7.1 Introduction

The head and neck region is composed of multiple structures in close proximity that are at risk for acute and late treatment effects. It is the juxtaposition of these sensitive tissues, which include the major organs for sensation (eyes, ears, nose and mouth), mucous membranes, salivary glands, teeth, base-of-skull and associated regions of brain and the hypothalamic-pituitary axis, which places multiple critical structures at risk for radiation damage. Approximately 40% of rhabdomyosarcomas arise in this region. Ewing’s sarcoma, osteosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, nasopharyngeal carcinoma, lymphoma, neuroblastoma, hemangioma and histiocytosis also occur in the head and neck. Consequently, late effects secondary to local treatment such as radiotherapy (RT) and surgery, as well as systemic therapy, are expected following treatment for tumors originating in this area. The current chapter reviews the pathophysiology and clinical manifestations of late effects in the head and neck region, outlines methods for screening and detection and suggests interventions that can be used for their management.

7.2 Pathophysiology

7.2.1 Normal Organ Development

At birth, the skin and mucous membranes, salivary glands, taste buds, bones and connective tissues, deciduous incisor crowns and auditory apparatus are all formed. These tissues of the head and neck region arise in the embryo from branchial arches, beginning
in the fourth week of gestation. Ectoderm, mesoderm and endoderm, along with migrating neural crest cells and myoblasts, give rise to the specialized structural and functional components of this region [42].

Sixty-five percent of the growth of the mandible, maxilla and alveolar ridge takes place from birth to puberty, with remaining growth completed by age 20. During childhood (age 4 through adulthood), mandibular growth is primarily forward, while the maxilla grows vertically. The permanent dentition is developing as well throughout childhood, with the more visible front teeth developing during the preschool years. Dental development may not be completed until 16 years of age [13]. Thus, therapy anytime during childhood can affect dentition. Long-term effects are dependent upon developmental status at the time of chemotherapy and radiotherapy. Manifestation of these effects becomes apparent with expected growth.

### 7.2.2 Organ Damage and Developmental Effects of Cytotoxic Therapy

The head and neck comprise a complex region with multiple tissue types, including mucosa, skin, subcutaneous tissue, salivary gland tissue, teeth, bone and cartilage. Each has a unique response to cytotoxic therapy. In general, two types of effects are seen. Acute effects that occur during or shortly after the course of treatment usually involve tissues that divide rapidly, resulting in erythema and pseudo-membrane vs. ulceration of mucosa, erythema and desquamation of skin, reduced serous output from salivary glands and reduction of taste acuity. Cell populations in “late-reacting” tissues proliferate slowly and may not manifest injury until months to years after treatment. Early changes within these tissues may also occur but are usually not detected by standard methods of observation. Late changes, however, can occur in all organs. Table 7.1 shows some of the more common late toxicities in relation to radiotherapy dose and type of chemotherapy.

#### 7.2.2.1 Skin and Mucous Membranes

Skin and mucosa exhibit early epithelial damage and delayed permanent vascular injury that are dependent on the total radiation dose, the fraction size and the volume of irradiated tissue. Early radiation injury to the skin is directly attributable to the effect of ionizing radiation on the stratum germinativum cells [20]. Release of vasoactive substances results in increased capillary permeability and dilatation that

---

**Table 7.1. Radiotherapy doses and types of chemotherapy attributed to late effects in head and neck region**

<table>
<thead>
<tr>
<th>Late effect</th>
<th>Radiotherapy dose</th>
<th>Type of chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Hypoplasia</td>
<td>RT dose ≥30 Gy</td>
<td>[23, 28, 33, 49]</td>
</tr>
<tr>
<td>Skin Necrosis/Ulceration</td>
<td>RT dose ≥70 Gy</td>
<td>[7]</td>
</tr>
<tr>
<td>Teeth Growth disturbances</td>
<td>RT dose ≥20 Gy</td>
<td>Cyclophosphamide, Vincristine, Vinblastine [18, 30, 33, 35, 36, 44, 47, 54, 57]</td>
</tr>
<tr>
<td>Salivary gland Xerostomia</td>
<td>RT dose ≥30 Gy</td>
<td>[5, 16, 23]</td>
</tr>
<tr>
<td>Ear Sensorineural hearing loss</td>
<td>RT dose ≥40 Gy</td>
<td>Cisplatin (cumulative dose ≥ 360mg/m²)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin [6, 13, 60]</td>
</tr>
</tbody>
</table>
manifest as skin erythema [55]. An increase in melanin-containing cells at 2–3 weeks enhances pigmentation. Moist desquamation that occurs 3–4 weeks from the initiation of treatment has been found to correlate with the development of severe delayed telangiectasias [2].

Late radiation effects are primarily caused by fibrosis and vascular damage, particularly to small vessels. Arterioles become narrow as a result of myointimal proliferation and destruction of capillaries and sinusoids [19]. Delayed histologic manifestations of these changes include fibrin deposition, ulceration and fibrosis. Telangiectasias are caused by endothelial cell depletion and basement membrane damage that causes capillary loops to contract into distorted sinusoidal channels.

Stomatotoxicity resulting from chemotherapeutic agents, such as methotrexate, Adriamycin, 5-fluorouracil, bleomycin and cytosine arabinoside, is not associated with long-term effects. However, when administered in conjunction with radiotherapy, the acute injury may be enhanced, resulting in an increased risk for long-term damage.

7.2.2.2 Bone and Connective Tissue

Irradiation of growing bone causes injury to actively dividing mesenchymal cells, osteoblasts and endothelial cells [20]; it also causes impairment of the osteoid formation. The long-term injury observed in irradiated growth centers includes atrophy, fibrosis of marrow spaces and a lack of osteocytes. Impaired vascularity and fibrosis of both periosteum and endosteum can occur.

The soft tissues may also be affected by radiation. Fibrosis occurs as a consequence of increased fibroblast proliferation, combined with collagen deposition, in children whose craniofacial structures are irradiated [21]. Hypoplasia also occurs. Mucosal atrophy, reduced tissue vascularity and tumor effects predispose to osteoradionecrosis, chondronecrosis and soft tissue necrosis, particularly with high radiation dose/time and large irradiated volume. Interstitial implants and intraoral techniques further enhance the likelihood of such outcomes.

7.2.2.3 Salivary Glands and Taste Buds

The parotid, submandibular and sublingual glands are the major salivary glands. Other (minor) salivary glands are variably distributed throughout the oral cavity and pharynx. In the resting state, saliva production comes primarily from the submandibular gland. With food intake, 60% of the saliva may originate from the parotid gland. The composition of saliva produced is characteristic of the specific gland. Parotid saliva production is primarily serous, while the minor salivary glands secrete a predominantly mucous fluid that is more viscous. The submandibular and sublingual glands produce mixed mucous and serous secretions. Radiation damages the serous cells to a greater extent than it does the mucous cells and epithelium of ducts. Histopathologic changes 10–12 weeks after initiation of RT to doses of 50–70 Gy consist predominantly of serous acini loss, mild fibrosis, dilatation and distortion of ducts and aggregation of lymphocytes and plasma cells [7]. There is little evidence that chemotherapy has a long-term effect on salivary gland function [39].

Modification in taste occurs as a result of changes in oral mucosa and saliva [38]. Patients retain the perception of sweet and salt more readily than that of sour and bitter. Dietary changes thus enhance dental decay in an environment already conducive to caries production [4]. Although the taste buds are considered relatively radioresistant, some taste alterations may be caused by damage to the microvilli.

7.2.2.4 Teeth

RT effects on dentition are influenced by the developmental stage of the tooth, with the most severe disturbances occurring in children younger than six years of age [9, 34, 56]. Prior to morphodifferentiation and calcification, irradiation may result in agenesis. Direct irradiation at a later stage may cause microdontia, enamel hypoplasia, incomplete calcification of enamel and arrested root development. Chemotherapeutic agents, such as cyclophosphamide, vincristine and vinblastine, have also been shown to affect dentition, resulting in hypodontia,
enamel hypoplasia, microdontia and root malformation [1, 11, 18, 30, 33, 35, 36, 44, 47, 54, 57].

7.2.2.5 Ear

Children who present with primary tumors of the head and neck area or brain frequently encounter radiation to the external, internal and middle ear during the course of their treatment [45]. There can be effects on the otic structures, both during the treatment sessions and months to years following therapy. The immediate effect on the ear is desquamation of the columnar epithelium, which lines the ears and covers the ossicles, leading to edema of the mucosa within the ear. Altered production of cerumen, in conjunction with epithelial desquamation, leads to plugging of the ear canals that may persist long after completion of therapy. More chronic effects from fibrosis and scarring can lead to chronic radiation otitis and hearing loss. Hearing loss secondary to radiation therapy is usually permanent and can be sensorineural or conductive, depending on the structures affected by the radiation. Direct effects of radiation on the cartilaginous structures can lead to stenosis or necrosis of the ear canal. Chondronecrosis may occur in the cartilage of the external ear as well.

Cisplatin and carboplatin have sensorineural effects, and these are most prominent in the high frequency ranges (which can be affected significantly by radiation – see Chapter 8).

7.3 Clinical Manifestation of Late Effects

7.3.1 Skin and Mucous Membranes

Mucosal atrophy after conventionally fractionated doses of 60–70 Gy over a period of 6–7 weeks is common, but necrosis, chronic ulceration and bone exposure rarely occur unless the delivery of dose is accelerated or the total dose exceeds 70 Gy in 7 wks [7]. Thrombosis of small blood vessels in the submucosa results in ischemia and the consequent appearance of ulcers and telangiectasias. This condition may become apparent as soon as six months after irradiation or as late as 1–5 years and is irreversible. Scarring and fibrosis of the nasal mucosa can alter sinus drainage and predispose patients to persistent rhinosinusitis. Children may complain of symptoms of chronic sinusitis, which include chronic nasal discharge, postnasal drip, headache and facial pain and headache. Smell acuity is significantly affected by radiation treatment of the olfactory mucosa, and, although this is not usually voiced as a specific complaint, it can contribute to decreased appetite and poor nutrition.

Severe skin reactions, including permanent hyperpigmentation, telangiectasias and skin ulcerations, are rarely seen with the use of modern day megavoltage RT, unless the skin is intentionally treated with a high dose. Doxorubicin and actinomycin can interact with radiation to produce severe skin reactions and may contribute to late skin effects. When these drugs are given early in the course of radiation such reactions may be seen after low doses of 20–30 Gy. If they are delivered after radiation, the phenomena of “radiation recall” may occur, in which skin reactions appear in the treated field [14, 26]. Skin often remains chronically dry due to damage to the sebaceous and eccrine glands. The sebaceous glands are as radiosensitive as the basal epithelial cells of hair follicles; eccrine glands are less sensitive [27]. Epilation within the treatment field usually occurs 2–3 weeks into the course of radiation treatment. The permanency of the epilation depends on the total dose of radiation delivered to the hair follicles, and this, in turn, depends on the treatment technique and beam energy. Single fraction doses of 7–8 Gy or more and total doses (after fractionated therapy) of greater than 40 Gy can result in permanent hair loss. After chemotherapy, hair begins to regrow within 1–2 months. It may be lighter in color and have a finer texture [20]. Microscopic analysis of hair samples of patients receiving chemotherapy has shown trichorrhexis, fragmentation, decrease in diameter and depigmentation of the hair shaft, all of which may account for the changes in color and texture [46].
7.3.2 Bone and Connective Tissue

Clinical manifestations of radiation include hypoplasia, deformities, fracture and necrosis. The craniofacial development of children is affected, resulting in reduced temporomandibular joint mobility, growth retardation and osteoradionecrosis [10]. Impaired growth of the mandible and facial bones can contribute to malocclusion. Chemotherapy may also affect the growing skeleton, although with limited long-term consequences. In the immature rat, the growth plate becomes thicker with methotrexate and thinner with doxorubicin. These agents do not appear to have a major effect on the ultimate height of treated children.

Varying degrees of facial asymmetry, including hemifacial microsomia and other craniofacial abnormalities, may necessitate interventions, including bimaxillary osteotomies and reconstruction with prostheses. The clinical effects of chemotherapy and radiation on dental and craniofacial development will be discussed later in this chapter. Radiation has been associated with malocclusion, reduced mobility of the temporomandibular joint, fibrosis, soft tissue necrosis and osteoradionecrosis. Eventual fibrosis of the temporomandibular joint results in muscle pain and headaches [11]. Tumor invasion of the temporomandibular joint, surgery and the use of large daily fractions further increase the risk of radiation-induced trismus. Combined modality therapy has a greater impact on facial structures when radiation doses are high; children receiving doses of 24 Gy or less to the temporomandibular joint have not demonstrated clinical signs of trismus [37]. The facial skeleton appears to be the most susceptible to high radiation doses before age six and at puberty, which are critical times of skeletal development. In a study of 26 children receiving a mean dose of 54 Gy for either nasopharyngeal cancer or rhabdomyosarcoma, cephalometric measurements utilizing CT showed deviations in the cranial vault, the anterior and mid-interorbital distances and lateral orbital wall length, compared with normal skulls [12]. The age at which RT is given is the most important factor determining orbital growth retardation in retinoblastoma. The orbit has three growth spurts, the first between 0–2 months, the second between 6–8 months and the third during adolescence. Radiation in children younger than 6 months of age is more damaging to orbital growth than at an older age [32]. Maxillary and mandibular hypoplasias are common dentomaxillofacial defects after chemoradiation. Linear cephalometric values suggest that the growth of the mandible may be more affected than that of the maxilla [41].

Rhabdomyosarcoma of the head and neck is a condition in which the long-term side effects of combined modality therapy has been extensively studied. Clinical or radiographic dentofacial abnormalities have been observed in 80% of patients with head and neck rhabdomyosarcoma at a median follow up of 12.2 years [18]. Abnormalities included enamel defects, bony hypoplasia/facial asymmetry, trismus, velopharyngeal incompetence, tooth/root agenesis and disturbance in root development. Bony hypoplasia and disturbance in root formation were the most common findings. The largest report on late effects in pediatric head and neck rhabdomyosarcoma comes from IRS II and IRS III, in which 213 patients were followed for a median length of 7 years. Seventy-seven percent had one or more late sequelae, including poor statural growth, facial and nuchal asymmetry, dental abnormalities and vision/hearing dysfunction [52]. Late side effects in children treated with combined modality therapy for head and neck rhabdomyosarcoma are usually seen within the first 10 years after treatment [49], given that most will have experienced their pubertal growth by that time. Bony hypoplasia of the orbit was noted in 50–60% of patients treated for orbital rhabdomyosarcoma in IRS-I and IRS-III [29, 53]. In both of these studies, orbital bone growth was inversely related to age at irradiation, which is reasonable, given that the growth potential is greater in younger children. The cosmetic effects become more apparent as normal growth proceeds in adjacent unirradiated areas.

In 1983, Guyuron et al. reported on 41 patients who had been treated as children with RT to the head and face. They noted that hypoplastic development of soft tissue and bone was a common finding [28]. Irradiation of the cranial base was often correlated with soft tissue deficits in the upper face and mid
face. Soft tissue was more vulnerable to RT than growing facial bones, with a threshold dose as low as 4 Gy (in contrast to 30 Gy for facial bones). In 1984, Jaffe reported on the maxillofacial abnormalities seen in 45 patients who had been treated as children with megavoltage RT for lymphoma, leukemia, rhabdomyosarcoma and miscellaneous tumors [33]. Forty-three of the 45 patients also received chemotherapy (including vincristine, actinomycin-D, cyclophosphamide, methotrexate, 6-mercaptopurine, prednisone, procarbazine or nitrogen mustard in various combinations). In 82% of the radiated patients, dental and maxillofacial abnormalities were detected, including trismus, abnormal occlusal relationships and facial deformities. The most severe radiation deformities were seen younger patients who received higher radiation doses. Those who received median doses of only 24–30 Gy for leukemia and Hodgkin’s disease did not have facial deformities or temporomandibular joint deficits. In contrast, 50% of the patients with rhabdomyosarcoma who received a median dose of 55 Gy developed trismus, nasal voice, caries and maxillary/mandibular and facial deformities.

In 1986, Fromm evaluated the late effects in 20 patients who, as children, had received radiation therapy and combination chemotherapy with vincristine, dactinomycin and cyclophosphamide (and, in some cases, doxorubicin) for sarcomas of the head and neck [23]. The median follow up was 5.5 years. Age at irradiation was an important factor, as all 16 children younger than 9 years of age developed facial growth abnormalities, while the remaining 4 patients, all of whom were older than 11 years, did not develop deformities. “Mild” deformity was seen in 7 patients, with a median 5.1 yr follow up and a median dose of 40–50 Gy. “Severe” deformities were seen in patients who had received a median dose of 50–60 Gy and were only observed at a median follow up of 8.6 yrs. The length of follow up, as well as total dose received, are important factors in the severity of defects seen in survivors of childhood cancer. Paulino found that 11 of 15 children treated for head and neck rhabdomyosarcoma with RT and chemotherapy developed facial asymmetry in the RT field at doses between 44–60 Gy [49]. Sonis studied 97 patients with acute lymphoblastic leukemia (ALL) who received either chemotherapy alone or with 18–24 Gy cranial RT [56]. The treatment fields routinely included temporomandibular joints, posterior tooth buds and the ramus of the mandible. A significant dose–effect relationship was seen between 18 and 24 Gy (2 Gy/fraction). Children under the age of 5 who received 24 Gy of cranial RT and chemotherapy had a 90% incidence of craniofacial abnormalities, but no craniofacial abnormalities were seen in children over the age of 5 or in those receiving only 18 Gy of cranial RT and chemotherapy. No craniofacial abnormalities were noted after chemotherapy alone. It is unlikely that chemotherapy alone contributes to bony or soft tissue abnormalities, although it clearly does affect dental development in relation to age at treatment [40, 44].

Radiation therapy has an effect on wound healing that may be critical for those who require a surgical procedure in the irradiated region [13]. RT may also affect the connective tissues and bone, leading to fibrosis and osteoradionecrosis. In the Fromm series, two patients developed temporomandibular joint fibrosis with limitation of jaw motion [23]. Osteoradionecrosis has been well described in the adult head and neck literature; however, little has been written on its incidence in the pediatric population. Osteoradionecrosis usually develops in the mandible and its risk is directly correlated with total radiation dose, fractionation dose, tumor size and bony involvement by the tumor. The risk is also increased in dentulous patients and even more so if these patients receive postirradiation extraction, compared with pre-irradiation extraction. Amifostine may confer radioprotection of craniofacial bone growth inhibition. Pretreatment with amifostine, 20 minutes before 35 Gy RT, resulted in significant preservation of linear bone growth, bone volume and bone mineral density in the rabbit orbital-zygomatic complex, compared with controls [22].

7.3.3 Salivary Glands and Taste Buds

Salivary gland dysfunction may occur when one or more of the major salivary glands are irradiated. Permanent damage can lead to xerostomia, predisposing
to dental caries, decay and osteoradionecrosis. Studies of salivary function in children after RT are limited. Fromm found that 8 of 11 parotid glands that had received >45 Gy to greater than 50% of the volume failed to secrete saliva, whereas all parotid glands receiving <40 Gy retained the ability to secrete [23]. More recent studies in adult patients have shown a lower dose–response effect. Chao found that only 25% of the pretreatment stimulated saliva was present when both parotid glands received a mean dose of 32 Gy; salivary flow rate was reduced by approximately 4% per Gy of the mean parotid dose [5]. Eisbruch found no measurable output or recovery over time in parotid glands receiving >26 Gy mean dose [16].

Chemotherapy for children with acute leukemia alters salivary function [39]. Mansson-Rahemtulla and colleagues showed decreased thiocyanate concentration in saliva following cytotoxic chemotherapy, which can lead to an alteration in function of the salivary peroxidase system, as well as increased oral complications. Patients who undergo bone marrow transplantation are also at risk. Xerostomia, as has been noted in patients with chronic graft-versus-host disease, can persist for as long as a year and results in a high risk for developing dental caries [3].

7.3.4 Teeth

Late effects on dentition in children can be attributed directly to the cytotoxic effects on the growing tooth buds and indirectly to salivary gland damage. Salivary gland damage results in a pronounced shift toward highly acidogenic and cariogenic oral microflora, which promotes dental caries [7].

The severity and frequency of long-term dental complications due to RT are related to the type of RT given, the total dose, the size and location of RT fields and the age of the patient. Growing tooth buds may be arrested with <10 Gy, while doses >10 Gy can completely destroy buds [38]. Root shortening, abnormal curvature, dwarfism and hypocalcification are noted with doses of 20–40 Gy [33, 56].

Age at the time chemotherapy is administered influences the degree of dental effects. Disturbances of dental development noted with chemotherapy include V-shaped and blunted roots [56]. The effects are most pronounced in children less than five years of age. All such children have V-shaped roots, compared with 36% of those older than five years. Blunted roots occur in 12% of children less than five years old and in 9% of those older than five years. Jaffe reported that five of 23 children treated with chemotherapy for non-head and neck region tumors had acquired amelogenesis imperfecta, microdontia of bicuspid teeth and thinning of roots with an enlarged pulp chamber; none of the 23 patients developed craniofacial abnormalities [33]. Similarly, Alpaslan found significant differences in plaque index, enamel hypoplasias, discolorations and agenesis in 30 chemotherapy-treated survivors, compared with matched healthy control subjects [1]. Children treated with RT and chemotherapy likewise develop dental complications. Another study showed that all children with head and neck rhabdomyosarcoma receiving RT to developing teeth, the alveolar portion of the mandible or the lingual surface of the maxilla developed dental abnormalities, including microdontia, root stunting and dental caries [49]. Kaste found radiographically identifiable dental abnormalities, including agenesis, microdontia and root stunting in 77% of children with head and neck rhabdomyosarcoma treated with chemotherapy and RT [34].

Information regarding dental outcome after bone marrow transplants (BMT) is limited [8, 30, 58]. Neuroblastoma patients who received 12 Gy fractionated total body irradiation (TBI)-based or non-TBI-based transplants were not different in the incidence of microdontia and missing teeth [30], although TBI was associated with more severe root defects and a higher chance of permanent damage to teeth. The incidence of tooth abnormalities, including agenesis, was 62.9% in another study in which most of the children were treated with a TBI-based BMT regimen [58]. A study that compared mandibular root surfaces according to treatment regimen showed that patients receiving TBI and chemotherapy had a smaller mandibular root surface area, compared with children receiving chemotherapy alone [15].
7.3.5 Ear

RT has long been associated with various forms of ototoxicity. The exact mechanism of radiation-induced ototoxicity is unknown. Some physicians hypothesize that direct damage to the ossicles and tympanic membrane may lead to conductive hearing loss and fibrosis. Direct damage to the cochlea may also be seen. Other physicians believe that late radiation effects to small vessels cause hypoxia to inner ear structures, leading to hearing loss. Damage to the brainstem through radiation may also lead indirectly to hearing loss.

In categorizing deleterious effects of radiation on the ear, three clinical syndromes are found [25, 48]. The first of these is acute radiation oitis. The effects of acute radiation oitis can be seen during or shortly after the completion of radiation. It is associated primarily with erythema of the tympanic membrane and external canal and occasionally with middle ear effusion and tinnitus. Radiation doses equal to or greater than 30 Gy have been implicated. According to some studies, 15–30% of pediatric patients will be affected. Acute radiation oitis is usually self-limiting but in severe cases requires further therapy. The second, and most common, clinical syndrome is that of chronic radiation oitis. Clinically, patients present with dry cerumen, thickened tympanic membrane and, occasionally, slight hearing loss (both conductive and sensorineural). Chronic radiation oitis usually occurs several months after RT has been completed. Radiation doses of 45 to 65 Gy are required, and in some studies this syndrome has been found in up to 70% of patients receiving radiation therapy [48]. The third, and most rarely seen, clinical syndrome is late radiation-associated deafness. This is seen in cases of radiation to the brainstem and ear. Patients experience an irreversible, unilateral, profound hearing loss, which may progress over weeks or months to the contralateral ear. Symptoms tend to occur 3–10 years following RT.

Specific antineoplastic agents have been shown to enhance the ototoxic effects of radiotherapy. In particular, the platinum-based agents, cisplatin and carboplatin, have well-documented effects on hearing, and radiation has been shown to be synergistic in terms of ototoxicity. Children with primary brain tumors, osteosarcoma, germ cell tumors and neuroblastoma are most at risk for this added ototoxicity, because they are more likely to receive platinum-based chemotherapy and may require RT as well. The exact mechanisms of ototoxicity related to chemotherapy are not known, but they seem to affect the cochlea, specifically the outer hair cells in the organ of Corti. Cisplatin ototoxicity has been reported in 9–91% of patients, depending on the dose, duration and circumstances surrounding its use. The initial effects are on high frequency hearing (above 8000 Hz), but lower frequencies can also be affected at higher doses. In one study, 14 of 25 children who received a cumulative cisplatin dose of 474 mg/m² developed hearing loss in the 250–2000 Hz range, while only four of 29 children had hearing loss in the same range with a cumulative dose of 410 mg/m² [6]. Hearing loss with cisplatin is irreversible and symmetric bilaterally. Cohen et al. have shown that the threshold for high-frequency hearing loss in patients receiving cisplatin is lower than for patients who have brain tumors treated with RT [6]. Information regarding the effects of timing the treatment with platinum-based chemotherapy and RT on patients has not been well characterized. Walker hypothesized that RT given concurrently with or prior to cisplatin administration was associated with a worsening of hearing [60].

More recent advances in RT may lead to fewer ear-related, radiation-induced effects. Intensity-modulated radiation therapy (IMRT) and 3D Conformal Radiotherapy (3D CRT) have been associated with reduced ototoxicity in pediatric patients receiving RT and cisplatin for the treatment of medulloblastoma [31]. Due to the precise delivery of RT with the conformal techniques, patients can receive full doses to the target volume while receiving lower doses to the auditory structures [24, 50].

7.4 Detection and Screening

The successful evaluation, diagnosis and management of late effects require a multidisciplinary approach. All children with head and neck cancers need prolonged follow up by a pediatric oncologist and
radiation oncologist. They must also have access to specialists in endocrinology, ophthalmology, otolaryngology and dentistry. In addition, psychological counseling should be available, as some of these children have suffered trauma secondary to cosmetic changes from tumor and/or treatment. Abnormalities in any of the head and neck or dental structures should be noted at diagnosis and prior to treatment. Children with head and neck cancers should receive an annual assessment of growth, pubertal status and growth function, as well as frequent ophthalmologic and dental exams.

The initial dental exam for children who have received chemotherapy and RT should consist of a full mouth series of radiographs, including periapical, bitewing and panoramic views of the teeth. Asymptomatic patients are often found on radiographic exam to have dental disease. Horizontal and vertical alveolar bone loss, retained root tips, deep caries and periapical pathoses can usually be visualized only on intraoral radiographs [51]. It is critical to assess crown and root development, as abnormalities can predispose a tooth to premature loss. Changes in root development are critically important to recognize, as they may affect decisions regarding the removal of permanent teeth. To assess abnormal tooth and root development, it is recommended that patients receive a dental exam every six months, with special attention to early caries, periodontal disease and gingivitis. Careful evaluation of root and crown status is required before tooth extraction, endodontic and orthodontic procedures. With time, the risk of periodontal bone loss increases; it is, therefore, critical that proper periodontal prophylaxis be offered to patients, including professional cleaning and meticulous oral hygiene. When areas of the periodontium exposed to radiation are treated, or in cases where the risk of infection is increased with trauma, antibiotics may be given.

Radiation-induced changes in salivary pH and quantity produce an environment conducive to the development of caries. Xerostomia and a high carbohydrate diet can predispose the pediatric cancer patient to radiation-induced caries. Frequent dental visits to identify early caries, periodontal disease, infection, gingival recession and soft tissue ulcers are important. Salivary flow studies are helpful in assessing xerostomia, and salivary substitutes may be offered to symptomatic patients. Nutritional counseling on the importance of avoiding fermentable carbohydrates and maintaining excellent oral hygiene is critical. Mouth rinsing is essential and daily topical fluoride applications (either as a solution for mouth rinsing, a gel delivered on a tray or brushed on as a paste or gel) are all effective in reducing the risk of radiation caries [17].

In children who have received high doses of radiation to the developing facial bones and soft tissues, the use of screening to identify craniofacial abnormalities and problems with jaw movement is important for early detection and management. Trismus, crepitus, limited mandibular movement and abnormal growth associated with the temporomandibular joint may be present [37].

Routine ear, nose and throat evaluation, including inspection of the oral mucosa for ulcers, indirect and direct laryngoscopy and nasopharyngoscopy may be included in the screening process to ensure a thorough assessment of the mucosa. It is important to look for nasal scarring, as this may interfere with the normal movement of mucus and sinus drainage, leading to recurrent sinusitis. The soft tissue of the head and neck should be evaluated for muscle hypoplasia, fibrosis and ulceration. Irradiated skin often has impaired vascularity and the resultant “thin skin” is highly susceptible to minor trauma.

Both an otoscopic exam and inspection of the auricle are necessary to rule out the presence of otitis externa and chondronecrosis, respectively. Detailed inspection of the ear canal can detect cerumen impaction and tympanic scarring, both of which can lead to conductive hearing loss. In addition, the patient should be evaluated for the possible presence of otitis media or tympanic membrane perforation. In children receiving cisplatin or high-dose radiation to the inner ear, pure tone audiometry should be done at baseline and every 2–3 years to evaluate for sensorineural hearing loss [43]. Finally, the physician following a child cured from cancer should always be aware of the possibility of secondary malignancies, particularly in irradiated fields.
7.5 Management of Established Problems and Rehabilitation

7.5.1 Oral Cavity

One of the best ways to manage late effects of the teeth is preventative care. Ideally, all patients should undergo a dental evaluation and treatment of any existing dental problems prior to undergoing treatment for their cancer. Patients who are younger at diagnosis and who have received higher radiation doses will require more watchful attention for future problems. Patients should have dental exams and cleanings every six months, and these should include fluoride applications [17]. For those who develop malocclusion or other structural abnormalities, consultation with an orthodontist who has experience in the management of childhood cancer survivors who have undergone irradiation is preferred. All patients should have at least a baseline Panorex examination prior to dental procedures to evaluate their root development, since root thinning and shortening occur fairly frequently. Symptomatic treatment of temporo-mandibular joint dysfunction may be required and involve exercises and pain control.

When major periodontal disease is present, care should be taken to minimize trauma to the oral cavity. Prophylactic antibiotics may be required prior to specific dental procedures in patients who have received high doses of radiotherapy to the extraction or procedure site. Oral infections that occur after procedures should be aggressively treated with antibiotics. Care should be taken to avoid tight sutures and trauma during use of orthodontics.

Patients should be evaluated yearly for xerostomia. Symptomatic care with saliva substitutes, moistening agents and sialogogues such as pilocarpine may be required. Fungal infections are more likely to occur in patients with xerostomia, so special care should be taken to treat with appropriate antifungal medications, either topically or systemically.

7.5.2 Bone and Connective Tissue Disease

Many bone and connective tissue late effects may require extensive surgical correction, often staged procedures, spanning many months to years. A craniofacial team, consisting of a head and neck plastic surgeon and neurosurgeon may be necessary in restoring function and cosmesis to an affected child.

Patients who have experienced radiation to the region requiring operation will also experience poor wound healing and increased susceptibility to infection. Patients who develop infections of the soft tissue regions will require not only aggressive antibiotic therapy, but also possible surgical debridement and supportive care of pain and swelling. Soft tissue and bone necrosis can be devastating to the patient, both physically and psychologically, so measures should be taken to prevent trauma to areas affected by radiation.

Chronic sinusitis is more likely to occur in patients who have a history of atopy or hypogammaglobulinemia. Aggressive management of sinus infections with the guidance of ENT specialists is required. Patients should have their sinuses evaluated at least yearly by history and physical exam, and CT of the sinuses should be obtained as clinically indicated.

7.5.3 Ears

Younger patients and those who have received higher radiation doses are more likely to experience sclerotic side effects and eustachian tube dysfunction. They are also at greater risk for developing sensorineural hearing loss. Patients should have audiograms or brainstem auditory evoked response (BAER) tests performed yearly, or as clinically indicated. Speech and language evaluations should be performed at the end of treatment and as needed for clinical concerns. Those children with hearing loss will require routine speech and language therapies. Special educational interventions may be required as well, including alternative learning methods, individualized education plans (IEP) and preferential seating in the classroom. Table 7.2 lists various amplification and assisted living devices currently available. The use of a hearing aid can help amplify any residual hearing. Personal
devices, such as FM trainers, can aid in reducing the signal-to-noise ratio in various listening situations, e.g., in the classroom, where, at times, there may be significant background noise.

For those suffering with chronic otitis, ENT referral is indicated. Treatment usually includes antibiotic therapy, myringotomy and/or the placement of pressure-equalizing tubes. Chronic cerumen and obstruction of the ear canal will require routine cleaning and the use of agents to soften the cerumen. Some patients may require treatment for otitis externa with the use of topical otic drops. These patients should avoid submersion in water without protective earplugs.

References


Table 7.2. Amplification and assisted listening devices for children with hearing loss

<table>
<thead>
<tr>
<th>Amplification</th>
<th>Assisted listening devices and personal systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional analog hearing aid</td>
<td>FM trainers</td>
</tr>
<tr>
<td>Digital hearing aid</td>
<td>Telephone devices with volume controls</td>
</tr>
<tr>
<td>Bone conduction hearing aid</td>
<td>and couplers for hearing aids</td>
</tr>
<tr>
<td>Bone-anchored hearing aid</td>
<td>Closed captioning television</td>
</tr>
<tr>
<td></td>
<td>Signaling devices</td>
</tr>
</tbody>
</table>

Chapter 7
25. Goldwein JW et al. Late radiation-associated deafness in children treated for medulloblastoma and brainstem tumors, a newly recognized sequela of radiation treatment. Oncolink website, University of Pennsylvania
60. Walker DA et al. (1989) Enhanced cis-platinum ototoxicity in children with brain tumors who have received simultaneous or prior cranial radiation. Med Pediatr Oncol 17:48–52