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UNIVERSITY OF CALIFORNIA
LOS ALAMOS SCIENTIFIC LABORATORY
(CONTRACT W-7405-ENG-36)
P. O. Box 1663
Los Alamos, New Mexico 87544

IN REPLY REFER TO: H-2

June 22, 1976

Morton M. Kligerman, M.D.
Director
Cancer Research and Treatment Center
The University of New Mexico
900 Camino De Salud, NE
Albuquerque, New Mexico 87131

Dear Doctor Kligerman:

The last Human Studies Committee met on June 11th to consider a protocol describing Pion Meson therapy of skin nodules in selected patients.

Approval is hereby granted to proceed with the protocol describing Pion therapy of skin nodules in selected patients. In order to expedite initiation of these studies the LASL Human Studies Committee has elected to approve the skin nodule protocol separately and will consider the solid tumor protocol at a later date. The following modifications are suggested to avoid ambiguity in the protocol and in the consent for:

1. Revised Pion dosage and schedule are to be included in a revised protocol.

2. In paragraph 11.2 of the protocol omit the first sentence, "Autopsies will be performed on all studied patients".

3. Consent form should be revised to the first person throughout as in Items 2B and C.

4. The committee felt that a patient cost statement similar to that in the previous consent form during the first Pion study should be included. A suggested inclusion might be, "The cost of your transportation to and from Albuquerque; tests performed at CTRC to evaluate your condition before treatment; transportation to and from Los Alamos; room and board while at Los Alamos receiving treatment and other medical expenses resulting from radiation treatment at Los Alamos will be borne by CTRC research funds".

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Morton M. Kligerman, M.D.

June 22, 1976

We trust that this approval will enable you to expedite what we consider a most worthwhile program and that the minor modifications may meet with your approval.

Robert S. Grier, M.D.
Chairman

Donald F. Peterson

Rosemary Griffith

Robert Dinegar

David Law, M.D.

Margaret Browne

Harry Schulte

RSG:h

Paul Lee, M.D.

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Pion Protocol
UNM/LASL 76-02
Rev. 5/76

EVALUATION OF RADIOBIOLOGICAL EFFECTS OF NEGATIVE PI MESONS ON MISCELLANEOUS LOCALLY-ADVANCED AND/OR RECURRENT HUMAN SOLID TUMORS AND SURROUNDING NORMAL TISSUES

Protocol for Human Radiobiology Studies of
Pi Meson Radiation Therapy at
University of New Mexico/Los Alamos Scientific Laboratory

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Morton M. Kligerman, M.D., Director
Cancer Research and Treatment Center
University of New Mexico
Albuquerque, New Mexico 87131

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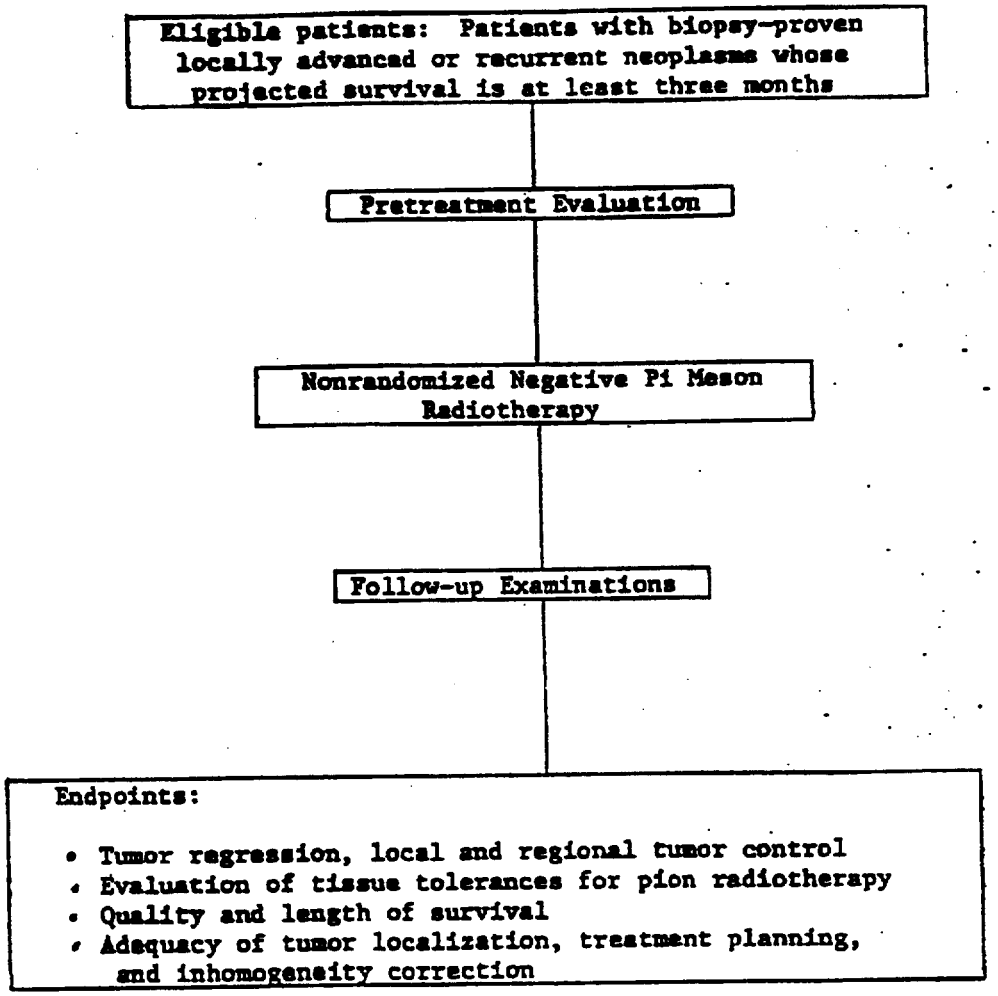
PROTOCOL: EVALUATION OF RADIOBIOLOGICAL EFFECTS OF NEGATIVE PI MESONS ON MISCELLANEOUS LOCALLY ADVANCED AND/OR RECURRENT HUMAN SOLID TUMORS AND SURROUNDING NORMAL TISSUES

0.0 Schema



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1.0 Summary of the Study

This is a nonrandomized pilot study to evaluate normal tissue and tumor response to pion radiotherapy in a wide variety of human tumor sites, all of which will be biopsy-proven, locally advanced or recurrent solid tumors. The study of local and regional tumor control as well as tissue tolerances will be the prime goal of this protocol. Additional valuable information will be gained regarding treatment planning, patient set-up and immobilization, assessment of tissue inhomogeneities, and other technical aspects of pion therapy.

Patients will be eligible if they are not undergoing chemotherapy or have not received previous radiotherapy to the area and have a life expectancy of at least three months.

2.0 Introduction and Objectives

During the pilot phase of pion radiotherapy, experience will be sought in patients with locally advanced and/or recurrent neoplasms to aid in establishing techniques of treatment, normal tissue tolerance and tumor response to pion beams before proceeding to randomized Phase III trials.

These patients may have tumors of a wide variety of sites provided they are locally advanced to the extent that conventional radiotherapy would have little or no chance of controlling the tumor.

Patients with radiosensitive lesions, widespread metastases, previous radiotherapy to the area, or undergoing concurrent chemotherapy would be excluded. Patients must be between the ages of 18 and 75.

The objectives of the study are:

1. To evaluate tumor response.
2. To study local and regional control of tumor.
3. To evaluate normal tissue response and tolerance to large field multi-fraction pion therapy.
4. To evaluate important aspects of treatment planning and technical aspects of delivering the radiation in an attempt to maximize the therapeutic ratio by minimizing the normal tissue volume to be irradiated.

3.0 Eligibility of Patients

3.1 Conditions of eligibility. The following conditions must be met before a patient can be admitted in the study:

1. Biopsy-proven malignancy.
2. Locally advanced or recurrent cancer.
3. Patient age between 18 and 75.

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3. Little or no chance of control with conventional radiotherapy.

4. Understanding by the patient of the provisions of the study and voluntary informed consent to participate in the study.

3.2 Conditions of ineligibility

1. Moderate to high chance of control by other treatment modalities.

2. Previous radiotherapy to site.

3. Ongoing chemotherapy.

4. Life expectancy less than three months or Karnofsky status of less than 60%.

5. Active uncontrollable infection in area of irradiation.

6. Medical, psychological or other contraindication to proposed treatment.

4.0 Treatment

4.1 Pretreatment evaluation. Pretreatment evaluation will be performed at the University of New Mexico Cancer Research and Treatment Center (CRTC) or by the referring physician at another institution, with findings verified and studies augmented as required by the CRTC study team. The evaluation will include:

1. Medical History.

2. Physical Examination.

3. Laboratory tests.

   a. CBC (including differential)
   b. Platelet count
   c. Urinalysis
   d. Serum Chemistry Profile
   e. Others as indicated

4. Chest X-Ray and others as indicated, particularly if tumor is in close proximity to bone.

5. Staging procedures as indicated with careful mapping and clipping of tumor where possible.

4.2 Admission to study. Any patient who meets the required eligibility and pretreatment evaluation criteria will be admitted to the protocol for pion radiotherapy at LAMPF. The following records will be generated by the study team and participating institutions for storage, retrieval and analysis at the CRTC study center in Albuquerque:

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1. Patient eligibility form

2. Pretreatment evaluation form. This form, documenting the history and physical information, laboratory tests and special studies including surgery, will be submitted on those patients referred for treatment.

3. Study entrance form (patient name, address, referring institution, referring physician, etc.)

4. Patient consent form

4.3 Treatment application. All patients will receive nonrandomized pion therapy at the Clinton P. Anderson Meson Physics Facility (LAMPF) in Los Alamos. For pion therapy, a safety factor based on results with earlier animal and human tests will be applied. Initially, multi-fraction pion treatment (five days per week) for three to six weeks will be utilized with a radiobiological equivalent of conventional x-ray doses for similar fractionation schemes less 40 percent. These doses may be altered subsequent to observation of radiation effects in a minimum of six patients receiving pion irradiation to the same anatomic site. Doses will vary, depending on the anatomical site to be irradiated, and no single numerical value can be assigned for all sites.

Single or multi-port techniques will be utilized to maximize the tumor/normal tissue dose ratio according to the anatomic site. Appropriate set-up and immobilization devices will be developed. Treatment planning will include use of hand-prepared plans as well as development of computer-produced isodose distributions. Where possible, assessment and compensation for tissue inhomogeneities will be accomplished. In vivo dosimetric measurement will be accomplished where feasible. Recording and scoring of acute and late reactions will be documented.

5.0 Endpoints

1. Tumor regression local and regional tumor control

2. Evaluation of tissue tolerances for pion radiotherapy

3. Quality and length of survival

4. Adequacy of tumor localization, treatment planning, and inhomogeneity correction

6.0 Statistical Considerations

This will be a nonrandomized pilot study. Patients will be entered with various tumor primaries until sufficient information on response and techniques of treatment planning has been accumulated to begin randomized trials.

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7.0 Post-Irradiation Evaluation

7.1 Follow-up plan and schedules. The referring physician will be encouraged to see the patient in accordance with his customary schedule.

The patient will be seen at the Cancer Research and Treatment Center at monthly intervals during the first year, semi-annually for the next two years and annually thereafter. If the patient cannot return to the CRTC, he will be seen by a radiotherapist representing the nearest participating institution to the patient's home town, or arrangements will be made to have him examined at another hospital by his private physician and a report of this examination submitted to the CRTC.

7.2 Follow-up information. The following information will be recorded on the follow-up form at each visit:

1. Brief interval history related to disease

2. Physical examination:

   a. Weight, blood pressure
   b. Temperature
   c. Appropriate aspects of physical examination
   d. Regression of palpable or visible tumor

3. Laboratory tests and routine x-rays; appropriate studies as indicated.

4. Specific diagnostic studies, or studies which gave the most reliable information regarding the initial extent of tumor will be repeated at periodic intervals.

5. Complications of treatment

6. Recording and scoring of late reactions and pathologic studies by re-biopsy/autopsy as indicated.

8.0 Additional Therapy

Clinical evidence of lack of tumor control should be documented by biopsy if possible. If such evidence is equivocal, re-exploration should be encouraged if the patient is a good surgical candidate, until such time as a pattern of recurrence is established and documented. In the event that surgery or biopsy is performed, the excised tissue or biopsy specimen should be carefully examined by the study pathologist with assistance from the involved radiation oncologist. If the primary tumor is not controlled, subsequent therapy should proceed at the discretion of the patient's responsible physician. The patient or physician will notify the investigator of any treatment instituted that has not been prescribed by the investigator.

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9.0 Study Parameters

Parameters to be recorded throughout the study include:

a. Degree and time of regression and regrowth

b. Assessment of acute radiation effects

c. Assessment of long-term radiation effects

10.0 Pathology

10.1 Initial surgical (biopsy) specimens. Biopsy specimens will be examined by pathologists at the participating institutions to confirm the diagnosis. Representative slides and copies of biopsy reports will be submitted to the study center for review by the study pathologists. Copies of the reports from the study pathologists will be forwarded to the referring and/or follow-up physician.

10.2 Subsequent surgical specimens. Any tissue surgically removed from anatomical sites will be examined by pathologists at the participating institution where surgery was performed. Appropriate microscopic slides and pathological reports will be forwarded to the study center for review by the study pathologists.

10.3 Autopsies. Autopsies are strongly urged on all study patients by pathologists at the participating institutions. Post-mortem studies should include a description of irradiated tissues and the character and extent of persistent, recurrent or metastatic tumor. Autopsy reports and representative microscopic slides will be forwarded to the study center for review by the study pathologists.

11.0 Records

Two copies of each study form must be submitted to the study center. Data will be recorded on standard forms to be supplied to participating institutions for storage retrieval, and analysis at the study center:

a. Photocopy of patient consent form

b. Patient eligibility form

c. Pretreatment evaluation form

d. Study entrance form

e. Radiation treatment summary. A daily schedule of pion therapy will be prepared at LAMPF. This report will also include an end of treatment examination to include weight, pertinent general physical examination, performance status, current medications, and, if possible, an assessment of tumor response.

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f. Follow-up examination form (see Section 7.2)

g. Pathology forms (see Section 10.0)

The necessary study forms to support data collection and analysis are currently being designed under the direction of the senior statistician assigned to the study team. The forms will be precoded to facilitate computerized data analysis.

12.0 Patient Consent and Peer Judgment

All institutional, Food and Drug Administration, and National Cancer Institute regulations requiring submission to the institutional human experimentation committee and the use of procedures for obtaining and recording informed consent will be followed A patient may be removed from the study if the study is not in the best interest of the patient. A patient may withdraw voluntarily from the study at any time, as will be indicated in the consent form.

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CANCER RESEARCH AND TREATMENT CENTER

University of New Mexico

Albuquerque, New Mexico

INFORMED PATIENT CONSENT FOR PARTICIPATION

IN PION PROTOCOL FOR HUMAN CANCERS

PATIENT'S NAME: _____

ADDRESS: _____

HOSPITAL/CLINIC: _____

HOSPITAL/CLINIC I.D. NUMBER: _____

SOCIAL SECURITY NUMBER: _____

1. I, _____, hereby agree to participate as a patient in a research project for treatment of cancer with pi meson radiation therapy using equipment at the Clinton P. Anderson Meson Facilities in Los Alamos, New Mexico, which will be conducted by Dr. Morton M. Kligerman as the Principal Investigator, and such qualified assistants as he may need and employ. (I understand that these assistants will be under the direct supervision of the attending physician appointed by Dr. Kligerman at all times during the course of the research.)

2. The procedures to be performed on me have been personally described to me by Dr. _____, and I fully understand them to be as follows:

   a. If you choose to enter the study and the physical examination and tests show you are eligible, you must agree to spend the required amount of time in Los Alamos for treatment. You must also agree to return to the U.N.M. Cancer Research and Treatment Center for the required follow-up examinations.

   b. You will receive pi meson radiation treatments at the Los Alamos Scientific Laboratory, Clinton P. Anderson Meson

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Physics Facility, for a period of _____ weeks. Treatments will be given each day, Monday through Friday, to appropriate portions of the body.

c. Standard preparatory procedures may be involved, including diagnostic x-ray pictures and nuclear medicine isotope scans. There will be a pre-irradiation aligning exercise without administering radiation to familiarize you with the process and to ascertain that radiation during treatment will be delivered to appropriate regions of your body. Plastic and flexible devices may be used for positioning.

d. The treatments will be administered in the manner demonstrated to you during the prealignment exercise. There will be no pain or sensation from the beam during treatment. You will be alone in the treatment room; however, the treatment personnel can view you at all times on closed-circuit T.V., and two-way voice conversation is possible any time via intercom equipment. A nurse is stationed immediately outside the treatment room and is available as needed.

e. You will be asked to participate in a variety of standard medical tests in the post-irradiation period: these will measure the progress and efficacy of the treatment.

f. While you are taking part in the study, your physician is still responsible for your treatment and can change your treatment or remove you from the study at any time if he believes it to be in your best interest. Your well-being is his primary concern. If you are receiving treatment in Los Alamos, your treatment will be managed in close cooperation with your physician, although he may not be administering the treatment himself.

3. Dr. _____ has informed me of the potential benefits to me and to others he anticipates will result from the research in which I have agreed to participate. The pi meson radiotherapy may be more effective in treating patients who require more than standard therapy.

4. Dr. _____ has explained and discussed the possible side effects and risks to me as follows:

We do not have complete information on the incidence and exact nature of the discomforts and risks which may occur with pi meson radiotherapy. Preliminary biology tests indicate that the procedure should not have significantly different adverse effects than usual treatment and the doses given you are designed to minimize the possibility of excessive discomfort and risk. Both pi meson radiation and conventional radiation could result in some or all of the following types of discomfort and risks, depending on the area of treatment. (See insert appropriate to tumor site to be treated).

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5. Dr. _____ has explained to me that there are alternative choices of treatment open to me and has described them as follows:

   a. Surgery

   b. Chemotherapy - Immunotherapy

   c. Conventional Radiotherapy

6. Dr. _____ has offered to answer any inquiries I might wish to make at any time during the course of the research.

7. No guarantees or assurances have been given to me or anyone regarding the treatment I may receive or the results that may be obtained.

8. I understand that while taking part in the study, Dr. _____ is responsible for my treatment and may change my treatment or remove me from the study at any time, if he believes it to be in my best interest.

9. I understand that this is not a release or waiver of my legal rights.

DATE:_____ TIME:_____ PLACE:_____

SIGNED:_____ WITNESS:_____
Patient

_____ WITNESS:_____
Parent or Legal Guardian When Indicated

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Possible Discomfort and Risks

The discomfort and risk you experience because of the radiation treatments should not be greater for pi meson radiation therapy than for conventional supervoltage radiation therapy. However, we do not have complete information on increased risk you may encounter with pi meson radiation therapy. Some of all of the types of discomfort and risk experienced by patients receiving any type of radiation treatments to the pelvis include:

1. Damage to the stomach and small or large intestine, such as ulceration or perforation might occur with pi meson radiation therapy, although in practice with conventional external beam treatment this has not been observed.

2. Mild to moderate effects on the blood, resulting in a decrease in one or more types of blood cells. (However, this is monitored at weekly intervals or more often when appropriate, so the condition can be treated promptly.)

3. Loss of hair in the treatment area.

4. Skin reaction in the treatment area (for example, redness and peeling).

5. Neurologic complications, such as weakening or paralysis of the legs (although this is rare in conventional treatment). In more than 50 consecutive cases analysed in one study, there was not a single case of paralysis.

6. Pain and swelling of normal tissues in the treatment area.

7. Diarrhea, possibly containing blood (usually readily controlled by approximate treatment and which usually disappears at the end of the x-ray treatments).

8. Nausea (also readily controlled by appropriate drugs and/or by slowing the rate at which radiation is given).

9. Urinary complaints, such as a more frequent need to urinate and burning pain with urination (which usually disappears at the end of treatment).

10. Impotence (40%)

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Possible Discomfort and Risks

We do not have complete information on the risk you may encounter with pi meson radiation therapy. Pi meson radiotherapy could result in some or all of the types of discomfort and risk experienced by patients receiving conventional types of radiation treatment to the pelvis, which include:

1. Damage to the stomach and small or large intestine, such as ulceration or perforation might occur with pi meson radiation therapy, although in practice with conventional external beam treatment this has not been observed.

2. Mild to moderate effects on the blood, resulting in a decrease in one or more types of blood cells. (However, this is monitored at weekly intervals or more often when appropriate, so the condition can be treated promptly.)

3. Loss of hair in the treatment area.

4. Skin reaction in the treatment area (or example, redness and peeling).

5. Neurologic complications, such as weakening or paralysis of the legs (although this is rare in conventional treatment). In more than 50 consecutive cases analyzed in one study, there was not a single case of paralysis.

6. Pain and swelling of normal tissues in the treatment area.

7. Diarrhea, possibly containing blood (usually readily controlled by appropriate treatment and which usually disappears at the end of the x-ray treatments).

8. Nausea (also readily controlled by appropriate drugs and/or by slowing the rate at which radiation is given).

9. Urinary complaints, such as a more frequent need to urinate and burning pain with urination (which usually disappears at the end of treatment).

10. Menstrual flow stoppage. This will almost certainly occur in female patients who are actively menstruating.

11. Vaginal discharge.

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Possible Discomfort and Risks

The discomfort and risks you experience because of the radiation treatments should not be greater for pi meson radiation therapy than for conventional supervoltage radiation therapy. However, we do not have complete information on increased risk you may encounter with pi meson radiation therapy. Some or all of the types of discomfort and risk experienced by patients receiving any type of radiation treatments to the pelvis may include:

1. Damage to the stomach and small or large intestine, such as ulceration or perforation might occur with pi meson radiation therapy, although in practice with conventional external beam treatment this has not been observed.

2. Mild to moderate effects on the blood, resulting in a decrease in one or more types of blood cells. (However, this is monitored at weekly intervals or more often when appropriate, so the condition can be treated promptly.)

3. Loss of hair in the treated area.

4. Skin reaction in the treatment area (for example, redness and peeling).

5. Neurologic complications, such as weakening or paralysis of the legs (although this is rare in conventional treatment). In more than 50 consecutive cases analyzed in one study, there was not a single case of paralysis.

6. Pain and swelling of normal tissues in the treatment area.

7. Diarrhea, possibly containing blood (usually readily controlled by appropriate treatment and which usually disappears at the end of the x-ray treatments).

8. Nausea (also readily controlled by appropriate drugs and/or by slowing the rate at which radiation is given).

9. Urinary complaints, such as a more frequent need to urinate and burning pain with urination (which usually disappears at the end of treatment).

10. Menstrual flow stoppage. This will almost certainly occur in female patients who are actively menstruating.

11. Vaginal discharge.

The incidence of these is known and has been established in conventional radiation therapy and surgery. What is not known is the increased—or decreased—incidence of these or other effects which may occur with pi meson radiotherapy.

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I understand that some discomforts (or side effects) and risks to my health and well-being may be associated with my participation. Dr. _____ has discussed these with me and has described them as follows:

1. Risks:

   a. Regardless of type of radiation treatment used, surgery may be required after the radiotherapy resulting in a permanent loss of voice.

   b. The possibility of nerve or spinal cord damage resulting in a weakening or paralysis of portions of the body (although the incidence is rare).

   c. The formation of fistulas, abnormal openings, which may heal themselves or may require surgical repair.

   d. Pain and swelling of normal tissues in the treatment area.

   e. Loss of normal bone and muscle tissue in the treatment area.

   f. Cavities in the teeth.

   g. Temporary or permanent ulcers of the lining of the mouth or throat.

   h. Difficulty in swallowing and sore throat.

   i. Cough.

   j. Difficulty breathing.

   k. Mild to moderate effects on the blood resulting in a decrease of one or more types of blood cells. (However, this is monitored at weekly intervals or more often when appropriate, so the condition can be treated promptly.

   l. Fever.

   m. Susceptibility to infection.

   n. Later development of cancer of the thyroid, although the incidence is rare.

2. Discomforts (or side effects)

   a. Skin reaction in the treatment area (for example, redness, peeling, and possibility of radiation skin burn, later possibly resulting in the development of skin cancer).

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b. Excessive moisture or dryness in the upper air and food passages.

c. Loss of taste (usually temporary).

d. Loss of hair in the treatment area.

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