CHAPTER

66 Benign Diseases

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DEFINITION AND CLASSIFICATION OF BENIGN DISEASES

Many diseases that are pathologically benign (nonmalignant) do not act clinically benign, causing significant symptoms or dysfunction to the patient. A number of these entities can be successfully treated with ionizing radiation. The use of irradiation for benign diseases dates back centuries, with initial uses coming from results obtained using x-rays for experimental purposes. Sokoloff reported positive results in radiotherapy of painful "rheumatoid diseases" as early as 1898.[1] The traditional classification of benign diseases amenable to radiotherapy as inflammatory, degenerative, hyperproliferative, functional, and other types of disorders is currently outdated. Worldwide, irradiation of benign diseases has become more important, although indications and treatment concepts have changed considerably with increasing information regarding acute and late effects of radiation therapy. Today, clear differences between countries do exist regarding radiation therapy use in nonmalignant conditions because of historical clinical traditions and differences in training.[2-6]

Indications for the Implementation of Radiotherapy

Benign diseases have several features that may justify the use of radiotherapy. They can grow invasively and aggressively. For example, desmoids (aggressive fibromatoses) and keloids can be cosmetically disfiguring and functionally disturbing. Endocrine orbitopathies may be life threatening. Refractory hepatic hemangiomas (Kasabach-Merritt syndrome) or juvenile angiofibromas in facial regions of children or adolescents may require radiotherapy. There may be an indication for irradiation when benign diseases have a lasting effect on quality of life by causing pain or other serious symptoms, or if other therapeutic options are not available, have failed, or may induce more side effects. Overall, however, radiotherapy is *rarely* the first option for treatment of most nonmalignant diseases. Therefore, the process leading up to informed consent must be especially thorough. Particular attention should focus on the risk for long-term consequences, such as the induction of secondary malignancies, including solid tumors or leukemia.

Long-Term Risk for Tumor Induction

Considering international data about the emergence of tumors and leukemias after whole-body exposure to ionizing radiation (United Nations Scientific Committee on the Effects of Atomic Radiation [UNSCEAR], Biological Effects of Ionizing Radiation [BEIR]), the risk for tumor induction can be calculated on gender- and age-related bases.[7] The average lifetime risk for exposure to radiation is lower in men (9.5%) than in women (11.5%). Table 66-1 summarizes the age- and gender-specific risks for tumor induction.

Principles of Irradiation of Benign Diseases

The principles of irradiation of benign diseases can be summarized in 10 statements (Box 66-1). These should be carefully considered for each patient in whom irradiation is being evaluated.

RADIOBIOLOGIC ASPECTS

The radiobiologic mechanisms, known from the treatment of malignant disease, and the identified proliferating target cells are only partially applicable to benign diseases. Other radiation-sensitive target cells and cellular and functional mechanisms should be considered as target points for ionizing radiation. However, radiotherapy is probably not working via one particular mechanism but rather through a complex interaction of different effects.

Reactions in Connective Tissue

Several mechanisms are triggered by ionizing radiation in connective tissues. Following any trauma or acute or chronic inflammation, several cell systems regulate the repair process where fibroblasts play a central role, particularly during the reparative phase, which is characterized by high cell production and stimulation of specific growth factors. Furthermore, ionizing radiation also has a pivotal influence on cellular differentiation.[8,9]

For some hyperproliferative events, fibroblast overreaction is responsible for the disease process (e.g., during the early stage of Dupuytren's contracture, during the early phase of Peyronie's disease, in keloids, and in the progression of aggressive fibromatosis [desmoid]). The increase in fibroblast production can be modified by ionizing radiation, which influences differentiation and suppresses cell proliferation.

Reactions in the Vascular System

The endothelial cells of the capillaries and the larger arterial and venous blood vessels possess a high proliferative potential and are the origins of various cytokine-mediated cellular reactions. Intercellular adhesion molecule 1 (ICAM-1), a mediator of the leukocyte-endothelial interaction, is induced by low radiation doses.[10] Similarly, selectins mediate the penetration of mononuclear blood cells into the interstitial tissue. Endothelial prostaglandin release is also modulated by ionizing radiation.[11] Cellular and membrane functions can be modified when they are exposed to radiation.

Large single or total doses may cause endothelial damage, leading to sclerosis and obliteration of small blood vessels. Higher fractionated doses or single doses are used for cerebral arteriovenous malformations (AVMs) or symptomatic vertebral hemangiomas, and lower single and total doses are applied to reduce inflammatory processes such as endocrine orbitopathy and pseudotumor orbitae.

TABLE 66-1 Tumor Induction Depending on Age and Gender: Relative Lifetime Risk

Age-group (Years)	Men (%/Sv)	Women (%/Sv)
≤10	25.0-26.0	32.0-33.0
11-20	15.0	19.0
21-30	13.0-14.0	17.0
31-40	7.0	8.0
41-50	5.0	6.0
51-60	4.5	5.0
61-70	3.5	4.5
71-80	2.5	3.0
>80	1.0	1.5

From Jansen JTM, Broerse J, Zotelief J, et al: Assessment of carcinogenic risk in the treatment of benign disease of knee and shoulder joint. In Seegenschmiedt MH, Makoski H-B, editors: Kolloquium Radioonkologie/ Strahlentherapie, Radiotherapie bei gutartigen Erkrankungen, Vol 15, Altenberge, Germany, 2001, Diplodocus Verlag, pp 13–15.

BOX 66-1 Principles of Irradiation of Benign Diseases

1. Estimate the natural course of disease without therapy.
2. Consider the potential consequences of nontreatment of the patient.
3. Review data about alternative therapies and their therapeutic results.
4. Conduct a risk-to-benefit analysis compared with other possible measures.
5. Prove that the indication is justified if conventional therapies have failed, if risks and consequences of other therapies are greater, and if nontreatment would have more dramatic consequences than irradiation for the patient.
6. Consider the potential long-term radiogenic risks to the individual patient.
7. Inform each patient about all relevant details of radiotherapy: target volume, dose concept (single and total dose), duration of single session and whole irradiation series, relevant radiogenic risks, and side effects.
8. Obtain written consent from the patient following thorough patient education.
9. Ensure long-term aftercare to document results.
10. Request a competent second opinion in case of doubt and if the provided patient's data or treatment decisions are uncertain.

Data from Seegenschmiedt MH, Katalinic A, Makoski H, et al: Radiation therapy for benign diseases. Patterns of care study in Germany. Int J Radiat Oncol Biol Phys 47:195–202, 2000; Micke O, Seegenschmiedt MH: The German Working Group guidelines for radiation therapy of benign diseases. A multicenter approach in Germany. Int J Radiat Oncol Biol Phys 52:496–513, 2002.

Reactions in Painful Processes

Degenerative processes in hypotrophic tissues such as tendons, ligaments, and joints can cause pain by chronic inflammation and trigger various forms of functional impairment of the musculoskeletal system. Radiation does not influence the degenerative process but may reduce inflammation and as a consequence, improve function of affected joints and limbs and achieve pain relief.[12,13]

Mechanism of Action

To know individual target cells and potential pathogenic mechanisms of the various benign diseases also means to coordinate the radiation therapy concepts accordingly and consistently. The dose concepts applied in benign diseases differ greatly from each other because of other potential mechanisms of action (Table 66-2).

TABLE 66-2 Mechanisms of Action and Dose Concepts

Mechanisms of Action	Single Dose (Gy)	Total Dose (Gy)
Cellular gene and protein expression (e.g., eczemas)	<2	<2
Inhibition of inflammation in lymphocytes (e.g., in pseudotumor orbitae)	0.3-1	2-6
Inhibition of fibroblast proliferation (e.g., in keloids)	1.5-3	8-12
Inhibition of proliferation in benign tumors (e.g., in desmoids)	1.8-3	45-60

BENIGN DISORDERS OF THE HEAD AND NECK AND CENTRAL NERVOUS SYSTEM

Benign tumors of the central nervous system (CNS) can lead to severe, life-threatening symptoms resulting from local expansion and pressure on neighboring normal structures. Depending on the growth rate, the surrounding normal tissues can potentially adapt and delay symptoms and the subsequent clinical diagnosis.

Pituitary adenomas, meningiomas, vestibular schwannomas, craniopharyngiomas, and chordomas are important benign CNS tumors treated with irradiation. These are covered fully in Chapters 23, 28, 29, and 30 and will not be discussed here.

Arteriovenous Malformation

Definition and Clinical Features

Intracranial AVMs are rare vascular abnormalities consisting of widened arteries with connections to the normal capillary bed that enables oxygenated blood to enter directly into the venous system. Approximately 80% of AVMs are located supratentorially. The incidence of AVMs is unknown. Its prevalence is below 0.01% (≈18:100,000) in the Western hemisphere. Most AVMs are discovered at the age of 20 years to 40 years. AVMs can extend to aneurysms and rupture (2% to 5% per year).[14] Neurologic symptoms associated with AVMs include headaches, hemorrhage, and cramp attacks, which may culminate in sudden death through bleeding. Increased risk of hemorrhage includes prior hemorrhage, exclusive deep venous drainage, associated aneurysms, and deep location, which can influence surgical and or radiosurgery decision making.[14,15] Lethality after the first bleeding episode occurs in up to 30%; 10% to 20% of survivors have long-term neurologic defects. Spontaneous regression is rare.[15] Diagnosis of AVMs is made with imaging techniques such as angiography and magnetic resonance imaging (MRI).

The aim of therapy is the prevention of bleeding by complete obliteration of the nidus, the improvement of neurologic malfunctions, if feasible, and preferably, minimal therapy-induced side effects. For this purpose, the options of minimally invasive endoscopic surgery, endovascular embolization, and stereotactic radiosurgery (SRS) are available. For therapy

TABLE 66-3 Arteriovenous Malformations: Obliteration Rate and Rate of Radiation Side Effects after Radiosurgery

Study (Chronological)	No. Patients	Obliteration (%)	Moderate Side Effects (%)	Severe Side Effects (%)
Steiner et al[19]	247	81	8	1
Engenhart et al[20]	212	72	4	4
Colombo et al[21]	153	80	6	2
Deruty et al[22,23]	115	82	10	Not stated
Flickinger et al[24]	197 351	72 75	5	3
Miyawaki et al	73	64	13	5
Chang et al[25]	254	79	3	2
Schlienger et al	169	64	4	1
Shin et al[26]	100	95 (5-year)	Not stated	4
Friedman et al[27]	269	53	4	1

planning, precise knowledge regarding the size, location, arterial feeders, and venous drainage of the nidus is required.

Surgical Treatment

The therapy of choice is the elective complete excision of the AVM vascular abnormality. Particularly with small AVMs in superficial, noneloquent regions of the brain, microsurgery results in high cure rates. Larger AVMs are treated initially with embolization before surgery or SRS. Only in special cases is surgery performed under emergency conditions to remove life-threatening brain hemorrhages.

Irradiation Options

Arteriovenous malformations are irradiated with SRT/SRS with a linear accelerator or Gamma Knife (see Chapters 7 and 23).

Stereotactic radiosurgery for AVMs dates back to the 1970s. The mechanism of action of SRT/SRS is linked to injury to the vascular endothelium, which causes proliferation of smooth muscle cells and the elaboration of extracellular collagen causing progressive stenosis and obliteration of the AVM.

Fractionated radiation with total doses of up to 60 Gy produced inadequate results.[16-18] Depending on the size and location of the AVM, a single dose of 15 Gy to 30 Gy is required to the periphery of the nidus. If therapy is successful, complete obliteration of the nidus will occur usually no sooner than 2 years from treatment, with many taking 3 years or longer. This delay in obliteration does leave the risk of bleeding until complete obliteration occurs. The obliteration rate after SRT or SRS is 65% to 95% (Table 66-3).

The side effects of SRT/SRS are mostly chronic and follow the time course of AVM obliteration: focal radionecroses or leukoencephalopathies occur 9 months to 3 years after SRT, but they may also appear after several weeks.[17,21,22,24,25,28-36] The risk correlates strongly with the irradiated brain volume, location of the AVM, and the total dose.[37-39] The brain volume irradiated with more than 10 Gy is an important predictive factor.[40,41]

Whether unruptured AVMs should be treated or observed has been a matter of debate. The ARUBA trial, a randomized trial of unruptured brain AVMs compared the risk of death and symptomatic stroke. Patients were randomized to either medical management for symptoms treated with pharmacologic agents alone or medical management with interventional therapy including neurosurgery, stereotactic radiotherapy, or embolization, alone or in combination. The trial was halted early because of the superiority of the medical management group because the risk of death or stroke was significantly lower compared to the intervention group.[42]

Glomus Tumor or Chemodectoma

Definition and Clinical Features

Glomus tumors (synonyms are chemodectomas or nonchromaffin paragangliomas) are rare benign tumors that can occur in multiple anatomic locations:

1. Paragangliomas occur at the carotid glomus, along the carotid, mostly near the bifurcation.
2. Jugular paragangliomas are found near the skull base in the region of the jugular bulb.
3. Paraganglioma of the tympanic glomus occurs in the region of the tympanum.
4. Other paragangliomas occur at the larynx, near the aorta, in pulmonary locations, and in the orbital cavity.

Approximately 50% of tumors are located near the skull base in the jugular fossa. The age peak is 45 years. The tumors are usually unilateral; only 10% to 20% are bilateral or multiple.[43] They grow slowly, rarely have endocrinologic activity, and degenerate into malignant forms in 5% to 10% of patients. They can also infiltrate bone, vessels, the middle ear, and cranial nerves (CN). The main symptoms are headaches, CN failure (CN V to XII), dysphagia, pulsatile tinnitus, vertigo, and hypacusis. Without therapy, there is the risk for CN injury; the swelling can be so extreme as to be life threatening. The diagnosis is made clinically and with high-resolution computed tomography (CT) and MRI.

Surgical Treatment

Although glomus tumors grow slowly, they can cause severe problems and, therefore, must be treated. In the carotid region, primary tumor resection after previous embolization is the therapy of choice. At the skull base or at the tympanum, neurosurgical interventions carry more risk, and therefore, fractionated radiation is often favored. In the case of incomplete surgery, the patient should initially be observed, and further treatment should only be started if the tumor grows.

Irradiation Options

Depending on the size and location of the lesions, the indication for RT may be either *primary* irradiation in the case of functional or other inoperability (mostly, jugular paragangliomas) or *adjuvant* irradiation for R1 to R2 resections or irradiation of *recurrence* if there is progression after surgery. Conventional fractionated three-dimensional (3D) conformal radiation therapy with 45 Gy to 55 Gy is the norm. The clinical target volume (CTV) is restricted to the tumor region with a safety margin to cover microscopic extensions.

Irradiation of paragangliomas produces control rates as good as or even better than surgery.[44] Even in large, diffusely growing or multiple tumors, radiation produces a local control rate of 88% to 100%.[26,27,44-46] Kim et al noted a recurrence rate of 22% with doses of less than 40 Gy, whereas recurrences occurred in only 1.4% with doses of more than 40 Gy.[45] Frequently, tumor rests are detectable on imaging for several years. Therapeutic success is usually assessed in terms of the regression of CN failures and the lack of tumor progression. A dose of 45 Gy to 50 Gy does not complicate surgery that might become necessary later.

Stereotactic single-dose radiation and Gamma knife therapy have efficacy in the treatment of paragangliomas.[26,27,44-51] The results are favorable compared to fractionated radiation, with excellent local control rates and acceptable side effects. Sheehan et al reported data regarding 134 patient procedures from eight Gamma knife centers including prior resection in 51 patients. The median tumor margin dose was 15 Gy. With a median duration of follow-up of 50.5 months (range, 5 months to 220 months), overall tumor control was 93% at last follow-up with an 88% actuarial tumor control 5 years after surgery. Worsening CN function was seen in 11% of patients despite radiological evidence of control.[52] No secondary malignancies were noted.

Irradiation of paragangliomas of the carotid glomus can acutely cause pharyngeal mucositis and chronically may lead to skin fibrosis and dryness of the pharyngeal mucosa on the irradiated side. Irradiation of jugular or tympanic paragangliomas can lead to acute skin reactions in the external acoustic canal, tube ventilation dysfunction, reduced sound conduction, and salivary retention may occur on the ipsilateral side.

Juvenile Nasopharyngeal Fibroma

Definition and Clinical Features

Juvenile nasopharyngeal fibromas (JNFs), which is a synonym is angiofibromas, are rare, benign, strongly vascularized tumors in the head and neck region, affecting mainly male juveniles. JNFs develop in the sphenoethmoidal suture and can spread from the epipharynx and the main nasal cavity via the sphenopalatine foramen and into the pterygopalatine fossa. After bony destruction, there is spread into the paranasal sinuses, the infratemporal fossa, the orbital space, and the middle cranial fossa.

Intracranial spread occurs in about 25% of cases. Typical symptoms are epistaxis and impaired nose breathing. Depending on the pattern of spread, facial swelling as well as orbital (e.g., blindness) and intracranial symptoms (e.g., CN failure) may occur. A biopsy can cause massive bleeding so that histologic confirmation of diagnosis is often not performed. The presence of hormone receptors shows the influence of androgynous hormones. Spontaneous remission after puberty is possible, but therapy can hardly be delayed when the symptoms increase and when complications are threatening.[53,54]

Surgical Treatment

In JNF, the main emphasis is placed on surgery combined with embolization to decrease the size of the tumor.[55,56] Small tumors that are restricted to the posterior nasal cavity and the nasopharynx can be completely removed after embolization. A JNF with lateral spread is also an indication for surgery. Endoscopic surgical approaches have been used in treating these tumors as a means of decreasing morbidity.[57,58] Through surgery, the local control rates for most JNFs without intracranial spread range up to 100% with minimal toxicity.[53,54,57,58]

Irradiation Options

Radiotherapy is an effective treatment for JNF. In locally advanced disease, complete resection is often not possible, and tumors with intracranial spread should receive primary irradiation. Other indications for radiation are tumor rests, inoperability, or local recurrence after initial surgical resection. With modern CT-based treatment planning, high control rates are achieved in locally advanced JNF as well. Intensity-modulated radiation therapy (IMRT) is often recommended.[59]

Total doses of 30 Gy to 55 Gy (1.8 Gy to 2 Gy per fraction) are said to be effective, but for large tumors, doses of 40 Gy to 46 Gy are currently recommended.[60-64] With conventional fractionated radiation, control rates of 80% to 100% can be reached. Remission of JNFs after radiation often requires several months[61]; sometimes, complete remission, as detected by imaging techniques, does not occur even after years, although there is no further growth.

Radiation side effects include mucositis, xerostomia and caries, dysfunction of the pituitary gland, CN failure, temporal lobe necrosis, osteoradionecrosis, growth impairment of the facial skull, cataract, glaucoma, and atrophic rhinitis, but these can be limited through careful radiation planning and highly conformal radiation. Radiation-induced tumors occur in up to 4% of cases, particularly in young patients; this has to be weighed against the risk for sudden death or severe morbidity after surgery.

BENIGN DISORDERS OF THE EYE AND ORBIT

Macular degeneration and endocrine orbitopathy (Graves' disease) are important benign diseases of the eye or orbit that are treated with irradiation. They are discussed in detail in Chapter 31 and will not be covered here.

Pterygium

Definition and Clinical Features

Pterygium is a wing-shaped fibrovascular proliferating tissue originating at the lens epithelium at the border between the conjunctiva and the cornea. It normally extends from the medial (nasal) corner of the eye to the cornea and beyond. The highest incidence occurs in hot, dusty, dry, and sun-exposed regions (desert belts). In such areas, even people in their 20s and 30s can be affected.[65,66] Typical symptoms are the sensation of having a foreign body in the eye and tearing. Motility problems are sometimes present. If the cornea is affected, vision may be impaired.

Surgical Treatment

Surgery is the mainstay of treatment, with treatment indicated if vision is threatened by the pterygium growing toward the pupil or if cosmesis is affected. Historically, the initial approach was bare sclera excision, which removes the pterygium from the cornea and conjunctiva, leaving the bare sclera exposed. Absent adjuvant therapy, recurrence rates have been reported to be as high as 88%.[67] Currently accepted therapeutic strategies include conjunctival or limbal autografts with or without mitomycin C intraoperatively or postoperatively. Amniotic membrane grafting has been used, but appears to be inferior to conjunctival or limbal autografting. With the use of the aforementioned adjuvants, recurrence rate reduction (compared to bare sclera excision alone) in both primary and recurrent cases is in the range of 40% to 95%. Vision-threatening and non-vision-threatening complications are relatively rare but can include scleral thinning or ulceration, delayed

conjunctival epithelialization, iritis, corneal edema, corneal perforation, symblepharon, corneal dellen, astigmatism, pyogenic granuloma formation, ocular pain, photophobia, and foreign body sensation.[67-70]

Irradiation Options

Radiotherapy is indicated after local resection of a recurrent pterygium, but some centers also report success with primary or preoperative radiation of the pterygium.[71] Besides rare orthovoltage therapy,[72] brachytherapy with beta radiators and eye applicators is usually employed. Normally, radionuclide strontium-90, a fission product of uranium-235 (half-life period, 28 years), which decays to yttrium-90 (half-life period, 64 days) is used. Strontium-90 radiation has a maximum energy of 0.546 MeV; for yttrium-90 it reaches 2.27 MeV.[73] The eye applicators have an effective diameter of 8 mm to 12 mm. The affected lesion is generously covered by the applicator for a certain time. If lesions are large, they are treated with a circular motion toward the corneal limbus.[74]

Most clinical studies have used postoperative radiation for recurrence prophylaxis with subsequent relapse rates of 1.5% to 11%. Van den Brenk[75] observed only 1.4% recurrences in 1300 treated pterygia (1064 patients). Irradiation was carried out once a week (days 0, 7, and 14 postoperatively). Paryani et al[74] achieved a recurrence rate of only 1.7% in 825 eyes with 60 Gy in six fractions of 10 Gy (once a week). Wilder et al[65] report a recurrence rate of more than 11% in 244 eyes after 24 Gy in three fractions of 8 Gy (once a week). In comparison to placebo irradiation, a Dutch double-blind randomized study with one fraction of 25 Gy showed significantly lower recurrence rates (local relapse in the irradiation arm in only 3 of 44 tumors and in the placebo arm in 28 of 42 tumors).[76]

Radiogenic consequences such as severe scleromalacia and corneal ulcerations occur in up to 4% to 5% of cases after application of higher total doses and after single-dose radiation of 20 Gy to 22 Gy.[77,78]

Choroidal Hemangioma

Definition and Clinical Features

Choroidal hemangiomas are slowly growing benign vascular tumors originating from the vessels of the choroid. The *diffuse type* (ages 5 years to 10 years, almost always associated with Sturge-Weber syndrome) and the *local type* (ages 30 years to 50 years) can be distinguished.[79] Symptoms are determined by the size and location of the tumor. If the hemangioma is located close to the papilla or macula, vision changes, metamorphopsia, and secondary retinal detachment are observed. In case of direct macular involvement, chronic glaucoma frequently develops. A threat to vision can occur and is the main indication for therapeutic intervention. On ophthalmoscopic examination, hemangiomas appear as a red-orange swelling with concomitant clinical phenomena (e.g., glaucoma, retinal detachment). Further diagnostic procedures are ultrasound, fluorescence angiography, CT, MRI, and scintigraphy (phosphorus-32).[80]

Nonradiotherapeutic Treatment

Indications for therapy depend on the progression of the lesion and the severity of symptoms (visual impairment, retinal detachment, or secondary glaucoma). Small lesions outside the field of central vision are treated with photodynamic therapy, photocoagulation, or transpapillary thermotherapy (e.g., to prevent retinal detachment).[81,82] Lesions near the macula or papilla are not coagulated because there is a risk for central scotoma. The same holds for incomplete retinal detachment and for the diffuse type (Sturge-Weber syndrome). In general, the currently favored therapeutic intervention is photodynamic therapy. Intravitreal bevacizumab alone, or in combination with local therapy, has also been used.[83-86] Patients with small, well-circumscribed lesions and patients with a history of longstanding visual loss can potentially be observed.[87,88]

Irradiation Options

Irradiation can be delivered by photons, protons, or brachytherapy. It is typically indicated in cases of no or minimal response to other local therapies and particularly in cases of critical proximity to the macula or papilla because invasive measures can threaten vision.[80] After successful irradiation, the primary lesion flattens, the retina reattaches partially, or perhaps, completely, and the eye and vision are maintained. Visual acuity is often improved. A loss of visual acuity affects almost exclusively eyes with existing location-dependent maculopathy. Early initiation of radiation can potentially lead to better long-term results.[89,90]

Schilling et al[90] irradiated 36 localized and 15 diffuse hemangiomas with 20 Gy in 10 fractions of 2 Gy. After 5 years, 23 eyes (64%) of the localized type achieved complete retinal reattachment. Visual acuity was stable in 50% and improved in 50%. Favorable results were also achieved for the diffuse type. In locally advanced cases, irradiation of the hemangioma cannot conserve visual acuity but can often maintain the eye as a whole.

Radiation with photons or protons is typically conventionally fractionated (1.8 Gy to 2 Gy per fraction) to total doses of 18 Gy to 20 Gy (local type) or 30 Gy (diffuse type). In cases of unilateral location, a lateral stationary field that tilts slightly posterior is used to protect the other eye and the chiasm. In bilateral disease, opposing lateral fields with lens protection are used.

Brachytherapy is carried out in localized hemangiomas with eye plaques, with iodine-125 seeds being the preferred source. Doses from the apex to the base of the lesion vary between 30 Gy and 240 Gy. Results are excellent in the sense of a permanent resorption of the subretinal edema, complete retinal attachment, and maintenance of vision.[89,91-94]

Potential radiogenic side effects are retinopathy and papillopathy with doses of more than 30 Gy. Despite lens-protecting radiation techniques, cataracts occasionally develop as well. With external beam techniques, protons may have the additional benefit of minimizing the risk of secondary malignancy induction compared to photons, which is an issue of particular relevance in pediatric cases.[95-99]

Idiopathic Orbital Inflammation or Pseudotumor Orbitae

Definition and Clinical Features

Lymphoid diseases of the orbit are rare and have a broad range, including pseudotumor orbitae (PO) and malignant lymphomas.[97,100] There are three possible nonmalignant causes: (1) an infectious process, for example, in transmitted sinusitis; (2) an autoimmune process; or (3) a fibroproliferative process.

PO typically occurs in patients of middle age, with clinical signs and symptoms that can result in a broad differential diagnosis. Thus, other causes of orbital space involvement such as granulomatous diseases (e.g., sarcoidosis, Wegener's granulomatosis), local infections, malignancies, or autoimmune diseases have to be excluded. Frequently, the acute onset of symptoms, unilateral disease, and impaired eye motility point to pseudotumor. On imaging, the infiltrates appear in retrobulbar adipose tissue (≤80%), enlarged eye muscles (≤60%), thickening of the optic nerve (≤40%), and proptosis (≤70%). On the basis of clinical diagnosis and diagnostic imaging, it can be difficult to differentiate between

benign and malignant changes; therefore, biopsy is essential.[101]

Nonradiotherapeutic Treatment

Surgical excision can be used in accessible lesions, but recurrences are frequent.[102] Corticosteroids are the most important component of medical therapy, but up to 50% do not respond adequately.[96,103] Some patients are forced to discontinue corticosteroid use secondary because of untoward side effects.[94,104] Beyond corticosteroids, there is increased interest in nonspecific as well as targeted immunomodulatory therapies in the management of PO. However, there are a limited number of studies demonstrating overt clinical benefit with these agents in patients not responding to initial corticosteroid therapy.[96] Without therapy, visual acuity can deteriorate seriously and permanently. The potential for malignant transformation of orbital pseudotumors is unclear.

Irradiation Options

Irradiation is typically reserved for patients who have not responded to initial corticosteroid therapy. As noted by Lambo et al, radiotherapy has response rates of 70% to 100%.[100,101,104-107] Recommended doses vary between 0.5 Gy and 3 Gy per fraction and total doses of 20 Gy to 35 Gy.

In Europe, a treatment attempt with a low dose of two fractions of 0.5 Gy per week up to a total dose of 5 Gy (first series) has been used.[107] In the case of nonresponse after 4 weeks, irradiation is changed to daily 1.5 Gy to 2 Gy fractions up to 30 Gy to 40 Gy as a total dose (second series). In the United States, most patients are treated with initial doses of approximately 20 Gy to 30 Gy at standard fractionation.[108]

Irradiation Technique

After CT planning, patients are treated via anterior and lateral fields with 1:3 weighting and wedged filters for dose homogenization while the patient's eyes are open. In bilateral disease, parallel opposing lateral fields with a half-block technique[102] or two anterior electron fields are used.

Irradiation Side Effects

With careful treatment planning, serious radiation-related side effects are rare (keratitis, retinopathy, cataracts, etc.).

BENIGN DISEASES OF JOINTS AND TENDONS

Dose Concepts

It has been known since the beginning of the 20th century that low doses of ionizing radiation may have analgesic and anti-inflammatory effects.

Nonradiotherapeutic Treatment

Numerous conservative measures, such as oral, local, or systemic application of medications, lifestyle modifications, physical therapy, and so on are the mainstay of management. Radiation therapy is rarely used in the United States for primary management of these diseases, but its use is certainly more common in other countries.

Irradiation Options

In Germany, guidelines and dose concepts for radiotherapy of benign diseases were developed during the past 10 years to 15 years, where a dose per fraction of 0.5 Gy to a total dose of 6 Gy can, and has been, used.[2,3,109] Conditions that have been treated include bursitis, tendonitis, subacromial syndrome (rotator cuff syndrome), tennis elbow (epicondylopathia humeri), calcaneodynia (heel spur), and degenerative joints with cartilaginous destruction (osteoarthritis).[108,110-115]

BENIGN DISEASES OF CONNECTIVE TISSUE AND SKIN

Desmoid (Aggressive Fibromatosis)

Definition and Clinical Features

A desmoid is a benign growth of connective tissue originating in the deep muscular-aponeurotic structures in the region of muscle fascias, aponeuroses, tendons, and scar tissue. The incidence of new cases is two to four per 1 million inhabitants per year. Women are affected twice as frequently as men (1:1.5 to 2.5). Desmoids occur most frequently during the third and fourth decades of life, but children can be affected as well. Mesenteric desmoids are commonly associated with the *APC* gene mutation as in Gardner's syndrome.[116]

Desmoids are differentiated into extraabdominal (≈70%) and intraabdominal (≈10%) desmoids and those located in the abdominal wall (≈20%). Extraabdominal forms tend to recur locally. Intraabdominal forms are associated with the autosomal dominantly inherited Gardner syndrome. Histologically, desmoids are similar to low-grade (G1), highly differentiated fibrosarcomas. Mitotic activity is low, and cellular atypia is rare. Locally infiltrating growth and nonencapsulation has earned the name of "aggressive fibromatosis" for this disease. Local recurrences after resection alone are quite common particularly after marginal or intralesional excision.[117,118] Pretreatment imaging with MRI is used to estimate the size and infiltration into other organs and incision biopsies are performed to distinguish benign from malignant lesions. Although prognosis for survival is good, these lesions may impair function, impact quality of life, and cause life-threatening events.

Nonradiotherapeutic Treatment

Desmoids can regress spontaneously or they can grow to a huge size, but they rarely cause death.[119] Surgery with a safety margin of 2 cm to 5 cm is considered the gold standard. After R0 resection, no adjuvant therapy is usually required. After R1 resection, treatment options include observation if the lesion is in a site where re-resection is feasible; if not, postoperative radiation is reasonable. Good long-term control can be achieved by resection alone, but up to 50% of patients develop local recurrence, which requires surgical and other measures subsequently.[120] Hormonal intervention with tamoxifen, progesterone, and toremifene can exert growth inhibitory effects.[121-123] Overall antiestrogens produce an effect in approximately 50% of patients as determined by systematic review.[124] Nonsteroidals, vitamin C, and chemotherapeutic agents have been tested.[125,126]

Irradiation Options

Radiotherapy is indicated in cases of local inoperability and after R2 resection and in R1 resection if repeated surgery would not be feasible or has already been performed for local recurrence. Radiotherapy is often used adjuvantly or as primary treatment. Adjuvant radiotherapy significantly reduces local recurrence rates compared with surgery alone. With total radiation doses of more than 50 Gy, the local recurrence rate decreases from 60% to 80% with surgery alone to 10% to 30% after adjuvant RT. With normal fractionation and single doses of 1.8 Gy to 2 Gy, a total dose of 50 Gy to 55 Gy is recommended postoperatively. For inoperable or recurring desmoids, some recommend a total dose of 60 Gy to 65 Gy.

After primary radiotherapy, the local control rate does not differ substantially from that after adjuvant irradiation.[3,117,120,127-133] A recent Phase II pilot study evaluated the response of patients with inoperable progressive disease of primary, recurrent, or incompletely resected desmoids receiving 56 Gy in 28 fractions and demonstrated a 3-year local control rate of 81.5%.[134]

Irradiation Results

In most studies, tumor size has no prognostic influence on local control rates. According to a meta-analysis (698 cases in 13 studies), the local control rate after R0 resection and radiotherapy was improved by 17% compared with that of surgery alone. For macroscopic (R2) and microscopic (R1) tumor residual, patients treated with adjuvant radiotherapy had even better results.[135,136] In 2001 to 2002, patterns of care study on the use of radiotherapy for treatment of desmoids were carried out in Germany; 345 patients were subjected to evaluation. The desmoids were distributed in the extremities (81.2%; 280 tumors), the trunk (13.9%; 48 tumors), and the head and neck region (4.9%; 17 tumors). A total of 204 patients (59%) were irradiated for locally recurrent or unresectable desmoids: 141 (40.8%) for high-risk situations postoperatively, 44 for unclear resection status, 49 after R1 resection, and 28 after R2 resection. Most patients were intensively pretreated, on average with two (range, one to five) operations. The median time of observation after therapy was 43 (range, 4 to 306) months. A total of 67 recurrences (19%) were seen after radiation. The long-term local control rate was 81.4% after primary radiotherapy of nonresectable desmoids and 79.6% after postoperative irradiation of resected desmoids. A precise topographic analysis of recurrences was possible in 124 patients or 22 recurrences (18%); 12 (54%) of the recurrences were located within and 10 (46%) were located outside the target volume or at the edge of the field.

Peyronie's Disease

Definition and Clinical Features

Peyronie's disease is a chronic and mostly progressive inflammation and connective tissue excrescence of the tunica albuginea in the cavernous bodies of the penis.[137] It usually affects men between the ages of 40 years to 60 years. Its cause is unknown. Strands of scar lead to the typical bending of the penis, which may cause severe pain during erections. Spontaneous remission is described only rarely.

Nonradiotherapeutic Treatment

There is no simple and successful standard treatment. Vitamin E, para-aminobenzoate, and steroids are said to have a favorable influence during the early phase. There are also local therapeutic attempts with ultrasound or shock waves as well as with corticoid, procaine, and hyaluronic acid injections. Surgery is the standard of care for stable Peyronie's, disabling deformity, or erectile dysfunction unresponsive to drug therapy. Several different surgical procedures are used including tunical shortening or lengthening and the use of penile prostheses. Each surgical procedure comes with potential complications and differing levels of postoperative satisfaction; thus, no one surgical treatment is considered standard.[138]

Irradiation Options

Although radiation therapy has been used in the treatment of Peyronie's, results have been mixed. Low-dose radiation appears to be effective in early stages in patients with painful erections not improving over time or by using oral or intralesional methods. Ionizing radiation can delay further induration and lead to softening of lumps and strands that cause pain, bending, and functional problems of the penis. Radiotherapy can be used during the early stages of Peyronie's disease, but in the later stages, there are hardly any radiosensitive fibroblasts and inflammatory cells left. Irradiation is carried out with gonadal protection (lead apron or capsule), and the glans penis is spared. The nonerect penis is pulled forward manually by the patient and is irradiated via a dorsal stationary field with orthovoltage or electrons up to 6 MeV with a 5-mm to 10-mm bolus.

Conventional fractionation is 20 Gy in 2-Gy fractions, but it is possible to use hypofractionation with a single dose of 2 Gy to 4 Gy two to three times per week up to a total dose of 12 Gy to 15 Gy.[139-142]

However, the actual effectiveness of radiation is unknown because of the absence of criteria for success. As well, randomized, controlled trials comparing interventions do not exist. This leads some to recommend that radiation not be used in this setting.[138]

Irradiation Results

Within 12 months to 24 months, radiotherapy leads to an improvement of symptoms in two thirds of all patients with early-stage disease. Local pain and associated clinical symptoms decrease in up to 75%. Angulation (25% to 30%) and dysfunction of the penis (30% to 50%) show less response because these symptoms often indicate that the disease is already in a more locally advanced stage.[140-142]

Dupuytren's Contracture (Morbus Dupuytren) and Morbus Ledderhose

Morbus Dupuytren (MD) (Dupuytren's contracture) and morbus Ledderhose (ML) are two spontaneous connective tissue diseases in which the palmar or plantar aponeurosis is affected. Two thirds of patients show bilateral involvement. The disease is more common in the hands (MD) than in the feet (ML). It mostly appears from the age of 40 years onward. Depending on geographic region and racial factors, its prevalence is 1% to 3%. Initially, subcutaneous lumps with skin fixation appear; later, there are strands that may reach as far as the periosteum. With increasing connective tissue hardening, flexion contractures develop in the metacarpophalangeal or proximal interphalangeal joints, and grabbing (MD) or walking (ML) is impaired. Mostly, the fourth and fifth phalanges of the hand (MD) or the first and second toes of the foot (ML) are affected. The extent of the extension deficit determines clinical staging in MD.

Nonradiotherapeutic Treatment

Spontaneous regression is initially possible. Without therapy, more than 50% of people affected show disease progression after 5 years. Surgery is indicated if there is functional impairment.

Irradiation Options

Radiotherapy can be considered during the early stages of disease. The target cells are the strongly proliferating radiosensitive fibroblasts and inflammatory cells. The aim of therapy is to avoid further progression. Normal fractionation is 2 Gy per fraction to a total dose of 20 Gy or 3 to 4 Gy per fraction to a total dose of 12 Gy to 15 Gy.

Irradiation Results

Many studies demonstrate a good response to radiotherapy in the form of stabilized disease (70% to 80%). Only a small number of patients with early-stage disease, however, experience degeneration of lumps and strands (20% to 30%). Only a

few studies have controlled long-term observation for more than 2 years.[143] Betz et al reported the results of long-term results of 208 hands irradiated in 135 patients treated with orthovoltage therapy.[143] Patients received 30 Gy in 10 fractions treated split course with a 6- to 8-week break between courses. Patients were staged according to a modified version of staging described by Tubiana et al.[144] In this staging system, patients with stage N/I had clinical symptoms in addition to minor defects in extension (1 degree to 5 degrees). Eighty-seven percent of patients with stage N and 70% of patients with stage N/I stabilized or regressed. With more advanced stages, disease progression was seen in 62% of stage I patients (clinical symptoms with extension deficits of 6 degrees to 45 degrees), and 86% of stage II patients (clinical symptoms with extension deficits of 46 degrees to 90 degrees). No benefit was seen in patients with more advanced extension deficits. Also, the time period from first recognition of symptoms to radiation therapy onset influenced success, with better long-term results seen when irradiation was used within the first year of diagnosis versus those treated after 48 months ($p < 0.001$). Long-term relief of such symptoms as pruritus and scratching, tension, pressure, and burning occurred in 66% of patients. There was no increase in postsurgical complications, and only 32% of patients experienced minor late toxicity such as dry desquamation or skin atrophy. No evidence of secondary malignancy was seen. The authors concluded that radiation therapy is effective in the prevention of progress and relief of patient symptoms in early-stage contracture.

Keloids and Hypertrophic Scars

Definition and Clinical Features

Keloids are excessive tissue excrescences in the region of scars, and they may occur in case of skin injury from surgery, burns, chemical burns, or inflammation (e.g., acne) or even spontaneously. They differ from hypertrophic scars by their infiltrating character, causing local pain and inflammation reactions or even triggering long-term progression. Hypertrophic scars show thickening without surrounding reaction and can flatten spontaneously.

Keloids appear mostly in the upper body and in regions with high skin tension (e.g., above the sternum, at the earlobes, and in the joint regions). The cause of the disorder is still undetermined, but there is a genetic and race-specific predisposition.

Nonradiotherapeutic Treatment

Besides surgical excision of hyperplastic tissue with cosmetic disfigurement and functional disruptions, it is possible to use a conservative procedure with pressure and silicon bandages, steroids, plant extracts, or steroid injections for smaller lesions. In more than 50% of cases, there is local recurrence after excision of keloids alone.

Irradiation Options

Indications for irradiation are either demonstrated recurrences postoperatively or a high-recurrence risk (e.g., marginal resection borders, wider spread, unfavorable location). Fibroblasts, mesenchymal cells, and inflammatory cells are the target cells. Prophylactic irradiation immediately after excision of the recurrence is most effective. The local recurrence rate after postoperative irradiation is 20% to 25%.

Irradiation is initiated 24 hours after surgery at the latest. Orthovoltage (70 kV to 150 kV), electrons (<6 MeV), and brachytherapy with iridium-192 implants or with strontium-90 dermaplate are used.[145-148] The target volume is limited to the scar plus a 1-cm safety margin. The recommended dose is 12 Gy to 25 Gy, typically with 3-Gy to 4-Gy fractions.[109,147,149-152] Single-dose irradiation with 7.5 Gy to 10 Gy is effective.[153] Keloids in certain areas such as the chest wall tend to have a higher risk of recurrence, possibly because of tension placed on the tissue after surgical excision. Data from Ogawa et al suggest that doses of 20 Gy in 4 fractions should be considered for these areas. Recurrences on the chest wall decreased from 39% with 15 Gy in 3 fractions to 14.3% with 20 Gy.[149]

Other Diseases of Connective Tissue and Skin or Cutaneous Appendages

Acute and chronic inflammatory changes of the skin (furuncle, carbuncle), of the nailbed (paronychia), and those that affect the sweat glands of the armpit and groin (hidradenitis suppurativa) can lead to chronic and therapy-refractive inflammation that is painful and can seriously impair the function of those affected by the disease. If all local treatment measures are exhausted, if there is a confirmed resistance to antibiotics, and if further surgical measures are rejected, irradiation can be implemented with single doses of 0.5 Gy to 1 Gy daily up to a total dose of 10 Gy.

Gynecomastia

Radiotherapy for gynecomastia, a benign proliferation of breast tissue, is most commonly used in the setting of hormonal therapy for prostate cancer as either a prophylactic measure or as a treatment for painful gynecomastia in patients. The prevalence of gynecomastia in patients undergoing complete hormonal blockade is 15%, increasing to 75% with antiandrogen monotherapy.[154] Radiotherapy, when used prophylactically, appears to significantly decrease the incidence of gynecomastia but does not appear to relieve mastodynia.[155,156] Bilateral radiotherapy of the mammary region is performed with 8-MeV to 12-MeV electrons. Historically, four to five fractions of 3 Gy, up to a total dose of 12 Gy to 15 Gy, have been used to prevent pain or further growth of the mammary gland.[157] More recently, studies have evaluated the use of single-fraction radiation therapy.[154,158] Tyrrell et al published the results of a randomized, sham-controlled, double-blind, parallel-group multicenter trial involving 106 men with prostate cancer and no gynecomastia/or breast pain.[158] Patients received either a single dose of 10-Gy electron beam radiotherapy or sham radiotherapy. Bicalutamide was administered for 12 months from the day of radiotherapy. Physician-assessed gynecomastia was significantly lower with radiation therapy compared with sham radiotherapy (52% versus 85%; $p < 0.001$) with the incidence of ≥5 cm gynecomastia (measured by calipers being 11.5% with radiation therapy versus 50.0% for sham radiotherapy). More patients in the sham group experienced moderate to severe gynecomastia compared to the radiation therapy group (48% versus 21%). Radiation therapy also slowed the development of gynecomastia. There was no statistical difference in the incidence of breast pain with radiotherapy (83%) and sham radiotherapy (91%). There was a nonsignificant reduction in patients experiencing breast pain with prophylactic radiation therapy.

However, radiotherapy cannot reverse gynecomastia.

Plantar Warts

Plantar warts can be painful and functionally as well as cosmetically disturbing. In older studies, control rates of more than 80% were achieved with orthovoltage irradiation (10 Gy in one fraction, or 15 Gy in five fractions of 3 Gy). The warts fell off without consequences after several weeks.[159] Over the past several decades, the use of radiation for plantar warts has declined, so it is rarely used.

BENIGN DISORDERS OF BONY TISSUES

Aneurysmal Bone Cysts

Definition and Clinical Features

Aneurysmal bone cysts are benign vascular cystic lesions in the metaphasis of bones, which can cause functional impairment, pathologic fractures, and damage to neighboring structures. They can infiltrate the surrounding soft tissue. Despite their nonmalignant character, cysts can lead to bone destruction and thus lead to serious problems, which is why treatment is recommended once a cyst has been diagnosed, particularly if the vertebral column is affected.[160-162]

Surgical Treatment

Therapy is primarily surgical (resection or curettage with or without bone grafting) as long as this does not lead to a considerable functional impairment. Following curettage alone, cysts recur in up to 60% of patients, with lower rates reported in patients with allografting.[163,164] After complete resection, the risk of recurrence is minimal.[160-162]

Irradiation Options

Radiotherapy can be used in patients with cysts that cannot be treated by surgery or if curettage is difficult because of the size or location of cysts. Cyst progression or repeated recurrences are also indications for radiotherapy. Because more than 50% of patients are 10 years to 19 years old, radiation doses should be kept as low as possible, with strong consideration for the utilization of protons if at all possible.[95] Nobler et al[165] reported one recurrence in a total of 11 patients who were irradiated with total doses of 12 Gy to 31.6 Gy. A dose of 10 Gy to 30 Gy in 1.8-Gy to 2-Gy fractions over 1 week to 3 weeks seems to be adequate to control aneurysmal bone cysts reliably.[166-168]

Pigmented Villonodular Synovitis

Definition and Clinical Features

Pigmented villonodular synovitis (PVNS) is a rare proliferative disease affecting the synovia of joints and the tendon sheaths.[169] There are two types of disease: the strictly localized and the diffuse involvement of synovial membranes.[170] In most cases, the lesion is restricted to one joint, though can spread to muscles, tendons, and skin.

Surgical Measures

Surgical excision normally consists of synovectomy, which is rarely complete, particularly in large joints such as the knee.[171] Joint replacement has also been used.[172] Recurrence is seen in up to 45% of patients[173]; therefore, the addition of perioperative or postoperative irradiation is appropriate in patients with high-risk disease.[174,175]

Irradiation Options

O'Sullivan et al[170] reported on 14 patients who were irradiated with 30 Gy to 50 Gy in 15 to 35 fractions at Princess Margaret Hospital. The patients had different risk factors: microscopic residual tumor (7), macroscopic tumor (7), tumor more than 10 cm (5), tumor 5 cm to 10 cm (7), recurrences (8), and skin infiltration with ulceration (2). During an average observation period of 69 months (13 months to 250 months), 1 patient had persistent tumor 8 months after radiotherapy with 30 Gy in 15 fractions. All but 2 patients had tumor control. On the basis of the Princess Margaret Hospital results, radiation with a dose of 40 Gy in 20 fractions has been recommended.

Other institutions have evaluated their results with adjuvant irradiation after surgical resection and have achieved similar results. The German Cooperative Group on Radiotherapy in Benign Diseases (GCG-BD) conducted a pattern-of-care analysis of the results of postoperative RT for PVNS in 41 patients from 14 institutions.[174] The radiation dose ranged from 30 Gy to 50 Gy (median, 36 Gy; median single dose, 2 Gy). Local control was achieved in 95% of patients.

Vertebral Hemangiomas

Definition and Clinical Features

Vertebral hemangiomas are benign vascular lesions that can lead to a resorption of the affected bone.[176-178] Normally, only one vertebral body is affected. Hemangiomas are usually diagnosed by their radiologic picture of rarefaction with vertical, dense trabeculae in a honeycomb pattern. Most lesions require no therapy. In most cases, symptoms occur during the fourth or fifth decade of life.[179-182] Women are affected more frequently than men.[183] Spread of the tumor into the extradural space, hemorrhage, or rare compression fractures can lead to bone marrow compression.

Surgical Treatment

Surgical relief can become necessary, but it can be difficult owing to the danger of hemorrhage.[184-187] In most cases, only partial resection is possible, and postoperative irradiation can be considered.[176,177] Recently, less radical options such as vertebroplasty have been effectively used.[188-190]

Irradiation Options

The GCG-BD evaluated the results of radiation for vertebral hemangiomas in 84 patients from seven German institutions.[191] The RT dose ranged from 4.5 Gy to 45 Gy (median, 34 Gy; median single dose, 2 Gy). The overall response (complete plus partial response) was 90.5%, with long-term local control of 80.9%.

Rades et al[192] analyzed data from 339 patients with symptomatic vertebral hemangiomas from publications of the past 50 years. There were 222 patients who had to be excluded, either because surgery was part of the treatment (98 patients) or because the data were incomplete (124 patients). Of the remaining 117 patients, 54 patients received 36 Gy to 44 Gy (group A) and 62 patients 20 Gy to 34 Gy (group B). After a median observation period of 36 months (range, 6 months to 312 months), 39% of group A and 82% of group B patients had complete pain relief. The researchers recommend a total dose of 40 Gy.

Heterotopic Ossification

Definition and Clinical Features

Heterotopic ossification (HO) can appear following trauma or surgery of the hip (total hip replacement) in 10% to 80% of cases, and with varying degrees of severity. HO consists of real bone and is located in the periarticular soft tissues.[193] Ten percent develop extensive HO, causing pain and functional impairment. Patients with HO frequently complain of pain only a few days after surgery. Radiologic studies detect calcified structures with blurred contours 3 weeks to 6 weeks postoperatively.

The etiology of HO is only partially known. It is assumed that the pluripotent mesenchymal cells, which are present ubiquitously in periarticular soft tissue, develop into osteoblastic stem cells under certain conditions.[194]

For all patients with an indication for a hip replacement, there should be an individual estimation of the risk of HO before carrying out surgery. Patients who already have ipsilateral or contralateral HO carry the greatest risk. After a second surgery, 90% to 100% of those patients redevelop HO.[195-197]

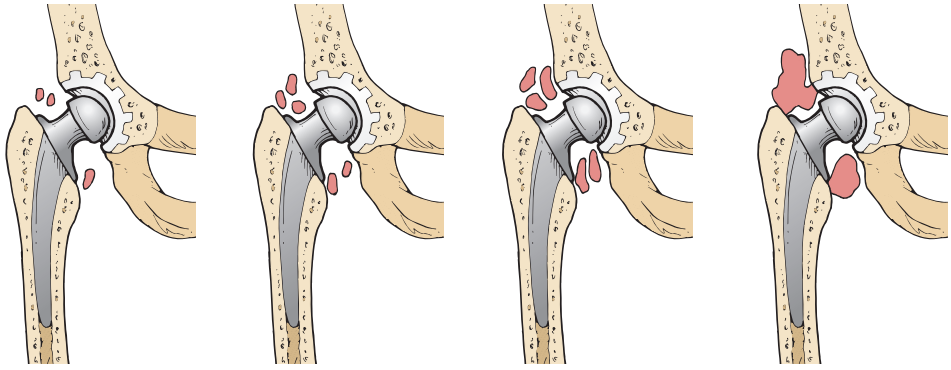

Figure 66-1 Staging of heterotrophic ossifications. **Grade I,** Bone islands within soft tissue around hip. **Grade II,** Exophytes of pelvis or proximal femur end with a minimum distance of 1 cm. **Grade III,** Exophytes of pelvis or proximal femur end with a distance of less than 1 cm. **Grade IV,** Bony ankylosis between proximal femur and pelvis.
From Brooker AF, Bowerman JW, Robinson RA, et al: Ectopic ossification following total hip replacement. J Bone Joint Surg 55A:1629–1632, 1973.

Patients with moderate or severe osteophytes at the femoral head and socket also have a high risk for HO, with an incidence of more than 50%.[198,199] After acetabular fractures, HO appears in 90% of hips. Fifty percent of those patients develop HO with clinical pathology.[200,201] Ankylosing spondylitis and the (rare) idiopathic hyperostosis of the skeleton are other influencing factors.

Diagnosis and Classification

Extensive ossifications lead to mobility impairment of the hip joint and cause pain. If HO is suspected, radiographs of the hip should be taken. Discrete changes in the radiograph can be seen at 2 weeks after surgery at the earliest. The literature provides a multitude of staging approaches. The most frequent one is the classification of HO according to Brooker et al[193] (Figure 66-1). To keep it simple, HO grades III and IV, according to Brooker et al, are designated as severe or clinically relevant, although there may not be any pain or mobility impairment.

Nonradiotherapeutic Treatment

Surgery

Clinically relevant (i.e., usually ankylosing) HO that has appeared after surgery should be removed to mobilize the joint and to remove pain. Complete removal of HOs is not essential if this is difficult and burdened with a higher risk. Most authors consider it necessary to wait for maturation of the forming ectopic bone and to reoperate only after 6 months to 1.5 years.

Medical Therapy

A number of medical options have been evaluated as prophylaxis against the development of HO. Although ethane hydroxy-diphosphates (EHDPs) have been used as prophylaxis, the treatment results are not convincing.[202-205] In contrast, some studies show that nonsteroidal anti-inflammatory drug (NSAID) use (indomethacin being the most commonly used), is effective in patients with a high risk of HO, with one meta-analysis noting that perioperative NSAID use resulted in a one half to two thirds reduction in the risk of HO development.[206-212] Selective cyclooxygenase-2 inhibitors have been tried, with promising results; though the concern for potential cardiovascular toxicity has tempered their use, particularly in patients with preexisting cardiovascular disease.[205]

Irradiation Options

Radiotherapy for prophylaxis of HO has been employed since the late 1970s and has proved to be effective. The initial dose was 20 Gy in 10 fractions.[213-218] Multiple dose schedules have been used. Various authors have pointed out that radiotherapy should be started no later than day 4 after surgery.

In three randomized studies, a dose of 10 Gy was compared with 20 Gy,[216] or with 17.5 Gy in five fractions,[219] and a single fraction of 8 Gy versus 10 Gy.[220] There was no significant difference between the effectiveness of high and low doses. Severe ossification occurred in 7% of patients with low and 5% of patients with high irradiation doses. No difference could be observed between fractionated and single-dose irradiation.

Preoperative radiation treatment with 7 Gy to 8 Gy in one fraction has been used successfully in patients with high-risk disease.[221] There appears to be no significant difference in clinically relevant HO compared with patients who are irradiated postoperatively.[222]

The relative roles of RT, indomethacin, and other NSAIDs for HO prophylaxis have been discussed by Pakos et al.[223-226] In a 2004 meta-analysis of seven randomized trials by Pakos et al,[223] irradiation was demonstrated to be more effective than NSAIDs for HO prophylaxis in preventing grade-3 to grade-4 ossification, but the absolute risk difference was only 1.2%. Pakos et al[225] subsequently reported a randomized trial in 96 patients comparing postoperative radiation (7 Gy in a single fraction) plus indomethacin (first 15 days postoperatively) to indomethacin alone (same 15 days) for HO prophylaxis. Patients receiving the combined treatment of radiation plus indomethacin had a lower rate of subsequent HO (4 versus 13 patients; $p < 0.05$). A systematic review of studies comparing indomethacin to radiation prophylaxis by Blokhuis and Frolke demonstrated an overall HO rate of 8.3% (5 of 60 patients) with radiation versus 8.9% (20 of 224 patients) with indomethacin. Although small, this difference was statistically significant.[227]

Irradiation is tolerated well. Neither fractionated irradiation nor high-single doses lead to an increased frequency of wound-healing disturbances, and there have been no documented cases of radiation-induced malignancies after prophylactic radiation.[228] Because radiation-induced tumors appear rarely and only after latencies of 10 years to 30 years, this risk is virtually irrelevant for most patients because the median age of patients is 65 years.

Irradiation Technique and Procedures

The irradiation field contains the typical localizations of periarticular ossifications, where the cranial field border is located approximately 3 cm above the acetabulum, and the irradiation field includes about two thirds of the implant shaft. Normally, the field size is 14 cm × 14 cm.

The effect of radiotherapy on the ingrowth of bone and fixation of noncemented implants was investigated in dogs[221] and rabbits.[229] After irradiation with 10 Gy (in five or four fractions), the fixation was significantly decreased within 2 weeks to 6 weeks.[229,230] Sumner et al[231] were also able to show that irradiation initially decreases the grade of fixation during the early postoperative phase, but after 4 weeks, the implants in irradiated and nonirradiated bone had the same strength.

In clinical application, the protection of the hip prosthesis with blocks as recommended by Jasty et al,[232] and the use of smaller blocks restricted to acetabular and femoral parts of the prosthesis can lead to ossifications underneath the block. Inadequate irradiation fields led to HO in 13 of 18 hips (76%) after irradiation with 7 Gy.[233] An open irradiation field covers the entire periarticular risk region more completely. Nonfixation of cementless implants was not observed after 6 Gy in one fraction,[234] after 7 Gy in one fraction,[235] or after 17.5 Gy in five fractions.[219,236,237] Because of the animal experimental and clinical studies, there appears to be no objection to irradiating hips with noncemented prostheses without a block. Strong consideration should be given to the utilization of testicular shielding in men interested in fertility as shielding can reduce testicular dose.[238]

Radiation for HO prophylaxis has also been used in patients with elbow trauma requiring surgical fixation. Although it does appear to be safe, a small prospective randomized study did note a significant difference in the nonunion rate between patients who received radiation and those who did not (38% versus 4%, $p = 0.007$).[239-241]

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