



Radiation Therapy for Benign Disease

Arteriovenous Malformations, Desmoid Tumor, Dupuytren Contracture, Graves Ophthalmopathy, Gynecomastia, Heterotopic Ossification, Histiocytosis

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KEYWORDS

- Radiation therapy • Benign disease • Arteriovenous malformations • Gynecomastia
- Heterotopic ossification • Histiocytosis • Desmoid tumor • Dupuytren contracture
- Graves ophthalmopathy

KEY POINTS

- Although the use of ionizing radiation in malignant conditions has been well established, its application in benign conditions has not been fully accepted and has been inadequately recognized by health care providers outside of radiation therapy.
- Radiation therapy has been shown to be effective as one of the treatment modalities for several benign conditions.
- Most patients experience no or few symptomatic side effects while achieving good long-term control and improved quality of life.
- Clinicians must still carefully balance all the potential risks against the benefits before proceeding with radiation therapy, especially in younger patients and children.

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INTRODUCTION

Once the imaging capabilities of x-rays were discovered in 1895 by Wilhelm Röntgen, their observed biological effect to create inflammation led other scientists to propose its use in treating medical disease. The first known successful use of x-rays for benign disease was by Leopold Freund in 1896, who demonstrated the effective use of x-rays on a 5-year-old girl suffering from a large hairy nevus on her back.¹ Initial clinical successes in the experimental use of x-rays led to many benign conditions treated with radiation. With improved understanding of radiobiology and late sequelae, there has gradually been more judicious use of radiation as well decreased number of patients treated with radiation for benign conditions.

Although the use of ionizing radiation in malignant conditions has been well established, its application in benign conditions has not been fully accepted and has been inadequately recognized by health care providers outside of radiation therapy. Most frequently, radiation therapy in these benign conditions is used along with other treatment modalities, such as surgery, in instances where the condition causes significant disability or could even lead to death. Radiation therapy can be helpful for inflammatory/proliferative disorders. For example, patients undergoing major orthopedic surgeries may benefit from adjuvant low-dose radiation therapy to help prevent heterotopic bone formation, and radiation therapy can help prevent progression and need for surgery in Dupuytren disease. Low to intermediate doses of radiation have been shown to provide effective improvement in conditions, such as Graves ophthalmopathy and keloid recurrence. Eye pterygium can be treated with brachytherapy using a strontium applicator. Arteriovenous malformations (AVMs) can be obliterated successfully with precise stereotactic radiosurgery (SRS). This article discusses the current use of radiation therapy on some of the more common benign conditions but excludes certain benign tumors, such as meningiomas and pituitary adenomas, that are frequently discussed in major textbooks or are very rare.

RADIOBIOLOGICAL BASIS

The therapeutic effect of radiation therapy is a result of energy interacting with matter and causing ionization or excitation. Ionization, which is the ejection of a charged particle from an atom, is important clinically due its resultant direct and indirect effects on DNA. Direct effects cause damage when the charged particles interact with DNA, whereas indirect effects lead to the production of intermediary products that then cause damage to the DNA. For example, charged particles react with water to create highly reactive free radicals. The free radicals form a hydroxyl radical that then interacts with DNA to cause lethal cellular damage, like a DNA double-strand break. Because mammalian cells are 80% water, indirect effects of radiation drive the majority of the resultant DNA damage.² Oxygen facilitates the production of free radicals. As well-oxygenated tumor cells are killed and hypoxic tumor cells gain a better vascular supply, reoxygenation of previously hypoxic cells makes subsequent doses of radiation more efficacious. Fractionation of radiation allows for the exploitation of reoxygenation. It also takes advantage of the reassortment of cells from more radioresistant phases of the cell cycle to more radiosensitive phases, specifically Gap 2 (G2 [subphase of interphase in the cell cycle])/mitosis. As the sensitive cells are eliminated, the surviving cells progress through the cell cycle to radiosensitive phases. Therefore, when the next dose of radiation is administered, the cells render themselves more sensitive to radiation.³ A cell's ability to delay the progression to the G2 phase may correspond to its resistance to irradiation. Regardless, some cells appear intrinsically more radiosensitive

to radiation therapy than others. Whether radiation directly or indirectly causes damage to the cell, sublethal damage can be repaired by cells if given enough time. Cancer cells, however, often have aberrant DNA repair mechanisms, so they are less able to repair DNA damage and subsequently die when they attempt to undergo mitosis prior to repairing damage. For cancers cells that survive, there is an accelerated regrowth of cells seen after irradiation that is called repopulation. The timing and length of radiation therapy must take into account the 5 radiobiologic principles that define the interaction of radiation with mammalian tissue during conventionally fractionated radiation: reoxygenation, reassortment, repair, repopulation, and radiosensitivity.⁴ The goal is to achieve optimal disease control while allowing for sufficient sparing of normal tissue.

RADIATION TOXICITY AND TISSUE TOLERANCE

Radiation therapy can produce acute and late side effects, which depend on the volume of tissue receiving dose above a tissue-specific threshold. The risk of side effects in the treatment of benign diseases is generally uncommon because the dose of radiation used often is lower than that used in the treatment of malignancies. Furthermore, with modern radiation therapy techniques, radiation treatment plans are optimized with dose-volume constraints to minimize the risk of side effects in nontarget tissues. These constraints are based on the radiation tolerance of each organ system, which depend on the organization of the organ (such as in series or parallel) and intrinsic cellular properties of the tissue (Table 1 lists example tissue constraints). The variable radiation tolerance of different tissues demonstrates that the risk of toxicity from radiation therapy depends on the site being treated and the nearby structures. For example, skin toxicities, such as acute dermatitis and late fibrosis, are of concern when treating an extremity target, whereas bowel toxicities, such as acute nausea and vomiting and late risk of bowel necrosis, are of concern when treating an abdominal target. Normal tissue tolerance and the risk of toxicities stratified by dose and volume of tissue treated are published with the results of radiation therapy clinical trials.⁵⁻⁷

ARTERIOVENOUS MALFORMATIONS

AVMs are complex congenital lesions of the cerebral vasculature in which blood flows directly from feeding arteries to draining veins without passing through a capillary

Tissue	Toxicities	Common Constraints (Reference Trial)
Brain stem	Necrosis	Volume receiving 60 Gy <0.03 mL (RTOG 0825)
Heart	Pericarditis	V30 Gy <50% of organ (RTOG 1308)
Lung	Pneumonitis	V20 Gy <25% (RTOG 1010)
Optic chiasm	Blindness	V56 Gy <0.03 mL (RTOG 0825)
Parotid	Xerostomia	Mean dose to organ <26 Gy (RTOG 1016)
Rectum	Proctitis/necrosis	V75 Gy <15% (RTOG 0815)
Stomach	Ulceration/perforation	Maximum dose to organ <54 Gy (RTOG 0848)

Note, these constraints are for radiation delivered in 1.8 Gy to 2 Gy per fraction. Normal tissues are more sensitive to higher doses of radiation per fraction (20 Gy in 1 fraction does not equal 20 Gy in 5 fractions of 4 Gy each).

Abbreviation: RTOG, Radiation Therapy Oncology Group; V, volume receiving.

system. The annual risk of AVM hemorrhage is approximately 3%.⁸ During the first year after hemorrhage, the risk of another hemorrhage increases to 6% to 15%.⁸ AVMs may be observed or treated with surgical resection, embolization, or SRS. For AVMs that are less suitable to surgical intervention, such as those with deep venous drainage or in high-risk areas of the brain, or for patients who are not surgical candidates, SRS is an effective treatment strategy to ablate the AVM and reduce the risk of hemorrhage.⁹ SRS may be delivered using cobalt beams (as with Gamma Knife), protons, or linear accelerators.

Radiosurgery works by injuring vascular walls within the AVM, thereby causing sclerosis of the lesion.¹⁰ Response to SRS typically takes 2 years to 4 years.⁸ The goal of treatment is complete obliteration of the lesion. Obliteration is associated with an 85% risk reduction of hemorrhage.⁸ After SRS, but before obliteration, there is a 54% reduction in bleeding risk.¹¹ SRS is generally recommended for lesions less than 3.5 cm in diameter,⁵ but staged radiosurgery, in which different parts of the lesion are treated in separate sessions, can be used for larger lesions.¹² The ideal management strategy for AVMs is an ongoing topic of debate, especially after recent randomized data suggested that medical management may be preferable for unruptured AVMs.¹³ **Fig. 1** shows a typical AVM case treated with linear accelerator-based SRS. **Table 2** presents published outcomes using radiation therapy to treat AVMs.

DESMOID TUMOR

Desmoid tumor (also known as aggressive fibromatosis) is a locally aggressive benign growth arising from connective tissue in the muscular aponeurotic structures. The name, desmoid, is derived from the Greek word, *desmos*, meaning relating to bonds, connections, or ligaments, and was originally used in the nineteenth century to describe a growth with tendon-like consistency. The estimated incidence of occurrence is 2 million to 4 per million people, with slightly more incidence in women.²⁰ Although desmoid tumors are benign without the potential for metastatic spread, they have a high rate of local recurrence with surgical excision, especially in the presence of positive margin status.²¹ Desmoid tumors can occur in most body sites, but they are differentiated into extra-abdominal (70%), abdominal wall (20%), and intra-abdominal (10%), with APC mutations associated with intra-abdominal and abdominal wall locations.²² **Fig. 2** demonstrates a recurrent desmoid tumor along the right elbow as well as a clinical setup for the treatment. Although most desmoid tumors arise

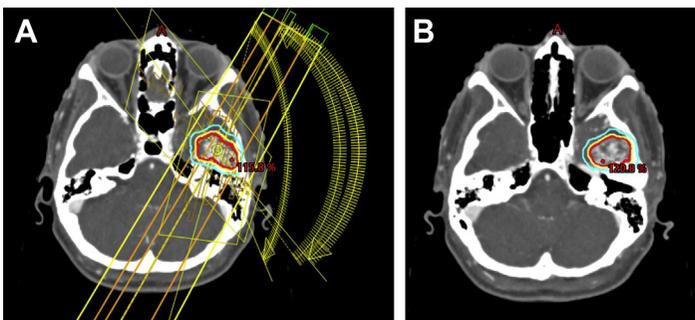


Fig. 1. AVM in the Left temporal lobe and a volumetric modulated arc therapy treatment plan using a linear accelerator (Linac). (A) Three noncoplanar arcs were used to treat the lesion. (B) Isodose lines, from out to in, 60%, 90%, and 100%. The prescription dose was 17.5 Gy in 1 fraction.

Table 2 Summary of selected treatment results for arteriovenous malformations				
Author, Year	Total No. Patients	Technique	Dose	Results (%)
Hanakita et al, ¹⁴ 2016	292	GKS	20 Gy	73 obliteration at 6 y 53 bleeding risk reduction after RS 85 bleeding risk reduction after obliteration
Ding et al, ¹⁵ 2015	66 elderly, ≥60 y	GKS	21.7 Gy (mean)	77 obliteration at 10 y 1.1 hemorrhage risk after RS
Yen et al, ¹⁶ 2014	31	GKS	15–26 Gy	61 obliteration (at median 51 mo) 6.5 hemorrhage
Starke et al, ⁹ 2013	1012	GKS	21.2 Gy (mean)	69 obliteration at mean 8 y 8.7 hemorrhage
Sirin et al, ¹² 2008	28 with large AVMs	GKS (staged volume)	16 Gy (median)	AVM volume range 10.2–57.7 cm ³ 39 total or near-total obliteration (only half followed >36 mo) 14 hemorrhage
Maruyama et al, ¹¹ 2005	500	GKS	20 Gy	91 obliteration at 6 y 6.6 complication rate 5.8 hemorrhage after RS
Vernimmen et al, 2005 ¹⁷	64	Protons	10–22 GyE	67 obliteration rate (vol <14 cm ³) 43 obliteration rate (vol ≥14 cm ³)
Nicolato et al, ¹³ 2005	63 children, <16 y	GKS	16–26 Gy	77 obliteration rate at 4 y 2 with complications No hemorrhage reported
Zabel et al, ¹⁸ 2005	110	Linac SRS	18 Gy	67 obliteration at 4 y 0 complications 8 hemorrhage after RS
Bollet et al, ¹⁹ 2004	118	Linac SRS	10–25 Gy	77 obliteration rate 6.7 complications 6 hemorrhage

Abbreviations: GKS, Gamma Knife radiosurgery; RS, radiosurgery.

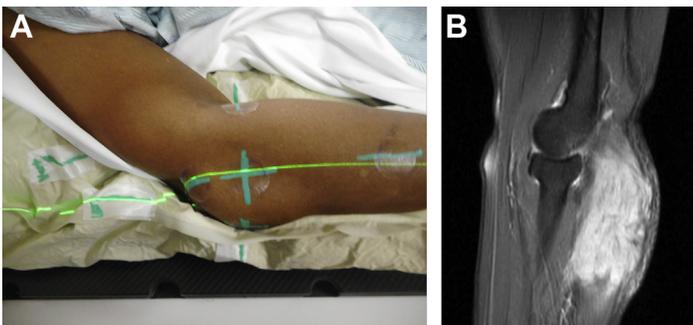


Fig. 2. Extra-abdominal desmoid tumor of the right elbow. (A) The clinical setup of the right elbow for the AP/PA treatment of the right elbow. (B) T1 Sagittal postcontrast MRI demonstrating the desmoid tumor along the right elbow. AP, anterior-posterior; MRI, magnetic resonance imaging; PA, posterior-anterior.

sporadically, approximately 7.5% to 16% arise from familial adenomatous polyposis.²³ Diagnosis of desmoid tumor is achieved through biopsy, with histologic identification of elongated clonal spindle-shaped cells in fibrous stroma.

Desmoid tumors can regress spontaneously, and, as such, close observation may be used for asymptomatic tumors, especially locations associated with significant morbidity after resection.^{24,25} Per current National Comprehensive Cancer Network (NCCN) guidelines, surgery is a first-line treatment of desmoid tumors that are symptomatic or impairing or threatening in function as well as for tumors that have progressed after proceeding with observation. When proceeding with surgery, obtaining negative margins should be attempted and would require re-resection for positive margins due to the increased rates of local recurrence associated with positive margins.^{26,27} There is also evidence, however, that status of surgical margins is not predictive of recurrence.^{28,29} When negative margins are obtained, no further therapy is needed.

Radiation therapy is an effective definitive treatment of patients with unresectable desmoid tumors, and radiation alone, to doses of 50 Gy to 56 Gy using conventional fractionation of 1.8 Gy to 2.0 Gy per fraction, is associated with local control rates of 75% to 83%.^{30–32} Keus and colleagues³¹ performed a multicenter phase II study for moderate-dose radiotherapy for inoperable desmoid tumors, delivering 56 Gy using 28 fractions of 2 Gy per fraction and demonstrated 3-year local control rate of 81.5% as well as demonstrating a slow response, with some cases demonstrating continued response after 3 years. Radiation therapy also is used in the postoperative for resections with microscopic (R1) and macroscopic (R2) margins. The utility of radiation in R1 resections has been more debated, with NCCN giving a category 2B recommendation for adjuvant radiation in that setting. The retrospective study from MD Anderson Cancer Center demonstrated a benefit for resection combined with radiation versus surgery alone for postoperative cases,²⁷ whereas an Italian experience³³ and a cohort from Memorial Sloan Kettering Cancer Center²⁸ did not demonstrate a significant association between positive margins and local recurrence. There was a recent meta-analysis, however, looking at 16 studies and a combined 1295 patients demonstrated improved recurrence rates with adjuvant radiation for patients with primary tumors and recurrent tumors who had incomplete surgical resection.³⁴ There also was evidence of a higher risk of local recurrence for patients who had microscopic positive resection margins after receiving surgery alone, with a relative risk of 1.78.

A limited number of studies from Princess Margaret Hospital may indicate a role for neoadjuvant radiation for desmoid tumors. In the largest study, 58 patients were treated with preoperative radiation using 50 Gy in 25 fractions, and with median follow-up of 69 months, there were 11 local recurrences (19%), with major wound complications in 2 patients (3.4%).³⁵ Systemic therapy also remains a component of the treatment cascade, with effects of antiestrogen agents contributing growth inhibitory effects and often may be used in combination with nonsteroidal anti-inflammatory drugs (NSAIDs).^{36,37} Per NCCN guidelines, systemic therapy can be used as frontline treatment or can be used in instances of gross residual disease or recurrence. In addition to noncytotoxic options of antiestrogen agents and NSAIDs, targeted therapy with imatinib (Bcr-Abl tyrosine kinase inhibition) and cytotoxic chemotherapy remain options for treatment. **Table 3** summarizes some of the selected treatment results.

DUPUYTREN CONTRACTURE

Dupuytren contracture is a noncancerous condition where the fingers can become permanently bent in a flexed position, typically occurring in individuals over 50 years

Table 3 Summary of selected treatment results of desmoid tumor				
Authors, Year	No. Lesions	Dose	Recurrence	Comments
Janssen et al, ³⁴ 2017	1295	35–66 Gy although some doses were not reported	Positive margins Primary tumor Surgery alone: LC 60% Surgery + RT: LC 77% Recurrent tumor Surgery alone: LC 22% Surgery + RT: LC 59%	Meta-analysis that demonstrates reduced risk of recurrence with adjuvant radiation for positive margins.
Keus et al, ³¹ 2013	44 (17 were recurrent)	56 Gy in 28 fractions	3-y LC 81.5%	Single modality radiation demonstrated good control in primary and recurrent setting.
Zlotecki et al, ³² 2002	65	50–56 Gy	5-y LRC 83%	There was a decreased probability of control with multiple prior recurrences.
Ballo et al, ³⁰ 1998	75	60 Gy (range 46–66 Gy)	After GTR: 5-y LC 82% Gross disease: 5-y LC 69%	There were increased rates of complications >56 Gy. Doses >50 Gy were associated with higher control rates.
O'Dea et al, ³⁵ 2003	58	Neoadjuvant 50 Gy in 25 fractions	At median 69 mo, LC was 81%	Demonstrates efficacy of preoperative radiation for desmoid tumors

Abbreviations: GTR, gross total resection; LC, local control; LRC, locoregional control; RT, radiation therapy.

of age. The underlying cause is unknown, but there is thought to be an abnormal formation of connective tissue in this condition. Patients present with nodules and cord-like structures in the palm of their hands, stretching from their palms to fingers. The contraction of these tendons can cause permanent flexion of the fingers, most

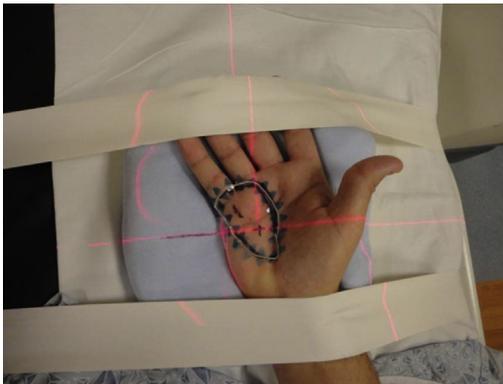


Fig. 3. This patient with Dupuytren contracture is receiving radiation treatment to the affected hand.

commonly affecting the fourth and fifth digits. Symptoms can include pain, burning, or itching in the affected area.^{38–42}

Dupuytren contracture can be treated with surgery, injections, or radiation. The choice of treatment largely depends on the degree the affected finger(s) is bent toward the palm. A staging system is used to characterize the degree of flexion, and this is called the Dupuytren staging system. For patients with a contracture between 0° and 10°, radiation is the primary treatment modality (Fig. 3). In addition, if there are only nodules and cords present in the palm without contracture, radiation can be used. Patients that have contractures greater than 10° are usually offered surgery, collagenase injections, or needle aponeurotomy. Radiation is not offered to patients with severe Dupuytren contracture, because these patients have a greater chance of worsening disease if treated with radiation alone.^{38–42}

A total dose of 30 Gy in 10 fractions is the typical treatment; 5 treatments are given consecutively every day and then a 6-week to 8-week period follows to allow the targeted area to respond and the surrounding tissue time to heal. After that 6-week to 8-week period, the last 5 treatments are completed. Patients also may receive a total dose of 21 Gy in 7 fractions.^{39,42–44} This regimen has comparable long-term control over the disease to the standard total dose of 30 Gy divided in 10 fractions but has more acute side effects, such as redness and skin irritation. Patients and health care providers may decide on the 21-Gy regimen if the longer course is not possible in accommodating a patient's schedule. Treatment fields consist of proximal/distal margin of 1 cm to 2 cm and lateral margin of 1 cm. Orthovoltage treatment consists of 120-kv to 150-kv photons with bolus and electron treatment consists of 6 MeV to 9 MeV with bolus, with preference of electrons to photons given superior target coverage.⁴⁵

The most common short-term side effect is erythema and long-term side effect is hand atrophy. No secondary malignancies have been identified, although follow-up for most studies has been limited to 5 years.^{2,46} Although there have been some studies in analyzing radiotherapy in Dupuytren contractures, these have been mostly retrospective in nature and do not always differentiate the stage of contracture. Further randomized controlled studies are required to confirm the efficacy of radiation in treating early-stage Dupuytren contracture and to understand the possible long-term effects. Table 4 presents some of the selected treatment results.

Study	No. Patients	Dose	Results
Keilholz et al, ⁴⁰ 1996	96	30 Gy in 10 fractions	77% with no progression and 23% with progression
Adamietz et al, ³⁸ 2001	99	30 Gy in 10 fractions	Stage N 84% and stage N/I 67% of cases with no progression. Stage I 65% and stage II 83% showed progression.
Seegenschmiedt et al, ⁴¹ 2001	129	Group A: 30 Gy in 10 fractions Group B: 21 Gy in 7 fractions	Group A: 93% showed no progression. Group B: 91% showed no progression.
Betz et al, ⁴² 2010	135	30 Gy in 10 fractions	69% showed no progression.
Zirbs et al, ⁴⁴ 2015	206	32 Gy in 4 fractions	80% showed no progression.

GRAVES OPHTHALMOPATHY

Graves ophthalmopathy is an inflammatory condition of the orbital tissues and the extraocular muscles. It is thought to be autoimmune in nature and frequently occurs in women aged 40 years old to 44 years old and 60 years old to 64 years old.⁴⁷ It is most commonly associated with hyperthyroidism, because 20% to 25% of patients with Graves hyperthyroidism have Graves ophthalmopathy,⁴⁸ but it also can occur in euthyroid or hypothyroid patients.

Histologic features include interstitial edema, widespread lymphocytic infiltration, and varying degrees of muscle damage. Inflammatory reaction leads to venous engorgement, inadequate drainage of interstitial fluid, periorbital edema, proptosis, and ultimately compression of the optic nerve.⁴⁹ This compression may cause irreversible neuronal death and diminished nerve function that can manifest as decreased visual acuity and pupillary dysfunction as well as constriction of the visual fields. The most common clinical presentation of Graves ophthalmopathy usually involves the constellation of proptosis, periorbital edema, upper eyelid retraction, and excessive tearing.⁵⁰

Management of this disease process can be medical, surgical (orbital decompression, eye muscle, or lid surgery), or radiologic or involve a combined modality approach.⁵¹ High-dose systemic glucocorticoids are the first line of treatment. Favorable results have been reported in 60% of patients.⁵² Orbital decompression may help in some cases that are resistant to steroid treatment, particularly in the presence of marked proptosis and optic neuropathy.⁵³ Although 1 study showed no benefit of radiation therapy,⁵⁴ many other investigators have found radiation therapy, usually in combination with steroids, as an alternative and efficacious anti-inflammatory therapy, with response rates of 50% to 88%.^{55–58} A meta-analysis showed that a combination of radiation therapy with corticosteroids was better than either therapy alone.⁵⁹ If combination therapy is utilized, intravenous corticosteroids seem better tolerated and more effective than oral corticosteroids.⁵⁸ Other therapies, such as immunosuppressive drugs, intravenous immunoglobulins, and plasmapheresis, have resulted in less than significant outcomes.⁶⁰ When severe ophthalmopathy is present, permanent control of thyroid hyperfunction by radioiodine or thyroidectomy is sometimes recommended.⁶¹

Radiation therapy should be reserved for those who are symptomatic, who have not responded to a course of high-dose systemic steroids, or for whom steroids are contraindicated (those who have optic neuropathy or corneal ulceration).⁶² Because of the risk of worsening retinopathy, diabetes mellitus can be a relative contraindication for radiation.⁶³ **Table 5** summarizes some of the results of radiation therapy treatments.

The most common dose of radiation is 20 Gy, which is administered using opposed lateral fields with posterior angulation. **Fig. 4** illustrates a common opposed lateral field design with a half-beam block posterior to the lens and the corresponding isodose color wash. Radiation treatment requires several weeks to take effect and may transiently cause increased inflammation. Thus, patients are sometimes maintained on steroids during the first few weeks of treatment.

Potential side effects include cataract formation, radiation retinopathy, and radiation optic neuropathy, which often manifests between 6 months and 3 years after ophthalmic radiation but may occur as late as 7 years after treatment.^{66,67} The risk of cataract formation does not appear to be higher than the risk in the general population when radiation is delivered with modern linear accelerators.⁶⁸ In addition, the use of intensity-modulated radiation therapy may further reduce the risk of cataract

Author, Year	Number of Patients	Treatment	Results	Comments
Kulig et al, ⁶⁴ 2004	101	20 Gy/2 wk + steroids	Donaldson ophthalmopathy index decreased significantly. Right eye: from 6.35 to 1.2; left eye: from 6.1 to 1.15.	Combined therapy is effective. Persistent diplopia in 16/101 patients
Prummel et al, ⁵⁵ 2004	88 (RT vs sham RT)	20 Gy/2 wk	52% vs 27% responded	Less need for follow-up in RT group
Alpert et al, ⁶³ 2003	47 (30 with optic neuropathy)	20 Gy/10 fx	75% improved. (retropulsion improved in 83%)	Early intervention (<6 mo) better
Pitz et al, ⁵⁷ 2002	104 (29 RT, 75 RT + steroids)	10–20 Gy	75% pain improved 25% motility improved	No additional benefit seen with steroids No adverse side effects up to 16 y
Mourits et al, ⁵⁶ 2000	60 (RT vs sham RT)	20 Gy/10 fx	Qualitative improvement (diplopia): 60% vs 31% Proptosis, lid swelling not better	25% RT patients spared from additional strabismus surgery
Beckendorf et al, ⁶⁵ 1999	199	20 Gy/2 wk	26% excellent response 50% partial response 19% stable 5% progression	Patients treated within 7 mo after having ophthalmopathy had better responses.
Marcocci et al, ⁵⁸ 2001	82 (RT + IV GC (41) vs RT + oral GC (41))	20 Gy/10 fx	87.8% response with RT + IV GC vs 63.4% in RT + oral GC	IV GC resulted in fewer side effects than oral GC (56.1% vs 85.4%)

Abbreviations: fx, fraction(s); GC, glucocorticoids; IV, glucocorticoids; RT, radiation therapy.

formation, with a cataract formation rate of 1.72% presented in a single-institution retrospective study.⁶⁹ These side effects generally do not occur if treatment is appropriately fractionated and carefully planned.

GYNECOMASTIA

Gynecomastia is a benign proliferation of glandular male breast tissue usually caused by an imbalance between estrogen and testosterone. The most common pathologic cause of gynecomastia is the use of antiandrogen therapy (AT) for treatment of prostate cancer. Gynecomastia can occur in 60% to 70% of patients receiving AT for prostate cancer.⁷⁰ Hormone-induced gynecomastia is usually bilateral and often

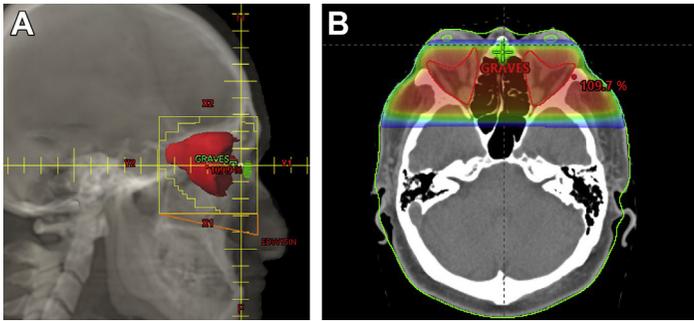


Fig. 4. (A) A typical half-beam block approach posterior to the lens to help with lens sparing. (B) The corresponding isodose color wash for treatment of Graves ophthalmopathy using opposed lateral fields.

accompanied by painful swelling. These side effects can lead to patients discontinuing AT in up to 16.4% of cases.⁷¹ This issue is increasingly relevant, given an increasing life expectancy in patients.

There are several treatment options for hormone-induced gynecomastia, including low-dose radiotherapy. This is an effective method for both the prevention and treatment of gynecomastia.^{72,73} Radiation is more effective if given prophylactically before the administration of antiandrogens, but it also has been used with some success for patients with existing gynecomastia. The largest randomized trial comparing radiation therapy for prevention of gynecomastia versus existing gynecomastia was conducted in 2003. For the prevention arm, gynecomastia rates decreased from 71% to 28%. For treating existing gynecomastia, 33% of patients had visible improvement and 39% experienced improvement in pain.⁷⁴ **Fig. 5** shows a patient with symptomatic gynecomastia after 6 months of hormonal therapy for prostate cancer. His symptoms were relieved with low-dose radiotherapy. **Table 6** summarizes several studies, including the aforementioned largest randomized trial, for evaluating radiotherapy for gynecomastia. Although this section focuses on radiotherapy in treating gynecomastia, it is important to recognize other treatment alternatives for gynecomastia. Tamoxifen has demonstrated its efficacy in treating hormone-induced gynecomastia via a small randomized trial.⁷⁶



Fig. 5. Gynecomastia after hormonal therapy for prostate cancer.

Study	No. Patients	Dose	Results
Ozen et al, ⁷⁵ 2010	125 (prophylactic RT vs no RT)	12 Gy/1 fx	15.8% had gynecomastia in prophylactic RT arm, and 50.8% had gynecomastia in the nonprophylactic arm ($P < .001$). Breast pain rate 36.4% and 49.2% in prophylactic and non-RT arms, respectively
Perdona et al, ⁷⁶ 2005	151 (AT only vs AT + tamoxifen vs AT + RT)	12 Gy/1 fx	69% developed gynecomastia in AT only arm, 1% in tamoxifen arm, and 34% in RT arm
Van Poppel et al, ⁷⁷ 2005	65 with existing gynecomastia	12 Gy/2 fx	Gynecomastia improved or resolved 33%; breast pain improved or resolved 39%
Tyrrell et al, ⁷⁸ 2004	106 (prophylactic RT vs no RT)	10 Gy/1 fx	Gynecomastia rate: 52% vs 85% ($P > .001$)
Widmark et al, ⁷⁴ 2003	253 (prophylactic RT vs no RT)	12–15 Gy/1fx	Gynecomastia rate: 28% vs 71% ($P > .001$)

Abbreviations: fx, fraction(s); RT, radiation therapy.

Tamoxifen has shown more effective in treating gynecomastia compared with radiotherapy, but tamoxifen must be taken concurrently with AT, whereas radiation may take up to only a few sessions.^{79,80} Additionally, aromatase inhibitors or mastectomy with liposuction also can be used.^{81,82}

Dosing typically is anywhere from 12 Gy in 2 fractions to 20 Gy in 5 fractions for existing gynecomastia.^{77,83} For prophylaxis, 10 Gy to 15 Gy in 1 to 3 fractions has been published in the literature.^{5–9} Radiation portal fields should cover the entire breast bud. Generally, electrons are used due to shallow depth–dose characteristics. Electron energy should be chosen depending on the thickness of the chest wall, typically 6 MeV to 12 MeV. Side effects tend to be minimal when treating gynecomastia. The most common side effect is mild skin erythema. Secondary malignancies, in particular breast cancer, from radiation therapy for gynecomastia is low.⁸⁴

HETEROTOPIC OSSIFICATION

Heterotopic ossification (HO), ossification of soft tissues around the hip, is a potential complication after total hip arthroplasty, hip trauma, acetabular fracture, or central nervous injury. Primitive mesenchymal cells surrounding soft tissues can be transformed into osteoblastic tissue, which then forms mature bones. The most common location of HP is around the femoral neck or adjacent to the greater trochanter. Other less common locations include jaw, elbow, spine, and other joints after trauma. HO occurs in approximately 43% of the patients who underwent hip arthroplasty, with the incidence greater than 80% in those who have a history of HO, either ipsilateral or contralateral.⁸⁵ Among patients with a history of hypertrophic osteoarthritis, ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, and Paget disease, the incidence of HO can be more than 60%.⁸⁶

The most common presenting symptom is hip stiffness, not hip pain. A majority of the patients with radiographically low-grade or early HO are asymptomatic. Those with severe HO may develop signs of inflammation, such as fever, joint erythema, swelling, warmth, and tenderness. Further work-up is needed to rule out infection. Plain films usually are sufficient for diagnosis. Ossification can be visualized on plain films within 4 weeks postoperatively. Bone scan typically shows increased uptake in the soft tissue next to the hip but it is not specific. The most widely adopted HO classification system is the Brooker system. It grades HO based on an anteroposterior radiograph of the pelvis and hip.⁸⁷ Bones that appear to be bridging, however, may be located either anterior or posterior to the hip, which may not cause significant loss of range of motion.

Table 7
Summary of selected radiation treatment results of heterotopic ossification prophylaxis

Study	Design	N	Results	Conclusion
Lo et al, ⁹³ 1988	Retrospective postoperative 7 Gy in 1 fx	24	No grade 3–4 HO	Single fraction of 7 Gy appears effective.
Pellegrini et al, ⁹⁴ 1992	PRT of postoperative 8 Gy (1 fx) vs postoperative 10 Gy (5 fx)	62	Grade 1–4 HO: Single fraction 21% Fractionated 21%	Single fraction appears equally effective as fractionated RT.
Gregoritch et al, ⁸⁶ 1994	PRT of 7–8 Gy (1 fx) preoperative vs postoperative	124	Grade 1–4 HO: preoperative 26%; postoperative 28%	Preoperative may be similar to postoperative in HO prevention.
Healy et al, ⁹⁵ 1995	Retrospective study of postoperative 7 Gy (1 fx) and postoperative 5.5 Gy (1 fx)	107	Grade 1–4 HO: 7 Gy 10%; 5.5 Gy 63% (P = .03)	5.5 Gy (1 fx) is insufficient.
Seegenschmied et al, ⁹⁶ 1997	PRT of preoperative 7 Gy (1 fx) vs postoperative 17.5 (5 fx)	161	Grade 1–4 HO: preoperative 24%; postoperative 5% (P = .05)	Preoperative inferior to postoperative for HO prevention
Padgett et al, ⁹⁷ 2003	PRT of postoperative 5 Gy (2 fx) vs 10 Gy (5 fx)	59	Grade 1–4 HO: 5 Gy 69%; 10 Gy 43% (P = .09)	5 Gy (2 fx) may be inferior to 10 Gy (5 fx) for HO prevention.
Burd et al, ⁹⁸ 2003	PRT of RT (8 Gy in 1 fx) vs indomethacin 6 wk	166	Grade 3–4 HO: RT 7%; indomethacin 14%; (P = .22)	NSAIDs not statistically inferior to RT for HO prevention but may be due to small sample size
Pakos and Ioannidis, ⁹⁰ 2004	Meta-analysis 7 PRTs of RT vs NSAIDs	1143	Grade 3–4 HO: OR 0.42 (95% CI, 0.18–0.97) favoring RT	RT more effective than NSAIDs for HO prevention. 1.2% absolute risk difference

Abbreviations: fx, fraction(s); PRT, prospective randomized trial; OR, odds ratio; RT, radiation therapy.

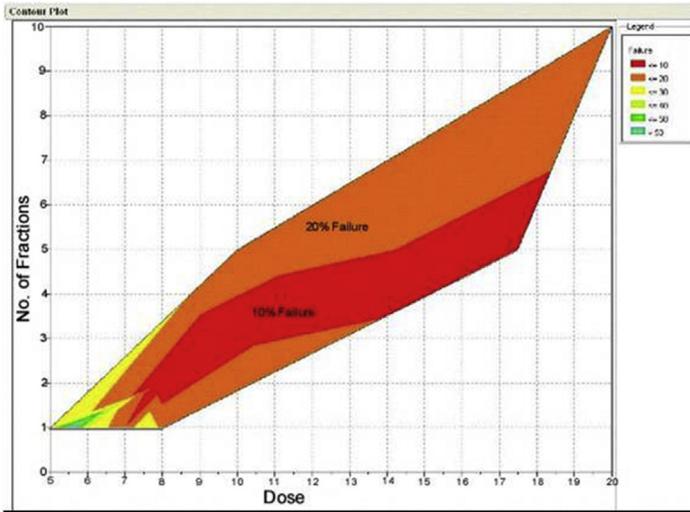


Fig. 6. Graphic retrospective analysis of 32 studies. Red (center) represents a failure rate of less than 10%. The lowest dose and number of fractions to achieve failure rate of less than 10% seems to be 7 Gy in 1 fraction. (From Luh JY, Cavanaugh SX, Eng TY, et al. A graphic retrospective analysis of 32 studies investigating optimal dose and fractionation schedules in the prevention of heterotopic ossification after hip arthroplasty. *Int J Radiat Oncol Biol Phys* 2004;60(15):5547; with permission.)

The general treatment regimen for HO is surgical excision with HO prophylaxis, which may include NSAIDs, or external beam radiation therapy (EBRT) because recurrence rate after surgical excision alone is high. Effective prophylaxis of HO generally should be given to patients at high risk of HO. Indomethacin is the most common NSAID used for HO prophylaxis. The recommended dose of indomethacin is 75 mg/d to 100 mg/d and should be continued for 7 days to 14 days postoperatively. Matta and Siebenrock⁸⁸ showed indomethacin was not effective in preventing ectopic bone formation. Other NSAIDs also have been used. Bleeding and gastrointestinal side effects are potential disadvantages of using NSAIDs.

EBRT is another effective option for HO prophylaxis. A prospective randomized study showed both EBRT and indomethacin are effective in postoperative HO prevention.⁸⁹ A 2004 meta-analysis of 7 randomized studies comparing EBRT with NSAIDs demonstrated that EBRT is more effective.⁹⁰ Various radiation doses have been used. A 2010 retrospective study by Pakos and colleagues⁹¹ showed great efficacy of combined EBRT and indomethacin in preventing HO after total hip arthroplasty. A fractionated total dose of 10 Gy does not seem to offer additional benefit compared with a single dose of 7 Gy. Several randomized studies demonstrated that the failure

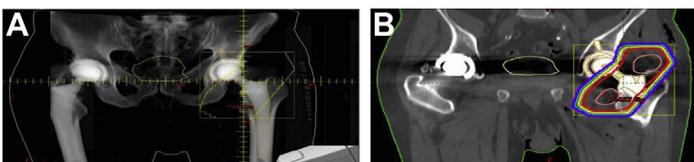


Fig. 7. (A) A small treatment field encompassing the soft tissue surrounding the hip joint and hardware but avoiding the bowels and genitals. (B) Isodose plan.

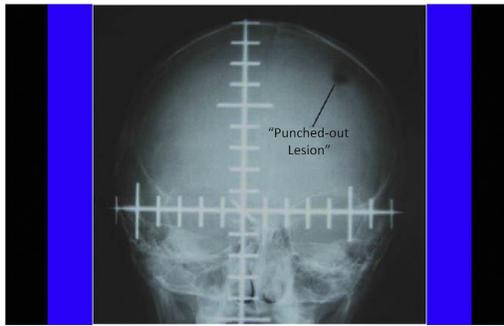


Fig. 8. A typical punched-out skull lesion in a 10-year-old boy who had histiocytosis.

rates are similar among those who received EBRT preoperatively (within 4 hours) or postoperatively (within 72 hours).^{86,92} Delivering radiation preoperatively helps reduce patients' discomfort but scheduling is challenging, especially if surgery is delayed.

Table 8					
Summary of selected treatment results of histiocytosis					
Authors, Year	No. Patients	Follow-up	Treatment	Outcome	Comments
Laird et al, ¹¹⁵ 2018	39	Med 45 mo	7.5–50.4 Gy/ varied fx sizes	LC 89% (100% in bone lesions)	Bone lesions well controlled with low doses of RT
Kotecha et al, ¹¹⁹ 2014	69	Med 6 y	2.5–45 Gy using 0.66–6 Gy per fraction	LC 91.4%	Increased long- term morbidity in pediatric patients
Jahraus et al, ¹¹⁶ 2004	24	Med 28 mo	3–20 Gy/varied fx sizes	1.8–2.0 Gy/fx, score 1.29; if <1.8 Gy/fx, score 2.1 (<i>P</i> = .013)	Recommended fx <1.8 Gy
Rosenzweig et al, ¹²⁰ 1997	14 diabetes insipidus	7.3 y	6–14.4 Gy/3–9 fx med 7.5 Gy	14% CR	Early disease responded
Minehan et al, ¹²¹ 1992	47 diabetes insipidus	Med 14.7 y	10–11 Gy mean (hypothalamic- pituitary RT vs no RT)	RT: 22% CR, 14% PR No RT: 0% CR/PR	Actuarial survival at 40 y was 65%
el-Sayed and Brewin, ¹¹¹ 1992	15	1–20 y	Low doses RT	14/15 bone CR; 2/2 (DI) responded	
Selch and Parker, ¹¹² 1990	22 (40 bony, 16 soft tissue sites)	1–13 y	6–26 Gy Med 9 Gy (bone) Med 15 (soft tissue)	All LC 82% Bone 88% Soft tissue 69%	Pediatric LC 100%

Score system: 1, CR; 2, greater than 50% PR; 3, less than 50% PR; 4, NR.

Abbreviations: CR, complete response; DI, diabetes insipidus; fx, fraction; LC, local control; med, median; NR, no response; PR, partial response; RT, radiation therapy.

Table 7 summarizes some of the selected treatment results. **Fig. 6** shows a graphic analysis of radiation doses and failure rates of HO prevention. **Fig. 7** illustrates a typical radiation treatment field used in HO.

Secondary malignancy induced by single-fraction radiation therapy is extremely rare. The University of Mississippi reports a 51 year-old patient who developed high grade undifferentiated sarcoma of the proximal thigh 16 months after prophylactic RT.⁹⁹ There is a relative contraindication for radiation in patients who have a posterior hip dislocation with a femoral head fracture because there is a theoretic risk of contributing to avascular necrosis or nonunion.

HISTIOCYTOSIS

Langerhans cell histiocytosis (LCH), previously known as histiocytosis X, is a rare disorder that consists of a cohort of idiopathic mononuclear cell regulation derangements¹⁰⁰ that present as infiltrative collections of monocytic cells with telltale cytoplasmic inclusions (Birbeck granules). LCH received its name from the due to the resemblance of the morphology and immunophenotype to Langerhans cells. LCH cells were discovered to be myeloid dendritic cells distinct from Langerhans dendritic cells of skin using gene expression array.¹⁰¹ LCH is a monoclonal disorder characterized by the by the accumulation of CD207⁺ dendritic cells with BRAF V600E mutation in stem cell and dendritic cells demonstrating support for LCH being a myeloid neoplasia.¹⁰²

LCH may present in multiple organ sites with a wide number of presentations,¹⁰³ many of which possess eponymous historical designations (for example, the classic exophthalmos, punched-out cranial lesions, and diabetes insipidus of Hand-Schüller-Christian disease or the pediatric hepatosplenomegaly, anemia, and hemorrhagic diathesis of Letterer-Siwe syndrome).¹⁰⁴ LCH has a predilection for bone involvement but may also include many other sites, including skin, lymph nodes, bone marrow, liver, and lungs.¹⁰⁵ **Fig. 8** shows a 10-year-old boy who has a typical punched-out skull lesion. He was treated with low-dose radiation therapy and had a complete response.

Multiple treatments exist for the treatment of LCH, including steroids, systemic therapy, and surgery.^{106–110} The role of radiation in LCH has not been well defined^{111,112} because treatment strategies have been changing over time. Bone pain and vertebral lesions remain an area that may benefit from radiation¹¹³; however, there is a decreased need for radiation, with cure rates of 70% to 90% with frontline surgical intervention.¹¹⁴ When surgery is contraindicated, or for palliation of multifocal, persistent, or osseous disease, low-dose conventional fractionation of 6 Gy to 10 Gy may be utilized with good results.^{113,115–118} Multiple series report local control greater than 80% with radiotherapy and local control in more than 90% of localized bone lesions.^{112,115,117,119} **Table 8** summarizes some of the results of radiation therapy in LCH.

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