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REVIEW ARTICLE

Assessment of post-radiotherapy salivary glands

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ABSTRACT. Salivary glands are usually irradiated during radiotherapy for head and neck cancers, which can lead to radiation-induced damage. Radiation-induced xerostomia (oral dryness) is the most common post-radiotherapy complication for head and neck cancer patients and can reduce the patient's quality of life. Accurate and efficient salivary gland assessment methods provide a better understanding of the cause and degree of xerostomia, and may help in patient management. At present, there are different methods for the assessment of salivary gland hypofunction; however, none of them are considered to be standard procedure. This article reviews the value of common methods in the assessment of post-radiotherapy salivary glands.

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Major salivary glands are situated in the lateral facial and submandibular regions where they are commonly included in or close to the target volume in radiotherapy of head and neck cancers. Parotid glands are commonly irradiated with high-radiation doses in two-dimensional (2D) radiotherapy (conventional radiotherapy) for some head and neck cancers like nasopharyngeal carcinoma (NPC) because they are usually in close proximity to, or within, the radiation field. High-radiation dose can damage salivary glands and lead to xerostomia (oral dryness owing to reduced salivary secretion from the impaired salivary glands). Saliva is produced by acinar cells, drained to the excretory duct though ductal cells and finally secreted into the oral cavity [1]. Saliva is mainly composed of water (99.5%) and the remaining 0.5% includes amylase, inorganic salts, mucin and bicarbonate [2]. It is important to normal daily life because saliva is responsible for moistening and softening food during ingestion, protecting oral mucosa and teeth, and breaking down starch using amylase. Xerostomia could seriously impair health-related quality of life and even the social activities of long-term survivors following head and neck radiotherapy [3–5]. This is because xerostomia can lead to alterations in speech and taste, malnutrition and difficulty in mastication and deglutition [4, 6, 7]. Oral mucosal dryness can also change the oral pH level and predispose patients to mucosal ulcerations, fissures, dental caries and oral infection [6, 8, 9].

Clinically, fractionated doses of 50–70 Gy are prescribed over 5–7 weeks (*i.e.* 2 Gy per day for 5 successive days per week) for common head and neck cancers [10]. However, Eisbruch et al [11] reported that a mean dose of 26 Gy or above to the parotid gland shows significant decrease or immeasurable salivary flow upon stimulation. One must note that radiation-induced xerostomia is an irreversible complication for the parotid gland which has received radiation with a mean dose of 26 Gy or above [11]. The study suggested that a mean dose of 26 Gy was a threshold dose for stimulated parotid glands. Other studies have shown different thresholds of radiation dose for the parotid gland, ranging from 20 Gy to 40 Gy [12]. However, some studies suggested that irreversible xerostomia could occur with a mean dose of over 60 Gy [10, 13]. This discrepancy in different threshold mean doses might be due to different methodologies used in these studies, such as different radiotherapy techniques, treatment protocols and methods in assessing salivary function. Although reduced risk of xerostomia with the use of intensity modulated radiotherapy (IMRT) has been reported, IMRT could not always achieve the suggested mean threshold dose for parotid glands because extensive tumours situated close to the parotid glands in advanced diseases inevitably deliver a high-dose to the glands [12, 14–16]. Kwong et al [17] reported that the mean dose to the parotid glands could be as high as 32.0–46.1 Gy for early stage NPC patients treated with IMRT. Eneroth et al [18] found that radiation as low as 2 to 3 doses of 2 Gy could cause radiation-induced xerostomia. It has also been found that a significant decrease in salivary secretion could appear in the first week of radiotherapy [19]. Hence, head and neck cancer patients treated with radiotherapy could develop different degrees of xerostomia. To accurately assess post-radiotherapy changes of salivary glands or xerostomia, different assessment methods have been reported in the literature. Improvement in the assessment of xerostomia or salivary gland function may allow more accurate evaluation of the dose conformity to the target and the normal structure sparing capability of advancing radiotherapy technologies in the head and neck. Accurate assessment of salivary gland morphological and functional changes after radiotherapy

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may also help to better understand the mechanism of post-radiotherapy xerostomia, which in turn aids the investigation of methods to relieve symptoms of xerostomia and improve the quality of life of the patient. It is also important to identify the post-radiotherapy changes of the salivary glands and differentiate these from other salivary gland diseases to ensure accurate diagnosis and appropriate disease management of this group of patients. Although more conformal radiotherapy techniques such as IMRT and three-dimensional conformal radiotherapy are replacing conventional radiotherapy for better treatment outcomes of head and neck cancers, it is still necessary to prove the worthiness of the new techniques for better disease control and lower risk of complications including post-radiotherapy salivary gland impairment.

Currently there are various methods for the assessment of post-radiotherapy salivary glands and radiation-induced xerostomia, which include histological evaluation, sialometry, MRI, ultrasonography, scintigraphy, CT and questionnaires. This article reviews the value of these methods in assessing post-radiotherapy changes in salivary glands.

Anatomy of salivary glands

In humans there are three pairs of major salivary glands: the parotid, submandibular and sublingual glands, as well as numerous minor salivary glands scattered thoughout the oral cavity.

Parotid gland

The parotid gland is the largest salivary gland located in the retromandibular fossa (Figure 1). It is composed of serous acinar cells, which produce serous saliva, mainly water in content. The imaginary plane formed by the facial nerve divides the parotid gland into superficial and deep lobes. The main salivary duct of the parotid gland is Stensen's duct, which drains saliva at the upper second molar tooth level. The parotid gland mainly secretes saliva in stimulated conditions like chewing, when it secretes up to 60% of total saliva.

Submandibular gland

The submandibular gland is the second largest salivary gland located under the floor of the oral cavity (Figure 1). It is composed of both serous and mucous acinar cells, which produce thicker and more viscous saliva. Its main salivary duct is Wharton's duct, which drains saliva near the lingual frenula. The submandibular gland mainly secretes saliva in non-stimulated conditions, producing up to 90% of total salivary output during the resting state, but contributes only 20–40% of total saliva in stimulated conditions.

Sublingual gland

The sublingual gland is the smallest among the three pairs of major salivary glands, which are located in the floor of the oral cavity and medial to mandible. Similar to the submandibular gland, the sublingual gland is composed of both serous and mucous acinar cells, which produce 2–5% of the total saliva upon stimulation. The intraglandular ducts of sublingual glands may either drain into the Wharton's duct or empty into the floor of the oral cavity directly.

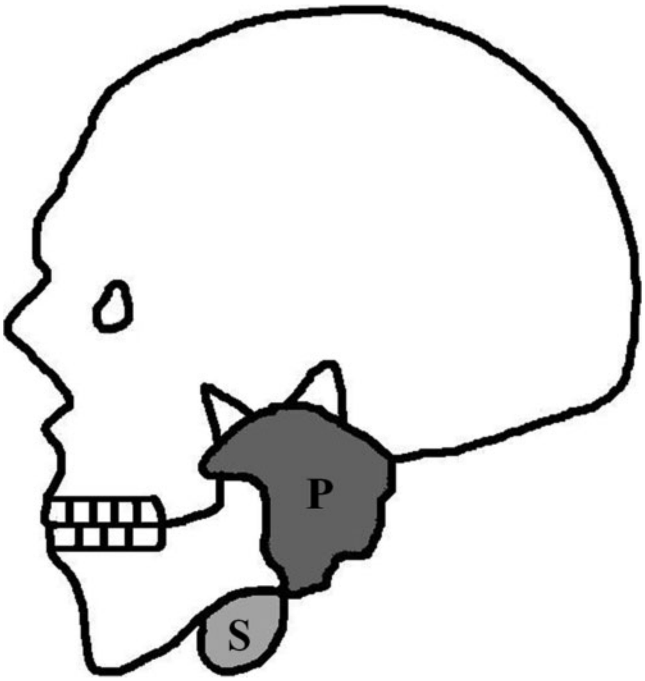

Figure 1. Schematic diagram shows the relative position of parotid gland (P) and submandibular gland (S) in the head and neck region. The parotid gland is located in the retromandibular fossa while the submandibular gland is located under the mandible and in the floor of the oral cavity.

Histological evaluation

Histological evaluation can assess post-radiotherapy changes of the salivary glands because functional change is closely related to histological change [20]. In animal studies, it has been found that normal parotid glands were characterised by homogeneous pure serous acinar cells with densely packed translucent granules and branching intercalated ducts [6, 20, 21]. The densely packed acini and the intercalated ducts were surrounded by myoepithelial cells [21]. Acini were well differentiated from the interlobular excretory ducts and the striated ducts [21]. On the other hand, a normal submandibular gland consisted of both mucous and serous acinar cells and they were slightly vacuolated [20].

Radfar et al [20] investigated the histological changes in salivary glands of Hanford minipigs (a small-sized pig that is a common animal model used to examine post-radiotherapy salivary gland damage) following a fractionated irradiation scheme of 70 Gy, which was commonly prescribed in human head and neck cancer radiotherapy. They found that both irradiated parotid and submandibular glands were characterised by parenchymal loss, acinar atrophy and interstitial fibrosis, duct proliferation, dilated intercalated and striated duct.

Loss of secretory granules in acinar cells and infiltration of inflammatory cells like lymphocytes and plasma cells were also found. However, acinar destruction and degranulation were more obvious in submandibular glands, suggesting that histological change in submandibular glands was more prominent than that in parotid glands. Prince et al [22] performed a similar study on monkeys with 50–55 Gy irradiation, and found similar histological changes in post-radiotherapy parotid and submandibular glands. In addition, they also found that the size of parotid and submandibular glands was reduced after irradiation. However, owing to size reduction of the salivary glands, they argued that there should be an increase in the number of ducts per unit volume in each gland rather than duct proliferation as Radfar et al [23] reported. Moreover, Henriksson et al [21] found mast cells and hyaluronic acid infiltration in irradiated salivary glands of rats, and they believed that the presence of mast cells and hyaluronic acid might be the key elements in activating fibrosis in glands after radiotherapy.

Grehn et al [24] performed an animal study and reported that the loss of acini in parotid glands was dose-dependent. With a radiation dose of 30 Gy, there was a slight decrease in acinar cells from 75.2% in the non-irradiated glands to 69.8% in the irradiated glands. However, with 40 Gy a more significant decrease in acinar cells from 77.3% in non-irradiated glands to 31.9% in irradiated glands was found. Compared with 30 Gy, a radiation dose of 40 Gy induced over 50% reduction in parotid acinar density.

Histology can provide information about the histological variation of post-radiotherapy salivary glands. However, the accuracy of histological findings could be influenced by ageing. Ageing causes a loss of acinar cells, for example around 30% of acinar tissue are lost between 20 and 90 years of age [25]. Scott [26] reported that uniform and densely packed parenchymal tissue of submandibular glands in young people are replaced by loosely fibroadipose tissue with advancing age.

Although the value of histological examination in assessing post-radiation salivary glands has been reported in animal studies, histological evaluation of salivary glands has not yet been established in clinical practice for humans. This is because xerostomia is not a life-threatening condition, and the conduction of the risk-bearing gland biopsy may not be justified for routine clinical practice. Biopsy is an invasive procedure and it may cause complications such as infection, poor wound healing and fistula formation [27]. Hence, safer or non-invasive assessment methods such as salivary flow measurement or medical imaging are commonly employed in the clinical assessment of xerostomia. Nevertheless, histological studies based on animal models have provided an invaluable insight in predicting the radiation response or post-radiotherapy changes of salivary glands in the human population.

Sialometry

Sialometry (salivary output measurement) has been widely used in assessing salivary gland function. It directly measures the function of salivary glands, and can be classified into the whole mouth salivary output measurement and selective salivary gland output measurement. Both methods involve the collection of saliva over a period of time (usually for at least 5 min), and the saliva volume and the salivary flow rate (usually expressed as ml min^{-1}) are determined [6]. In sialometry, both unstimulated and stimulated salivary outputs are measured in order to assess salivary gland function at rest and upon stimulation, such as eating [6].

Whole mouth salivary output measurement can be simply achieved by drainage, spitting or weighing cotton wool balls soaked with saliva in the mouth [6]. The procedure is fast, easily performed and inexpensive; however, it cannot evaluate the function of the individual salivary gland. Parotid saliva collection can be done by catheterisation of the Stensen's duct or using a suction cup such as Lashley cup and Carlson-Crittenden cup attached to the buccal mucosa surrounding to the duct orifice [1, 6, 11, 28]. Submandibular saliva can be collected by gentle suction at the Wharton's duct orifice of the submandibular gland using a micropipette [25, 29]. However, submandibular secretion is actually the combination of saliva from the submandibular gland and sublingual gland as sublingual saliva also drains into Wharton's duct [28, 30, 31]. Therefore, evaluation of submandibular secretion and function by this method should be performed with caution.

Previous studies have used sialometry in the investigation of post-radiotherapy changes of salivary glands. Eisbruch et al [11] found that parotid glands receiving a mean dose higher than 24 Gy and 26 Gy showed no measurable salivary flow and did not recover 12 months after completion of radiotherapy. Hence, 24 Gy and 26 Gy were the respective threshold doses of unstimulated and stimulated salivary flow. In addition, Eisbruch et al [28] studied 84 head and neck cancer patients who received conformal radiotherapy and IMRT thoughout a 2 year post-radiotherapy follow-up, and both stimulated and unstimulated parotid salivary flows were investigated. They demonstrated that in the bilateral neck irradiation group, the salivary flow rate of contralateral parotid glands receiving a mean dose of 21.9 Gy decreased in the early post-radiotherapy period but increased continually afterward and nearly returned to the pre-radiotherapy level after 12 months. The contralateral parotid glands in the unilateral neck irradiation group receiving relatively lower doses (mean dose, 4.1 Gy) showed continuous salivary flow improvement during the second year after radiotherapy and even higher than the pre-radiotherapy level, indicating a compensatory mechanism [1, 28]. However, in both bilateral and unilateral neck irradiation groups, no salivary flow could be detected in the ipsilateral parotid glands, which received a mean dose higher than 30 Gy [28]. Submandibular glands in the unilateral neck irradiation group demonstrated retention of about 50% of the pre-radiotherapy salivary flow in the first 3 months after radiotherapy, but the flow rate increased continually to the pre-radiotherapy level after 1 year [28]. The authors only measured the total output of both submandibular glands, but the contralateral glands received a much lower mean dose compared with the ipsilateral glands (14.7 Gy *vs* 51.4 Gy). Therefore, they believed that the salivary output was mainly contributed by the contralateral glands. In the bilateral neck irradiation group, the salivary flow rates of submandibular glands remained very low in most patients, in which ipsilateral and contralateral glands received mean doses of 66.9 Gy and 57.6 Gy, respectively [28].

Pow et al [32] used sialometry to study the sparing of salivary gland in IMRT for NPC. They found that both stimulated parotid and whole mouth salivary flow were higher in IMRT compared with 2D radiotherapy at 2, 6 and 12 months after radiotherapy. Also, the recovery of salivary flow was only noted in patients receiving IMRT but not in the 2D radiotherapy group.

Although sialometry can directly measure the salivary gland function, there are limitations in the evaluation of post-radiotherapy salivary functional change. Low reproducibility of sialometry may lead to an inconsistent result in the assessment [6]. Ageing may also be a factor leading to the decrease in salivary flow rate, which affects the accuracy of post-radiotherapy salivary gland assessment [25, 30, 33].

Magnetic resonance imaging

MRI is a useful imaging modality for follow-up of head and neck cancer patients treated with high-dose radiotherapy [27]. MRI has excellent spatial resolution, and it is superior to CT in delineating soft-tissue structures. Moreover, it does not involve ionising radiation and allows visualisation of deeply situated tissues, such as the deep lobe of the parotid gland [34].

Nomayr et al [35] evaluated the appearances of radiation-induced changes in normal cervical structures including salivary glands using MRI. They found that volume reduction in the parotid glands occurred after radiotherapy of 60–70 Gy, and the hyperintense signal was detected in 22% of post-radiotherapy parotid glands, and 31% of post-radiotherapy submandibular glands in T_2 weighted (T_2W) images. In follow-up examinations, the signal intensity of the glands decreased in T_2W images but the gland volume continually reduced [35]. Volume reduction and increased signal intensity in salivary glands after radiotherapy were also documented in other studies using MRI for post-radiotherapy evaluation [2, 36]. Increased signal intensity in T_2W images suggested the presence of oedema in the glands owing to the damage of blood and lymph vessels and resulted in reduced lymph transport with accumulation of interstitial fluid [35, 37].

Nomayr et al [35] found that there was a volume reduction of parotid glands in all patients with primary neck tumours after radiotherapy, and such volume reduction might be due to the loss of acinar cells. It is believed that reduced gland parenchyma is mainly due to serous acinar cell loss. A larger extent of parenchyma loss occurs in parotid glands compared with submandibular glands upon irradiation because parotid glands constitute more serous acini [35]. Parotid glands are therefore believed to be more radiosensitive than submandibular glands. However, the difference in the radiosensitivity of parotid and submandibular glands is still controversial. Some studies report the radiosensitivity in parotid and submandibular glands should be similar as they are equally vulnerable to radiotherapy [5, 15, 16].

Apart from conventional MRI, a more advanced MRI technique called MR sialography is becoming popular in the clinical assessment of radiation-induced changes in salivary glands. MR sialography uses heavily T_2W sequences to show salivary ducts, and saliva appears as a hyperintense signal while the surrounding salivary gland tissues appear hypointense [2, 38]. Unlike conventional X-ray sialography, MR sialography does not involve any ionising radiation and cannulation of the salivary ducts, and does not require the introduction of contrast medium, which avoids the uncomfortable feeling during the procedure, radiation risk and possible allergy. Astreinidou et al [38] showed that MR sialography could provide high-quality three-dimensional images of both parotid and submandibular ductal architectures with high reproducibility. They suggested that MR sialography could be used in follow-up examinations to detect the location of potential radiation-induced changes in salivary ducts in post-radiotherapy patients. Astreinidou et al [1] also found that there was no significant change in the visibility of the salivary ducts in the post-radiotherapy compared with the pre-radiotherapy stage in a low-dose level of below 20 Gy. However, reduced visibility of the ducts occurred in the salivary glands that received more than 20 Gy, and increased visibility occurred 6 months post-radiotherapy compared with 6 weeks post-radiotherapy, indicating that the gland had a recovery mechanism [1]. Wada et al [36] also noted the poor visualisation of the intraglandular ducts (main ducts and branches) in stimulated post-radiotherapy parotid and submandibular glands, indicating radiation-induced injury of the glands. It has been reported that the poor visualisation of small intraparotid ducts on MRI after radiotherapy may be due to the increased signal intensity in post-radiotherapy salivary gland tissues or damage of the ducts [1].

Although MRI is capable of showing post-radiotherapy morphological changes in salivary glands and salivary ducts, it has a number of limitations which have restricted its wide clinical application. MR sialography is not effective in detecting or visualising small branches of the salivary ducts [31]. Compared with other imaging modalities, MRI is relatively expensive and more susceptible to motion artefacts owing to its long image acquisition time [34]. Also, MRI is not suitable for claustrophobic patients or patients with metallic implants such as pacemakers, bullets, non-MRI compatible surgical clips and other ferromagnetic implants [31].

Ultrasonography

Ultrasonography is widely used in cancer imaging and screening as it is safe, non-invasive, inexpensive, widely available and carries no radiation hazard [39]. It is useful in delineating superficial soft-tissue structures including those in head and neck regions like the thyroid gland, lymph nodes and salivary glands. Although it is commonly used in the assessment of salivary gland diseases like neoplasms, Sjogren's syndrome, sialadenitis and sialolothiasis, there is scant information in the literature about ultrasound evaluation of radiation-induced xerostomia or post-radiotherapy changes in the salivary glands [40].

Ultrasonography allows the visualisation of the whole submandibular gland, sublingual gland and the superficial lobe of the parotid gland. However, the deep lobe of the parotid gland cannot be assessed by ultrasound because it is obscured by the acoustic shadow of the mandibular ramus [41–43]. In ultrasonography, a normal parotid gland appears as a homogenous speckle pattern structure [42, 44]. The parotid gland is markedly or slightly hyperechoic compared with the adjacent muscle (Figure 2), and echogenicity is determined by the amount of fatty glandular tissue deposited in the gland [42, 45]. Normal intraparotid lymph nodes are usually observed at the pre-auricle level or at the tail of the gland, which is demonstrated as hypoechoic oval structures with hyperechoic central hilus [45]. Normal intraglandular ducts are rarely visualised but they may appear as slightly echogenic linear structures (Figure 3) [43, 45].

A normal submandibular gland is shown on ultrasonographs as a triangular structure in the transverse scan plane [43]. Similar to the parotid glands, the normal submandibular gland appears as a homogeneous structure with markedly or slightly hyperechoic compared with the adjacent muscle (Figure 4) [41, 42]. The normal non-dilated intraglandular ducts of the submandibular gland are rarely seen on ultrasonographs [43].

To the best of our knowledge, there is only one study that documented the post-radiotherapy changes of salivary gland on ultrasonographs. Ying et al [40] used high-resolution ultrasound to compare the sonographic appearances of normal and post-radiotherapy parotid glands. They found that greyscale ultrasound could be used to assess the size, echogenicity and internal architecture of the parotid glands. The post-radiotherapy parotid glands were described as a heterogeneous structure, hypo- or isoechoic relative to adjacent muscles, with multiple hyperechoic lines or spots and hypoechoic areas (Figure 5). Slightly higher conspicuity of intraparotid ducts was noted in post-radiotherapy parotid glands compared with the normal group. The heterogeneous appearance of the post-radiotherapy glands might be due to the patches of inflammatory infiltrate appearing as multiple hypoechoic areas, while the presence of the hyperechoic lines or spots might reflect fibrosis [40]. Fibrosis was characterised with hyperechoic lines of irregular course and thickness but not parallel to each other, in contrast to the intraparotid ducts which were demonstrated as hyperechoic lines with regular course and thickness and parallel to each other [40]. Higher conspicuity of intraparotid ducts in the post-radiotherapy parotid glands might be due to fibrosis or proliferation of the ducts, which provided higher reflective interfaces for ultrasound beam and thus increased ductal echogenicity [40]. In Doppler ultrasound, the authors found that the mean peak systolic velocity (PSV), resistive index (RI) and pulsatility index (PI) of normal parotid glands were significantly higher than that of post-radiotherapy parotid glands [40]. The relatively lower vascular resistance and PSV in post-radiotherapy parotid glands might be due to the lower compression pressure on the vessels by the reduced number of surrounding acinar cells and granules [40]. Although this study documented the sonographic appearances of the post-radiotherapy parotid glands,

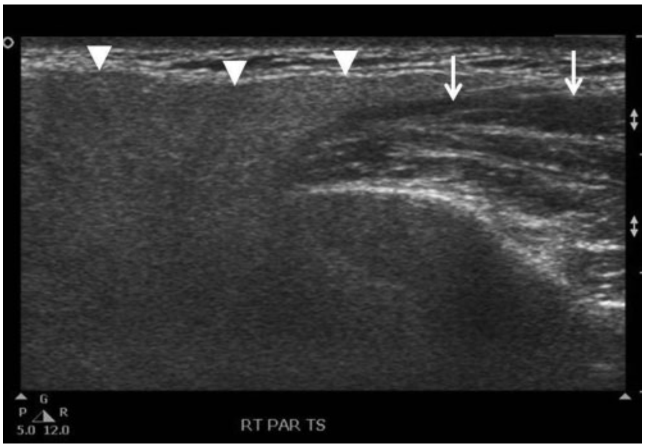

Figure 2. Sonogram shows a transverse scan of a normal parotid gland (arrowheads), which is hyperechoic compared with the adjacent masseter muscle (arrows).

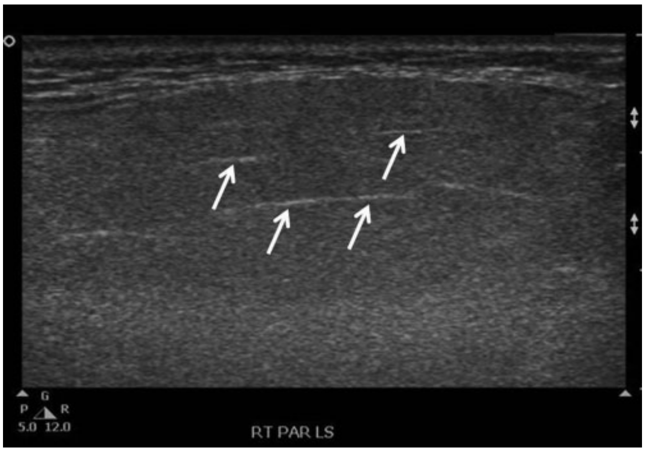

Figure 3. Sonogram shows a longitudinal scan of a normal parotid gland with homogeneous echotexture. The intraglandular ducts (arrows) are marginally seen.

Figure 4. Sonogram shows a transverse scan of a normal submandibular gland (arrowheads) with homogeneous echotexture. The gland is hyperechoic compared with the adjacent mylohyoid muscle (black arrows) and the intraglandular ducts (white arrows) are marginally seen.

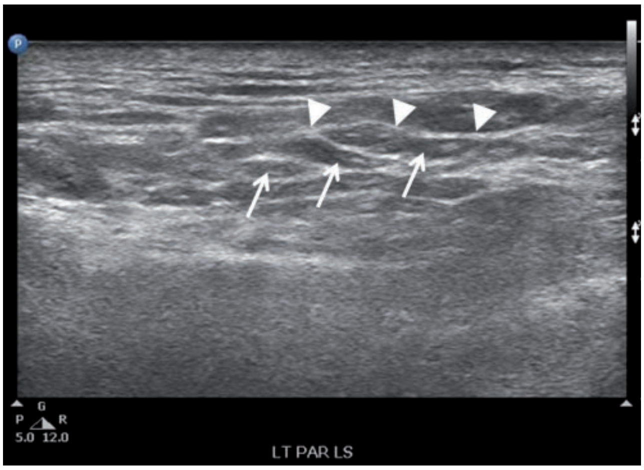

Figure 5. Sonogram shows a longitudinal scan of a parotid gland in a patient treated with conventional radiotherapy. There are multiple hypoechoic areas (arrows) within the gland, and the intraglandular ducts (arrowheads) are obviously seen.

the sample size of the study was small (n=10). Moreover, the study focused on the assessment of the parotid glands in NPC patients treated with conventional radiotherapy.

There are few limitations of using ultrasonography in the assessment of post-radiotherapy changes in the salivary glands. The reported sonographic appearances of the parotid gland in Sjogren's syndrome were similar to those observed in the post-radiotherapy parotid changes, including heterogeneous echotexture, multiple hypoechoic areas and multiple hyperechoic lines or spots [46–48]. Such similarity in sonographic appearances could be confusing when differentiating post-radiotherapy changes with Sjogren's syndrome, leading to inaccurate diagnosis. Ultrasound can not evaluate the deep lobe of the parotid gland as it is obscured by the acoustic shadow of the ramus of mandible [43, 42]. Therefore, the size of the parotid gland cannot be fully evaluated. Operator dependency is also a limitation of ultrasonography [39].

Scintigraphy

Salivary gland scintigraphy has been used in the assessment of salivary gland function including the post-radiotherapy salivary functional change for decades. It makes use of the absorption and excretion properties of radioisotopes such as ^{99m}Tc at the salivary glands for functional assessment [2, 30]. It has been found that ^{99m}Tc is readily trapped and secreted in the ductal epithelium of salivary glands and excreted in the saliva, which allows salivary gland scintigraphy to be performed and provides quantitative information on the glandular function [49, 50]. Apart from minimal invasiveness, scintigraphy has a low radiation dose, good patient tolerance, no interference with the normal physiology of the salivary glands and ready availability of ^{99m}Tc, which make it valuable to salivary functional studies [30, 50]. Scintigraphy provides results for several parameters in salivary functional assessment such as time-activity curve analysis, visual interpretation, salivary target to background ratio and salivary excretion fraction (SEF) [51]. Although parameters help the assessment of different functions of the glands, there is a lack of standardisation in the use of certain parameters, such as SEF, for physicians interpreting salivary scintigrams. Nevertheless, SEF is commonly used to assess radiation-induced xerostomia or other salivary gland diseases [30, 49, 52, 53].

Liem et al [49] found that many post-radiotherapy salivary glands showed impaired saliva excretion with a large amount of radiopharmaceutical (*i.e.* ^{99m}Tc) retained in the salivary glands, and there was no decline in time-activity curves even though the glands were stimulated. As damaged salivary glands fail to excrete saliva into the oral cavity, the radiopharmaceutical cannot be removed by saliva from the gland and it accumulates and is retained within the gland. They also found that there was a dose–response relationship of both the parotid and submandibular glands, which demonstrated that higher radiation doses cause greater reduction in SEF of the salivary glands. A rapid decrease in SEF could occur in salivary glands receiving a radiation dose of 30–70 Gy as early as 1 month after radiotherapy, but SEF can remain unchanged in the glands receiving radiation of less than 24 Gy. A persistent decrease in SEF for 6 and 12 months after radiotherapy was seen in both parotid and submandibular glands receiving more than 30 Gy of radiation [49]. Kohn et al [30] also demonstrated a positive correlation between the salivary flow rate and the scintiscan rating (the summary score of different salivary gland scintigram parameters including initial uptake of the tracer, appearance of unstimulated radionuclide in the oral cavity, radiopharmaceutical concentration in the glands and response to stimulation) of salivary gland scintigraphy in xerostomia patients.

Although salivary gland scintigraphy could reflect the functional change of salivary glands after radiotherapy, its spatial resolution was low and not suitable for the evaluation of morphological change of the glands [30]. Moreover, scintigraphy may not be sensitive enough in detecting slight changes in salivary gland excretion [54]. Hermann et al [51] found that SEF could only distinguish Sjogren's syndrome or radiation damage from normal salivary glands but not from each other, which reflected the poor specificity of scintigraphy in identifying radiation-induced injury in salivary glands. The complexity of the procedure including a range of patient preparation and co-operation, such as fasting and post-imaging radiation management, and the involvement of ionising radiation restrict the use of scintigraphy in routine clinical assessment of salivary gland function.

Computed tomography

CT has been widely used in head and neck cancer imaging. However, there is scant information regarding the application of CT in post-radiotherapy salivary gland evaluation. CT has been proven to be an effective imaging method in the assessment of salivary glands, with nearly 100% sensitivity in detecting salivary gland lesions [34, 35]. A normal parotid gland is a fatty glandular tissue encapsulated by a dense capsule, which is shown as a radiolucent structure in CT compared with the surrounding muscles [55, 56]. In CT, parotid ducts are hardly seen. However, the introduction of iodinated contrast medium increases the sensitivity in the detection of parotid ducts [55, 57]. CT can demonstrate the entire physical volume of the parotid glands.

In CT, the superficial portion of a normal submandibular gland is usually shown as a globular soft-tissue structure superior and lateral to the hyoid bone on CT images [55]. It is more radio-opaque than parotid gland but with a similar opacity to the adjacent muscle [55, 56]. The deep portion of the gland and the intraglandular ducts are well visualised on CT scans [55].

Bronstein et al [56] reported an increased image density in post-radiotherapy salivary glands on contrast-enhanced CT scans (Figure 6). They found that increased image density was associated with a high dose of irradiation to the glands (>45 Gy). Both parotid and submandibular glands showed a similar degree of increased image density after radiotherapy, and the increased image density might be due to the contrast medium stored in the expanded extracellular space resulting in the loss of acinar cells after radiotherapy [56].

Since CT generates cross-sectional images of the region of interest, localisation and volume determination of organs and lesion are possible. Previous studies have found that there was a decrease in parotid gland volume with a rate of 0.6–0.7% volume loss per day during radiotherapy for head and neck cancers, and the median parotid volume loss at the end of treatment was 21.3% [58] or 28.1% [59]. Apart from volume reduction, medial shift of parotid gland with median values of 5.26 mm [58] and 3.1 mm [59] after radiotherapy was also noted. The reduced volume and positional change of salivary glands are important for physicians to determine the post-radiotherapy changes in salivary glands and treatment planning since the change in volume or position may lead to a higher dose received by the glands than expected in the initial treatment planning, especially in IMRT [58]. Hence, replanning within the treatment course may be necessary to ensure the optimal treatment outcomes.

There are some limitations in using CT to assess post-radiotherapy salivary gland changes. Increased image density of salivary glands occurs in radiation doses higher than 45 Gy, but salivary gland dysfunction or radiation-induced xerostomia can happen with a radiation dose below 45 Gy [12, 19, 60]. Also, increased image density was noted in salivary gland tumours and hence image density variations of the glands might not be an accurate indicator to show post-radiation changes [56]. Moreover, a decrease in CT number of salivary gland owing to ageing and increase in adipose tissue [61], and spray artefact from dental filling, would also limit the use of CT on salivary gland diagnosis [62]. CT involves ionising radiation, and iodinated contrast medium is usually required for the examination, which increases the risk of radiation and risk of allergic reaction towards the contrast agents. The use of contrast medium in CT is also contraindicated to patients with poor renal function.

Xerostomia questionnaire

A xerostomia questionnaire is a useful tool in assessing the quality of life for patients with radiation-induced xerostomia. Some questionnaires have been validated to

(a) (b)

Figure 6. (a) Axial CT scan of skull in a nasopharyngeal carcinoma patient before radiotherapy. The image density of the parotid gland (P) is about the same as the adjacent masseter muscle (M). (b) Axial CT scan of a skull in the same patient after radiotherapy. There is an increased image density of the parotid gland (P) when compared with the pre-radiotherapy scan. The image density of the parotid gland is greater than that of the adjacent masseter muscle (M).

evaluate the quality of life of post-radiotherapy xerostomic patients by assessing the ease or difficulty of different oral activities in their daily life [28, 63].

To quantify the quality of life of patients with xerostomia, a visual analogue scale or an 11-point ordinal Likert scale is usually used to evaluate the oral dryness or oral discomfort of the patient [7, 28, 63]. The summation of the score of each item (xerostomia score) in the questionnaire is used to indicate the severity of xerostomia [28].

Eisbruch et al [11] showed that the xerostomia score obtained from the patients after head and neck radiotherapy was significantly higher than the score obtained from the same group of patients before radiotherapy. This demonstrated that the xerostomia questionnaire could detect oral discomfort owing to reduced salivary secretion after radiotherapy. In the follow-up examinations significant decreases in xerostomia scores were found in patients indicating improvement in oral dryness and discomfort. Eisbruch et al [4] reported a lower xerostomia score (less oral dryness) in patients receiving radiotherapy with parotid glands sparing than those treated with conventional radiotherapy.

Similar to other assessment methods, there are limitations of using questionnaires in the assessment of xerostomia. The assessment method is subjective and does not provide quantitative analysis of the function of the salivary glands. There was a weak correlation between xerostomia score and the salivary flow [19, 28, 49]. This weak correlation may be due to the large variation in normal salivary flow rate and the discrepancy between mucosa hydration status and salivary output [28]. Moreover, oral sensory change or alteration in the perception of oral dryness in the mucosal tissue may occur after radiotherapy [29].

Conclusions

A variety of methods are currently available for the evaluation of radiation-induced xerostomia or salivary gland changes. Although there is still a lack of a standardised method for the assessment, morphological assessment methods (*i.e.* histological evaluation, CT, MRI and ultrasonography) and functional assessment methods (*i.e.* sialometry, MR sialography and scintigraphy) can be used together for a more accurate assessment of post-radiotherapy salivary gland. Nevertheless, more effort should be made in the improvement of evaluation of radiation-induced salivary gland changes for better clinical management of patients treated with head and neck radiotherapy.

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