Chapter 12

Radiation Therapy

12.1. INTRODUCTION

The Collaborative Ocular Melanoma Study (COMS) has established a Radiation Therapy and Physics Committee (RTPC) that has major responsibility for the proper conduct of the study, particularly those aspects pertaining to administration of radiation therapy for patients who are assigned at random to be treated with radiation. The general objectives of the RTPC are:

- To develop specific guidelines for treatment of patients with radiation and to revise these as necessary over the course of the Study;
- To develop procedures for monitoring compliance with the COMS radiation treatment protocols at COMS clinical centers;
- To develop and maintain procedures for certifying radiation oncologists and radiation physicists;
- To assess compliance with the COMS protocols for radiotherapy.

The Radiological Physics Center is responsible for receiving and evaluating documentation of radiation treatment. The staff of that center communicates directly with radiation oncologists and physicists of clinical centers in which problems are identified. Persistent problems are called to the attention of the Quality Assurance Committee. If the problem is not resolved, the COMS Steering Committee may suspend enrollment of COMS patients at any center not in compliance with the protocol.

A patient eligible for either of the COMS randomized trials may be randomly assigned to radiation therapy:

- Eyes of patients with tumors from 2.5 mm to 10 mm in apical height *and* a basal diameter of 16 mm or less are treated with a radioactive plaque if randomized to radiation.
- Eyes of patients with tumors measuring greater than 10 mm in apical height *or* greater than 16 mm in basal diameter and patients with a juxtapapillary tumor greater than 8 mm in apical height are treated with preoperative external beam radiotherapy if randomly assigned to radiation.

12.2. RADIOACTIVE PLAQUE TREATMENT

12.2.1. Isotope and Activity Verification

Only ^{125}I is used in COMS plaques. A review of factors considered in selecting ^{125}I has been published.[1] Exhibit 12-1 illustrates differences in isodose curves between ^{125}I in COMS plaques and Cobalt-60.

Each seed (pellet) is assayed separately using an ionization chamber that has been calibrated by the user with an ^{125}I seed calibrated at the National Institute of Standards and Technology or an Accredited Dosimetry Calibration Laboratory (ADCL) *(viz.* K&S Associates in Nashville, TN, or the University of Wisconsin). Alternatively, the institution's well ionization chamber may have a calibration factor assigned by an ADCL. In either case, the calibration must be obtained for the particular seed type(s) used by the institution, model 6711 and/or model 6702. Chamber factor constancy is checked prior to each use by a long-lived check source (e.g., AM-241) whose equivalent ^{125}I activity also was determined with the calibrated seed. Records of the constancy of the chamber factor are to be maintained for review by the Radiological Physics Center.

Every institution participating in the COMS trial of radioactive plaque for medium tumors must have a system that can be used to verify the constancy of the manufacturer's stated activity reliably. There are three levels of verification.

1. The institution *must* maintain records relating ionization reading to the manufacturer's stated strength of a specially-calibrated seed purchased with each new batch of seeds. This procedure is used to identify batch-to-batch gross inconsistencies in stated or measured strengths.
2. It is highly recommended that the institution has a long-lived check source (e.g., Am-231, Cs-137) that can be used *on the same electrometer scale* as ^{125}I . This procedure is used to verify the constancy of the system factor.
3. It is recommended that the institution obtain an ^{125}I seed with NST-traceable calibration from K&S or the University of Wisconsin Accredited Dosimetry Calibration Laboratories. This seed is then used to assign a calibration factor to the institution's system. The constancy of this factor is checked as in level 2 above. This procedure enables the institution to calibrate each seed and verify the manufacturer's stated values.

12.2.2. Plaque Design

Standardized plaques are manufactured by Trachsel Dental Studio, Inc., Rochester, MN. Gold outer plaques and flexible inner plastic plaques are available in six standard sizes. They are described in Section 23.5. The participating clinical centers are responsible for ordering the standard plaques or obtaining approval of plaques made elsewhere, ordering radioactive iodine seeds for local use, and preparing plaques for insertion.

Radiation oncologists at COMS clinical centers may elect to manufacture their own plaques, modeled after the standard plaques. However, such plaques must be approved in advance by the Radiation Therapy and Physics Committee. The Radiological Physics Center should be contacted for instructions regarding the procedures to obtain approval for designs other than the standard plaques. The following information must be provided:

- General design of the plaque:
  - Material and thickness of the shield, with an estimate of radiation transmission;
  - Shape and size of the lip;
  - Distance from the surface of the seeds to the sclera;
  - Typical source distribution.
- Sample plaque:
  - Source distribution
  - Description of tumor
  - Dose distribution.

12.2.3. Plaque Construction

Plaques are constructed as follows:

- ^{125}I seeds are sandwiched between a gold outer plaque and an inner plastic seed carrier. The gold outer plaque has a lip or edge shield which encircles the plaque and extends to the sclera. The activity and number of seeds is chosen so that the dose rate at the prescription point (apex of the tumor if 5 mm or more at apex; 5 mm from the scleral surface if between 2.5 mm and 5 mm at apex) is at least 0.42 Gy/hr (42 cGy/hr), but no more than 1.05 Gy/hr (105 cGy/hr).
- The plaques are designed so that there is 1.0 mm of plastic between the surface of the seeds and the scleral surface of the plaque.
- Plaques are provided with suture holes on the periphery of the plaque.
- ^{125}I seeds are arranged in an outer ring near the edge of the plaque (within 1.5 mm of the edge) and in concentric rings throughout the plaque. The loading should be such that the 85 Gy isodose

surface passes through the prescription point, encompasses the tumor, and extends to or beyond the edge of the gold plaque.

12.2.4. Plaque Size

The plaque size is chosen so that the tumor base and a tumor-free margin of 2 mm to 3 mm are covered entirely by the plaque. The tumor base is defined for COMS purposes to include all pigmented areas.

An exception may be made if the tumor border is within 2 mm of the optic nerve. In this case, the plaque may be trimmed around the optic nerve so that the posterior edge of the plaque lies between the optic nerve and the posterior edge of the tumor, provided that the tumor does not subtend more than a 90° angle around the optic nerve. Alternatively, a notched plaque of the same design, including a lip around the notch, may be used. Notched plaques are also available from Trachsel Dental Studio, Inc.

12.2.5. Radiation Dose

For tumors 5 mm or greater in apical height, the tumor dose is prescribed at the apex of the tumor. For tumors from 2.5 mm to 5 mm in apical height, the prescription point is 5 mm from the interior surface of the sclera.

The absorbed dose at the prescription point is 85 Gy* (8,500 cGy) delivered at the rate of at least 0.42 Gy/hr (42 cGy/hr) but no more than 1.05 Gy/hr (105 cGy/hr).

12.2.6. Definition of Tumor Thickness

The thickness of the tumor is defined for COMS purposes to be the distance from the interior surface of the sclera to the apex of the tumor. The sclera is assumed to be 1 mm thick. Thus, if a tumor is said to be 5 mm in apical height, the point of dose prescription in the COMS is 6 mm from the surface of the radioactive plaque (i.e., 5 mm tumor thickness plus 1 mm scleral thickness). If the plaque lies on an oblique muscle, the plaque must be considered to be 1 mm from the external surface of the sclera.

12.2.7. Dose to Critical Structures and Other Points of Calculation

COMS eligibility criteria have been formulated so that patients are not eligible for assignment to radioactive plaque if treatment of their tumor would require so much radiation that loss of the eye secondary to radiation would be likely. The location of the following critical structures, relative to the plaque, are determined by the ophthalmologist and radiotherapist and noted on the retinal drawing or map (see Exhibit 9-1).

- *Sclera:* Necrosis of the sclera is a dose-limiting factor. For purposes of this Study, the dose to the sclera is estimated and reported at a point on the central axis of the plaque 1 mm from the surface of the plaque. This point is usually coincident with the internal surface of the sclera near the center of the tumor. Calculated doses to other points of concern or interest also may be reported.
- *Macula and optic nerve:* The COMS investigators are cognizant of potential loss of vision following plaque therapy. Efforts to shield the macula and optic disc by the lip of the plaque are encouraged. However, treatment is not compromised, beyond that discussed in Section 12.2.4, because of the optic nerve dose. For COMS purposes, the dose to the optic nerve is calculated and reported at the center of the optic disc and the macular dose is calculated and reported at the foveola (the base or bottom of the fovea centralis).
- *Retina:* Radiation maculopathy is believed to be unlikely to occur with doses of 5000 cGy or less but is expected as the dose to the fovea approaches 10,000 to 15,000 cGy. The dose to the retina opposite the tumor must be calculated and reported. The dose is calculated 22 mm from the scleral

*Note: 85 Gy corresponds with 100 Gy prior to the TG43 dosimetry formulation.[2])

surface at the base of the tumor measured along a diameter of the globe passing through the apex of the tumor.

- *Lens:* The lens is very radiosensitive and cataracts can be expected with radiation treatment of more anterior tumors. Because cataracts can be managed surgically, cataract formation is considered an acceptable side effect. The dose to the center of the lens is calculated and reported.

For tumors greater than 5 mm in apical height, the dose prescription point is the apex of the tumor; however, the dose also is recorded at the point 5 mm from the scleral surface on the central axis of the tumor.

12.2.8. Plaque Assembly

The troughs in the seed carrier insert of the plaque provide a snug fit for the ^{125}I seeds. However, because of the flexibility of the insert, it is relatively easy to dislodge the seeds. Therefore, care must be taken when handling the insert with seeds installed, and attention must be paid to inspection (visual and/or radiographic) of the completed plaque assembly. Seed insertion and removal in a pan of water adds shielding and protection from seed loss.

Experience with the seed carrier insert indicates that it is advisable to use a bonding agent between the insert and the metal shield to enhance plaque integrity. For this purpose, a very small amount of silicone adhesive is used (Silastic Medical Adhesive Silicone, Type A). Three drops of adhesive evenly spaced around the periphery of the plaque secures the insert satisfactorily. To ensure that the seeds are not glued to the insert, the adhesive is applied to the inner surface of the lip around the metal shield and the metal shield is pressed down over the seed carrier.

To disassemble the plaque, a thin blunt-ended instrument (such as the end of a pick-up), when inserted under the edge of the seed carrier, can be worked gently around the circumference of the plaque, freeing the seed carrier insert. Recovery of the seeds and reuse of the insert are often possible. However, if the insert is torn, reuse is inappropriate and the insert should be discarded.

12.2.9. Plaque Sterilization

The recommended sterilization procedures for the assembled radioactive plaque are "flashing" (steam autoclave cycle) or gas sterilization. Either method is acceptable, though gas sterilization requires a significantly longer cycle. Both methods require a suitable metal (shielding) container that does not interfere with the sterilization process.

The assembled plaque should not be sterilized in a liquid such as Cidex. Some of the liquid sterilizing agent may be trapped between the gold plaque and the seed carrier insert and not removed by brief flushing with sterile water. The trapped sterilizing liquid could then leak out while the plaque is in place on the eye.

Note that the acrylic template ("dummy plaque") should not be autoclaved, because it may deform at the temperature employed. The template may be sterilized in a gas cycle or in a sterilizing liquid.

12.2.10. Management of Plaqued Patients

Patients with radioactive plaques in place often are hospitalized until the plaque is removed. However, patients may be cared for on an outpatient basis provided that national and local radiation safety regulations and guidelines are satisfied. See Nuclear Regulatory Commission guidelines, Part 10 CFR 35, and Exhibit 12-2 for issues to consider in such circumstances.

12.2.11. Data to Submit for Quality Assurance Review

The following information is submitted to the Radiological Physics Center following construction of a radioactive plaque and application of it to the eye of a COMS patient:

- Plaque dosimetry data (COMS Form RP, Part I).
- Diagram (or photograph) of the plaque showing placement of seeds. Enough details must be supplied to determine the relative orientation of the seeds and the distance from the seed to the surface of the applicator.
- Map (fundus-view diagram) of the interior of the eye showing the position of the various critical structures (see Section 12.2.7).
- Seed strength in units of air Kerma Strength, U, (with date exact).
- Apparent seed activity in units of mCi (with date exact).
- Number of seeds.
- Total time of irradiation.
- Dose distribution perpendicular to the plaque through the apex of the tumor. The tumor must be outlined on this distribution, indicating at least the tumor thickness and base diameter. If this distribution does not include the central axis of the plaque, a second dose distribution perpendicular to the plaque, through the central axis of the plaque, with the point of scleral dose calculation indicated, also should be submitted.

12.2.12. Management of Treatment Failures

If, after brachytherapy, >2 mm extrascleral extension of the melanoma, severe eye pain, visual acuity <20/200, or documented expansion of the tumor is observed (see Section 11.7), radiation therapy is considered to have failed for COMS purposes. Any tumor for which treatment failure has been documented may be managed at the discretion of the ophthalmologist.

The clinical center staff must continue to follow the patient according to the schedule described in Chapter 8. The reason for judging that treatment has failed and the selected management of the eye must be reported on COMS Form TF.

12.2.13. Dosimetry Information

For COMS purposes, dosimetry is that recommended by Task Group 43 of the AAPM Radiation Therapy Committee[2]. The following assumptions are made:

- the point source approximation is used[a],
- anisotropy is ignored[a],
- the effects of the gold backing on scatter and attenuation are ignored[b],
- the silastic insert is assumed to be water equivalent[b], and
- shielding effects of the rim are ignored[c].

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[a] Anisotropy corrections: For COMS purposes, all anisotropy corrections should be removed and the seeds should be treated as isotropic point sources, using the above formulations and parameters. Individual seed angular anisotropy corrections, if left in, have little or no effect on dose to the prescription point, although calculations of doses to critical structures may be affected.

[b] Influence of gold plaque and silastic insert: The effect of the gold plaque and the silastic insert on dose to the target volume is to be neglected until the magnitude of these effects can be unequivocally determined in the physics literature.

[c] Shielding of critical structures by the rim of the gold plaque: Dose should be reported with the shielding effect of the rim neglected.

The TG-43 formalism reduces to the equation:

$$\dot{D}(r) = \left(S_k \bullet \Lambda \bullet r_0^2 / r^2 \right) \bullet g(r)$$

where,

S_k is the air kerma strength of the source in U (μGy m^2 h^{-1})

Λ is the dose rate constant, in cGy h^{-1} U^{-1}

Λ (model 6711 ^{125}I seed) = 0.88 cGy h^{-1} U^{-1} .

Λ (model 6702 ^{125}I seed) = 0.93 cGy h^{-1} U^{-1} .

g(r) is the radial dose function (Table VII of ref. 2)

r is the distance from the source center, in cm.

r_0 = 1 cm (the reference distance).

For institutions whose treatment planning system is incompatible with the TG-43 formalism (e.g. the planning system does not support specification of seed strength in units of air kerma strength), dosimetry, for COMS purposes, may be accomplished through the equation:

$$\dot{D}(r) = A \bullet \Gamma \bullet f \bullet \frac{g(r)}{r^2}$$

where,

A is the apparent activity of the source, in mCi .

For ^{125}I seeds, the conversion to air kerma strength is 1.270 U / mCi .

Γ is the exposure rate constant.

For ^{125}I seeds, Γ = 1.45 R h^{-1} cm^2 mCi^{-1}.

f is the exposure to dose conversion factor.

f (model 6711 ^{125}I seed) = 0.771 cGy / R .

f (model 6702 ^{125}I seed) = 0.815 cGy / R .

g(r) is the radial dose function (Table VII of ref. 2)

r is the distance from the source center, in cm.

12.3. EXTERNAL BEAM RADIOTHERAPY

12.3.1. Radiation Sources

Photon beams from cobalt-60 or accelerators of 4 to 10 MV are acceptable. *Electron treatments are not allowed.* Multiple fields with wedges are recommended. Anterior and lateral oblique wedged fields with a hinge angle of less than 45° yield a triangular dose distribution which corresponds closely to the bony orbit; see Exhibit 12-3. A single appositional field is allowed if it meets the dose uniformity criteria specified below (see Exhibit 12-4). A 5-cm wide field is usually adequate.

12.3.2. Target Volume

The tumor, the posterior half of the globe, the first 1 cm of the optic nerve, and structures immediately posterior to the globe are considered the tissues at risk. For COMS purposes, the target volume is defined as the tumor, the posterior half of the globe, and a 1 cm margin lateral and posterior to the globe. Bolus must be used for 10 MV photon beams as well as for situations in which the dose prescription point otherwise would be in the dose buildup region (i.e., in front of d_{max}).

12.3.3. Prescribed Dose and Dose Uniformity

The prescribed dose is 20 Gy (2000 rad) delivered in five daily fractions of 4.0 Gy (400 rad) each in five to eight days. Enucleation should follow as soon as possible, preferably the same day that the last

fraction of radiation is administered. Enucleation must be performed within 80 hours of the last radiation fraction.

For wedged-pair delivery, the dose is prescribed at the intersection of the axes of the two fields. For a single appositional field, the dose is prescribed at 2 cm depth from the globe surface on the central axis of the beam.

The total target volume must receive a dose within ± 10% of the prescribed dose.

12.3.4. Data To Submit for Quality Assurance Review

The following information must be submitted to the Radiological Physics Center after each treatment of a COMS patient using external beam irradiation:

- *External Beam Radiotherapy Form* (COMS Form XR).
- Copy of portal films of each treatment port.
- Copy of daily radiotherapy treatment records.
- Copy of dosimetry calculations including an isodose distribution. The globe should be outlined on the distribution, verifying that the target volume is encompassed within ± 10% of the prescribed dose. See Exhibit 12-4.

12.4. REFERENCES

1. Earle JD, Kline RW, Robertson DM: Selection of Iodine 125 for the Collaborative Ocular Melanoma Study. *Arch Ophthalmol* 100:763-764, 1987.
2. Nath R, Anderson LL, Luxton G, Weaver KA, Williamson JF, Meigooni AS: Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM Radiation Therapy Committee Task Group No. 43. *Med Phy* 22:209-234, 1995.

EXHIBIT 12-1

Comparison of Isodose Curves for Radioactive Plaques:
COMS ^{125}I Plaque vs. Co-60 Plaque

IODINE 125 COBALT 60

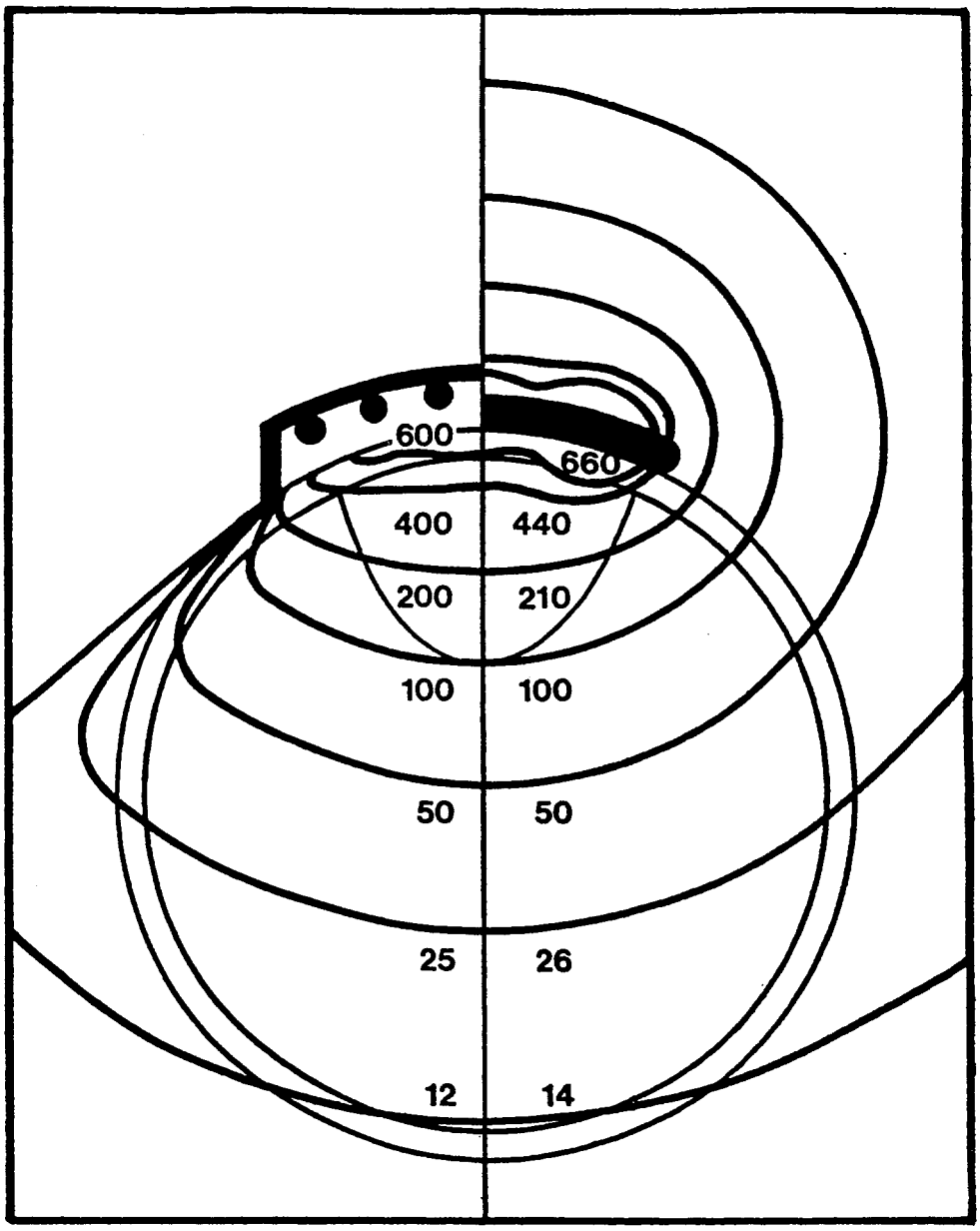


EXHIBIT 12-2

Radiation Safety Issues for Outpatients Wearing ^{125}I Plaques

- Federal regulations; see NRC Part I CFR 35. Also, see local and state regulations.

- Willingness and ability of the patient to comply with radiation safety instructions based on federal, state and local regulations.

- Safety of family members and visitors

  Recommendations:

  - Lead-lined eye patch
  - Limited time together
  - No contact with pregnant women or children under 18 years of age

- Safety of other community members

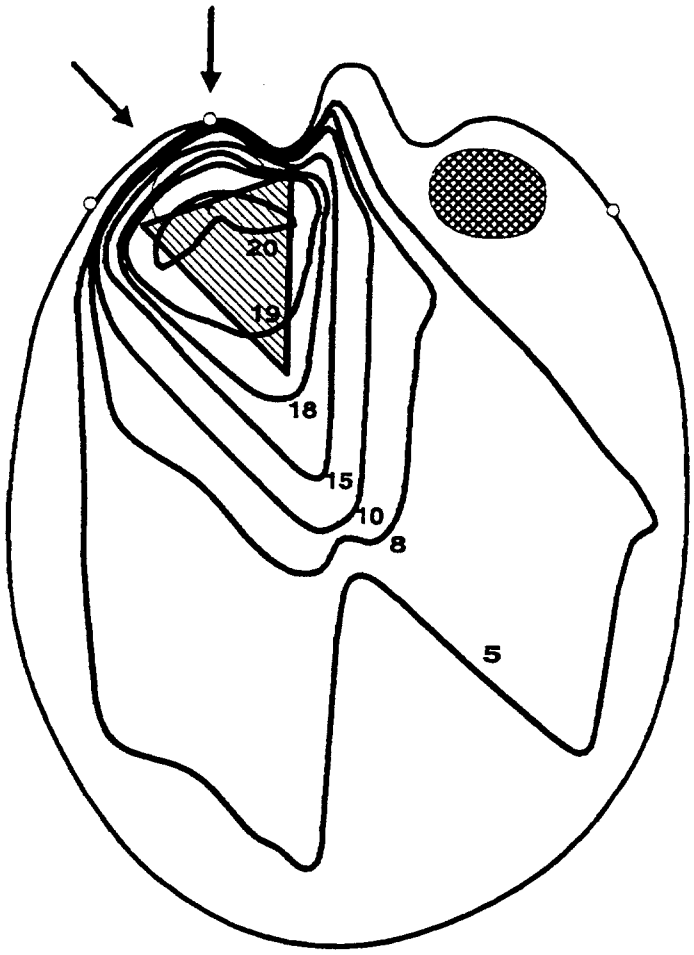
  Recommendation: Restriction of activities to home and backyard

- Safety of emergency medical workers and/or eye bank workers in case of a motor vehicle accident or other serious accident

  Recommendation: Identifying bracelet

EXHIBIT 12-3

Wedged-Pair Technique of External Beam Radiotherapy



CA 167601X-01

Wedged-pair treatment approach using 6 MV x-rays.
(Courtesy of Department of Radiotherapy, Mayo Clinic.)

EXHIBIT 12-4

Sample Isodose Curves for Single Appositional Field of External Beam Radiotherapy