Journal of
Nuclear Medicine & Radiation Therapy

Bhandare and Mendenhall, J Nucl Med Radiat Ther 2012, S:2
DOI: 10.4172/2155-9619.S2-009

Review Article Open Access

A Literature Review of Late Complications of Radiation Therapy for Head and Neck Cancers: Incidence and Dose Response

Niranjan Bhandare* and William M Mendenhall

Department of Radiation Oncology, University of Florida, Gainesville, USA

Abstract

Depending on the time of its occurrence, toxicity from cancer therapy is classified as acute or delayed. Acute toxicity develops during or shortly after completion of treatment. It is often temporary and usually can be managed by conservative means. Delayed toxicity occurs months or years after treatment and is often permanent. The underlying processes of many delayed toxicities are not well understood, thus limiting the scope for their treatment and management. Delayed toxicities may exhibit severe manifestations that can affect a patient's quality of life significantly. This report reviews some late complications of head and neck after radiation therapy and relevant dose-response information.

Keywords: Xerostomia dental issues; Osteoradionecrosis; Soft tissue fibrosis; Carotid artery injury; Trismus; Dysphagia; Esophageal toxicity; Dysphonia; Myelitis; Dry-eye syndrome; Pituitary-hypothalamic dysfunction; Thyroid disease; Damage to vision apparatus; Ototoxicity

Introduction

Depending on the stage and extent of the disease, when treating head and neck cancer, radiation therapy (RT) can be used either as the primary treatment modality in combination with chemotherapy, as adjuvant therapy following surgical resection, or for palliation. Regardless of the clinical intent, RT produces tissue changes that may profoundly affect patients' quality of life later. Toxicities from radiation therapy (RT) for head and neck cancers are classified as early (acute) or late (delayed) effects based on the time course of their development relative to the RT. Early effects develop during the course of RT or shortly after completing RT (about 2-3 weeks) and usually subside thereafter. Late effects manifest months to years after completing RT.

Although organ sparing is an important consideration when selecting surgical methods, treatment techniques, and fractionation schedules for the treatment of head and neck cancers, anatomical preservation of organs does not necessarily translate into functional preservation. Preservation of function depends on multiple factors, including radiation dose and fractionation, which play a major role in the occurrence of radiation morbidities.

Late side effects of RT for head and neck cancers include xerostomia, osteoradionecrosis, soft tissue fibrosis, carotid artery injury, trismus, dysphagia, esophageal toxicity, myelitis, pituitary-hypothalamic dysfunction, thyroid disease, ocular toxicity and ototoxicity. This article presents a short review of delayed complications after RT for head and neck cancers.

Xerostomia

Parotid gland

Parotid glands produce 60% to 70% of the total stimulated salivary output along with other glands. Submandibular, sublingual, and other small salivary glands contribute primarily to unstimulated (resting) salivary production [1]. Radiation damage to the parotid, submandibular, and minor salivary glands can lead to xerostomia. Serous parotid glands are suggested to be more susceptible to radiation damage than nonserous submandibular, sublingual, and minor salivary tissue. Salivary tissue effects include loss of acinar-cells; alterations in duct epithelium, fibrosis, and fatty degeneration [2]. Compromise in salivary function can be seen 1 to 2 weeks into the course of RT and may persist thereafter. Unless the damage is severe, salivary function often recovers within 2 years after RT [3,4] and may even over shoot (recovery>100%). While post-RT xerostomia may improve with time, it is still the most common delayed complication of radiation therapy and chemotherapy for head and neck cancers. Xerostomia can have a negative effect on quality of life by greatly impairing a patient's ability to speak, chew, swallow, and taste.

The magnitude of dysfunction is related to dose and the volume of salivary tissue irradiated. Minimal gland dysfunction can be observed at mean doses of 10 to 15 Gy and mean doses >40 Gy to the parotid can result in a 75% reduction in function [3,5]. One imaging study observed a decline in salivary function at even lower doses [6]. Reduction in saliva production was observed to occur in a more or less linear fashion with dose. A linear correlation with 5% loss of function per 1 Gy of mean dose to the parotid with no threshold has been reported. The TD 50/5 for the parotid (that is, the uniform dose resulting in a 50% complication probability at 5 years) was 38 to 46 Gy, with gradual improvement in parotid flow after radiotherapy [7]. The dysfunction is considered to be irreversible at doses >54 Gy [2].

It is suggested that sparing of at least one parotid gland or a submandibular gland may reduce the risk of xerostomia [8]. When the mean dose of at least one parotid gland was kept ≤ 26 Gy, the incidence of xerostomia was significantly reduced and could return back to pretreatment levels when the mean dose was <25 to 30 Gy [3,9]. Patients receiving <30 Gy to the contralateral parotid experienced no xerostomia or mild subjective xerostomia [10]. A complete recovery of salivary production is suggested to be possible when the volume of the

***Corresponding author:** Niranjan Bhandare, Department of Radiation Oncology, University of Florida Health Science Center, 2000 SW Archer Road, P.O. Box 100385, Gainesville, FL 32610-0385, USA, Tel: 352-265-0287; Fax: 352-265-0759; E-mail: bhandn@shands.ufl.edu

Received July 14, 2012; **Accepted** August 25, 2012; **Published** August 31, 2012

Citation: Bhandare N, Mendenhall WM (2012) A Literature Review of Late Complications of Radiation Therapy for Head and Neck Cancers: Incidence and Dose Response. J Nucl Med Radiat Ther S2:009. doi:10.4172/2155-9619.S2-009

contralateral parotid receiving a mean dose >40 Gy is 33% [11]. A recent review of literature suggests limiting the mean dose to one parotid to 20 Gy or that of both glands to 25 Gy to avoid severe xerostomia (long-term salivary function of <25% of baseline) [12].

Submandibular gland

Doses to both the parotid and submandibular glands were significant on multivariate analysis for patient-reported xerostomia [8]. Both stimulated and unstimulated salivary flow rates were observed to decrease exponentially with dose to the submandibular glands [13]. Dose modeling for the submandibular gland suggested that the submandibular gland may be more radioresistant than the parotid. Both stimulated and unstimulated flow rates were observed to recover 2 years after RT when the mean dose was ≤ 39 Gy [13].

Osteoradionecrosis

Osteoradionecrosis (ORN) is defined as the exposition of devitalized bone in a previously irradiated area, without histological evidence of tumor recurrence, occurring within 3 to 6 months after RT. Vascular obliteration from RT and reduced vascular supply leads to hypovascular areas with associated tissue hypoxia and subsequently ORN. Although it is usually diagnosed within months of RT, it may be diagnosed years after RT in some patients [14]. It may manifest as a small, asymptomatic bone exposure that remains for months to years and heals with conservative management, or it may gradually progress, leading to fistulas and infections with severe necrosis requiring surgical intervention and reconstruction [15,16].

The incidence of mandibular ORN in head and neck cancer patients managed with radical or postoperative irradiation has varied widely in the literature, ranging from 0.4% to 56% [17]. Suggested approximate overall lifelong risk of ORN for patients who have undergone high-dose RT for head and neck tumors is 15% [2]. A systematic review of 43 articles published between 1990 and 2008 reported a weighted prevalence of ORN by type of RT treatment as follows: conventional radiotherapy, 7.4%; intensity-modulated radiotherapy (IMRT), 5.1%; chemoradiation (CRT), 6.8%; and brachytherapy, 5.3% [2,15]. The risk factors for ORN include primary site, T stage, proximity of tumor to bone, poor dentition, type of treatment (i.e., external-beam RT, brachytherapy, surgery, and chemotherapy), RT dose, and acute and chronic injury or trauma (i.e., surgery, dental extractions, infection) to the mandible or maxilla.

The mandible is the most common site of ORN, partly due to its vicinity to tumors of the oral cavity and oropharynx and partly because the blood supply may be less abundant relative to the maxilla [16]. One study reported an 85% incidence of ORN in dentulous patients and 50% of adentulous patients at doses >75 Gy and none for <65 Gy [18]. Another study reported that only 6.6% of patients with ORN at doses <65 Gy underwent resection, while the rest were manageable by conservative means, and they reported an incidence around 40% for doses >65 Gy that required resection [19]. ORN is essentially reported to occur at cumulative doses ≥ 66 Gy on the mandible (standard fractionation) applied to a significant volume [20]. Mandibular ORN is almost never seen below 60 Gy with conventional fractionated RT [21]. Maxillary osteonecrosis is rare and usually seen in cases of nasopharyngeal cancer [5]. RT doses >70 Gy were found to be significant for maxillary ORN [5].

Radiation Fibrosis

Radiation fibrosis (RF) describes the insidious pathologic fibrotic tissue sclerosis that often occurs in response to radiation exposure. The term radiation fibrosis syndrome (RFS) describes the myriad clinical manifestations of progressive fibrotic tissue sclerosis that result from radiation treatment [22]. The development of radiation-induced fibrosis is influenced by multiple factors, including the radiation dose and volume, fractionation schedule, previous or concurrent treatments, genetic susceptibility, and co-morbidities such as diabetes mellitus. Contrary to the original assumption that radiation-induced fibrosis is a slow, irreversible process; contemporary studies suggest that it is not necessarily a fixed process [23]. Depending on the tissue, fibrosis is generally associated with total radiation doses of >40 Gy in both connective and vascular tissues and with total radiation doses of 60 Gy or higher [23]. RT-induced fibrosis may result in muscle stiffening, immobility, pain, and, in severe cases, flexion contractures. Trismus is a frequent late morbidity in head-and-neck patients that is caused by inflammation and fibrosis of muscles of mastication [24].

Trismus

Trismus is defined as a tonic contraction of the muscles of mastication and results in restricted mouth opening [25]. It is attributed to a combination of fibrosis of the muscles of mastication, spasm, and contraction of muscles responsible for the movement of the temporomandibular joint [26]. The precise mechanism that leads to trismus is unknown, but exposure of the temporomandibular joint (TMJ), pterygoid muscle, and massater muscle to high-dose radiation is suggested [27]. Fibrosis of the pterygoid (medial, lateral), temporalis, and masseter muscles gradually leads to trismus [28].

While the commonly used functional definition of reduced mouth opening is an interincisor distance of ≤ 35 mm, a 20 mm to 40 mm interincisor distance is suggested as indicative of trismus [25]. A severe limitation is defined as distances of 18 to 20 mm [24,29]. Severity of trismus is associated with configuration of fields, radiation source, and radiation dose [30].

The reported incidence of post-RT trismus varies significantly from 6% to 86% of patients receiving radiation to the temporomandibular joint (TMJ) and masseter/pterygoidmuscle, or both, with variable severity [26,31]. A lower incidence of approximately 5% has been observed with newer techniques using IMRT (Itensity Modulated Radiation Therapy) that minimize the dose to the TMJ and muscles of mastication [32]. A systematic review of the literature on post-RT trismus found a mean incidence of 25% in patients treated with conventional RT and 30.7% for patients treated with RT and chemotherapy [26].

A steep dose-effect relationship between mean dose to the masseter and pterygoid muscles and the probability of trismus has been observed. In one study, a 47% incidence of trismus in cancer patients following >55 Gy to the masseter, pterygoid muscles, or both was observed [33]. Another study reported a 24% increase in the probability of trismus for every 10 Gy in the pterygoid muscle after a dose of 40 Gy [34]. A limiting dose of 50 Gy to the TMJ is suggested to prevent trismus [32].

Late Esophageal Toxicity: Stricture and Dysphagia

Dysphagia is the inability to swallow safely or efficiently. Severe dysphagia necessitates an indwelling gastrostomy tube (GT), which may cause infection and weight loss. Patients may suffer sensory loss in the laryngeal and pharyngeal structures, leading to absence or reduction in the cough reflex, subjecting patients to a high risk of silent aspiration.

Dysphagia after CRT may be related to a number of issues including

mucositis and severe dysfunction of the base of tongue, larynx, and pharyngeal muscles [35,36]. CRT results in an increased severity of side effects compared with RT alone [37]. There is an approximately 12% to 21% incidence of symptomatic strictures [37,38] and 50% to 64% incidence of dysphagia after CRT in patients with oral, pharyngeal, and laryngeal squamous cell carcinoma [38,39].

Formation of fibrosis is considered the primary source of post-RT dysphagia [40]. The National Institute of Health (NIH) Laryngeal Study Section presented preliminary data that has allowed for an improved understanding of the neuromuscular etiology of chronic dysphagia after CRT [41,42]. The formation of strictures after CRT has also been linked to the development of dysphagia [37]. The suggested structures for predicting complications related to swallowing include superior, middle, and inferior pharyngeal constrictor muscles, the cricopharyngeous muscle, 1 cm of the muscular compartment of the esophageal inlet [43], and the glottis and supraglottic larynx [44].

In one prospective study, the mean dose to pharyngeal constrictors and the partial organ dose for both the constrictors and larynx correlated significantly with the occurrence of aspiration [44]. The volume of larynx and inferior constrictor receiving ≥ 50 Gy were statistically associated with aspiration and stricture, and the mean larynx dose was statistically associated with aspiration [45]. Dose to the superior constrictor has also been found to be strongly significant [45,46]. A dose-volume analysis presented dose-volume parameters for the inferior pharyngeal constrictor (IPC) and cricoid pharyngeal inlet (CPI) that would decrease the risk of dysphagia and gastrotomy tube as follows: IPC V65<15%, IPC V60<40%, IPV mean<55 Gy, and CPI D_{max}<60 Gy [47]. In another study, the probability of a swallowing disorder increased 19% per 10 Gy after 55 Gy to the superior constrictor muscle. With a mean dose of 51 Gy, 48 Gy, and 32 Gy to the superior, middle, and inferior constrictor muscles, respectively, an overall probability of incidences of 2%, 10%, 20% and 50% were estimated at 22 Gy, 44 Gy, 55 Gy, and 74 Gy to the superior constrictor muscle using a logistic model. Brachytherapy (20 to 22 Gy) to the primary site (base of tongue) was significant on multivariate analysis [43]. An increased incidence of dysphagia [37,48] and aspiration [44] (after CRT has been observed). A relationship between xerostomia and dysphagia is suggested [48], and a mean radiation dose to the parotid gland of approximately 26 Gy or less should be the goal to reduce the risk of both toxicities [49].

Arterial Injury

Carotid artery and delayed cerebrovascular consequences

Carotid atherosclerosis usually remains undetected until symptoms associated with arterial stenosis or occlusion occurs. In a dataset of 910 patients subjected to between 40 and 50 Gy of cervical irradiation, the incidence of stroke was 6.3%, abnormal phonoangiograms (an average of 5 years after neck irradiation) was 25%, and abnormal oculoplethysmogram was 17% [50]. The mean dose for patients with abnormal carotid phonoangiography was 39.4 Gy. This study did not specify the estimated dose to parts of the carotid in the field. In another series, 30% of patients who received ≥ 50 Gy had moderate to severe carotid disease when examined by duplex scanning 28 months after RT, which was 5-fold higher than the unirradiated group [51]. The severity of disease did not seem to correlate with the radiation dosage [52,53]. The time interval between RT and manifestations of symptoms of cerebral vascular insufficiency shows significant variation between 1-34 years [54,55].

Carotid artery blowout (CB) is a rare but serious complication of salvage reirradiation [56] and postoperative catastrophe in the irradiated neck, especially with trifurcate incision [50]. Predisposing factors include surgery, diabetes mellitus, and prolonged corticosteroid use.

Pituitary-Hypothalamic Dysfunction

High doses of definitive external-beam RT to the hypothalamic pituitary axis (HPA) during the treatment of pituitary tumors [57], nasopharyngeal malignancies [58,59] and primary brain tumors [60] may lead to hypopituitarism. Hypopituitarism has also been observed after prophylactic cranial irradiation for acute lymphoblastic leukemia [61] and following total body irradiation (TBI) [62]. Both the pituitary and hypothalamus may be affected by radiation leading to hypopituitarism [63,64]. Development of RT-induced hypopituitarism is insidious and its effects are diverse and complex because of a wide variety of combined hormonal deficiencies that may occur.

The extent and time of onset of HPA dysfunction after fractionated RT depends upon total dose, fractionation, CRT, and volume of HPA subjected to radiation [57,65]. The onset of biochemical hormonal deficiency has been reported as early as 1 month to 1 year after RT [66]. Lam et al. [58] have reported on the overt expression of hypopituitarism 2 to 5 years after RT with a median latent interval of 3.8 years. Low doses around 20 Gy can cause growth hormone (GH) deficiency. Higher doses of 30 to 50 Gy will lead to deficiencies in thyroid-stimulating hormone, adrenocorticotropic hormone, and gonadotropin. Deficiency of one or more hormones with rapid onset of symptoms usually occurs with higher doses or larger radiation fraction sizes [57]. However, another study reported a lower incidence of anterior pituitary deficiencies with large doses (>45 Gy) [67]. Surgical manipulation prior to RT may influence the risk of HPA deficit [57]. Risk factors for HPA dysfunction include concomitant irradiation of the hypothalamus [68], higher dose [68,69], and larger baseline tumor volume in cases of nonfunctioning adenomas [70].

HPA dysfunction is believed to be more likely in the pediatric patient population than in adults [71,72]. A decrease in GH response to growth-hormone-releasing hormone (GHRH) was observed in pediatric patients who received total body irradiation (TBI) to12 Gy in 5 fractions. TBI represents a unique setting in which both the central (HPA) and peripheral (endocrine) glands are exposed to radiation. A direct effect of radiation to the endocrine organs was suggested to be the primary contributing factor to endocrine dysfunction [73]. A GH deficiency and reduction in height was reported in pediatric patients who received 12 Gy in 6 fractions [74], yet another study did not find any primary deficit 2 to 11 years after irradiation [75].

Thyroid Dysfunction

Thyroid dysfunction can result from direct radiation damage to the thyroid, known as primary hypothyroidism (PH), or direct functional damage to the HPA, known as central hypothyroidism (CH) subsequent to hypopituitarism. PH is the most common delayed morbidity in patients undergoing cervical neck node RT to doses of 30 to 70 Gy [76]. The reported incidence of PH varies significantly from 3% [77] to 47% [78], although most investigators report an incidence of 20% to 30% [76]. The occurrence of PH also varies, with some studies reporting clinical hypothyroidism while others report chemical hypothyroidism or subclinical hypothyroidism without manifestations of clinical/overt hypothyroidism.

Although PH can develop after doses as low as 20 Gy, the incidence

of HP after 30 to 45 Gy to the thyroid is more commonly documented [79-81]. The association between the total dose to the thyroid and an increased risk of PH is reported in some studies [82-84] and disputed in others [85]. The percentage of volume receiving >30 Gy (v30) is suggested as a possible predictor of PH [86].

Ocular Toxicity

Delayed radiation-induced damage to components of the visual system results in morbidities varying in severity and latency. Most common delayed morbidities of the ocular system include cataracts, chronic dry eye syndrome, retinopathy, and optic neuropathy. Iris neo vascularization, secondary glaucoma, strabismus, scleral atrophy, scleral necrosis, choroidal neo vascularization, and, less commonly, globe perforation, have also been observed [87-89].

Radiation-induced cataracts are often described as posterior sub capsular cataracts (PSCs). Irradiation of mitotically active cells in the germinative zone leads to cell death, compensatory mitosis, and differentiation into fiber cells resulting in defective lens-fiber formation, and migration to the posterior pole [90]. The severity of cataract formation is related to total dose and fractionation [91]. Cataract formation usually occurs within 2 to 3 years (range, 6-64 months) [92]. A threshold for detectable opacity has been suggested to be 2 Gy in a single exposure [93]. In one study, the adult lens was observed to tolerate a total dose of 5 Gy after fractionated RT [94], while another study reported that radiation-induced cataracts generally occur at doses >8 Gy to 10 Gy [95].

Dry eye refers to a conglomerate of chronic symptoms resulting from the effects of radiation on the conjuctival epithelium, goblet cells, corneal surface, and lacrimal glands. Changes in quality and quantity of tear production lead to impairment of the dynamic stability of the tear film resulting in chronic dry eye [96]. For doses >45 Gy, symptoms of dry eye developed within 1 month after radiation, and corneal opacification and vascularization were observed in 9 to 10 months [96]. Another study reported on the median time to manifestation of corneal injury to be 9 months (range, 1-31 months) [97]. A 58% incidence of keratitis for doses ≤ 40 Gy and a 30% incidence of dry eye for doses >40 Gy were reported in one study [97]. Parsons et al. [96] observed a 19% incidence for doses ≤ 45 Gy and 100% for doses >57 Gy. For doses between 30 and 39 Gy, Bessell et al. [98] noted a 4.5% incidence of dry eye, increasing to 23% for doses ranging from 40 to 49 Gy.

Non proliferative retinopathy (NPR) is the early form of radiation-induced retinopathy (RIRN) and involves capillary and arterial damage that may lead to capillary closure, retinal ischemia, necrosis of nerve tissue, and fibrovascular proliferation [92,99,100]. Capillary closure may lead to severe capillary non perfusion and ischemia resulting in neovascularization in the retina, often referred to as "proliferation radiation retinopathy" (PRR) [100,101]. With a median of 1.5 to 2 years, the latency for clinical manifestations of RIRN varies from 7 months to 8.5 years [102,103]. For patients receiving doses between 45 to 55 Gy to half or more of the retina, Parsons et al. [96] were reported an incidence of 53%; excluding patients with diabetes mellitus, chemotherapy, and high dose-per-fractions, it was 22%. The upper limit of a safe dose was suggested to be 35 Gy in one early study [104], but cases of retinopathy have been reported after doses as low as 20 Gy [105-107] and have been associated with intensive chemotherapy in conjunction with RT, diabetes mellitus, and Grave's disease. The incidence of RIRN increases with the total dose received by the retina and increased fraction sizes above the standard fraction size of 1.8 to 2.0 Gy [102]. Hyper fractionation was associated with a lower incidence of RIRN [102].

The effect of radiation on the optic nerve is not fully understood. Vascular, cytopathic chromosomal, and auto allergic factors have been considered [108-111]. The reported incidence of radiation-induced optic neuropathy (RION) after fractionated RT was 10.6% by Parsons et al. [89] and 8.8 % by Bhandare et al. [112]. With a median latency of 28 to 30 months, the latency of RION shows significant variation (from 7 months to 14 years) [89,97, 112]. The incidence of RION increases with an increase in the total dose to the optic nerve >55 Gy using conventional fractionation [89,97,112], although optic chiasmal injury at 50 Gy has been observed [97]. Fraction sizes exceeding the standard fraction size of 1.8 to 2.0 Gy have been associated with the incidence of RION [89, 112]. A possible benefit of hyper fractionation for reducing the incidence of RION has been suggested [112].

Ototoxicity

RT-associated delayed morbidities in the auditory system can affect the external ear (i.e., necrosis of pinna, chronic otitis externa, external auditory canal stenosis, osteonecrosis of the external auditory canal), the tympanic membrane (thickening of the tympanic membrane and sclerosis), the middle ear (i.e., Eustachian tube dysfunction, chronic otitis media with effusion, conductive hearing loss, fibrosis of the middle ear, ossicular atrophy), and the internal ear (i.e., labyrinthitis, canal paresis, vertigo balance problems, sensorineural hearing loss (SNHL)).

Early studies exhibited a tolerance dose for chronic external otitis between 65 and 70 Gy [113,114] with another study showing a 5% increased risk for each 5 Gy increase with doses > 50 Gy to the external ear. An association between dose and incidence of chronic external otitis, atrophy, and canal stenosis was reported above 55 Gy to the external ear [115].

The incidence of tympanic membrane perforation and otitis media with effusion (OME) increased above doses of 50 Gy to the middle ear [115]. Radiation dose has been associated with deterioration of the passive opening function of the Eustachian tube. A dose to the isthmus of the Eustachian tube below 52 Gy and a dose to the middle ear cavity below 46 Gy are reported to decrease the incidence of OME [116]. Another study reported deceased OME with a dose to the middle ear cavity and isthmus of the Eustachian tube below 47 Gy [23]. The reported incidence of sensory-neural hearing loss varies significantly from 0% to 54% [27,117-119].

High-frequency (≥ 4 KHz) hearing loss is more prevalent than low-frequency hearing loss (0.5-3 KHz) [118,120]. Sensory-neural hearing loss has been reported to occur after a total dose as low as 30 Gy [121]. Several studies have reported a total dose to the inner ear above which incidences of SNHL increased. These include 40 Gy (at 2 Gy per fraction) [120], 45 Gy (fractionation unspecified) [122], a mean cochlear dose of 48 Gy delivered by either conventional RT or IMRT followed by a twice-daily boost [123], and 50 Gy delivered at 1.8 to 3.0 Gy per fraction [124].

Nervous System

Brain

Temporal lobe necrosis (TLN) can be a serious and potentially life-threatening late RT complication in nasopharyngeal cancer patients [125,126]. Patients with stage III or IV disease often present with extensive base of the skull invasion or cavernous sinus involvement. A definitive radiation dose between 66 and 70 Gy given to the gross tumor volume and 54 to 60 Gy to the clinical target volume often exposes

parts of the temporal lobes to doses over 60 Gy, thereby increasing the risk of TLN.

The reported incidence of TLN ranges from 1% and 6% at 10 years after conventional fractionation and can be 35% in 3.5 years after accelerated fractionation to 71.2 Gy [126-131]. Although relatively rare, radiation-induced TLN is reported to be responsible for 65% of radiation-related deaths in patients with nasopharyngeal carcinoma [55,132].

The development of radiation-induced TLN is associated with total radiation dose, fractionation schedule, and possibly the administration of chemotherapy [133]. Different fractionation schemes were compared using a biologically effective dose (BED) with an α/β ratio of 3[134]. With standard fractionation, side-effect incidences of 5% and 10% occur at BEDs of 120 Gy (range, 100-120 Gy) and 150 Gy (range,140-170 Gy), respectively (corresponding to 72 Gy (range 60-84) and 90 Gy (range 84-102) in 2 Gy fractions). With twice-daily fractionation, the occurrence of toxicity increases sharply when the BED is >80 Gy. For a once-daily large fraction size (>2.5 Gy), the incidence and severity of toxicity is unpredictable.

Brainstem

Depending on the location of the tumor, the dose to the brainstem can be critical in the treatment of head and neck cancers. Symptoms of brain stem injury include motor, sensory, and cerebellar dysfunctions or a complex combination of the three [135]. Radiation-induced brainstem damage may be seen as bulbar palsy, ataxia, trigeminal and facial cranial neuropathy, hearing loss, hemianopsia, and hemihypesthasia [136]. Development of symptoms may occur 3 months to 9 years after RT and can result in death [135-137]. The common toxicity criteria of cancer therapy evaluation program (CTEP) grades brainstem injury on the basis of symptoms [138]. The planning constraints used to limit brainstem injury shows significant variation. For treatment with megavoltage X-rays they include absolute volume at a dose of 65 Gy (AV65) to <3 ml and AV60 to <5 ml with twice-daily fractionation [139], maximum dose <50 Gy [140], dose to 1% volume (D1%) of ≤ 54 Gy [141], AV55 to <0.1 cc [142], and, for particle treatment, they are as follows: surface ≤ 63 Cobalt Gray Equivalent (CGE) and center ≤ 54 CGE [116] and surface ≤ 64 CGE and center ≤ 54 CGE [135,143]. It has been suggested that the entire brainstem may be treated to 54 Gy using conventional fractionation with a limited risk of severe or permanent neurological effects [144]. Smaller volumes of brainstem may be irradiated to a maximum dose of 59 Gy for dose fractions ≤ 2 Gy [145].

In one large study involving skull-base tumors treated with megavoltage photons and protons, multivariate analysis revealed that the risk of brainstem toxicity significantly increased with AV60>0.9 mL CGE, the number of surgical procedures, and the prevalence of diabetes or high blood pressure, while univariate analyses revealed an association with brainstem D_{max}>64 CGE, AV50>5.9 ml, and AV55>2.7 ml [135]. Median doses of 63.1 CGE (range, 49.6-68.1 CGE) and 48.5 CGE (range, 15.8-63.3 CGE) to the surface were tolerable in another study [116].

Myelitis

The term radiation myelopathy in the radiation of the head and neck includes 2 distinct clinicopathological entities: (1) a common but mild and transient subacute myelopathy and (2) a less-common catastrophic delayed progressive myelopathy. Spinal cord neoplasm and vascular malformations have also been associated with therapeutic radiation [141].

Transient myelopathy occurs between 1 and 30 months after RT with peak onset at 4 to 6 months [146,147] and manifests as parethesias or an "electric shock" sensation radiating down the spine (L hermitte's phenomenon). The condition resolves gradually over 1 to 9 months and has been observed in patients receiving a total spinal dose of>50 Gy and a daily fraction size of >2 Gy [148].

Severe delayed radiation myelopathy usually begins 9 to 15 months after RT with parethesias and other sensory disturbances that progress into motor signs within 2 to 4 years after RT [149,150]. Clinical signs and symptoms include a combination of motor and sensory deficits depending on the location of cord injury. The signs and symptoms of radiation myelopathy may be nonspecific and include a diminished sense of proprioception, temperature sensation, and minor motor weakness, and they may progress to gait, incontinence, Brown-Sequard syndrome, hyperreflexia, plegia, paresis, spasticity, and Babinski sign. If the damage occurs at the upper cervical level, it can be fatal [151]. When radiation is delivered by standard fractionation of 1.8 to 2.0 Gy per fraction, the risk of delayed cervical myelopathy is no more than 0.3% after a total dose of 45 to 50 Gy and approximately 5% after total doses of 57 to 61 Gy [133,152-156]. An evidence-based recommendation is that the tolerance dose of the spinal cord in 2 Gy per fraction is 50 Gy (BED2=100 Gy; EQD2/2=100 Gy) and represents a low risk of permanent myelopathy [149,157,158]. For reirradiation with standard fractionation, investigators recommend a cumulative BED2 ≤ 100 to 120 Gy and EQD2/2 ≤ 50 to 60 Gy [159].

Cranial nerve palsy and peripheral nerve plexopathies

Muscle fibrosis of the neck, total radiation dose, hypo fractionation technique, and use of chemotherapy are suggested to be significant factors in the development of plexopathies of cranial and brachial nerve palsy (CNP) [128,124]. In addition to a detailed history, a physical examination is needed to exclude recurrence-induced CNP. Additional assessments or extended follow up (6–12 months) may be required for diagnosis of RT-induced CNPs [160,161]. Reported incidence rates of RT-induced cranial and/or sympathetic nerve palsies in the literature varies widely, from 0.4% to 47% [126,130,162-164]. Cranial nerves 9, 10, 11, and 12 are the most commonly affected by RT to the head and neck [126,128,129,162,164]. CNPs of the 3rd, 4th, 5th, and 6th nerves have also been reported [119,165]. CNP can appear between 1 and 19 years after completing RT [166,167]. A review of the published literature suggests that the use of doses per fraction in the range of 2.2 to 4.58 Gy with total doses between 43.5 to 60 Gy can cause a significant risk of brachial plexopathy ranging from 1.7% to 73%. The risk of plexopathy was <1% for regimens with a dose per fraction between 2.2 and 2.5 Gy to tal doses between 34 and 40 Gy [168].

Conclusion

Radiation-induced toxicity is a major cause of long-term disability after cancer treatment. Late toxicities can be life-threatening or significantly erode the patient's quality of life and functional status. The difficulties of accurately assessing and quantifying the risks and severity of late toxicities stem from competing risks of disease-related morbidity and mortality and loss to follow-up.

References

1. Dawes C, Wood CM (1973) The contribution of oral minor mucous gland secretions to the volume of whole saliva in man. Arch Oral Biol 18: 337-342.
2. Oral Complications of Chemotherapy and Head/Neck Radiation (PDQ®) (2012) National Cancer Institute.
3. Blanco AI, Chao KS, El Naqa I, Franklin GE, Zakarian K, et al. (2005) Dose-

volume modeling of salivary function in patients with head-and-neck cancer receiving radiotherapy. Int J Radiat Oncol Biol Phys 62: 1055-1069.

4. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, et al. (2001) Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys 50: 695-704.
5. Chao KS, Deasy JO, Markman J, Haynie J, Perez CA, et al. (2001) A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. Int J Radiat Oncol Biol Phys 49: 907-916.
6. Buus S, Grau C, Munk OL, Rodell A, Jensen K, et al. (2006) Individual radiation response of parotid glands investigated by dynamic 11C-methionine PET. Radiother Oncol 78: 262-269.
7. Braam PM, Roesink JM, Moerland MA, Raaijmakers CP, Schipper M, et al. (2005) Long-term parotid gland function after radiotherapy. Int J Radiat Oncol Biol Phys 62: 659-664.
8. Saarilahti K, Kouri M, Collan J, Kangasmaki A, Atula T, et al. (2006) Sparing of the submandibular glands by intensity modulated radiotherapy in the treatment of head and neck cancer. Radiother Oncol 78: 270-275.
9. Li Y, Taylor JM, Ten Haken RK, Eisbruch A (2007) The impact of dose on parotid salivary recovery in head and neck cancer patients treated with radiation therapy. Int J Radiat Oncol Biol Phys 67: 660-669.
10. Portaluri M, Fucilli FI, Castagna R, Bambace S, Pili G, et al. (2006) Three-dimensional conformal radiotherapy for locally advanced (Stage II and worse) head-and-neck cancer: dosimetric and clinical evaluation. Int J Radiat Oncol Biol Phys 66: 1036-1043.
11. Meirovitz A, Murdoch-Kinch CA, Schipper M, Pan C, Eisbruch A (2006) Grading xerostomia by physicians or by patients after intensity-modulated radiotherapy of head-and-neck cancer. Int J Radiat Oncol Biol Phys 66: 445-453.
12. Deasy JO, Moiseenko V, Marks L, Chao KS, Nam J, et al. (2010) Radiotherapy dose-volume effects on salivary gland function. Int J Radiat Oncol Biol Phys 76: S58-S63.
13. Murdoch-Kinch CA, Kim HM, Vineberg KA, Ship JA, Eisbruch A (2008) Dose-effect relationships for the submandibular salivary glands and implications for their sparing by intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys 72: 373-382.
14. Cheng SJ, Lee JJ, Ting LL, Tseng IY, Chang HH, et al. (2006) A clinical staging system and treatment guidelines for maxillary osteoradionecrosis in irradiated nasopharyngeal carcinoma patients. Int J Radiat Oncol Biol Phys 64: 90-97.
15. Peterson DE, Doerr W, Hovan A, Pinto A, Saunders D, et al. (2010) Osteoradionecrosis in cancer patients: the evidence base for treatment-dependent frequency, current management strategies, and future studies. Support Care Cancer 18: 1089-1098.
16. Mendenhall WM (2004) Mandibular osteoradionecrosis. J Clin Oncol 22: 4867-4868.
17. Jereczek-Fossa BA, Orecchia R (2002) Radiotherapy-induced mandibular bone complications. Cancer Treat Rev 28: 65-74.
18. Morrish RB Jr, Chan E, Silverman S Jr, Meyer J, Fu KK, et al. (1981) Osteonecrosis in patients irradiated for head and neck carcinoma. Cancer 47: 1980-1983.
19. Beumer J, Harrison R, Sanders B, Kurrasch M (1984) Osteoradionecrosis: predisposing factors and outcomes of therapy. Head Neck Surg 6: 819-827.
20. Berger A, Bensadoun RJ (2010) [Normal tissue tolerance to external beam radiation therapy: the mandible]. Cancer Radiother 14: 295-300.
21. Hoebers FJP, Ferguson PC, O'Sullivan B (2010) Bone. In: Human Radiation Injury. Shrieve DC, Leoffler J (Eds.), Philadelphia: Lippincott Williams & Wilkins 481-498.
22. Stubblefield MD (2011) Radiation fibrosis syndrome: neuromuscular and musculoskeletal complications in cancer survivors. PM R 3: 1041-1054.
23. Weiss E (2012) Clinical manifestations and treatment of radiation-induced fibrosis.
24. Sciubba JJ, Goldenberg D (2006) Oral complications of radiotherapy. Lancet Oncol 7: 175-183.
25. Dijkstra PU, Kalk WW, Roodenburg JL (2004) Trismus in head and neck oncology: a systematic review. Oral Oncol 40: 879-889.
26. Bensadoun RJ, Riesenbeck D, Lockhart PB, Elting LS, Spijkervet FK, et al. (2010) A systematic review of trismus induced by cancer therapies in head and neck cancer patients. Support Care Cancer 18: 1033-1038.
27. Goldstein M, Maxymiw WG, Cummings BJ, Wood RE (1999) The effects of antitumor irradiation on mandibular opening and mobility: a prospective study of 58 patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 88: 365-373.
28. Dijkstra PU, Sterken MW, Pater R, Spijkervet FK, Roodenburg JL (2007) Exercise therapy for trismus in head and neck cancer. Oral Oncol 43: 389-394.
29. Dijkstra PU, Huisman PM, Roodenburg JL (2006) Criteria for trismus in head and neck oncology. Int J Oral Maxillofac Surg 35: 337-342.
30. Dahllof G, Krekmanova L, Kopp S, Borgstrom B, Forsberg CM, et al. (1994) Craniomandibular dysfunction in children treated with total-body irradiation and bone marrow transplantation. Acta Odontol Scand 52: 99-105.
31. Keus RB, Pontvert D, Brunin F, Jaulerry C, Bataini JP (1988) Results of irradiation in squamous cell carcinoma of the soft palate and uvula. Radiother Oncol 11: 311-317.
32. Chen YY, Zhao C, Wang J, Ma HL, Lai SZ, et al. (2011) Intensity-modulated radiation therapy reduces radiation-induced trismus in patients with nasopharyngeal carcinoma: a prospective study with >5 years of follow-up. Cancer 117: 2910-2916.
33. Louise Kent M, Brennan MT, Noll JL, Fox PC, Burri SH, et al. (2008) Radiation-induced trismus in head and neck cancer patients. Support Care Cancer 16: 305-309.
34. Teguh DN, Levendag PC, Voet P, van der Est H, Noever I, et al. (2008) Trismus in patients with oropharyngeal cancer: relationship with dose in structures of mastication apparatus. Head Neck 30: 622-630.
35. Smith RV, Kotz T, Beitler JJ, Wadler S (2000) Long-term swallowing problems after organ preservation therapy with concomitant radiation therapy and intravenous hydroxyurea: initial results. Arch Otolaryngol Head Neck Surg 126: 384-389.
36. Lazarus CL, Logemann JA, Pauloski BR, Colangelo LA, Kahrilas PJ, et al. (1996) Swallowing disorders in head and neck cancer patients treated with radiotherapy and adjuvant chemotherapy. Laryngoscope 106: 1157-1166.
37. Lee WT, Akst LM, Adelstein DJ, Saxton JP, Wood BG, et al. (2006) Risk factors for hypopharyngeal/upper esophageal stricture formation after concurrent chemoradiation. Head Neck 28: 808-812.
38. Francis DO, Weymuller EA Jr, Parvathaneni U, Merati AL, Yueh B (2010) Dysphagia, stricture, and pneumonia in head and neck cancer patients: does treatment modality matter? Ann Otol Rhinol Laryngol 119: 391-397.
39. Nguyen NP, Sallah S, Karlsson U, Antoine JE (2002) Combined chemotherapy and radiation therapy for head and neck malignancies: quality of life issues. Cancer 94: 1131-1141.
40. Martin M, Lefaix J, Delanian S (2000) TGF-beta1 and radiation fibrosis: a master switch and a specific therapeutic target? Int J Radiat Oncol Biol Phys 47: 277-290.
41. Hutcheson KA, Lewin JS (2012) Functional outcomes after chemoradiotherapy of laryngeal and pharyngeal cancers. Curr Oncol Rep 14: 158-165.
42. Martin S, Chung B, Bratlund C, Kearney P, Mathews B, et al. (2010) Movement trajectories during percutaneous stimulation at rest of the hyolaryngeal muscles in head and neck cancer patients treated with radiation therapy (abstract). Dysphagia 25.
43. Levendag PC, Teguh DN, Voet P, van der Est H, Noever I, et al. (2007) Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. Radiother Oncol 85: 64-73.
44. Eisbruch A, Schwartz M, Rasch C, Vineberg K, Damen E, et al. (2004) Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys 60: 1425-1439.
45. Caglar HB, Tishler RB, Othus M, Burke E, Li Y, et al. (2008) Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 72: 1110-1118.
46. Feng FY, Kim HM, Lyden TH, Haxer MJ, Feng M, et al. (2007) Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys 68: 1289-1298.

47. Li B, Li D, Lau DH, Farwell DG, Luu Q, et al. (2009) Clinical-dosimetric analysis of measures of dysphagia including gastrostomy-tube dependence among head and neck cancer patients treated definitively by intensity-modulated radiotherapy with concurrent chemotherapy. Radiat Oncol 4: 52.

48. Logemann JA, Pauloski BR, Rademaker AW, Lazarus CL, Mittal B, et al. (2003) Xerostomia: 12-month changes in saliva production and its relationship to perception and performance of swallow function, oral intake, and diet after chemoradiation. Head Neck 25: 432-437.

49. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA (1999) Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 45: 577-587.

50. Elerding SC, Fernandez RN, Grotta JC, Lindberg RD, Causay LC, et al. (1981) Carotid artery disease following external cervical irradiation. Ann Surg 194: 609-615.

51. Moritz MW, Higgins RF, Jacobs JR (1990) Duplex imaging and incidence of carotid radiation injury after high-dose radiotherapy for tumors of the head and neck. Arch Surg 125: 1181-1183.

52. Marcial-Rojas RA, Castro JR (1962) Irradiation injury to elastic arteries in the course of treatment for neoplastic disease. Ann Otol Rhinol Laryngol 71: 945-958.

53. Jones TR, Frusha JD (1986) Carotid revascularization after cervical irradiation. South Med J 79: 1517-1520.

54. Levinson SA, Close MB, Ehrenfeld WK, Stoney RJ (1973) Carotid artery occlusive disease following external cervical irradiation. Arch Surg 107: 395-397.

55. Conomy JP, Kellermeyer RW (1975) Delayed cerebrovascular consequences of therapeutic radiation. A clinicopathologic study of a stroke associated with radiation-related carotid arteriopathy. Cancer 36: 1702-1708.

56. McDonald MW, Moore MG, Johnstone PA (2012) Risk of carotid blowout after reirradiation of the head and neck: a systematic review. Int J Radiat Oncol Biol Phys 82: 1083-1089.

57. Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Applegate G, et al. (1989) Hypopituitarism following external radiotherapy for pituitary tumours in adults. Q J Med 70: 145-160.

58. Lam KS, Tse VK, Wang C, Yeung RT, Ma JT, et al. (1987) Early effects of cranial irradiation on hypothalamic-pituitary function. J Clin Endocrinol Metab 64: 418-424.

59. Samaan NA, Vieto R, Schultz PN, Maor M, Meoz RT, et al. (1982) Hypothalamic, pituitary and thyroid dysfunction after radiotherapy to the head and neck. Int J Radiat Oncol Biol Phys 8: 1857-1867.

60. Harrop JS, Davies TJ, Capra LG, Marks V (1976) Hypothalamic-pituitary function following successful treatment of intracranial tumours. Clin Endocrinol (Oxf) 5: 313-321.

61. Shalet SM, Price DA, Beardwell CG, Jones PH, Pearson D (1979) Normal growth despite abnormalities of growth hormone secretion in children treated for acute leukemia. J Pediatr 94: 719-722.

62. Littley MD, Shalet SM, Beardwell CG, Robinson EL, Sutton ML (1989) Radiation-induced hypopituitarism is dose-dependent. Clin Endocrinol (Oxf) 31: 363-373.

63. Arnold A (1954) Effects of x-irradiation on the hypothalamus: a possible explanation for the therapeutic benefits following x-irradiation of the hypophysial region for pituitary dysfunction. J Clin Endocrinol Metab 14: 859-868.

64. Samaan NA, Bakdash MM, Caderao JB, Cangir A, Jesse RH Jr, et al. (1975) Hypopituitarism after external irradiation. Evidence for both hypothalamic and pituitary origin. Ann Intern Med 83: 771-777.

65. Darzy KH, Shalet SM (2003) Radiation-induced growth hormone deficiency. Horm Res 59: 1-11.

66. Wang LF, Kuo WR, Ho KY, Lee KW, Lin CS (2004) A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. Otol Neurotol 25: 168-173.

67. Grossman A, Besser M, Wass J, Rees L (1984) Treatment of prolactinomas with megavoltage radiotherapy. Br Med J (Clin Res Ed) 288: 2002.

68. Pai HH, Thornton A, Katznelson L, Finkelstein DM, Adams JA, et al. (2001) Hypothalamic/pituitary function following high-dose conformal radiotherapy to the base of skull: demonstration of a dose-effect relationship using dose-volume histogram analysis. Int J Radiat Oncol Biol Phys 49: 1079-1092.

69. Bhandare N, Kennedy L, Malyapa RS, Morris CG, Mendenhall WM (2008) Hypopituitarism after radiotherapy for extracranial head and neck cancers. Head Neck 30: 1182-1192.

70. Pollock BE, Cochran J, Natt N, Brown PD, Erickson D, et al. (2008) Gamma knife radiosurgery for patients with nonfunctioning pituitary adenomas: results from a 15-year experience. Int J Radiat Oncol Biol Phys 70: 1325-1329.

71. Samaan NA, Schultz PN, Yang KP, Vassilopoulou-Sellin R, Maor MH, et al. (1987) Endocrine complications after radiotherapy for tumors of the head and neck. J Lab Clin Med 109: 364-372.

72. Brauner R, Czernichow P, Rappaport R (1986) Greater susceptibility to hypothalamopituitary irradiation in younger children with acute lymphoblastic leukemia. J Pediatr 108: 332.

73. Kauppila M, Koskinen P, Irjala K, Remes K, Viikari J (1998) Long-term effects of allogeneic bone marrow transplantation (BMT) on pituitary, gonad, thyroid and adrenal function in adults. Bone Marrow Transplant 22: 331-337.

74. Brauner R, Adan L, Souberbielle JC, Esperou H, Michon J, et al. (1997) Contribution of growth hormone deficiency to the growth failure that follows bone marrow transplantation. J Pediatr 130: 785-792.

75. Snead FE, Amdur RJ, Morris CG, Mendenhall WM (2008) Long-term outcomes of radiotherapy for pituitary adenomas. Int J Radiat Oncol Biol Phys 71: 994-998.

76. Jereczek-Fossa BA, Alterio D, Jassem J, Gibelli B, Tradati N, et al. (2004) Radiotherapy-induced thyroid disorders. Cancer Treat Rev 30: 369-384.

77. Zohar Y, Tovim RB, Laurian N, Laurian L (1984) Thyroid function following radiation and surgical therapy in head and neck malignancy. Head Neck Surg 6: 948-952.

78. Kuten A, Lubochitski R, Fishman G, Dale J, Stein ME (1996) Postradiotherapy hypothyroidism: radiation dose response and chemotherapeutic radiosensitization at less than 40 Gy. J Surg Oncol 61: 281-283.

79. Bajorunas DR (1980) Disorders of endocrine function following cancer therapies. Clin Endocrinol Metab 9: 405-430.

80. Hancock SL, McDougall IR, Constine LS (1995) Thyroid abnormalities after therapeutic external radiation. Int J Radiat Oncol Biol Phys 31: 1165-1170.

81. DeGroot LJ (1988) Radiation and thyroid disease. Baillieres Clin Endocrinol Metab 2: 777-791.

82. Hancock SL, Cox RS, McDougall IR (1991) Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 325: 599-605.

83. Groover TA, Christie AC, Merritt EA, Coe FO, McPeak EM (1929) Roentgen irradiation in the treatment of hyperthyroidism: a statistical evaluation based on three hundred and five cases. JAMA 92: 1730-1734.

84. Bhandare N, Kennedy L, Malyapa RS, Morris CG, Mendenhall WM (2007) Primary and central hypothyroidism after radiotherapy for head-and-neck tumors. Int J Radiat Oncol Biol Phys 68: 1131-1139.

85. Posner MR, Weichselbaum RR, Fitzgerald TJ, Clark JR, Rose C, et al. (1985) Treatment complications after sequential combination chemotherapy and radiotherapy with or without surgery in previously untreated squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 11: 1887-1893.

86. Yoden E, Soejima T, Maruta T, Demizu Y, Nishimura H, et al. (2004) [Hypothyroidism after radiotherapy to the neck]. Nihon Igaku Hoshasen Gakkai Zasshi 64: 146-150.

87. Finger PT (1997) Radiation therapy for choroidal melanoma. Surv Ophthalmol 42: 215-232.

88. Shields JA, Shields CL (2007) Non-neoplastic conditions that can simulate posterior uveal melanoma. In: Intraocular tumors: An atlas and text. (2ndedn), Philadelphia: Lippincott Williams & Wilkins 171-205.

89. Parsons JT, Bova FJ, Fitzgerald CR, Mendenhall WM, Million RR (1994) Radiation optic neuropathy after megavoltage external-beam irradiation: analysis of time-dose factors. Int J Radiat Oncol Biol Phys 30: 755-763.

90. Cogan DG, Donaldson DD, Reese AB (1952) Clinical and pathological characteristics of radiation cataract. AMA Arch Ophthalmol 47: 55-70.

91. Durkin SR, Roos D, Higgs B, Casson RJ, Selva D (2007) Ophthalmic and adnexal complications of radiotherapy. Acta Ophthalmol Scand 85: 240-250.

92. Anteby I, Ramu N, Gradstein L, Miskin H, Pe'er J, et al. (1998) Ocular and orbital complications following the treatment of retinoblastoma. Eur J Ophthalmol 8: 106-111.

93. Hall EJ (2000) Radiobiology for the Radiologist. 5 ed Lippincott Williams & Wilkins, Philadelphia.

94. Henk JM, Whitelocke RA, Warrington AP, Bessell EM (1993) Radiation dose to the lens and cataract formation. Int J Radiat Oncol Biol Phys 25: 815-820.

95. Schipper J, Tan KE, van Peperzeel HA (1985) Treatment of retinoblastoma by precision megavoltage radiation therapy. Radiother Oncol 3: 117-132.

96. Parsons JT, Bova FJ, Fitzgerald CR, Mendenhall WM, Million RR (1994) Severe dry-eye syndrome following external beam irradiation. Int J Radiat Oncol Biol Phys 30: 775-780.

97. Jiang GL, Tucker SL, Guttenberger R, Peters LJ, Morrison WH, et al. (1994) Radiation-induced injury to the visual pathway. Radiother Oncol 30: 17-25.

98. Bessell EM, Henk JM, Whitelocke RA, Wright JE (1987) Ocular morbidity after radiotherapy of orbital and conjunctival lymphoma. Eye (Lond)1: 90-96.

99. Irvine AR, Alvarado JA, Wara WM, Morris BW, Wood IS (1981) Radiation retinopathy: an experimental model for the ischemic--proliferative retinopathies. Trans Am Ophthalmol Soc 79: 103-122.

100. Irvine AR, Wood IS (1987) Radiation retinopathy as an experimental model for ischemic proliferative retinopathy and rubeosis iridis. Am J Ophthalmol 103: 790-797.

101. Kinyoun JL, Lawrence BS, Barlow WE (1996) Proliferative radiation retinopathy. Arch Ophthalmol 114: 1097-1100.

102. Monroe AT, Bhandare N, Morris CG, Mendenhall WM (2005) Preventing radiation retinopathy with hyperfractionation. Int J Radiat Oncol Biol Phys 61: 856-864.

103. Chan RC, Shukovsky LJ (1976) Effects of irradiation on the eye. Radiology 120: 673-675.

104. Chacko DC (1981) Considerations in the diagnosis of radiation injury. JAMA 245: 1255-1258.

105. Kim MK, Char DH, Castro JL, Saunders WM, Chen GT, et al. (1986) Neovascular glaucoma after helium ion irradiation for uveal melanoma. Ophthalmology 93: 189-193.

106. Viebahn M, Barricks ME, Osterloh MD (1991) Synergism between diabetic and radiation retinopathy: case report and review. Br J Ophthalmol 75: 629-632.

107. Robertson DM, Buettner H, Gorman CA, Garrity JA, Fatourechi V, et al. (2003) Retinal microvascular abnormalities in patients treated with external radiation for graves ophthalmopathy. Arch Ophthalmol 121: 652-657.

108. Atkinson AB, Allen IV, Gordon DS, Hadden DR, Maguire CJ, et al (1979) Progressive visual failure in acromegaly following external pituitary irradiation. Clin Endocrinol (Oxf) 10: 469-479.

109. Glantz MJ, Burger PC, Friedman AH, Radtke RA, Massey EW, et al. (1994) Treatment of radiation-induced nervous system injury with heparin and warfarin. Neurology 44: 2020-2027.

110. Raskind R (1967) Central nervous system damage after radiation therapy. Int Surg 48: 430-441.

111. Sheline GE, Wara WM, Smith V (1980) Therapeutic irradiation and brain injury. Int J Radiat Oncol Biol Phys 6: 1215-1228.

112. Bhandare N, Monroe AT, Morris CG, Bhatti MT, Mendenhall WM (2005) Does altered fractionation influence the risk of radiation-induced optic neuropathy? Int J Radiat Oncol Biol Phys 62: 1070-1077.

113. Burman C, Kutcher GJ, Emami B, Goitein M (1991) Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 21: 123-135.

114. Emami B, Lyman J, Brown A, Coia L, Goitein M, et al. (1991) Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21: 109-122.

115. Bhandare N, Antonelli PJ, Morris CG, Malayapa RS, Mendenhall WM (2007) Ototoxicity after radiotherapy for head and neck tumors. Int J Radiat Oncol Biol Phys 67: 469-479.

116. Weber DC, Rutz HP, Pedroni ES, Bolsi A, Timmermann B, et al. (2005) Results of spot-scanning proton radiation therapy for chordoma and chondrosarcoma of the skull base: the Paul Scherrer Institut experience. Int J Radiat Oncol Biol Phys 63: 401-409.

117. Anteunis LJ, Wanders SL, Hendriks JJ, Langendijk JA, Manni JJ, et al. (1994) A prospective longitudinal study on radiation-induced hearing loss. Am J Surg 168: 408-411.

118. Kwong DL, Wei WI, Sham JS, Ho WK, Yuen PW, et al. (1996) Sensorineural hearing loss in patients treated for nasopharyngeal carcinoma: a prospective study of the effect of radiation and cisplatin treatment. Int J Radiat Oncol Biol Phys 36: 281-289.

119. Rong X, Tang Y, Chen M, Lu K, Peng Y (2012) Radiation-induced cranial neuropathy in patients with nasopharyngeal carcinoma. A follow-up study. Strahlenther Onkol 188: 282-286.

120. Honore HB, Bentzen SM, Moller K, Grau C (2002) Sensori-neural hearing loss after radiotherapy for nasopharyngeal carcinoma: individualized risk estimation. Radiother Oncol 65: 9-16.

121. Raaijmakers E, Engelen AM (2002) Is sensorineural hearing loss a possible side effect of nasopharyngeal and parotid irradiation? A systematic review of the literature. Radiother Oncol 65: 1-7.

122. Pan CC, Eisbruch A, Lee JS, Snorrason RM, Ten Haken RK, et al. (2005) Prospective study of inner ear radiation dose and hearing loss in head-and-neck cancer patients. Int J Radiat Oncol Biol Phys 61: 1393-1402.

123. Chen WC, Liao CT, Tsai HC, Yeh JY, Wang CC, et al. (1999) Radiation-induced hearing impairment in patients treated for malignant parotid tumor. Ann Otol Rhinol Laryngol 108: 1159-1164.

124. van der Putten L, de Bree R, Plukker JT, Langendijk JA, Smits C, et al. (2006) Permanent unilateral hearing loss after radiotherapy for parotid gland tumors. Head Neck 28: 902-908.

125. Lee AW, Poon YF, Foo W, Law SC, Cheung FK, et al. (1992) Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976-1985: overall survival and patterns of failure. Int J Radiat Oncol Biol Phys 23: 261-270.

126. Lee AW, Ng WT, Hung WM, Choi CW, Tung R, et al. (2009) Major late toxicities after conformal radiotherapy for nasopharyngeal carcinoma-patient- and treatment-related risk factors. Int J Radiat Oncol Biol Phys 73: 1121-1128.

127. Leung SF, Kreel L, Tsao SY (1992) Asymptomatic temporal lobe injury after radiotherapy for nasopharyngeal carcinoma: incidence and determinants. Br J Radiol 65: 710-714.

128. Kong L, Lu JJ, Liss AL, Hu C, Guo X, et al. (2011) Radiation-induced cranial nerve palsy: a cross-sectional study of nasopharyngeal cancer patients after definitive radiotherapy. Int J Radiat Oncol Biol Phys 79: 1421-1427.

129. Schinagl DA, Marres HA, Kappelle AC, Merkx MA, Pop LA, et al. (2010) External beam radiotherapy with endocavitary boost for nasopharyngeal cancer: treatment results and late toxicity after extended follow-up. Int J Radiat Oncol Biol Phys 78: 689-695.

130. Chen CY, Han F, Zhao C, Lu LX, Sun Y, et al. (2009) Treatment results and late complications of 556 patients with locally advanced nasopharyngeal carcinoma treated with radiotherapy alone. Br J Radiol 82: 452-458.

131. Mould RF, Tai TH (2002) Nasopharyngeal carcinoma: treatments and outcomes in the 20th century. Br J Radiol 75: 307-339.

132. Mou YG, Sai K, Wang ZN, Zhang XH, Lu YC, et al. (2011) Surgical management of radiation-induced temporal lobe necrosis in patients with nasopharyngeal carcinoma: report of 14 cases. Head Neck 33: 1493-1500.

133. Marcus RB Jr, Million RR (1990) The incidence of myelitis after irradiation of the cervical spinal cord. Int J Radiat Oncol Biol Phys 19: 3-8.

134. Lawrence YR, Li XA, el Naqa I, Hahn CA, Marks LB, et al. (2010) Radiation dose-volume effects in the brain. Int J Radiat Oncol Biol Phys 76: S20-S27.

135. Debus J, Hug EB, Liebsch NJ, O'Farrel D, Finkelstein D, et al. (1997) Brainstem tolerance to conformal radiotherapy of skull base tumors. Int J Radiat Oncol Biol Phys 39: 967-975.

136. Holdorff B, Schiffter R (1971) [Late radiation necrosis of the brain stem, including the hypothalamus after irradiation with ultra hard x-rays and high-speed electrons. Concerning the problem of radiation sensitivity of the brain stem]. Acta Neurochir (Wien) 25: 37-56.

137. Bhansali A, Banerjee AK, Chanda A, Singh P, Sharma SC, et al. (2004) Radiation-induced brain disorders in patients with pituitary tumours. Australas Radiol 48: 339-346.

138. Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, version 4.0 In: National Institute of Health, National Cancer Institute, U.S. Department of Health and Human Services.

139. Jian JJ, Cheng SH, Tsai SY, Yen KC, Chu NM, et al. (2002) Improvement of local control of T3 and T4 nasopharyngeal carcinoma by hyperfractionated radiotherapy and concomitant chemotherapy. Int J Radiat Oncol Biol Phys 53: 344-352.

140. Hoppe BS, Stegman LD, Zelefsky MJ, Rosenzweig KE, Wolden SL, et al. (2007) Treatment of nasal cavity and paranasal sinus cancer with modern radiotherapy techniques in the postoperative setting--the MSKCC experience. Int J Radiat Oncol Biol Phys 67: 691-702.

141. Daly ME, Chen AM, Bucci MK, El-Sayed I, Xia P, et al. (2007) Intensity-modulated radiation therapy for malignancies of the nasal cavity and paranasal sinuses. Int J Radiat Oncol Biol Phys 67: 151-157.

142. Schoenfeld GO, Amdur RJ, Morris CG, Li JG, Hinerman RW, et al. (2008) Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 71: 377-385.

143. Debus J, Hug EB, Liebsch NJ, O'Farrel D, Finkelstein D, et al. (1999) Dose-volume tolerance of the brainstem after high-dose radiotherapy. Front Radiat Ther Oncol 33: 305-314.

144. Merchant TE, Chitti RM, Li C, Xiong X, Sanford RA, et al. (2010) Factors associated with neurological recovery of brainstem function following postoperative conformal radiation therapy for infratentorial ependymoma. Int J Radiat Oncol Biol Phys 76: 496-503.

145. Mayo C, Yorke E, Merchant TE (2010) Radiation associated brainstem injury. Int J Radiat Oncol Biol Phys 76: S36-S41.

146. Word JA, Kalokhe UP, Aron BS, Elson HR (1980) Transient radiation myelopathy (Lhermitte's sign) in patients with Hodgkin's disease treated by mantle irradiation. Int J Radiat Oncol Biol Phys 6: 1731-1733.

147. Goldwein JW (1987) Radiation myelopathy: a review. Med Pediatr Oncol 15: 89-95.

148. Fein DA, Marcus RB Jr, Parsons JT, Mendenhall WM, Million RR (1993) Lhermitte's sign: incidence and treatment variables influencing risk after irradiation of the cervical spinal cord. Int J Radiat Oncol Biol Phys 27: 1029-1033.

149. Schultheiss TE, Higgins EM, El-Mahdi AM (1984) The latent period in clinical radiation myelopathy. Int J Radiat Oncol Biol Phys 10: 1109-1115.

150. Wong CS, Van Dyk J, Milosevic M, Laperriere NJ (1994) Radiation myelopathy following single courses of radiotherapy and retreatment. Int J Radiat Oncol Biol Phys 30: 575-581.

151. Schultheiss TE, Stephens LC, Peters LJ (1986) Survival in radiation myelopathy. Int J Radiat Oncol Biol Phys 12: 1765-1769.

152. Kim YH, Fayos JV (1981) Radiation tolerance of the cervical spinal cord. Radiology 139: 473-478.

153. McCunniff AJ, Liang MJ (1989) Radiation tolerance of the cervical spinal cord. Int J Radiat Oncol Biol Phys 16: 675-678.

154. Jeremic B, Djuric L, Mijatovic L (1991) Incidence of radiation myelitis of the cervical spinal cord at doses of 5500 cGy or greater. Cancer 68: 2138-2141.

155. Schultheiss TE (2008) The radiation dose-response of the human spinal cord. Int J Radiat Oncol Biol Phys 71: 1455-1459.

156. Kirkpatrick JP, van der Kogel AJ, Schultheiss TE (2010) Radiation dose-volume effects in the spinal cord. Int J Radiat Oncol Biol Phys 76: S42-S49.

157. Saunders MI, Dische S, Hong A, Grosch EJ, Fermont DC, et al. (1989) Continuous hyperfractionated accelerated radiotherapy in locally advanced carcinoma of the head and neck region. Int J Radiat Oncol Biol Phys 17: 1287-1293.

158. Schultheiss TE (1990) Spinal cord radiation "tolerance": doctrine versus data. Int J Radiat Oncol Biol Phys 19: 219-221.

159. Schultheiss TE, Kun LE, Ang KK, Stephens LC (1995) Radiation response of the central nervous system. Int J Radiat Oncol Biol Phys 31: 1093-1112.

160. Heng DM, Wee J, Fong KW, Lian LG, Sethi VK, et al. (1999) Prognostic factors in 677 patients in Singapore with nondisseminated nasopharyngeal carcinoma. Cancer 86: 1912-1920.

161. Bajrovic A, Rades D, Fehlauer F, Tribius S, Hoeller U, et al. (2004) Is there a life-long risk of brachial plexopathy after radiotherapy of supraclavicular lymph nodes in breast cancer patients? Radiother Oncol 71: 297-301.

162. Yeh SA, Tang Y, Lui CC, Huang YJ, Huang EY (2005) Treatment outcomes and late complications of 849 patients with nasopharyngeal carcinoma treated with radiotherapy alone. Int J Radiat Oncol Biol Phys 62: 672-679.

163. Lin YS, Jen YM, Lin JC (2002) Radiation-related cranial nerve palsy in patients with nasopharyngeal carcinoma. Cancer 95: 404-409.

164. Lee AW, Sze WM, Yau TK, Yeung RM, Chappell R, et al. (2001) Retrospective analysis on treating nasopharyngeal carcinoma with accelerated fractionation (6 fractions per week) in comparison with conventional fractionation (5 fractions per week): report on 3-year tumor control and normal tissue toxicity. Radiother Oncol 58: 121-130.

165. Vaphiades MS, Spencer SA, Riley K, Francis C, Deitz L, et al. (2011) Radiation-induced ocular motor cranial nerve palsies in patients with pituitary tumor. J Neuroophthalmol 31: 210-213.

166. Powell S, Cooke J, Parsons C (1990) Radiation-induced brachial plexus injury: follow-up of two different fractionation schedules. Radiother Oncol 18: 213-220.

167. Johansson S, Svensson H, Denekamp J (2000) Timescale of evolution of late radiation injury after postoperative radiotherapy of breast cancer patients. Int J Radiat Oncol Biol Phys 48: 745-750.

168. Galecki J, Hicer-Grzenkowicz J, Grudzien-Kowalska M, Michalska T, Zalucki W (2006) Radiation-induced brachial plexopathy and hypofractionated regimens in adjuvant irradiation of patients with breast cancer--a review. Acta Oncol 45: 280-284.

This article was originally published in a special issue, **Surgical oncology: Clinical Importance** handled by Editor(s). Dr. Liqiang Zhang, Arizona State University, USA; Dr. Salomone Di Saverio, Surgery and Trauma Surgery Unit, Italy