachers and parents, it was planned to select only 3 ASHA schools of the nearby area where the investigator is working as a samples from the population. After consideration the population it was further planned to select only the following ASHA schools-

Table: ASHA schools taken as a Sample.

Sl.No.	Name of ASHA school with establishment
1	ASHA Specials, Jhansi Cantt. Jhansi, U.P.
2.	ASHA Special School, Bibina Cantt. Babina M.P.
3.	ASHA Special school, Gwlior Cantt, Gwalior, M.P.

All the teachers working under the selected ASHA schools and the parents of all the beneficiaries were taken as a sample of the study. The details of the beneficiaries and the teaching staff at the different schools are as under-

Status of Beneficiaries and Staff

Sl. No.	Name of ASHA school	No. of Beneficiaries	No. of teaching staff
1	Babina	30	12
2	Jhansi	26	10
3	Gwalior	32	12

To solve the purpose of the research the selection or/ and development of the appropriate tool being always considered as of prime importance to the success of the study. For the purpose of current study no standardize tests were available but some suitable tests were taken into consideration and adopted for the study. Mainly they are teacher/ researchers made tests. The tools taken for the study are as under:-a) To study to opinion of the parents and the teachers towards the facilities in the schools, a tool developed by Sharma and Mahapatra (2005) was taken into consideration by their written consent for using it only for this study)

Data Analysis

Data collected through the sources were analyzed by using both parametric and non parametric statistical techniques. Information collected through questionnaire from the beneficiaries had been analyzed accordingly. Percentage and Chi-square techniques were applied on the questionnaires to analyze the data.

Result & Discussion

The opinion of the parents having the children with special needs towards facilities available in 'ASHA' special schools

The data was analyzed and the following findings were emerged out that-1. There was no significant difference found between the parents having the children with disabilities on the facilities available in ASHA special schools at Bibina, Jhansi and Gwalior. Although in the opinion of the parents, some shortcomings of the schools were emerged out for all the schools such as; (i) the building in some criteria was found poor; (ii) the heating, cooling and/ or lighting system in the classroom is poor; (iii) Labs are adequately secured to the children; (iv) Is the school Barrier Free; (v) Lack of instructional materials in the library; (vi) Inadequate aids/ equipment repairing services in the school; (vii) Teachers are often absent from the class in as month (viii) Teachers know the strengths and weaknesses of every child personally; (ix) There is a class test in every month to ensure the child' development; (x) You are compulsory to attend the parent teachers meeting; (xi) The test results shown to the parents in every parents meeting; (xii) School ensured that each and every child must wear a hearing aid; (xiii) Simple aid repair facilities are available in the school at minimum cost; (xiv) School have the psychological/ audio logical evaluation facilities, (xv) School organize parent training programme every year, (xvi) School often invites the parents to be a part of the therapy session; (xvii) School has parent counseling services regarding their child' problem; (xviii) Teachers and other staff are well cooperative to the parents and (xviv) Video equipment, tapes and films would be readily available and accessible in the school.

2. Disagreement of the parents towards the statements was shown in the study at a glance. This exhibits that the 'ASHA' school at Babina, Jhansi and Gwalior fulfils the expectations of the parents up to the some level. Although, some of the facilities like; (i) multimedia equipments as video tapes and films; (ii) barrier free environment; (iii) secured labs; (iv) teachers perception towards students' weakness and strengths; (v) regular class tests; (vi) regular parents teachers meeting; (vii) test results do not shown to the parents; (viii) no compulsion to wear the hearing aids; (ix) no audio logical and psychological facilities. Etc. are the shortcomings of the school which must be resolved.
3. Parents are somewhat agree with the statements such as (i) There is a lack of classroom space; (ii) Appropriate numbers of toilets' sanitation facilities are available in school (iii) enough computers are available for instruction; (iv) The class time in the school is sufficient to cover the syllabus, (v) Parents teachers meeting are organized in a month to discuss about the child problems. The reactions show that the parents are disagreed with the statements. It needs to be improved.

4. Parents feel there was a lacuna in the school and it needs to be improved. They reacts for the statements like; (i) Toilets are clean and proper ventilated; (ii) Instructional material (e.g. textbooks. charts, models) are lacking in the school; (iii) Lack of multi-media resources for instruction; (iv) Inadequate facilities for the fine arts/ vocational training in the school; (v) Fees structure of the school suits you; (vi) Playground facilities is available to the children; (vii) School has its own facility to take and drop the students from home. It means that the parents are somewhat not appreciating some of the facilities available in the school campus.
5. The overall impression towards the facilities by the parents shows a positive remark towards the school. A large group of the parents were reacting as the schools fit on their expectations but needed a lot.

The opinion of the Teachers of Children with special needs towards facilities available in 'ASHA' special school

1. A 70%-80% of the teaches of the ASHA special schools were found satisfied with the facilities available in the schools and there was no significant difference found between their opinions on the facilities. Most of the teachers reacts that a healthy and sustainable environment of working is found in these ASHA special schools such as: (i) they receive environment; (ii) building is fit for teaching learning environment; (iii) classrooms are properly ventilated; (iv) toilet facilities are good; (v) teachers are discussing with each others on the matter of teaching learning issues; (vi) the quality of TLMs like boards etc. are good; (vii) recreational facilities are available and they were ever being motivated to do innovations.
2. Some teachers were reacted and needs to be improve the conditions such as (i) psychological/ audio logical lab must be equipped and needs improvements, (ii) teachers should be given chance to lead the staff meetings rather than the administrative staff and the issues related to academics should be discussed in meeting (iii) teachers should be given time to relax; (iv) teachers should be given opportunity to go for the career development programs and the regular seminars/ workshops should be organized to help in improving skills among the teachers .

Suggestions for Future Researches-

Here are some suggestions for the future researchers and the investigators-1. They may take this study and elaborate it to the large sample covering all the 'ASHA' special schools in India.

2. The study may be focused to compare the cross school comparisons of the facilities available in the ASHA specials all over the country.
3. The future study may be undertaken to compare the opinion of the parents and teachers on the basis of Sex, Educational Qualification, Professional qualification and their Socio- economic status.
4. The study may be taken to compare the opinion between parents from the Army and Civil staff on the facilities available in ASHA special schools.
5. The future study may be taken as the opinion of teachers and the administrative staff of the ASHA special school.

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EFFECT OF ACHIEVEMENT IN ENVIRONMENTAL STUDIES ON ENVIRONMENTAL ETHICS AMONG SECONDARY LEVEL STUDENT

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Ethics is as old as philosophy, but the concept of environmental ethics is very new. Ethics refers to the philosophical science that deals with rightness and wrongness of human actions. His responsibility to make the appropriate choice of actions towards vulnerable things like persons, social institution and human communities. As far as nature was considered it was believed to be too vast and enduring to be vulnerable. But today we all know that nature itself is imperiled by deliberate human actions. Hence to set a standard of conduct based on moral principles to guide human relations with the environment became imperative. Thus in the early 1970s environmental ethics emerged as a new discipline of philosophy. Environmental ethics is a branch of philosophy that considers the moral relations between human beings and their natural environment. As a field of study, it assumes that humans have certain responsibilities towards the natural world, and it seeks to help people to act responsibly, when they do things that impact the natural world. Therefore as a specialized part of ethics, environmental ethics is concerned with the morality (right and wrong) of human actions towards the environment or the natural world we live in.

Keywords*: Ethics, Environmental Ethics, Philosophy, Human*

Many people associate the beginning of today's environmental ethics with the first Earth Day held on 22nd April, 1970 in the United States. Since then this is celebrated to make people and political leaders aware of the importance of caring for and preserving the environment. The first Earth Day launched the beginning of an environmental awareness in the United States and later around the world. It made many people realize that some sense of environmental responsibility should be developed and applied in our daily lives.

Most movements do not just suddenly happen they are usually preceded by many other influential events. In the environmental movement, perhaps the earliest of these was the 1949 publication of a book by American naturalist Aldo Leopold (1887-1948). Forest science in 1909, as a game management expert, he came to appreciate and understand how deeply humans affected the natural world. His idea of new philosophy about man and nature, or what would come to be called an environmental ethics was carried on by others after his death, when two decades later the first Earth Day was held.

In the vedantic philosophy the divine force pervades the entire cosmos and resides in each individual therefore all are fellow beings, living in the cosmos and so the relationship has to be of perception, understanding and harmony. This concept of sustainable living still permeates the Indian society. The Indian constitution is first in the world to recognize the importance of protecting the environment.

Seeing the graveness of the problem of environment degradation in India like all other countries environment education has become a part of school curriculum. With

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the introduction of environmental education it has been thought that with the increasing information about the natural world, children will become more sincere towards environment, which will help to develop harmony between humans and our ecosystem. This paper intends to find out, whether environmental education is able to develop an attitude and behaviors compatible with this new ethics.

Objective:

To find out relationship between achievement in environment studies and environmental ethics among secondary level students.

Hypothesis:

There is no significant relationship between achievement in environment studies and environmental ethics among secondary level students.

Methodology:

The study was conducted under the broad framework of descriptive method of research. Randomly selected sample consisted of 100 students (50 boys of and 50 girls) of class IX of Allahabad City. A self constructed tool of environmental ethics and achievement test of environmental education was used for data collection. Pearson product moment correlation was applied for data analysis.

Results & Discussion:

Table 1: Correlation between Achievement in Environment Studies and Environmental Ethics

N	r
100	0.033

On the basis of Pearson product moment correlation applied on the sample, value obtained is 0.033 which is not significant at .05 level, thus the hypothesis that there is no significant relationship between achievement in Environment Studies and Environmental Ethics stands accepted. This shows that being aware or having knowledge about something is different from adopting it in our behaviour. Many times people have knowledge about what is right and what is wrong but they consciously or unconsciously act according to their immediate requirements not bothering about the dire consequences it will lead to in future.

Today it is a known fact that environmental education is part of the school curriculum in almost all the countries of the world. But simply to create consciousness of environment in the students through school curriculum is not sufficient. Yenice Nilyun (2007) determined that environmental education introduced in schools does not effect ones environmental sensibility. Therefore what is required is to change the behaviour of the children towards the environment. Hence there is need to ensure that educational programmes reflect the importance of an ethics for living sustainably (14CN/UNEP/WWF, 1991, p.5) Kusmawan (2005) suggested the infusion of values in scientific action, reinforce students concern for environmental problems and foster positive attitude towards environment.

Conclusion:

We all know that all major resources in the country are in grave danger of irreparable damage. To save it moral and ethical education can help a lot in changing peoples attitude. It is therefore the need of the hour to propose environmental education with the essential elements of moral philosophy. This will alert the public towards the need of achieving global sustainable development and the likely consequences of failing to do so.

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OVERWEIGHT AND OBESITY AMONG CHILDREN OF AFFLUENT PUBLIC SCHOOL IN ALLAHABAD

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Purpose: To know the prevalence of overweight & obesity in affluent school children aged between 11-16 years and to analyze the association between overweight/obesity and physical activity.**Methodology:** A cross sectional study was carried out in 2 affluent schools of Allahabad city –Maharshi Patanjali Vidya Mandir and Tagore Public School. A total of 1146 ,school children studying between 6^{th} and 11^{th} standard aged between 11 to 16 years were studied and data regarding time spent on television viewing ,sleeping, playing computer/video games, indoor games, outdoor games and physical exercises was recorded in a pre designed and pre tested questionnaire.**Results:** Out of 1146 school children 223 (19.5%) and 119 (10.4%) were overweight and obese respectively. Proportion of overweight and obesity was more in boys (20.7 % and 12.2%) than girls (17.8% and 8.0%). Prevalence of overweight/obesity was observed significantly higher among children who watched television >20hrs/week($p<0.0001$), playing computer/video games>10hrs/week ($p=0.005$) On the other hand regular participation in outdoor games>30 min/day ($p=0.001$) and physical exercises >30min/day($p=0.01$) significantly lowers the prevalence of overweight/obesity. **Conclusion:**The overall prevalence of overweight and obesity in affluent school children was estimated to be 29.9%. Spending long hours on television viewing and playing computer/video games was found to be positively associated with overweight/obesity whereas participation in physical exercises and outdoor games was negatively associated with overweight/obesity.

Overweight , Obesity , Physical Activity

Keywords: *Body Mass Index, School children,*

Introduction

The rate of overweight and obesity among children worldwide have been increasing dramatically in the last few years among children and adolescents from developing countries [1,2]. In developing countries such as India, especially in urban population and affluent children , obesity is emerging as a major health problem [3,4,5].The magnitude of overweight ranges from 9% to 27.5% and obesity ranges from 1% to 12.9% among Indian children [6,7,8,9,10,11]. Childhood obesity is increasing being observed with the changing life style of families with increased purchasing power, increasing hours of inactivity due to addiction to television, videogames and computer, which have replaced outdoor games and other social activities[12] .

It is observed that 30% of obesity begins in childhood and out of that 50% to 80% become obese adults[13]. In the Harvard study, morbidity from cardiovascular disease , diabetes, obesity related cancers and arthritis was 50-100% higher in obese individuals who were also obese as children[14]. Similarly a study exploring the trends of disease and economic burden of obesity in youth from 1979-1999 with use of a national representative population sample of hospital discharges, the National Hospital Discharge Survey (NHDS) conducted by the National

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Center for Health Statistics had shown that in last two decades of the previous century have witnessed dramatic increase in health care cost due to obesity and related issues among children and adolescents[15] . Due to the difficulty of curing obesity and overweight in adults and many long term adverse effects of childhood obesity, the prevention of child obesity has been recognized as a public health priority [16]. Evidences also revealed prevention and management of childhood obesity is one of the effective way to prevent obesity in adult life [17]

The present study was done with the objectives to determine the prevalence of overweight & obesity in two affluent school children of Allahabad city studying between 6th and 11th standard and to find out the association between overweight/obesity and physical activity

Materials and methods

Two affluent co educational public school (where the annual fees is more than 22,000) of Allahabad city were selected by the simple random technique. Children of class 6th to 11thwere selected as study unit.2 sections were randomly selected from each class. From each school, It was assumed at least 100 children would be studied from every class 6-11.After taken the consent from the principal of schools height and weight of children were measured by adopting standard procedures and Body Mass Index was calculated. Standard charts for age and sex were used as reference standards [18]. Children with BMI above the 95th percentile were considered as obese and those between 85th and 95th percentile as overweight and those with BMI below the 5th percentile were considered as underweight [18] . BMI percentile for boys and girls is given in Table-1. Children were interviewed to collect information regarding their physical activities like time spent on T.V. Watching <20hrs/week or >20hrs/week, playing computer/video games <10 hrs/week or >10 hrs/week , indoor games <10 hrs/week or >10 hrs/week , sleeping <10hrs/day or >10 hrs/day, participation in outdoor games <30min/day or >30min/day, physical exercises/cycling <30min/day or >30min/day, in a pre designed and pre-tested questionnaire.

Children below 11years and above 16 years were excluded from the study. Prevalence of overweight and obesity is presented as percentages. Chi-square test and Odds ratio (OR) were done to analyze the results statistically. P<0.05 was considered as statistically significant.

Age in (years)	Boys			Girls		
	5th	85th	95th	5th	85th	95th
11	13.3	19.1	23.4	13.5	20.6	24.5
12	13.6	19.8	23.8	13.9	21.9	25.7
13	14.0	20.4	25.3	14.6	22.6	27.1
14	14.5	21.1	25.3	15.4	23.0	27.4
15	15.4	22.0	27.3	15.9	23.6	27.7
16	15.8	22.7	27.6	15.9	23.7	27.4

Table 1: BMI percentile for boys and girls

Results

A total of 1146 school children in the age group of 11-16 years were participated in the study. Out of them 657 (57.3%) were boys and 489 (42.7%) were girls. Among the total boys 136 (20.7%) were overweight and 80 (12.2%) were obese. Similarly among the girls 87(17.8%) were overweight and 39(8.0%) were obese. Overall, 223(19.5%) children were overweight while 119(10.4%) were obese. Therefore 342 (29.9%) children were either overweight or obese (Table-2). There was a higher prevalence of overweight and obesity in boys (32.9%) compared with girls (25.8%), and the difference was found statistically significant (p=0.009) (Table-4).

Grade	**Boys (657)**	**Girls (489)**	**Total (1146)**
Overweight	136 (20.7%)	87 (17.8%)	223 (19.5%)
Obesity	80 (12.2%)	39 (8.0%)	119 (10.4%)
Underweight	13 (2.0%)	1 (0.2%)	14 (1.2%)
Normal	428 (65.1%)	362 (74.0%)	790 (68.9%)

Table 2: Prevalence of overweight and obesity by sex

Age(yrs)	**Total children**	**Overweight**	**Obesity**	**Underweight**	**normal**
11	112	22(19.6%)	16(14.3%)	-	74(66.1%)
12	224	48(21.4%)	25(11.2%)	3(1.3%)	148(66.1%)
13	219	48(21.9%)	22(9.6%)	3(1.4%)	146(66.6%)
14	214	35(16.4%)	28(13.1%)	1(0.5%)	150(70.1%)
15	174	27(15.5%)	12(6.8%)	1(0.5%)	134(77.0%)
16	203	43(21.2%)	16(7.8%)	6(3.1%)	138(70.0%)
Total	1146	223(19.5%)	119(10.4%)	14(1.2%)	790(68.9%)

Table 3: Prevalence of overweight and obesity by age

Factors	**Total number (1146)**	**Overweight/obesity (342)**	**OR (95%CI)**	**X^2**	**P value**
Sex					
Boys	657(57.3%)	216(32.9%)	0.709(0.547-0.919)	6.77	0.009
Girls	489(42.7%)	126(25.8%)			
Age group					
11-13yrs	555(48.4%)	181(32.6%)	0.774(0.600-0.997)	3.94	0.047
14-16yrs	591(51.6%)	161(27.2%)			
Physical exercise					
<30 min/day	597(52.1%)	198(33.1%)	0.717(0.555-0.925)	6.57	0.01
>30 min/day	549(47.9%)	144(26.2%)			
Outdoor games					

<30 min/day	529(46.2%)	183(34.6%)	0.656(0.509-0.846)	10.59	0.001
>30 min/day	617(53.8%)	159(25.8%)			
Television Watching					
<20hrs/week	608(53.1%)	124(20.4%)	2.659(2.047-3.455)	55.21	<0.0001
>20hrs/week	538(46.9%)	218(40.5%)			
Playing computer/video games					
<10hrs/week	511(44.6%)	113(22.1%)	1.987(1.525-2.588)	7.79	0.005
>10hrs/week	635(55.4%)	229(36.1%)			
Indoor games					
<10hrs/week	613(53.5%)	185(30.2%)	0.966(0.749-1.245)	0.07	0.789
>10hrs/week	533(46.5%)	157(29.5%)			
Sleeping					
<10hrs/day	720(62.8%)	214(29.7%)	1.016(0.781-1.319)	0.01	0.908
>10hrs/day	426(37.2%)	128(30.0%)			

Table-4 : Associated factors of overweight/obesity

555 (48.4%) children belong to 11-13 years age group while the 591(51.6%) children belong to 14-16 years age group .The proportion of overweight/obesity was significantly higher (32.6%) in 11-13 years age group than (27.2%) in 14-16 years age group and the difference was found statistically significant (p=0.047) (Table 4).

Higher prevalence of overweight and obesity was observed in children watching television >20hrs/week (40.5%), playing computer/video games >10 hrs/week (36.1%), participated in outdoor games <30 min/day (34.6%), performing physical exercises <30 min/day (33.1%). The prevalence of overweight and obesity was found significantly higher in children watching television >20hrs/week (p=<0.0001) and playing computer/video games >10 hrs/week (p=0.005) whereas participation in outdoor games

>30 min/day (p=0.001) and doing physical exercises >30 min/day (p=0.01) significantly lowers the prevalence of overweight and obesity .Other factors like playing indoor games and sleeping were not found to be statistically significant. (Table 4)

Discussion

The overall prevalence of overweight and obesity was found to be 29.9% among affluent school children (overweight-19.5% and obesity-10.4%) in Allahabad . Ramachandran et al[7] reported the prevalence of overweight (including obese)in adolescent was 22% in better off schools in Chennai and Kapil U et al[6] reported prevalence of overweight was 31% of which 7.5% were obese in a Delhi school with tuition fees more than Rs.2,500 per month. Similarly ,Sharma et al[19] reported prevalence of overweight and obesity to be 22% and 6% respectively from Delhi.) whereas 10.95% and 5.63% of overweight and obesity was found in Amritsar, Punjab by Sidhu et al[9]while Aggarwal et al[5] reported 12.7 and 3.4% prevalence of overweight and obesity from Ludhiana. Wide variations were observed in the prevalence of overweight and obesity among affluent school children in

different parts of the country could be due to different definition being used to define overweight and obesity and differences in age group included in these studies.

In the present study prevalence of overweight and obesity was observed higher among boys compared to girls consistent with the results of earlier studies done by Kapil et al[6]; Valen C et al[20] and Patnaik et al[21] On the other hand Kumar S et al[22] reported higher prevalence in girls than boys. All these studies therefore indicate that the sex of the child has an affects on prevalence of overweight and obesity. In our study, tendency for overweight and obesity was observed significantly higher in the age group of 11-13years probably due to increased adipose tissue and overall body weight during puberty.

Physical inactivity like spending long hours on Television Watching and playing computer or video games were found to be significantly associated with overweight and obesity similar as shown by earlier studies [23,24,25,26,27] .The results clearly revealed that regular participation in physical activities like outdoor games and physical exercises is an important factor in reducing prevalence of overweight and obesity as observed by other studies [7,26].

Conclusion

The present study shows a high prevalence of overweight and obesity among affluent school children in Allahabad City. Greater time spent on television watching, playing computer/video games and less involvement in physical activities are found to be associated with higher prevalence of overweight/obesity. As a preventive strategy there is an urgent need to counsel children and their parents about consequences related to overweight/obesity as well as to encourage children to adopt healthy lifestyle.

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