Salivary Flow and Intensity-modulated Radiation Therapy

a report by
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Saliva's fluid characteristics allow cleansing and lubrication of the oral cavity and mucosa. It is responsible for facilitation of taste perception, mastication, swallowing and speech. It contains a number of proteins that serve to maintain oral health and function.[1] Any salivary gland dysfunction can result in reduced saliva secretion and inadequate composition, as well as xerostomia. The main causes of xerostomia due to hyposalivation include adverse reactions to some drugs, systemic disorders, particularly Sjögren's syndrome, chemotherapy, treatment of thyroid cancer with radioactive iodine and radiation therapy of head and neck tumours. In the treatment of head and neck cancer by radiotherapy, the salivary glands are often inevitably included in the treated volume. The impairment of salivary gland function that can result is an important cause of late morbidity following treatment. Evaluation of effects of radiotherapy may comprise subjective rating of oral symptoms or objective measures such as flow measurements. The most direct quantitative study of salivary gland dysfunction measures the salivary flow rate at rest or after stimulation. Selective measurement of the major salivary glands can be performed. The parotid glands produce about 60–65% of the total salivary volume during stimulation such as eating or chewing. Saliva of individual parotid glands can be collected by the use of suction cups placed over the openings of Stensen's ducts. This method is commonly used to measure radiation-induced hyposalivation. Stimulation with citric acid (the most potent gustatory stimulus) provides information about the secretory capacities of the glands. Salivary flow measurements are performed in patients before the initiation of radiation treatment and after the end of the treatment at various time intervals. The best indication of objective parotid gland toxicity appeared to be reduction of stimulated flow to <25% of the value before radiotherapy.[2]

Dose–Volume Effects

Depending on the dose received by the glands and the volume of the glands included in the radiation fields, xerostomia may become an irreversible, lifelong problem. Parotid glands included in the treatment volume have been shown to have markedly reduced stimulated flow rates several years after treatment.[3] Several studies have been performed to establish more precisely the radiation tolerance of the parotid glands as a function of total dose and volume irradiated. Two dose–volume response curves that are obtained from large patient groups measuring individual stimulated parotid gland flow are available.[4,5] Using planning computed tomography scans, dose–volume histograms were deduced from the dose distribution in each individual gland. In both studies a strong correlation was found between the mean dose to the parotid gland and the parotid gland function after radiotherapy. Parotids receiving higher radiation produce less saliva. The largest reduction in function was at one to three months after radiotherapy followed by gradual recovery. Most of the parotid glands receiving <25Gy have completely recovered their functionality in producing secretions under stimulated conditions. When a mean dose reached above 45–50Gy, nearly all patients had a severe decrease in parotid flow rate. Parotid gland function can continue to recover for years after radiotherapy. An improvement of the parotid flow rate of approximately 30% at five years compared with 12 months after radiotherapy completion was shown.[6]

Intensity-modulated Radiation Therapy

In head and neck cancer, conventional radiotherapy (CRT) in general results in high radiation dosage to both parotid glands and hence often leads to severely reduced salivary flow. The best way of managing xerostomia is preventing it by reducing the volume of the salivary glands in the radiation fields and the dose delivered to the glands. This is possible by implementing conformal radiotherapy techniques and especially intensity-modulated radiation therapy (IMRT). Although parotid sparing can also be obtained using conventional techniques,[7] it is generally accepted that IMRT can be applied to further reduce the dose to the parotid gland.[8–10] IMRT is an advanced form of conformal radiotherapy and provides a sophisticated method of dose delivery. IMRT techniques use modifications in intensity of the beams across the beam portals as an additional degree of freedom to enhance the capability of conforming dose distributions in three dimensions. Using IMRT, it is possible to deliver more conformal doses to the target volumes and consequently spare more of the parotid gland tissue than in conventional techniques (see *Figure 1*). The mean parotid dose values for IMRT reported in literature vary from 20 to 40Gy.[11,12] Reduction of the mean parotid dose below 25Gy might be possible. The dose–response curves indicate that such a reduction in dose will largely improve parotid gland function.

The fact that IMRT reduces the dose to the parotid glands and that a dose-response relationship exists that predicts a reduction in xerostomia complications has led to widespread use of IMRT to spare the parotid glands. Data objectively and prospectively quantifying the advantages of IMRT over conventional techniques with respect to parotid flow are, however, rare. One study has been published that objectively compares parotid gland function in patients treated with IMRT and CRT. In this prospective comparison between 27 IMRT patients and 14 patients treated conventionally, the parotid flow ratio correlated with the mean parotid dose and the mean parotid dose was lower in the IMRT group. However, use of IMRT versus CRT did not independently influence the functional outcome

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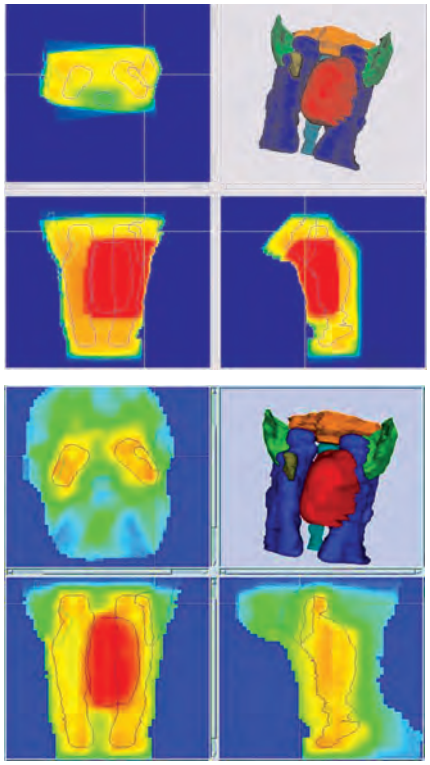
Figure 1: Dose Distribution of Conventional Radiotherapy and Intensity-modulated Radiation Therapy Plan



Dose distribution of conventional radiotherapy (top) and intensity-modulated radiation therapy (IMRT) plan (bottom) of the same patient in a transverse, coronal and sagittal plane. The IMRT plan appeared to be better at reducing the dose to the left parotid gland.

of the salivary glands in this study.[13] Another study by Braam et al.[14] showed that by using IMRT compared with CRT a dose reduction of 30% to the parotid gland can be achieved (48.1 versus 33.7Gy), which resulted in a reduction in flow complications from 83% after conventional treatment to 41% after IMRT at 12 months after treatment for oropharyngeal cancer (see *Table 1*). So, the number of complications was indeed lower for the IMRT technique than for conventional radiotherapy. However, further reduction of the number of complications is desirable. Much research and developmental work remains to be done to fully utilise the potential advantages of IMRT. Progress in computerised optimisation, leaf sequencing and multileaf collimator design are just some of the strategies that are currently under development.[15]

Future

With the development of IMRT, xerostomia-preventing radiotherapy was generally focused on protecting the parotid gland. A reduction in mean parotid gland dose using IMRT resulted in a higher parotid flow ratio and a reduction of objective complications, but no improvement in subjective xerostomia was found.[16] Roesink et al.[2] have shown that subjective patient

Table 1: Parotid Gland Function Parameters for Patients with Oropharyngeal Cancer Treated with Conventional Radiotherapy and Intensity-modulated Radiotherapy

Parameter	CRT (n=26)	IMRT (n=30)	p
Parotid gland dose (Gy)			
Mean	48.1	33.7	<0.005
Range	3.6-68.7	13.6-60.6	
Six Weeks			
Flow ratio (%)	11	41	
Complications (%)	87	55	<0.005
Six Months			
Flow ratio (%)	18	64	
Complications (%)	81	56	0.04
12 Months			
Flow ratio (%)	23	73	
Complications (%)	83	43	0.001

scoring for xerostomia does not correlate with the mean parotid dose, as the salivary flow measurements do. This may be due to the fact that the dose–volume response analysis is based only on the function of the parotid glands; the patient's subjective feeling for xerostomia, however, results most probably from the reduced salivary function of the whole salivary system including the submandibular glands, the sublingual glands and the minor salivary glands spread in the oral cavity.[17] The parotid gland is responsible for the main stimulated saliva production. During rest, however, the submandibular glands are responsible for the main saliva production. Owing to their location, the submandibular glands are seldom spared from radiation and a dose–response curve is not available. Submandibular gland sparing might also be achieved using IMRT. It has been reported that sparing the contralateral submandibular gland is feasible using IMRT and resulted in better maintained unstimulated salivary flow rates.[18] It should be noted that IMRT by itself would not solve all problems. In order for IMRT to be effective, accuracy in volume delineation and dose delivery are essential. Imaging is of vital importance to meet the requirements that IMRT poses on treatment planning. In CRT most often the salivary glands are irradiated fully and homogeneously. IMRT treatment planning allows for dose painting, and therefore can account for possible variations in radiosensitivity over the gland volume. It is important to know whether regional enhancements in radiosensitivity occur in order to select the proper dose constraints and plan strategy. Functional dynamic magnetic resonance sialography opens a new field of possibilities for studying the function of the salivary glands *in vivo*.[19]

Conclusions

A reduction of the dose to the parotid glands can be achieved by using IMRT compared with CRT, and indeed reduces the number of objective complications. However, further reduction of the parotid dose to values below 25Gy is desirable. The contribution of the submandibular and minor salivary glands on xerostomia is important, and IMRT should also be focused on submandibular and minor salivary gland sparing. ■

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