Teletherapy: Indications, Risks, and New Delivery Options

14

Thomas E. Merchant and Erin S. Murphy

Contents

T.E. Merchant, DO, PhD (✉)
Division of Radiation Oncology,
St. Jude Children's Research Hospital,
262 Danny Thomas Place, Mail Stop 220,
Memphis TN 38105, USA
e-mail: thomas.merchant@stjude.org

E.S. Murphy, MD
Department of Radiation Oncology, Cleveland Clinic,
9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: murphye3@ccf.org

14.1 Introduction

In the treatment of retinoblastoma, radiation therapy provides the benchmark for the evaluation of tumor control, for eye preservation, and for side effects. Its role has recently been diminished by the haunting prospect of long-term side effects and a move toward chemotherapy combined with local ophthalmic therapy (Chap. 11) [1]. SEER data demonstrates that upfront radiotherapy was utilized in 34.6 % of patients from 1985 to 1989 and declined to 6.5 % from 2000 to 2004 [2]. This chapter will discuss teletherapy and its indications, risks, and new delivery approaches. Chapter 10 provides more detail about brachytherapy in the treatment of intraocular retinoblastoma.

Although there is increasing tendency to use the International Retinoblastoma Staging Working Group system to classify extent of intraocular retinoblastoma for reporting chemotherapy outcomes, the Reese-Ellsworth classification is still used to report radiation therapy outcomes. Various classification and staging systems are discussed elsewhere (Chap. 3).

14.2 Indication and Efficacy

Prospective pilot studies in the 1990s demonstrated the utility of chemo reduction followed by focal therapy (plaque brachytherapy, laser photocoagulation, thermotherapy, and cryotherapy) as

A.D. Singh et al. (eds.), *Clinical Ophthalmic Oncology: Retinoblastoma*,
DOI 10.1007/978-3-662-43451-2_14, © Springer-Verlag Berlin Heidelberg 2015

Table 14.1 Considerations for external beam radiotherapy

Advanced stage disease at diagnosis
Early-stage disease at diagnosis when focal therapy is contraindicated or not available
Recurrence after focal therapy
Recurrence after chemotherapy
Post-enucleation with positive margins
Orbital extension
Metastases

a means of avoiding external beam radiotherapy and enucleation [3, 4]. Over 100 children with 264 tumors were treated on a prospective trial of 6 monthly cycles of vincristine, etoposide, and carboplatin combined with focal therapy with two main endpoints of need for external beam radiotherapy and need for enucleation [5]. Fifty-two percent of the eyes were classified as Reese-Ellsworth groups I–IV and 48 % group V. The need for external beam radiotherapy occurred in 25 % of eyes at 1 year and 27 % at 3 years with no increased risk at 5 years. The Reese-Ellsworth group significantly impacted the need for radiotherapy with external beam needed for 10 % of group I–IV eyes and 47 % of group V at 5 years. Therefore, external beam radiotherapy continues to play an important role in this disease particularly after failed focal therapy, which may occur in about half of group V eyes. External beam radiotherapy is also indicated when proximity of tumors to the macula or optic disk is prohibitive for safe use of focal therapies (Table 14.1).

When necessary, external beam radiotherapy is a highly effective nonsurgical treatment for retinoblastoma, but its effectiveness must be balanced against its potential for side effects because most patients are very young at the time of diagnosis and there is genetic susceptibility to further malignancy (Chap. 19).

14.2.1 Globe Preservation

Radiation therapy has an excellent track record in preserving the eye. In patients with the Reese-Ellsworth group I–II disease, tumor control rates measured at 5 years are in excess of 95 %. In patients with more advanced disease (Reese-Ellsworth groups III–IV), 5-year control rates reduce to approximately 50 %, owing partly to the greater tumor burden and intraocular extent of disease [6]. Patients with Reese-Ellsworth group Vb disease have 5-year eye-preservation rates of approximately 53 % [7]. Poor tumor control in advanced cases is often attributed to vitreous seeding.

14.2.2 Visual Acuity

Although data on visual acuity are relatively limited, most patients are reported to have good visual acuity (20/20–20/40) after radiation therapy; the rest have at least some prospect for functional vision (20/50–20/400) [8, 9]. Final visual acuity and field are affected by tumor location, which often depends on the patient's age at the time of diagnosis: younger patients are more likely to have tumors in the macula (Fig. 14.1) [10].

14.3 Side Effects and Secondary Malignancies

The side effects of radiation therapy have framed current clinical trials to include avoidance of radiation therapy for patients with retinoblastoma. These side effects include ophthalmic complications, such as retinal detachment, vitreous hemorrhage, cataract formation, and glaucoma; somatic complications, such as orbital hypoplasia; and the most daunting of all side effects, the second malignant neoplasm (Chap. 19) (Fig. 14.2).

14.3.1 Risk of Second Malignant Neoplasms

The risk of second malignant neoplasms is highest among patients with the germ-line mutation of the retinoblastoma gene (RB1). They may occur without the use of radiation therapy, but radiation-induced tumors are the most frequent, and bone and soft-tissue sarcomas are the most common.

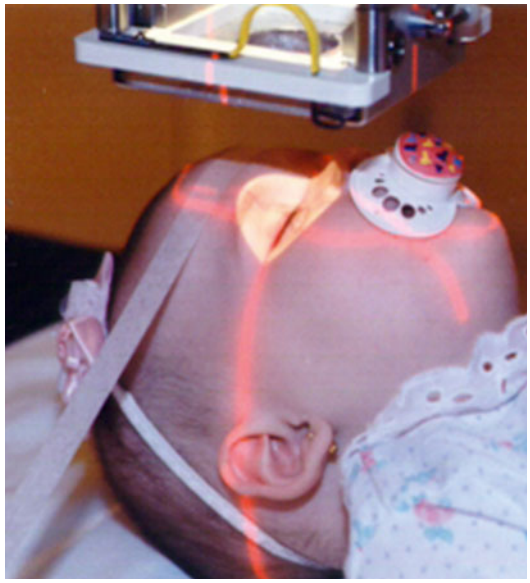

Fig. 14.1 A child receiving external beam radiation therapy

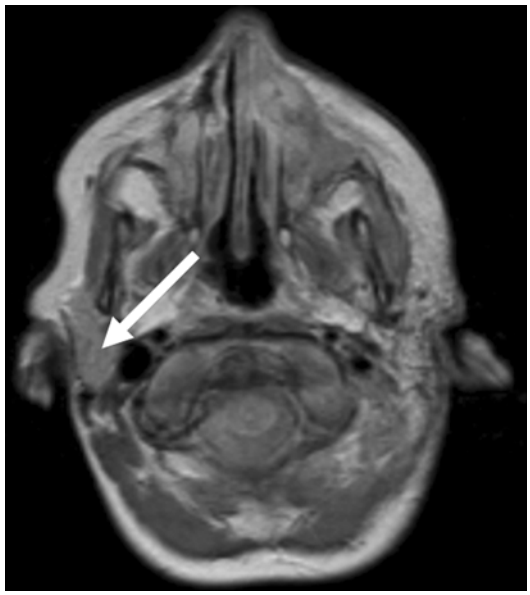

Fig. 14.2 Coronal magnetic resonance image showing a secondary malignancy (sarcoma indicated by *arrow*) in a patient treated for retinoblastoma

Radiation-induced sarcomas are the secondary malignancies that cause most deaths, and more patients die from second malignant neoplasms than from retinoblastoma itself. In a recent SEER analysis, second malignant neoplasm accounted for 52 % of deaths for children with bilateral retinoblastoma [11].

14.3.1.1 The 1914–1984 New York/ Boston Patient Series [12]

A report published in 1997 had a chilling effect on the use of radiation therapy in patients with retinoblastoma [12]. The report covered a 70-year experience (1914–1984) of treating 1,604 patients with bilateral retinoblastoma. The 50-year cumulative incidence of second malignant neoplasms in irradiated patients was 51 % (1 % per year) for patients with bilateral disease, but only 5 % for patients with unilateral disease (Fig. 14.3). The data clearly showed that radiation-induced tumors are the leading cause of death among long-term survivors. This article is the one most often quoted by parents whose child is referred to a radiation oncologist. It might seem irrational, on the basis of these results, to irradiate a child with retinoblastoma—the radiation oncologist is often put in a difficult position when the family is confronted with the news that external beam irradiation is the only option for ocular preservation.

14.3.1.2 The Incidence of Radiogenic Tumors Is Smaller in Other Series

Moll et al. reviewed 11 series reporting on malignancy induction, each including more than 50 patients, and published between 1966 and 1995, only four were without selection bias [13]. The 11 series included 35 second primary tumors, and three of the larger series showed cumulative incidences of second malignancy of 8 % at 18 years, 16 % at 20 years, and 19 % at 35 years (Fig. 14.3). The same group published an analysis of data from the Netherlands Cancer Registry [14], which included 639 patients diagnosed between 1945 and 1994; 241 had hereditary tumors, and more than 80 % were followed beyond 10 years. The cumulative incidence of a histologically confirmed second malignant neoplasm in patients with hereditary tumors was 3.7 % at 10 years and only 17.7 % at 35 years. Curiously, 7 of the 28 second malignant neoplasms in the data from the Netherlands Cancer Registry were melanoma. One might conclude that the lower incidence of

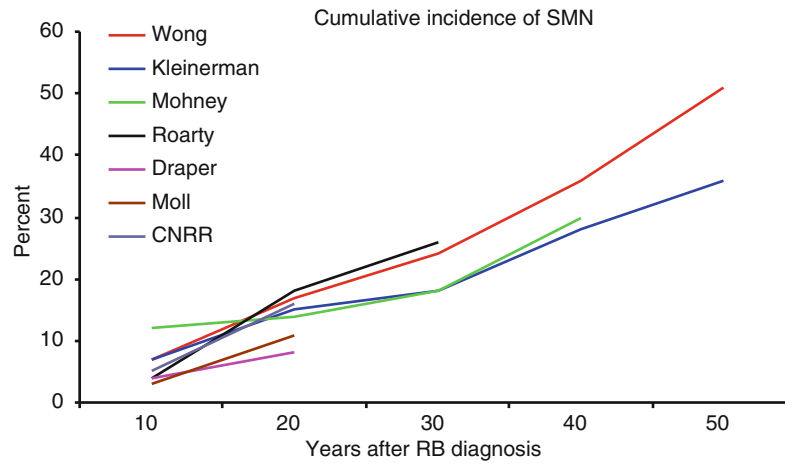

Fig. 14.3 Cumulative incidence of second malignant neoplasms reported in various studies identified by the author (Data derived from Moll et al. [17] and Kleinerman et al. [15])

second malignant neoplasms in this report than in the 1997 report [12] was due to the unique patient population that included central referral for an entire country, as well as the definition and types of second malignant neoplasms.

14.3.1.3 A 2005 Update on the 1914–1984 New York/Boston Patient Series

A recent report by Kleinerman et al. provided an update on some of the 1,601 previously studied retinoblastoma survivors through the year 2000 [15]. The analysis included nearly 1,000 patients with irradiated or non-irradiated tumors in patients with heritable retinoblastoma. The standardized incidence ratio (ratio of observed to expected cancers) was 22 in the irradiated group and 7 in the non-irradiated group, a threefold difference. The cumulative incidence of new cancers at 50 years was 38 % among those irradiated and 21 % in those not irradiated (Fig. 14.3). Sufficient data were available to determine risks of malignancy induction after orthovoltage irradiation (32.9 %) and modern megavoltage irradiation (26.3 %); this finding provided some indication that the use of newer radiation therapy modalities might reduce the risk of secondary malignancy. In this series, tissues calculated to receive a cumulative dose more than 0.4 Gy were considered at risk of radiation-induced malignancy. This definition augmented the risk of various tumors, from pineoblastoma to breast cancer. Although the authors justified their inclusion criteria on the basis of atom-bomb survivor data, the small number of events leading to the increased risk (three cases of breast cancer), and the lack of potentially influential clinical variables leaves these results open to debate among radiation oncologists. At face value, these results indicate that all external beam radiation modalities will result in an excess of secondary malignancies and that the use of any diagnostic x-ray procedure in the clinical assessment of patients with retinoblastoma should cease.

14.3.2 Patient Age at Radiation Appears to Be Important

In 1998, Abramson et al. determined that the risk of a second malignancy was smaller for patients older than 12 months than for patients younger than 12 months when they received radiation therapy [16]. The risk of secondary malignancies in patients irradiated when older than 12 months was equal to that in patients who did not receive radiation therapy. Therefore, delaying radiation therapy until the patient is older than 1 year appears to reduce the risk of a second malignancy. This information has played a prominent role in clinical decision making. Similar findings were observed by Moll et al., who reviewed the Dutch Registry of 1945–1997, which included 263 patients with heritable retinoblastoma [17]. In that series the cumulative incidence of second malignancy at age 25 years was 22 % in patients who were younger than 12 months of age at the time of irradiation and only 3 % in those irradiated after

age 12 months. The infield tumor induction rate was 11 % in the younger patients and 3 % in the older ones, but this difference was not statistically significant. The "infield" evaluation is meant to specify the location of the event within the irradiated volume determined by detailed review of radiation portals or two- or three-dimensional dosimetry. The authors concluded that the similarity of the infield failure rates suggested that factors other than radiation therapy are involved in the induction of malignancy in younger patients and that the estimation of the risk of second malignancy depends on how the second malignancy is defined, how carefully the irradiated volume is analyzed, and how the statistical analysis treats pineoblastoma. In that study, pineoblastoma was not defined as a secondary malignancy.

14.4 Reducing Side Effects from Radiation Therapy

A number of measures may be taken to reduce the likelihood of second malignant neoplasms and radiation-related treatment effects in children with retinoblastoma [1]: delay radiation therapy until the patient is at least 12 months old [2]; reduce the total dose of radiation [3]; use episcleral plaque brachytherapy; and [4] apply new external beam treatment methods and modalities, including conformal radiation therapy, intensity-modulated radiation therapy, and proton-beam radiation therapy (Box 14.1).

Box 14.1. Measures to Reduce Radiation-Related Treatment Effects in Children with Retinoblastoma

- Delay radiation therapy until the patient is at least 12 months old.
- Reduce the total dose of radiation.
- Use episcleral plaque brachytherapy (if applicable).
- Consider new external beam treatment methods including conformal radiation therapy, intensity-modulated radiation therapy, and proton-beam radiation therapy.

14.4.1 Delay Radiation

The fact that delay of radiation until after age 12 months reduced the risk of second malignant neoplasms [16] provides hope that teletherapy may still have a major therapeutic role in the eyes with advanced disease that have had their tumor load reduced but not eliminated by primary chemotherapy. It is now common practice in some retinoblastoma centers to use systemic chemotherapy in patients with bilateral advanced disease diagnosed before 1 year of age, delaying radiation until after the first birthday.

14.4.2 Lower the Radiation Dose

The standard dose for irradiation is 45 Gy. One of the largest studies to show the feasibility of low-dose irradiation included 49 eyes in 38 patients treated with 36 Gy between 1978 and 1998 [18]. At a median follow-up of 88 months, rates of tumor control in patients who had undergone low-dose irradiation therapy were equivalent to those attained with higher doses in other series. The estimated 10-year ocular preservation rate was 82 ± 6 %. The 5-year ocular preservation rate for patients with Reese-Ellsworth group I or II tumors was 95 ± 4 % and for patients with Reese-Ellsworth group III or IV tumors, 66 ± 11 %. Ocular preservation rates after external beam irradiation at various doses indicate that low-dose external beam irradiation may be an option for selected patients. The role of response-based radiotherapy dosing for stage 4a and 4b retinoblastoma is currently being evaluated in a Children's Oncology Group trial, ARET0321 (NCT00554788).

14.4.3 Use Episcleral Plaque Brachytherapy

Episcleral plaque brachytherapy has the advantages that it is highly focused, it allows irradiation of normal tissue to be limited, and it has a high rate of lesion control. Its applicability as a treatment technique has traditionally been limited to eyes with single isolated tumors that

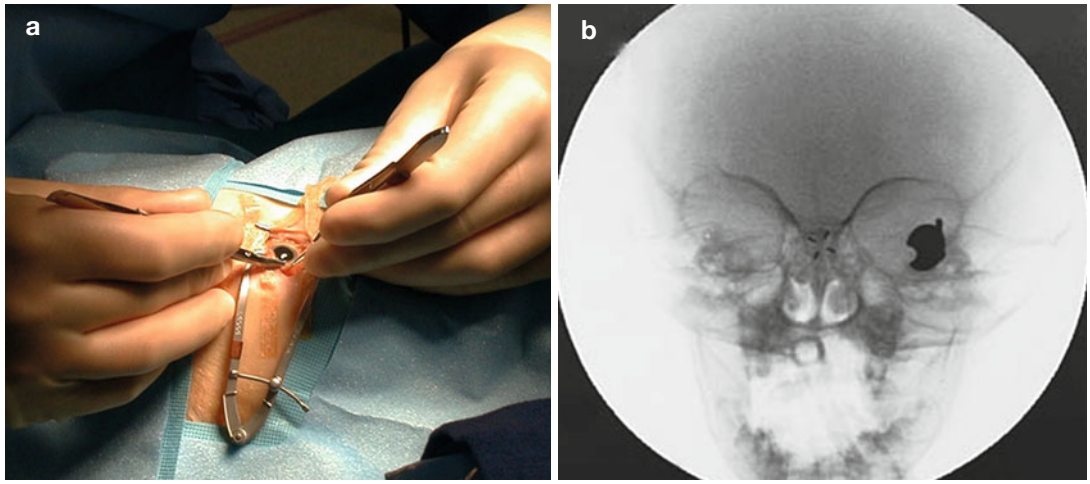

Fig. 14.4 Application of a notched episcleral iodine-125 plaque for brachytherapy (**a**). The corresponding x-ray image showing the episcleral plaque, abutting the optic nerve (**b**)

are located more than 3 mm from the optic disk or fovea. It requires extensive operator experience and in some instances produces significant adverse effects in the retina (Fig. 14.4). The standard dose is 40 Gy to the apex at 40–50 cGy per hour and may require inpatient admission. Common sources include iodine-125, but other sources have been investigated [19]. The St. Jude series included a relatively small number of cases and a lesion control rate of 96 % [20]. Response to episcleral plaque brachytherapy is seen rapidly and in some cases during the brief course of application. The role of brachytherapy has been evaluated in the setting of localized vitreous seeding with reasonable rates of control [21]. However, this role should be further evaluated accounting for the finding that vitreous seeding predicts for tumor recurrence in reports of long-term follow-up [19].

14.4.4 Use New Radiation Treatment Techniques

Discussion of all radiation techniques and measures taken to spare the lens and minimize irradiation of normal tissue is beyond the scope of this chapter. Indeed, given that a substantial number of patients are diagnosed with vitreous seeding (Reese-Ellsworth IVb) and require whole-eye irradiation after chemotherapy, it may be less important to reduce the total dose of radiation, spare the lens, or use a more focal radiation delivery technique [22, 23]. Nevertheless, the more commonly used new techniques are discussed below.

14.4.4.1 Conformal and Intensity-Modulated Radiation Therapy (IMRT)

Most clinicians are familiar with the D-shaped fields used to treat unilateral or bilateral disease, with the isocenter placed 2–3 mm behind the lens at the level of the surgical limbus (Fig. 14.5a). Less familiar are the unilateral or bilateral electron fields used for en face treatment (Fig. 14.5b). With the advent of three-dimensional radiation therapy, a variety of methods have been used to treat retinoblastoma, including intensity-modulated radiation therapy (IMRT). Various methods may be compared on a dosimetry basis by comparing dose-volume histograms for normal tissue, assuming adequate coverage of the targeted volume. Although each method may be used to achieve conformity (i.e., shaping the radiation field so that the highest doses are centrally focused on the targeted volume), each method has different characteristics in terms of normal tissue irradiation (Fig. 14.6). The advantages of intensity-modulated radiation therapy (IMRT) over three-dimensional conformal radiation therapy and conventional

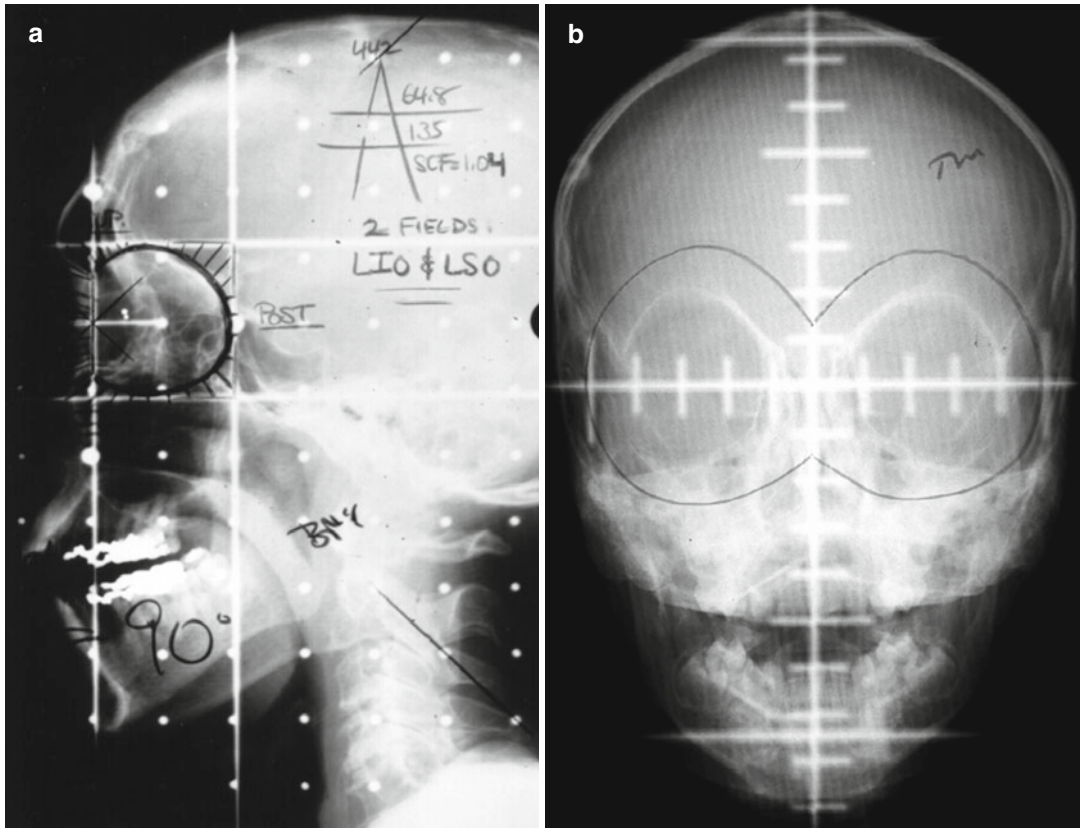

Fig. 14.5 The D-shaped field used in photon beam radiation therapy (**a**). An en face bilateral electron field (**b**)

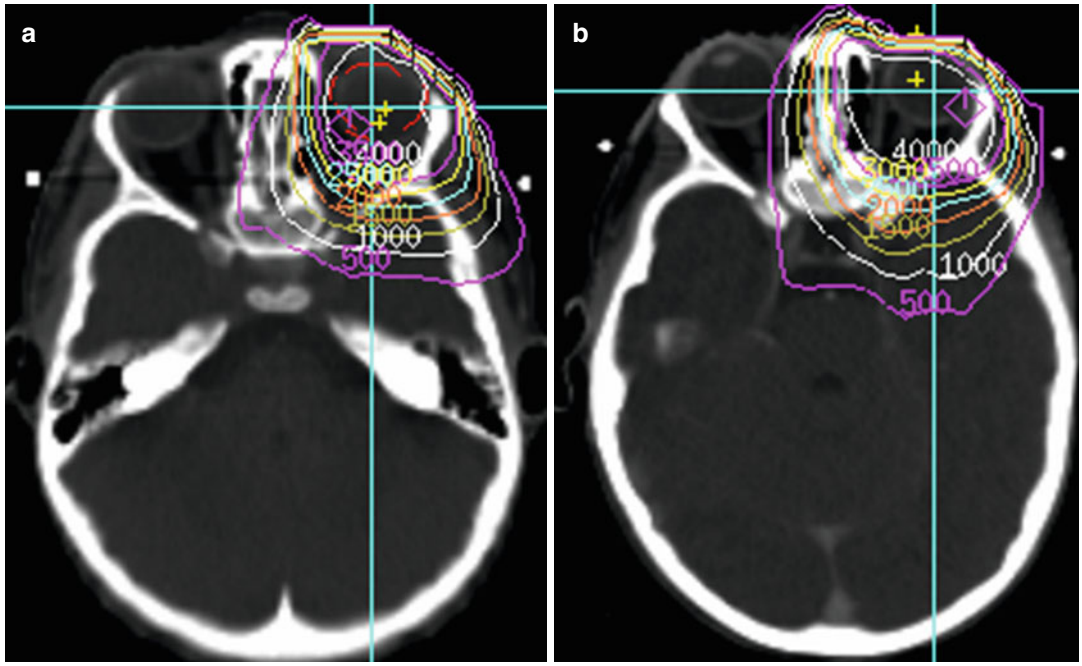

Fig. 14.6 Comparison of electron (**a**) and photon (**b**) dosimetry on axial CT images. Decreasing radiation doses are indicated by the curves delimiting the volumes surrounding the target volume

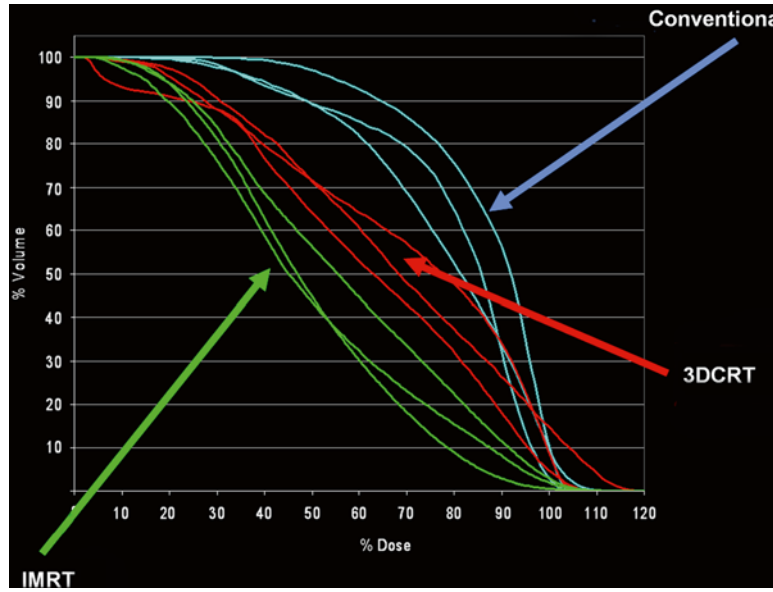

Fig. 14.7 Relation between irradiated volume and dose of radiation to the orbit to compare the dosimetric characteristics of conventional, conformal (*3DCRT*), and intensity-modulated (*IMRT*) radiation therapy

two-dimensional irradiation in terms of the dose delivered to normal tissue structures (Fig. 14.7) have been demonstrated [24]. Although, for most techniques, increasing the conformity of the highest doses results in a relatively sharp decline of the dose-volume curve at the higher doses, this gain comes at the expense of increasing the volume of normal tissue that receives the lowest doses. Consider the dose to the bony orbit, a common site of secondary malignancies: even optimally applied intensity-modulated radiation therapy will result in 50 % of the orbit receiving 50 % of the prescribed dose.

14.4.5 Proton-Beam Radiation Therapy

Although proton-beam radiation therapy has been available for decades, only recently have protons shown promise as external beams that can deliver a precise dose to the target yet minimize the dose to normal tissues. The proton beam has exquisite stopping power in tissue and produces essentially no lateral scatter, whereas photon beams traversing the tissue slowly lose energy and deposit decreasing doses of radiation along the path through the tissue (Fig. 14.8). Where the photon beam enters the tissue, it deposits most of its dose superficially and then continues to deposit dose gradually until it exits the patient. The proton beam, with its sharp Bragg peak (Fig. 14.8), can penetrate deeply and leaves no exit trail. The proton beam can be modulated to achieve a more widely spread Bragg peak and used to uniformly irradiate the tumor or target at a particular depth. Comparing photons or x-rays with protons, it is easy to see that proton-beam irradiation can be used to control tumors at any depth without the entrance and exit doses associated with photon beam irradiation that are largely responsible for the complications we see in patients given radiation therapy for retinoblastoma.

A recently published series suggests a reduction in the rate of second malignant neoplasms from proton therapy, with a 10-year cumulative incidence of radiotherapy-induced second malignant non-ocular neoplasm of 0 % for protons and 14 % for contemporary photon therapy [25]. Although the median follow-up for the patients who had received proton therapy is short at 6.9 years, this finding is noteworthy with some patients more than 24 years from radiotherapy.

The advantages of protons over photons in reducing doses to normal tissue (lens, lacrimal gland, bony orbit, and soft tissues) have been demonstrated during irradiation of tumors in

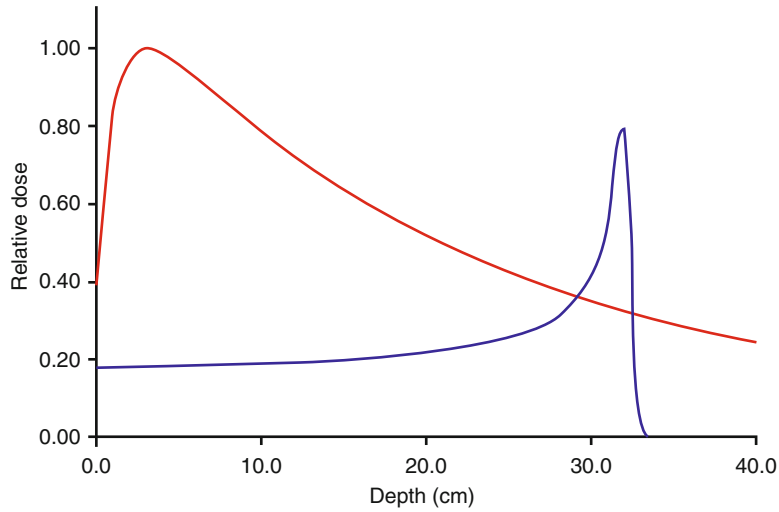

Fig. 14.8 The relation between dose and depth of penetration of the beam for protons (*blue curve*) and photons (*red curve*). The sharpness of the Bragg peak for the proton beam illustrates the potential tissue-sparing capacity of the proton beam

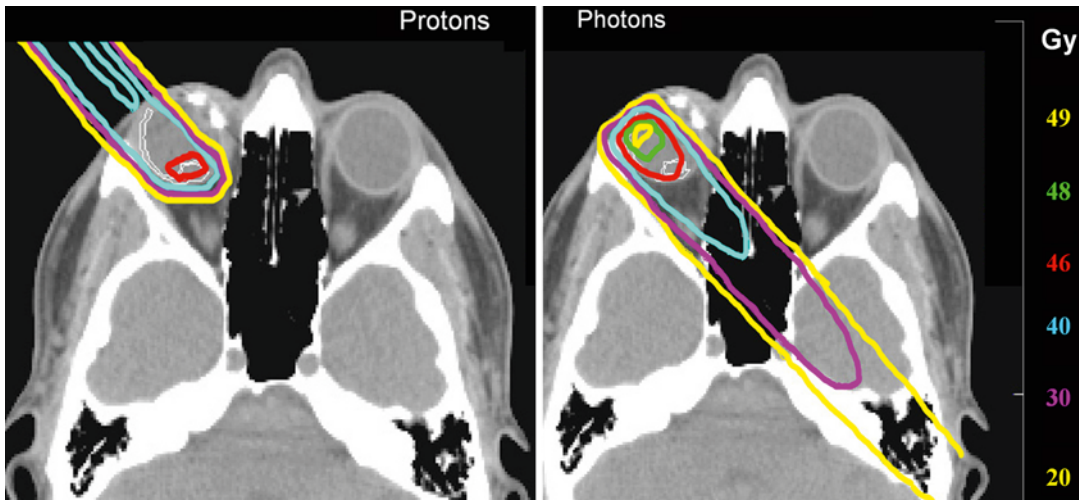

Fig. 14.9 Comparison of single-beam proton and photon irradiation (Courtesy of EB Hug, MD)

various sites in the retina (Fig. 14.9) [26]. One study showed that for tumors located in the nasal retina, central retina, or temporal retina, irradiation of normal tissue can be avoided by using beam positioning and eye positioning techniques. This finding opens up the possibility of selective retinal irradiation by using an external beam. Enhancements that allow fine-beam (pencil-beam) scanning and new methods of achieving stereotaxy (including image guidance and robotics) will enable very precise proton-beam treatment of the retina in patients with retinoblastoma. Given plans to increase the availability of proton-beam radiation therapy in the United States, the relatively small number of cases (based on current trends) that will require radiation therapy, and the obvious dosimetry advantages in these high-risk patients, proton-beam radiation therapy will become the standard modality for external beam irradiation of retinoblastoma.

14.5 Current Recommendations

Our recommendations for patients with newly diagnosed retinoblastoma include 36 Gy for Reese-Ellsworth group I or II disease and standard dose irradiation (45 Gy) for more advanced

(Reese-Ellsworth group III–V) disease. For patients whose disease progresses after chemotherapy, our bias is to irradiate with standard doses (outside a protocol) and to use episcleral plaque brachytherapy when possible. We recommend defining the clinical target volume as the optic globe and the treatment planning target volume as the optic globe with a 3–5 mm margin. Lens sparing can be accomplished on an individual basis when no evidence of vitreous or subretinal seeding is apparent. Additional individualized techniques include using a conventional split beam to spare the lens and using electrons, conformal irradiation, intensity-modulated radiation therapy, and proton-beam radiation therapy. New chemotherapy techniques including intravitreal, periocular, subtenon, and intra-arterial delivery may alter the role of chemotherapy but are unlikely to impact the indications for external beam radiotherapy.

References

1. Wilson MW, Rodriguez-Galindo C, Haik BG, et al. Multiagent chemotherapy as neoadjuvant treatment for multifocal intraocular retinoblastoma. Ophthalmology. 2001;108:2106–14; discussion 2114–5.
2. Broaddus E, Topham A, Singh AD. Survival with retinoblastoma in the USA: 1975–2004. Br J Ophthalmol. 2009;93:24–7.
3. Shields CL, De Potter P, Himelstein BP, et al. Chemoreduction in the initial management of intraocular retinoblastoma. Arch Ophthalmol. 1996;114:1330–8.
4. Gallie BL, Budning A, DeBoer G, et al. Chemotherapy with focal therapy can cure intraocular retinoblastoma without radiotherapy. Arch Ophthalmol. 1996;114:1321–8.
5. Shields CL, Honavar SG, Meadows AT, et al. Chemoreduction plus focal therapy for retinoblastoma: factors predictive of need for treatment with external beam radiotherapy or enucleation. Am J Ophthalmol. 2002;133(5):657–64.
6. Blach LE, McCormick B, Abramson DH. External beam radiation therapy and retinoblastoma: long-term results in the comparison of two techniques. Int J Radiat Oncol Biol Phys. 1996;35:45–51.
7. Abramson DH, Beaverson KL, Chang ST, et al. Outcome following initial external beam radiotherapy in patients with Reese-Ellsworth group Vb retinoblastoma. Arch Ophthalmol. 2004;122:1316–23.
8. Egbert PR, Donaldson SS, Moazed K, Rosenthal AR. Visual results and ocular complications following radiotherapy for retinoblastoma. Arch Ophthalmol. 1978;96:1826–30.
9. Hall LS, Ceisler E, Abramson DH. Visual outcomes in children with bilateral retinoblastoma. J AAPOS. 1999;3:138–42.
10. Brinkert AW, Moll AC, Jager MJ, et al. Distribution of tumors in the retina in hereditary retinoblastoma patients. Ophthalmic Genet. 1998;19:63–7.
11. Shinohara ET, DeWees T, Perkins SM. Subsequent malignancies and their effect on survival in patients with retinoblastoma. Pediatr Blood Cancer. 2014;61(1):116–9.
12. Wong FL, Boice Jr JD, Abramson DH, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA. 1997;278:1262–7.
13. Moll AC, Imhof SM, Bouter LM, Tan KE. Second primary tumors in patients with retinoblastoma. A review of the literature. Ophthalmic Genet. 1997;18:27–34.
14. Moll AC, Imhof SM, Bouter LM, et al. Second primary tumors in patients with hereditary retinoblastoma: a register-based follow-up study, 1945–1994. Int J Cancer. 1996;67:515–9.
15. Kleinerman RA, Tucker MA, Tarone RE, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. J Clin Oncol. 2005;23:2272–9.
16. Abramson DH, Frank CM. Second nonocular tumors in survivors of bilateral retinoblastoma: a possible age effect on radiation-related risk. Ophthalmology. 1998;105:573–9; discussion 579–80.
17. Moll AC, Imhof SM, Schouten-Van Meeteren AY, et al. Second primary tumors in hereditary retinoblastoma: a register-based study, 1945–1997: is there an age effect on radiation-related risk? Ophthalmology. 2001;108:1109–14.
18. Merchant TE, Gould CJ, Hilton NE, et al. Ocular preservation after 36 Gy external beam radiation therapy for retinoblastoma. J Pediatr Hematol Oncol. 2002;24:246–9.
19. Shields CL, Shields JA, Cater J, et al. Plaque radiotherapy for retinoblastoma: long-term tumor control and treatment complications in 208 tumors. Ophthalmology. 2001;108(11):2116–21.
20. Merchant TE, Gould CJ, Wilson MW, et al. Episcleral plaque brachytherapy for retinoblastoma. Pediatr Blood Cancer. 2004;43:134–9.
21. Francis JH, Barker CA, Wolden SL, et al. Salvage/adjuvant brachytherapy after opthalmic artery chemosurgery for intraocular retinoblastoma. Int J Radiat Oncol Biol Phys. 2013;87(3):517–23.
22. Blach LE, McCormick B, Abramson DH, Ellsworth RM. Trilateral retinoblastoma–incidence and outcome: a decade of experience. Int J Radiat Oncol Biol Phys. 1994;29:729–33.
23. Rodriguez-Galindo C, Wilson MW, Haik BG, et al. Treatment of intraocular retinoblastoma with vincristine and carboplatin. J Clin Oncol. 2003;21:2019–25.

24. Krasin MJ, Crawford BT, Zhu Y, et al. Intensity-modulated radiation therapy for children with intraocular retinoblastoma: potential sparing of the bony orbit. Clin Oncol (R Coll Radiol). 2004;16:215–22.
25. Sethi RV, Shih HA, Yeap BY, et al. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. Cancer. 2014;120(1):126–33.
26. Krengli M, Hug EB, Adams JA, et al. Proton radiation therapy for retinoblastoma: comparison of various intraocular tumor locations and beam arrangements. Int J Radiat Oncol Biol Phys. 2005;61:583–93.