Organ-sparing radiotherapy in head and neck cancer

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Summary

Intensification of radiotherapy (RT) treatment for locally advanced head and neck cancer (HNC) through the use of altered fractionation schedules and/or concomitant chemotherapy has resulted in significantly improved loco-regional control and survival rates. However, these improvements in outcome come at the cost of increased acute, and perhaps also late, toxicity. It is to be expected that technological advances such as intensity-modulated radiotherapy (IMRT) will further improve the therapeutic index of RT in HNC by limiting toxicity and possibly increasing local control. The organ-sparing potential of IMRT and other highly conformal radiotherapy techniques relies heavily on the appropriate selection and accurate delineation of the critical organs at risk (OAR), with the application of rigorous restrictions during planning.

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Introduction

Several groups have evaluated the major contributing factors to quality of life after RT for head and neck cancer.[1,2] It has been shown that both late xerostomia and swallowing disorders are the main causes of decreased quality of life.[2,3] These discomforts are the focus of this review. Some specific OAR such as the lens, the optic nerve and the chiasm (in sinonasal cancer) or temporal lobes (in nasopharyngeal cancer) will not be addressed.

Salivary glands

Since irreparable damage is caused to the salivary glands which are included in the radiation fields, a permanent dry mouth or xerostomia is one of the most common complications of conventional radiotherapy for head and neck cancer.[4] About 60 – 65% of the total salivary volume is produced by the parotid glands. Therefore, most attention has been directed to developing parotid-sparing techniques.[5,6] It is generally accepted that a significant reduction of xerostomia can be achieved by maintaining a mean parotid dose lower than 26 to 30 Gy as a planning criterion.[4] However, since lower doses (10 – 15 Gy) can also induce serious loss of function, the mean dose should probably be kept as low as possible.[7] If patients are carefully selected, parotid-sparing does not result in higher recurrence rates.[8,9]

Since the submandibular glands are responsible for most of the saliva production during stimulation, they could also play an important part in radiation-induced xerostomia.[4] *Saarilathi et al* were the first to demonstrate that sparing of the contralateral submandibular gland (mean dose < 25 Gy) is feasible with IMRT and results in prevention of xerostomia. Recently a group from the university of Michigan suggested a mean dose threshold of 39 Gy for submandibular gland sparing.[10,11] Although data on possible thresholds are currently lacking, the mean dose to the oral cavity, representing the RT effect on the minor salivary glands, may also be important in the prevention of xerostomia.[4]

Swallowing structures

Swallowing dysfunction during or after radiotherapy is correlated with compromised quality of life, anxiety and depression. It can also lead to life-threatening complications such as aspiration pneumonia.[12] Dysphagia is more and more recognized as being the dose-limiting toxicity of concomitant chemoradiotherapy for head and neck cancer.[13] It is to be expected that limiting the dose to the critical swallowing struc-

Table 1. Delineation guidelines for the swallowing structures.

OAR	Superior border	Inferior border	Anterior border	Posterior border
Superior pharyngeal constrictor muscle	caudal tip of the pterygoid plates (hamulus)	upper edge of hyoid bone	widest diameter of rhinopharynx, base of tongue, hyoid bone and larynx	cervical vertebra or pre-vertebral muscles
Middle pharyngeal constrictor muscle	upper edge of hyoid bone	lower edge of hyoid bone		
Inferior pharyngeal constrictor muscle	lower edge of hyoid bone	lower edge of cricoid cartilage		
Base of tongue	below soft palate (uvula)	upper edge of hyoid bone	posterior third of the tongue	
Supraglottic larynx (lumen excluded)	top of the piriform sinus and aryepiglottic fold	upper edge of the cricoid cartilage	anterior tip of the thyroid cartilage	cornu of the thyroid cartilage
Glottic larynx (lumen excluded)	at the level of the cricoid cartilage			
Upper esophageal sphincter including cricopharyngeus muscle	lower edge of cricoid cartilage	upper edge of trachea	subglottic larynx	cervical vertebra
Esophagus	upper edge of trachea	first 2cm	trachea	cervical vertebra

tures will reduce the incidence of dysphagia.[12] However, several questions regarding to which swallowing structures are essential and what volume and dose restrictions should be applied, remain to be answered. Based on a literature search, 8 relevant swallowing structures for organ-sparing RT can be identified: *(1)* superior pharyngeal constrictor muscle, *(2)* middle pharyngeal constrictor muscle, *(3)* inferior pharyngeal constrictor muscle, *(4)* base of the tongue, *(5)* supraglottic larynx, *(6)* glottic larynx, *(7)* upper esophageal sphincter, including the cricopharyngeus muscle and *(8)* the esophagus (*Table 1*). In most studies, the upper and middle pharyngeal constrictor muscles as well as the glottic and supraglottic larynx appear to be the most critical OAR, and reducing their radiation doses could lead to a clinical benefit.[14-17]

Auditory structures

Despite their apparent functional consequences, radiotherapy-induced ear injuries remain under-evaluated and under-reported. Up to 40% of patients suffer from acute middle ear side-effects (e.g. otitis media with effusion or transient conductive hearing loss), while about one third of patients develop late sensorineural hearing loss (SNHL) due to inner ear (cochlea) damage.[18] The use of concomitant chemotherapy (cisplatin), total RT dose and the tumor site (nasopharynx) seem to be the most important factors associated with the risk of hearing impairment.[18] Thus, reducing the radiation dose to the auditory structures should be attempted whenever possible. Researchers from the university of Michigan conducted a prospective study of SNHL in which the function of the cochlea ipsilateral to the tumor, which had received a high dose, was compared to the contralateral cochlea, which had received a low dose. They observed that SNHL risk started at doses of 40 – 45 Gy.[19] These results are consistent with other prospective studies that reported increased hearing loss risks associated with doses in the range of 40 – 50 Gy.[18]

Mandible and temporo-mandibular joints

Osteoradionecrosis (ORN) of the mandibular bone is a well-documented complication of conventional radiotherapy in HNC.[20] In general, bones are resistant to high radiation doses and will not sustain any overt damage as long as the overlying soft tissue remains intact and the bone is not subjected to excessive stress or trauma. A retrospective analysis of 176 HNC patients treated with IMRT at the university of Michigan revealed a 0% incidence of ORN, if a maximal dose restrictions of 72 Gy was respected.[21] Strict dental prophylactic care is probably the most essential factor in the prevention of ORN.[20,21]
Irradiation of the temporo-mandibular joints (TMJ) with high radiation doses can result in a slowly evol-

Key messages for clinical practice

OAR	D_{max}	D_{mean}	Volume restrictions
Spinal cord	45 Gy	-	-
Spinal cord extended (5mm margin)	-	-	> 50 Gy to ≤ 1%
Brainstem	54 Gy	-	-
Brainstem extended (1mm margin)	-	-	> 60 Gy to ≤ 1%
Parotid gland	1. mean dose to either gland (at least one) < 26 Gy or 2. at least 50% of either gland (at least one) < 30 Gy or 3. at least 20cc of combined volume of both glands < 20 Gy		
Submandibular gland	no restrictions, reduce dose as much as possible		
Oral cavity	-	< 40 Gy	-
Tongue	55 Gy	-	> 65 Gy to ≤ 1%
Pharyngeal constrictor muscles	no restrictions, reduce dose as much as possible		
Larynx	-	< 45 Gy	< 50 Gy to 2/3 of volume
Esophagus	-	< 45 Gy	-
Inner ear (cochlea)	-	< 50 Gy	> 55 Gy to ≤ 5%
External and middle ear	-	< 50 Gy	-
Mandible	70 Gy	-	> 75 Gy to ≤ 1 cc
Temporo-mandibular joints	70 Gy	-	> 75 Gy to ≤ 1 cc
Brachial plexus	60 Gy	-	-
Brain (temporal lobes)	60 Gy	-	> 65 Gy to ≤ 1%

Overview of restrictions for critical organs at risk (OAR) in recent RTOG trials on head and neck radiotherapy (adapted from www.rtog.org).

ving inability to open the mouth (trismus), with an incidence of 5 – 38% after conventional RT. Currently, no reliable dose-response relationship exists, but most problems are observed above a dose of 70 Gy.[20]

Brachial plexus

Concerns about the development of brachial plexopathy (mostly seen in patients irradiated for breast or lung cancer) after radiotherapy for HNC have prompted the radiation therapy oncology group (RTOG) to include brachial plexus dose restrictions ranging from 60 to 66 Gy in many recent protocols. However, a recent analysis showed that patients treated with IMRT often receive a brachial plexus dose > 60 Gy, with 70% and 30% of patients receiving doses of > 66 and > 70 Gy, respectively.[22] It should also be noted that the brachial plexus is best imaged, and delineated, with gadolinium-enhanced T1-weighted coronal and sagittal MRI sequences, and usually cannot be visualized on CT.[22]

Conclusion

If head and neck cancer patients are treated with IMRT or other highly conformal radiotherapy techniques, it is important that all relevant organs at risk are delineated and rigorous dose-restrictions are applied. It is to be expected that the prospective collection of dosimetric data along with the corresponding functional outcomes will allow the development of more precise dose-response curves.

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