महानिदेशक सशस्त्र सेना चिकित्सा सेवा चिकित्सा ज्ञापन क्रमांक–131
DG AFMS MEDICAL MEMORANDUM NO 131

विकिरण चिकित्सा (विकिरण अर्बुद्ध विद्या)
RADIOTHERAPY (RADIATION ONCOLOGY)

(फरवरी 1994 में जारी)
(Issued in February 1994)

(यह ज्ञापन महानि० स० से० चि० से० चिकित्सा ज्ञापन क्रमांक 23 को अतिक्रमित करता है।)
(This supersedes DGAFMS Medical Memorandum No 23)

वितरण :
Distribution :

(क) एक प्रति प्रत्येक चिकित्सा अधिकारी
(a) One copy per Medical Officer

(ख) एक प्रति प्रत्येक चिकित्सा यूनिट
(b) One copy per Medical Unit

(ग) एक प्रति प्रत्येक फार्मेशन मुख्यालय की चिकित्सा शाखा
(c) One copy per Medical Branch of the Formation Headquarters.

महानिदेशक सशस्त्र सेना चिकित्सा सेवा के प्राधिकार से जारी किया गया

Issued under the authority of
The Director General Armed Forces Medical Services

प्रकाशन नियंत्रक, भारत सरकार, प्रकाशन विभाग, (शहरी विकास मंत्रालय)
सिविल लाइन्स (पुराने सचिवालय के पीछे) दिल्ली-110 054 द्वारा वितरित
Distributed by the Controller of Publications, Govt of India. Department of Publications, (Ministry of Urban Development), Civil Lines (Behind Old Secretariat), Delhi-110 054.

(केस सं० 8547/डीजीएएफएमएस/डीजी-3 सी)
(Case file No. 8547/DGAFMS/DG-3C)

DGAFMS MEDICAL MEMORANDAM NO 131

RADIOTHERAPY (RADIATION ONCOLOGY)

INTRODUCTION

1. Radiation Oncology is a clinical speciality-practice of which involves use of ionising radiation in the treatment of cancer. The objective is eradication of cancer. Proper patient management includes pre-treatment evaluation and long term post-treatment observation as well as the actual treatment application by Radiation Oncologist (Radiotherapist).

2. Ionising radiations are used in two thirds of all cancer patients either for cure or for palliation. They deliver high energy which when obsorbed by the atom causes its ionisation resulting in highly reactive chemical radicals.

3. Radiation therapy has an advantage over surgery that its application is less influenced by concurrent medical problems of the patient. Moreover it is free from anatomic restrictions, and thus causes tumour destruction while preserving structure function and cosmesis. But prolonged time required for radiation treatment, displaces the patient from familiar surroundings.

PHYSICAL BASIS

4. The radiation used for treatment can either be electromagnetic (X-rays, gamma rays) or corpuscular (electrons, protons, neutrons, alpha particles, mesons). The basic physical mechanisms of action of all types of ionising radiations are the same. The differences observed are secondary to their energies.

5. The physical characteristics of ionising radiations gradually change over the spectrum of energies practical for clinical use.

A few decades earlier the ionising radiations available were in kilovoltage range known as superficial X-ray therapy (SXT) and Deep X-ray therapy (DXT). Modern era is of megavoltage or supervoltage therapy in which radiations are produced from upwards of one million volts. The megavoltage radiation has got the following advantages over the kilovoltage radiation.

(a) Better pentration in the tissues

(b) Reduced absorption in the bones

(c) Skin sparing effect

(d) Reduced sideways scattering

6. Gamma rays from Cobalt 60 have all the properties of megavoltage radiation.

DOSIMETRY

7. Following unit are used for measuring radiation

(a) Rotgen 'R'—This unit is used for measuring radiation exposure. One 'R' is the amount of X or gamma radiation such that the associated corpuscular emission, per 0.001293 grammas of air, produces in air ions carrying one electrostatic unit of charge of either sign.

static unit of charge of either sign.

(b) *Radiation absorbed dose*"*rad*". This unit is used for measuring radiation absorbed in the tissues. One "rad" is the amount of radiation such that 100 ergs of energy is absorbed by one gramme of tissue.

(c) *Gray*—'*Gy*'. One Gray is equivalent of 100 rads.

APPLICATION OF RADIOTHERAPY

8. Radiotherapy can be administered through the following means :—

(a) Teletherapy

(b) Brachytherapy

(c) Systemic therapy

Teletherapy

9. Radiation is administered from an external source and the patient is kept at a distance from the machine. Teletherapy is available to us by

(a) *Linear Accelerators or Betatrons.* These machines produce super voltage or megavoltage x-rays.

(*b*) *Gamma ray teletherapy machines.*—These machines use either cobalt 60 or caesium—137 to give out gamma radiation for external use.

Brachytherapy

10. Radioactive sources can be placed inside the body tissues. For the sake of radiation protection to the operators, brachytherapy now-a-days is administered by "After-loading" technique in which applicators are first placed inside the body tissues and are loaded wth radioactive isotopes subsequently. The various procedures are as follows :—

(*a*) *Interstitial.* Needles of radio active isotopes are put into the various tissues for giving localised and high dose. The cancers treated thus are cancers of the tongue, lips, cheek and breast.

(*b*) *Intracavitary.* Isotopes are put in the body cavities such as, uterus, nasopharynx, oesophagus, paranasal sinus and rectum.

(*c*) *Local Applicatior* The isotopes are kept next to the cancers, such as cancers of the skin.

Radio-active Isotopes used for Brachytherapy

11. The various isotopes used are Cobalt 60, Cesium-137 Iridium-192, Tantalum-182, Californium 252 and Gold-198. Radium-228 is no more considered as a suitable source for brachytherapy.

Systemic Therapy

12. The systemic use of radioactive isotopes such as Iodine-131 and Phosphorus-32, is made to treat cancer thyroid and Polychteaemia Vera.

BIOLOGICAL BASIS

13. Though the radiotherapy has been in practice for the last seventy years, the biological basis of its application has been discovered very recently.

Basic Mechanism of Cell Killing

14. Radiations dissipate energy by ionisation in the tissues. It is generally considered that production of irreparable damage to DNA by radiation is responsible for reproductive cell death. For irreparable damage to occur to DNA, presence of molecular oxygen in the cell is most essential. Thus, for a given absorbed dose, the probability that a cell will be killed is a function of the intracellular oxygen concentration at the time of irradiation. The biological effects of ionising radiation are directly proportional to the amount of energy absorbed (dose.).

15. The biological end point of most importance is loss of cellular reproductive ability or clonogenicity. An irradiated cell is considered "dead" if it is unable to proliferate indefinitely.

Radiosensitivity, Radio-resistance and response of Tumour to Radiation

16. Radiosensitivity is a measure of susceptibility to injury by ionising radiations. This injury may be lethal to the cell through interruption of the capacity to replicate indefinitely or (reproductive death) or through metabolic incapacitation or structural degeneration i.e. independent of progression through the reproductive cycle (interphase death).

17. Radio-resistance is the reciprocal reaction to radio-sensitivity and therefore, is relative rather than absolute. These terms are frequently misused in clinical oncology because of the misconception that the rate of gross reduction in the size of tumour is a meaningful measure of the effectiveness of radation. Such gross response depends not only on cellular susceptibility to damage but also on other factors. Such as the rate of clearance of dead cells and the proportion of intercellular components.

18. Another misconception is that there is a specific radiation dose that will kill all cells of certain type or all cells in a tumour, mass. Repeated specific radiation dose kills a constant fraction not an absolute number of cells of a particular type. Thus, initial radiation doses kill the largest absolute number of cells. Fruther reduction of cells incapable of causing a clinical recurrence is a fractional process governed in part by statistical rules of probability.

19. Lingering incorrect concepts of radio sensitivity may result in incorrect clinical use. Tumour location and extent rather than a potential for rapid gross response to ionising radiation, usually dictate whether or not radiation therapy is applicable. Thus adeno-carcionomas arising in an confined to the breast or uterus may be curable by radiation, whereas adenocarcinomas arising in the stomach and metastasising to the regional lymph nodes are not. Actually the most radio-curable cancers, (with the exception of a few, e.g. seminoma arising in the testes), usually are not the most responsive to radiation as measured by gross tumour disappearance. Thus, squamous cell carcinomas arising in the skin, uterine cervix or oral cavity are only moderately radio-responsive but are highly radio-curable.

Therapeutic Ratio

20. Therapeutic ratio is the ratio between the tumour lethal dose and the maximum dose of tissue tolerance. Sensitive tumours are those in which this ratio is high. Resistive tumours are those

in which the dose required to produce lethal action is almost as great as the destructive dose for normal tissue.

Enhancement of therapeutic Ratio

21. If the response of tumor and normal cells to ionising radiation could be modified to increase the therapeutic ratio (response of the tumour compared with the response of normal tissues), the effectiveness and applicability of the method could be usefully extended. Radiosensitivity can be modified by the following factors.

(a) Use of radio sensitisers
(b) Use of radiations of very high energies like neutrons
(c) Hyperthermia
(d) Synchronising cells in sensitive phases through the use of drugs.
(e) Use of hyperbaric oxygen.
(f) Modifying the fractionation based on the cell cycle of the tumour.
(g) Selectively protecting normal tissue.

FRACTIONATION

22. When a given dose of radiation is divided into several increments and delivered over a period of several days, the process is known as fractionation. The biologic effects in fractionation is less than if the radiation has been given in a single dose. This decreased response with daily fractionation appears to be related to cell recovery occuring between the increments. Those cells which survive the acute effects of an irradiation repair their sub-lethal damage is less than 24 hours. Thus the total dose of radiation has to be increased peri-passu with the increase in the overall period treatment.

23. If the overall period is prolonged the normal tissues get time to repair the radiation-induced damage as this damage initiates a feed-back mechanism that activates a reparative process. This has been called the homeostatic stimulus to normal tissue repair.

Melignant cells are little effected by this stimulus. Thus, it can be seen that fractionation enhances the therapeutic ratio.

24. There is a significant component of hyposic cells in any palpable cancerous mass. As the initial fraction of irradiation destroys oxygenated cells, the hypoxic cells move into the area of oxygenation. This process is known as re-oxygenation.

25. The advantages of fractionation can be summarised as follows :

(a) Fractionation exploits the differential recovery rates between normal tissues and neo-plastic tissues. Thus it enhances the therapeutic ratio.

(b) Through the process of re-oxygenation it overcomes partially the problem of hypoxic cell resistance.

(c) Blood vessels compressed by a growing cancer are decompressed as the cancer shrinks and thus improves the oxygenation of cells.

(d) Very high doses of radiation produce local oedem awhich can threaten life. This can be reduced by fractionation.

(e) The initial increments of a course of fractionated irradiation will often produce enough benefits such as cessation of haemorrhage, reduced infection and improved nutrition, so that the remaining fractions are better tolerated.

(f) Radiation sickness can be reduced through fractionatio n

(g) Fractionation permits greater flexibility in the overa l dosage and tissue volume irradiated.

CLINICAL BASIS

26. Like any other therapeutic modality radiation therapy has definite indications and contra-indications for clinical application. The use of this powerful modality which often eradicates cancer

may sometimes create substantial morbidity. Inoperability per se or psychological support of the patient and family is ill considered indications of radiation thereapy and is a disservice to both the patient and the modality. In evaluating a patient to determins whether or not radiation therapy might be helpful, there are factors to be considered that are related to the tumour itself and othere that are related to the host.

27. All the available therapeutic methods for cancer in the human may produce serious morbidity, or even ocasional mortality. Thus it is essential that histopathological diagnois of cancer is established prior to the institution of the treatment. However, there are rare exceptions to this when the biopsy itself may pose a threat to the patient, such as in patients with tumours of them mid-brain, brain-stem or optic tract.

28. Histological identification of the tumour type and an assessment of tumour cell activity within a particular tumour type (grading) are useful pre-therapeutic predictors of biologic behaviour. However, such evidence is poor predictor of radio-responsiveness or radio-curability. For example, squamous cell carcinoma and adenocarcinomas are equally radio-responsive, but the outcome of treatment varies considerably due to other factors, such as tumour site and extent. Likewise the advisability of radio therapy for squamous cell carcinoma arises in the floor of the mouth is related not to histologic differentiation but to other factors.

29. The anatomic site of origin and the extent of cancer are often more important than tumour type in deciding whether or not irradiation is appropriate. Thus, whereas a squamous cell carcinoma that is limited to a freely mobile vocal cord should be irradiated. local extension of such tumour from the true cord to adjacent structures or the sub-glottic region make surgery preferable. In contrast, although pulmonary squamous cell carcinoma without spread to the mediastinum should usually be resected extension of such a tumour to the mediastinum might make local irradiation preferable.

30. At times, when radiation therapy seems indicated for the cancer, it may be inappropriate becouse of host factors. For example, even in some palliative situations, radiation-therapy may be un-(acceptably vigorous. Thus, the relatively high radiation dose needed to open an oesophageal lumen obstructed by squamous cell carcinoma may not be tolerated by a frail, chronically ill, elderly patient. As with surgery and chemotherapy, treatment application may be prevented by irrational fears of the patients.

31. After evaluation, the objective of radiation therapy must be defined. If the cancer is potentially radio-curable, patient–inconvenience, high cost and a reasonable risk of serious treatment—related morbidity are acceptable.

32. If palliation in an incurable patient is the objective, these consequences of treatment usually are not acceptable.

33. In planning the actual treatmnent not only identifiable gross tumour but also sites of high risk of spread must be delineated. The doses of radiation to different sites in the same patient may vary, and actual delivery may require an integration of different types of radiations from several radiation sources. Thus, a cancer of uterine cervix or oral cavity may require radiation not only from an external source but also from brachytherapy.

E EFFECTS

34. The sequalae of treatment seen three to four decades earlier are rare now, because of accurate dosimetry, megavoltage equipment, basic understanding of normal tissue tolerances and availability of trained Radiation Oncologists. The incidence of treatment related side effects are dose dependant and have to be balanced with higher tumour control.

35. Early reactions occur during or immediately following radiation therapy. These include anorexia, nausea, vomiting, diarrhoea, oesophagitis, skin reactions (which are more marked in body folds), mucositis, epilation and bone marrow depression. These effects are self limiting and recover within four to six weeks of irradiation.

36. The late sequaelae are subsequent to the endarteritis caused by irradiation. This results in fibrosis. Serious injuries such as radiation myelopathy, bowel stenosis and necrosis of the bone are rare as dose is restricted to within the tolerance level of vital tissues. The tolerance level of some vital tissues are given below :—

Liver 300 rads	Lenss of the eye 600 rads
Kidneys 1500 rads	Retina 4000 rads
Lung 3000 rads	Spinal cord 4000 rds

COMBINATION THERAPY

37. Today is the era of multi-modal treatment in the management of cancer. Radiotherapy is increasingly being combined with chemotherapy, surgery, immunotherapy or any combination thereof Interactions with surgery date back to many years. The objective is the improvement of local and regional control of the tumour. Both surgery and radiotherapy in majority of cases are directed to the same anatomic site. Sometimes the two modalities may be directed to adjacent but different anatomic, sites.

38. Radiotherapy can be given either pre-operatively or post operatively depending on the different objectives of treatment and prejudices of the specialists involved. The interval between the application of each treatment method should be planned to minimise the additive complications without dissipating any advantage in tumour control. The interval will vary with the quality of radiations, radiation dose, irradiated volume, anatomic structures involved and extent of the surgery, but it usually ranges from 4 to 6 weeks.

39. Interations of radiotherapy and chemotherapy have increased strikingly over the past few years. Usually the objectives of each are complementary with irradiation of large tumor masses, often at the primary site and systemic treatment of wide-spread metastases, either documented or occult.

40. Planned interactions of agents that stimulate the human immune system and ionising radiations, which are immunosuppressive are the subject of current research.

41. From this discussion, of the necessity of correlating cancer biology in the human, basic radio-biology and physics, radiation

responses of cancers and normal tissues, and continuing evaluation of performance, it should be evident that the selection of patients for radiation therapy is beyond the capabilities of the referring doctor, regardless of competence in his or her chosen medical speciality. Thus, the selection of patients for radiation thereapv must be made by the radiation oncologist, just as the selection of surgery must be the decision of the surgeon.

Combination of Radiotherapy and Surgery

42. In selected sites the high incidence of local persistance after irradiation alone or after surgery alone has led to the trial of a great variety of combinations of the two modalities. Radiotherapy can be given either preoperatively or post-operatively.

PRE-OPERATIVE RADIOTHERAPY

43. Aims of preoperative Radiotherapy are :—

(a) To reduce the incidence of local recurrence.

(b) To render a locally non-resectable cancer, resectable.

(c) To make any malignant cell non-viable which otherwise would have been implanted in a wound during surgery.

(d) Increasing the resistance of the normal tissue to tumour cell implant and further tumour invasion.

44. *Optimum Pre-operative Dose of Radiation.* This dose is difficult to define. Optimum preoperative radiotherapy should yield the maximum cure rate compatible with an acceptable post-operative-morbidity. The commonly used dosage varies between 2000 rads in eight treatments and 5000 rads in twenty treatments However, the dosage will vary with anatomic site and cell type.

45. *Optimum Interval between Radiotherapy and Surgery.*—This period should be such that its normal tissues will recover from radiation damage so that wound healing will proceed uneventfully. Meanwhile it should not be long enough so that cancer cells can recover and proliferate. Moreover, if surgery is delayed then the late effects of radiation such as fibrosis may set in. Usually this period is between 3 to 6 weeks.

46. **Advantages of Pre-operative Radiotherapy :—**

(a) Peripheral extensions of cancerous mass are more radio-sensitive than the central cells. Thus pre-opetative radio-therapy will have maximum cell killing in this zone.

(b) Making a non-resectable cancer, resectable one.

(c) As the blood supply is intact, the effect of radio-therapy will be appreciably better if given pre-operatively.

(d) Reduces the incidence of viable cancer cells implantation.

47. **Disadvantages of Pre-operative Radiotherapy :**

(a) It impairs the wound healing.

(b) Delays curative surgery. Thus, the tumour mass may grow or occult distant metastasis may occur.

(c) Gross shrinkage of cancerous mass may tempt the surgeon to perform a less radical resection.

(d) Prolongs the stay in the hospital.

(e) The patient may feel better and refuse surgery.

48. Thus, it can be seen that the advantages and disadvantages have to be balanced in an individual patient and treatment has to be individualised depending on the experience of the treating clini-cians.

POST-OPERATIVE RADIOTHERAPY

49. Aims of Post operative Radiotherapy are to sterilise locally residual cancer after surgical excision, thus, reducing the incidence of local recurrence.

50. **Advantages of Post- operative Radiotherapy**

(a) The healing of surgical wound will be unaffected.

(b) As the healing has already occurred a higher dose of radiation can be administered.

(c) Surgically removed specimen can give a good idea about the size shape and location of the volume requiring irradiation.

51. **Disadvantages of Post operative Radiotherapy**

(a) As the blood supply is interfered with, cancers are not very radio-sensitive after surgery.

(b) The tolerance of the normal tissues to radiotherapy post-operatively is poor.

52. **Optimum Period for Post-operative Radiotherapy**—This period should be around 1 to 2 weeks after surgery.

53. **"Sandwitch" Technique.**—In this technique half dose of radiation is given before surgery and half after wards.

CLINICAL USE OF RADIOTHERAPY IN MANAGEMENT OF VARIOUS MALIGNANCIES

54. **Radiotherapy as the treatment of choice**—This may be due to :

(a) Tumours are radiosensitive

(b) Tumours are inaccessible sites

(c) The various cancers are :—

(i) Stage I and II — Hodgkin's Disease

(ii) Stage I and II — Non-Hodgkin's Lymphoma

(iii) Carcinoma Cervix

(iv) Carcinoma Vagina

(v) Carcinoma Nasopharynx

(vi) Early cases of cancer Laryn X and Hypopharynx

(vii) Carcinoma Oropharynx

55. **Radiotherapy and Surgery are equally effective :**

(a) Oral Carcinomas
(b) Cancers of the skin
(c) Anal carcinoma
(d) Carcinoma Penis

56. **Radiotherapy is combined with Surgery**

(a) Carcinoma Breast
(b) Carcinoma Oesophagus
(c) Carcinoma Prostate
(d) Carcinoma urniary bladder
(e) Renal cell carcinoma
(f) Testicular tumours
(g) Carcinoma ovary
(h) Carcinoma uterus
(j) Cancers of nose and paranasal sinuses
(k) Cancers of salivery glands
(l) Cancers of middle ear
(m) Late cancers of Larynx and Hypopharynx
(n) Brain tumours
(o) Lung cancer
(p) Cancer Rectum

57. **Radiotherapy is combined with chemotherapy**

(a) Stage III & IV Hodgkin's Disease
(b) Stage III & IV Non-Hodgkin's lymphoma
(c) Leukaemias
(d) Anaplastic Carcinoma of the lung

(e) Ewing's sarcoma and other paediatric malignancies.

(f) Multiple Myoloma.

58. **Radiotherapy used for palliation**

(a) Cancer Pancreas

(b) Cancer Vulva

(c) Bony metastases

(d) Cerebral metastases

(e) SVC obstruction

(f) Relief of pain

PROSPECTS FOR THE FUTURE

59. The clinical use of ionising radiations, dates to the discovery of X-rays in 1895 and the recognition of natural radio-activity in 1896. However, the physical foundations of therapeutic application, the development and distribution of megavoltage generators, the training of substantial number of physicians and para medical staff and an elementary knowledge of radio-biology began only a few years ago. The propspects for better therapeutic use of radiotherapy in the future are very good through continuous research. Research objectives include a betterunderstanding of cancer biology through modification of the radio-sensitivity of both tumours and normal tissues, better application of ionising radiations by improving the definition of targets and delivery systems, development of particle irradiation, improved use of adjuvants and more effective interaction with other modalities.

(P K Chakrabarti)

Lt Gen

Director General Armed Forces Medical Services

DATE 21 FEB 1994.

94/M/J(N)62DGAFMS—5,500—6-3-95—GIPS

C