ASPECTS OF SALIVARY GLAND SCINTIGRAPHY
WITH $^{99m}Tc$-PERTECHNETATE

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam,
op gezag van de Rector Magnificus
Prof. Dr. S.K. Thoden van Velzen
in het openbaar te verdedigen in de Aula der Universiteit
(Oude Lutherse Kerk, ingang Singel 411, hoek Spui),
op donderdag 21 januari 1988, te 15.00 uur

door

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geboren te Utrecht

Rodopi

AMSTERDAM 1988
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To Marianne, Jet and Annemartien
To my mother
Acknowledgement:
To all those who have contributed to the realization of this thesis I express my sincere gratitude
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Chapter 1

INTRODUCTION
In 1960 Richards was the first to suggest that technetium-99m, produced by the Brookhaven National Laboratories-U.S.A., might have useful medical applications and soon after that the isotope was introduced for brain and thyroid scanning (Harper et al., 1962, 1964; McAfee et al., 1964; Andros et al., 1965). The ability of the salivary glands to concentrate $^{99m}$Tc-pertechnetate had been recognized since the early days of brain scanning, but this phenomenon initially was considered a nuisance because it interfered with the proper interpretation of the cerebral structures, particularly on the vertex view. However, it was soon realized that active concentration of pertechnetate by the salivary glands provided a welcome opportunity to investigate various diseases of these organs and the first article solely dedicated to salivary gland scintigraphy with $^{99m}$Tc-pertechnetate was published by Börner et al. in 1965. In the following years a large number of publications on the subject appeared in the international literature, indicating a lively interest in the new procedure at a time when, from a practical point of view, only plain radiography and sialography were available to evaluate salivary gland disorders. More than two decades have elapsed since then, during which the initial enthusiasm for the method gradually subsided to a point where it is now probably being underutilized. This decline in interest resulted on the one hand from frustrated expectations as the limitations of the procedure, for instance in tumor diagnosis, became apparent, and on the other hand from the advent of newer and in some respects more rewarding techniques such as ultrasound, computed tomography, aspiration cytology and magnetic resonance imaging. Nevertheless, salivary gland scintigraphy with $^{99m}$Tc-pertechnetate still remains the only procedure with which the functional status of all major salivary glands can be studied simultaneously and as such it may offer information not obtainable by any other diagnostic technique. Provided, therefore, that the proper indications are observed, a greater application of salivary gland scintigraphy in clinical practice and for research purposes is certainly warranted.

The articles included in this thesis aim at promoting such wider use by investigating some fundamental and clinical aspects of the procedure. In particular, an attempt was made to answer the following questions:
- what is the origin of the oral activity seen on scintigraphic images and where is it located?; do dental restorations influence the appearance of this oral activity? (Chapter 4).
- is it feasible to shorten the scintigraphic examination time by ad-
ministering a salivary stimulant at 10 minutes instead of at 20 minutes after pertechnetate injection without forfeiting information? (Chapter 5).
-is there a reliable method for background subtraction? (Chapter 5).
- what is the present status of salivary gland scintigraphy, considering the advent of promising new techniques for evaluating salivary gland disorders? (Chapter 6).
- what is the effect of transoral sialolithectomy on submandibular gland function as measured by salivary gland scintigraphy? (Chapter 7).
- are there clinical situations in which the use of salivary gland scintigraphy is absolutely indicated? (Chapter 8).

References.

Chapter 2

TECHNETIUM-99m
Introduction.

Element No.43, the metal technetium, was discovered by Perrier and Segre in 1937. The name "technetium", derived from the Greek for "artificial", was proposed in 1947 and relates to the fact that this element was the first to be artificially produced by prolonged nuclear bombardment of molybdenum (Perrier and Segre, 1947). It falls in group VII A of the periodic table, together with manganese and rhenium. Today 28 technetium isotopes have been identified, all of which are radioactive (Shukla et al., 1984). Some of them have been detected in distant stars by spectral analysis, but the only natural technetium on earth is technetium-99, the isotope to which technetium-99m decays (Leading Article, Lancet I, 1968).

Physical characteristics of technetium-99m.

One of the isotopes of element No.43 is technetium-99m, presently by far the most frequently used radionuclide in diagnostic nuclear medicine (McIntyre et al., 1980). Technetium-99m in the form of heptavalent pertechnetate ($^{99m}$TcO$_4^-$) may be obtained daily from a $^{99m}$Mo-$^{99m}$Tc generator, originally developed by the Brookhaven National Laboratory (U.S.A.), by eluting the generator with a physiological saline solution. The parent nuclide molybdenum-99 ($^{99}$Mo) disintegrates to technetium-99m by beta decay with a physical half-life of 67 hours. The emitted beta minus particle, an electron, is the result of a neutron to proton transformation, thereby augmenting the charge of the nucleus, and therefore the atomic number, by one. This nuclear transition results in a transmutation from molybdenum to technetium and serves as a basis for the chemical separation of technetium-99m from molybdenum-99 in the generator. Technetium-99m decays by isomeric transition to technetium-99 while emitting gamma rays of 140 KeV with an almost 90% abundance. The physical half-life of this process is 6 hours. In addition to this principal gamma radiation, there is also generation of conversion and Auger electrons and of characteristic roentgen radiation. The nuclei of technetium-99m and technetium-99 contain 43 protons and 56 neutrons. The difference between them is that the nucleus of technetium-99m is in a metastable increased energy state, hence the addition of the superscript m after the mass number. Technetium-99 further decays by beta minus
emission to stable ruthenium-99 with a physical half-life of $2 \times 10^5$ years. Because of this exceptionally long half-life of technetium-99, the resulting secondary radioactivity is very low so that its presence is not considered to be biologically hazardous after diagnostic amounts of technetium-99m have decayed in vivo. Furthermore, since only a very small amount (less than $10^{-12}$ gram) of technetium-99m is used, there is no problem with chemical toxicity.

As mentioned above, technetium-99m is widely used in diagnostic nuclear medicine. This popularity is mainly based upon its favourable physical characteristics. The short physical half-life of 6 hours coupled with the near absence of particulate radiation permit relatively large doses of radioactivity to be administered with little hazard to the patient. Furthermore, the essentially mono-energetic gamma radiation of 140 KeV is almost ideal from the standpoint of external detection. Gamma rays of this energy suitably penetrate soft tissue with a half-value layer of 46 mm, so that the radiation leaves the body without too much absorption in the tissues. The half-value layers in lead and in sodium iodide (NaI) are 0.3 and 2.4 mm, respectively, and these data have been used to develop the scintillation camera for detection of low-energy gamma radiation. This scintillation camera (otherwise known as gamma camera) is equipped with a thin NaI (Tl) scintillation crystal, maximum 1.2 cm in thickness, which absorbs virtually 100% of the low-energy photons. Moreover, a balance between sensitivity and spatial resolution has been achieved by the design of special low-energy collimators with very thin lead septa.

Distribution and excretion of $^{99m}\text{Tc}$-pertechnetate in man.

After intravenous injection, $^{99m}\text{Tc}$-pertechnetate disappears rapidly from the blood. A disappearance curve, based on data collected during several hours after injection, can be fitted with 3 exponential components (Harper and Lathrop, 1972). Approximately 50 to 60% of the injected $^{99m}\text{Tc}$-pertechnetate leaves the blood within 1 to 2 minutes after injection. The curve then continues to decrease rapidly, showing a second component with a half time of 10 to 15 minutes, followed by a much slower third component with a half time of approximately 3 to 6 hours (McAfee et al., 1964; Andros et al., 1965; Beasley et al., 1966; Alberts, 1971). The marked initial decrease of the curve within the first minutes is due to rapid equilibration with extra-cellular fluid, as well as to early selective uptake and excretion of $^{99m}\text{Tc}$-pertechnetate by various organs. Of the total $^{99m}\text{Tc}$-pertechnetate activity circulating in the bloodstream 1 hour after injection, an average of 30% is contained in the red cell fraction and 70% in the plasma. Approximately 80% of the plasma activity is loosely bound to
protein, particularly albumin (Mc Afee et al., 1964; Hays and Green, 1973).

The early distribution of $^{99m}$Tc-pertechnetate is very similar to that of inorganic iodide in that both ions are selectively concentrated by the thyroid gland, the salivary glands, the stomach and the choroid plexus, and excluded from the cerebrospinal fluid. There are, however, quantitative differences between $^{99m}$Tc-pertechnetate and iodide kinetics in various organs and these are probably due to the above mentioned binding of pertechnetate to albumin (Hays and Berman, 1977).

A small fraction of $^{99m}$Tc-pertechnetate concentrates in the thyroid gland. However, in contrast to iodide, the pertechnetate ion is not organified by the thyroid and is released from the gland unchanged, a process that can be accelerated by oral administration of perchlorate. Normal pertechnetate uptake values in the human thyroid, expressed as a percentage of the administered dose, vary depending on the time and method of measurement. Mean values reported in the literature vary from 1.8 to 3.7% at 15 - 30 minutes after injection (Kuba et al., 1967; Shimmins et al., 1968; Alberts, 1971; Bousemann-Sokole et al., 1975) and from 2 to 4% at 1 - 2 hours after injection (McAfee et al., 1964; Andros et al., 1965).

Selective concentration of $^{99m}$Tc-pertechnetate also occurs in the major salivary glands. Quantification of this uptake was first attempted by Harden et al. (1967a). After correction for background activity, they found 30 to 35 minutes after injection a mean parotid gland uptake of 0.35% of the administered dose, with a somewhat lower uptake by the submandibular glands. Stephen et al. (1971, 1976), measuring the uptake during the first 15 minutes after injection, reported mean values of 0.30% of the administered dose in the parotid gland and 0.17% in the submandibular gland. At 15 minutes, however, parotid gland activity was still increasing, whereas by that time submandibular gland activity had reached a plateau or was already decreasing. Schall et al. (1972) and Hug (1973) found that parotid gland uptake, uncorrected for background activity, reached a maximum of 0.79% of the administered dose by 30 to 40 minutes after injection. These data from the literature are largely confirmed by our own observations presented in Chapter 3.

After intravenous injection of $^{99m}$Tc-pertechnetate, the highest level of radioactivity is observed over the stomach. The cells of the gastric mucosa apparently rapidly concentrate pertechnetate and excrete it towards the lumen. Harden et al. (1967b) studied the gastric uptake of $^{99m}$Tc-pertechnetate in a series of normal subjects and found at 6, 20 and 60 minutes after injection an average gastric uptake of 1.2, 3.0 and 6.8%, respectively. Very dynamic movement was noted by Lathrop and Harper
(1972), as 5% of the injected $^{99m}$Tc-pertechnetate appeared in the fundus within 5 minutes after injection and was suddenly swept into the antrum and duodenum by peristaltic action until no more than 1% remained in the entire stomach. This was followed by a rapid build-up to higher levels. As in the thyroid and salivary glands, pertechnetate uptake in the stomach can be discharged by administration of perchlorate.

$^{99m}$Tc-pertechnetate starts to be excreted in the urine soon after intravenous administration. Alberts (1971) found in the first 30 minutes an average urinary excretion of 3% of the injected activity, while Bartelink (1968) reported a 5% recovery during the first hour after injection. Even though a wide inter- and intraindividual variation exists, urinary excretion is maximal during the first 24 hours when an average of 27% of the injected activity is recovered in the urine. After the first day excretion decreases rapidly, so that at the end of a three day interval total urinary excretion of $^{99m}$Tc-pertechnetate averages 33% (McAfee et al., 1964; Andros et al., 1965; Beasley et al., 1966; Bartelink, 1968).

Excretion of $^{99m}$Tc-pertechnetate into the digestive tract occurs through the salivary glands, the stomach and the liver. Since pertechnetate is only partly reabsorbed in the small intestine, a considerable fraction accumulates in the large bowel and is excreted in the feces. In contrast to urinary excretion, fecal excretion reaches its maximum several days following administration of $^{99m}$Tc-pertechnetate. Beasley et al. (1966), using $^{95m}$Tc, found that maximum excretion of technetium occurred on the 4th day when about 25% of the dose was recovered in the stool. In their studies, total fecal excretion at this time was approximately 40% of the injected dose. Others, however, report a wide variation in total fecal excretion over a three day interval with values ranging from 10 to 45 percent (McAfee et al., 1964; Andros et al., 1965). The excretion rate and partition between urine and feces is quite variable among subjects and there is an apparent competition between the two routes which begins immediately after injection (Lathrop and Harper, 1972). Most authors agree, however, that the total recovery in both urine and feces in three days averages 50% of the injected dose (McAfee et al., 1964; Andros et al., 1965; Beasley et al., 1966).

**Handling of $^{99m}$Tc-pertechnetate by the salivary glands.**

It is generally assumed that in man pertechnetate is concentrated and secreted into saliva by the cells of the striated ducts. However, unequivocal evidence demonstrating these cells to be the site of pertechnetate transfer is still lacking. In fact, this assumption is based on animal experiments suggesting a ductal secretion of iodide on the one hand, and salivary
measurements in man indicating a common transport mechanism for iodide and pertechnetate on the other hand. Thus, the argumentation for a ductal transfer of pertechnetate in man involves several steps, which will now be considered in detail.

Evidence from animal experiments indicating a ductal transfer of iodide into saliva:

Using autoradiography of freeze-dried salivary glands, Cohen et al. (1955) and Logothetopoulos and Myent (1956) identified the structures associated with an iodide concentrating mechanism in the submandibular and parotid glands of hamsters and mice. From the pattern of blackening in the autoradiographs they concluded that in these animals the mechanism responsible for concentrating iodide-131 is localized in the proximal ducts of the submandibular gland and the more distal ducts of the parotid gland. Autoradiographs of rat salivary glands, however, showed no selective accumulation of iodide, which is in keeping with the observation that rats are unable to concentrate iodide in their saliva (Cohen and Myent, 1959). McGee et al. (1967), using a more refined autoradiographic technique which keeps the tissues solidly frozen from the time of removal until exposure is completed (Kinter et al., 1960), corroborated the above findings in hamsters but also reported an intense autoradiographic image over several larger distal or excretory ducts. After $^{99m}$Tc-pertechnetate administration, we too observed an autoradiographic label over ductal cells in the mouse submandibular gland (Fig. 1).

Further evidence for a ductal transfer of iodide has been provided by

![Fig. 1. Autoradiograph of the submandibular gland of the mouse showing $^{99m}$Tc-pertechnetate localization in an excretory duct (x 250).](image-url)
Burgen and Seeman (1957) and Burgen et al. (1959) in an experiment involving rapid injection of iodide-131 into the arterial supply of the dog parotid gland. The speed with which the ion appeared in the saliva suggested that iodide must have been secreted via the duct cells rather than the acinar cells.

Finally, Stephen et al., (1971) compared the salivary gland/plasma ratios for iodide and for pertechnetate in the submandibular glands of male and female mice and found a significantly higher ratio for both anions in the male submandibular gland. Since there is a sexual dimorphism in the mouse submandibular gland with a higher proportion of ducts in the male compared to the female gland (Lacassagne, 1940), this observation also supports the hypothesis that active concentration of iodide and pertechnetate occurs in the ducts.

**Extrapolation of the findings from these animal experiments to the human situation:**

Even though no direct information is yet available on the site of iodide concentration in human salivary glands, it is generally assumed that also in man iodide is transported by the cells of the proximal part of the ductal system, i.e. the striated ducts (Freinkel and Ingbar, 1953; Burgen and Emmelin, 1961). However, considering the marked differences between various species regarding the handling of iodide by the major salivary glands (Cohen and Myent, 1959), it is apparent that this assumption is the weakest link in the chain of argumentation mentioned above.

**Evidence from salivary measurements in man indicating the presence of a common transport mechanism for iodide and pertechnetate:**

Several authors have reported that in man a linear relation exists between both the salivary iodide and pertechnetate clearances and the flow rate. Moreover, at all flow rates the pertechnetate clearance is about half the iodide clearance, which suggests that iodide and pertechnetate share a common transport mechanism (Harden and Alexander, 1967; Walker et al., 1970). Further evidence for a shared mechanism has been presented by Harden et al. (1968a,b). These authors pointed out that if the iodide and pertechnetate ions are transferred into saliva by the same route, then the finite number of carrier sites in the salivary glands would demand that an increase in the plasma concentration of one anion (iodide) would result in saturation of the mechanism for both anions. Since such a mutual inhibition would be strong evidence for a common transport mechanism, they studied the relation between the plasma inorganic iodine concentration (PII) and the parotid saliva/plasma ratios for iodide and pertechnetate. It appeared that both the iodide and pertechnetate clearances decreased with an increasing PII concentration. Furthermore, at all flow rates and PII levels the ratio of salivary iodide and pertechnetate
clearances remained constant, the pertechnetate clearance being about half the iodide clearance. These iodine loading studies, therefore, once more indicate the presence in man of a common transport mechanism for iodide and pertechnetate.

The concentrating mechanism for iodide and pertechnetate in the human salivary glands is typical of an active ion transport system in that it can be inhibited by an excess of one of the ions in the source fluid, as described above, but also competitively by other ions, such as perchlorate. Harden et al. (1968b) and Stephen et al. (1973) investigated the inhibitory effect of perchlorate on the concentrating mechanisms for iodide and pertechnetate in the human parotid gland and showed that iodide and pertechnetate behave differently in the presence of perchlorate. They found that perchlorate depresses the pertechnetate saliva/plasma ratio to a greater degree than the iodide saliva/plasma ratio, so that the iodide/pertechnetate clearance ratio rises after perchlorate administration. The reason for this difference in the handling of iodide and pertechnetate is not clear. One explanation might be that although pertechnetate shares with iodide one transport mechanism, it is also transported by a mechanism shared not with iodide but with perchlorate.

Even though the above findings are usually accepted as evidence for a ductal site of iodide and pertechnetate transfer, there are also studies suggesting that acinar cells are active in the salivary uptake and secretion of these ions. Measuring the influence of flow rate on the salivary iodide concentration in man, Mason et al. (1966) found that the iodide concentration falls with increasing flow rate but remains constant at flow rates greater than 1 - 2 ml/min. They argued that this finding may be consistent with the presence of an acinar mechanism secreting iodide at a constant concentration in addition to the iodide secreting mechanism in the ducts. At low flow rates an acinar iodide secreting mechanism would contribute little to the salivary iodide, the majority being secreted via the duct cells. At rapid flow rates, however, most of the salivary iodide would be secreted via the acini, so that the salivary concentration would then be almost constant.

In an experiment in monkeys, Scott et al. (1984) studied the effect of unilateral experimental injury to the parotid gland (duct ligation and intraglandular injection of a sclerosing agent) on the glandular pertechnetate uptake. The pertechnetate uptake, expressed as the ratio of the operated to the unoperated side, was compared with the ratios of the weights of various salivary component tissues, such as acini and ducts, morphometrically determined at necropsy. The results suggest that in the monkey uptake levels of pertechnetate are influenced predominantly by the mass of acinar rather than ductal tissue present. However, a drawback
of such a quantitative approach is that the quality of the various tissue components is not taken into consideration. For example, in the glands subjected to experimental surgery the proportional volume of ducts increased but these ducts were often simple ductules indicating only limited regeneration of glandular epithelium. Hypothetically it is possible that the cells of these ductules do not possess the capacity for pertechnetate concentration, in which case Scott's conclusions would be invalidated.

Recently, Fox et al. (1986) provided evidence that in rats transport of $^{99m}$Tc-pertechnetate occurs in parotid acinar cells. They found that pertechnetate was present in saliva within the first minute after injection and that normal or induced fluctuations in fluid secretion from parotid glands were closely mimicked by fluctuations in $^{99m}$Tc-pertechnetate output. However, the saliva to plasma pertechnetate ratio was always smaller than unity, which is consistent with earlier reports indicating that rat parotid gland duct cells lack the ability to concentrate iodide (Logothetopoulos and Myent, 1956; Cohen and Myent, 1959). In vitro experiments further indicated that parotid acinar cells are capable of uptake and release of $^{99m}$Tc-pertechnetate. The transport mechanism of $^{99m}$Tc-pertechnetate in rat parotid acinar cells was studied by Helman et al. (1986). These authors investigated the relationship between pertechnetate transport and Cl$^-$ transport and found evidence that pertechnetate is taken up by the Na$^+$/$K^+$/$Cl^-$ cotransport system. When acinar cells were incubated in the presence of the loop diuretic furosemide, which inhibits Na$^+$/$K^+$/$Cl^-$ cotransport, pertechnetate uptake was completely inhibited. Replacement of K$^+$ or Na$^+$ in the extracellular medium resulted in a 50 to 90 percent decrease of pertechnetate uptake. Furthermore, when extracellular Cl$^-$ was replaced by iodide, uptake of pertechnetate decreased by almost 90 percent, but when the impermeant anion gluconate was used to replace Cl$^-$ a 300 percent increase in pertechnetate uptake was found. On the basis of these findings, Helman et al. (1986) concluded that pertechnetate is taken up by rat parotid acinar cells via the Na$^+$/$K^+$/$Cl^-$ cotransport system thought to be responsible for primary saliva formation.

In conclusion, there are strong indications from animal experiments that iodide and pertechnetate are transported into saliva by cells of the ductal system, even though there is also some evidence for a role of acinar cells in this respect. In the human salivary glands pertechnetate and iodide are probably transported by the same mechanism, but the exact site or sites of this transfer system are still uncertain. Further research would be required to elucidate this question.
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Chapter 3

SALIVARY GLAND SCINTIGRAPHY WITH $^{99m}$Tc-PERTECHNETATE IN NORMAL SUBJECTS
Introduction.

For a correct interpretation of abnormal results, a thorough knowledge of normalcy is required. This somewhat platitudinous but nevertheless accurate statement applies to all diagnostic procedures, and salivary gland scintigraphy is no exception to the rule. For this reason, a review of the available normal data from the literature, as well as our own results in normal subjects, are presented.

Salivary gland images and time-activity curves in normal subjects.

Salivary gland dynamics with respect to $^{99m}$Tc-pertechnetate can be visually evaluated by using a gamma camera. As a result of concentration, secretion and excretion of pertechnetate by the major salivary glands, the appearance of these glands on sequential images changes with time so that a visual assessment of their function can be made. Pertechnetate uptake in the parotid and submandibular glands can already be identified in the first 2 minutes after injection. Over the next hour, there is a progressive increase and subsequent decrease of radioactivity in the glands, resulting in marked changes on the sequential images. This is exemplified by Fig. 1, showing the variation in glandular and oral appearance during that period. Laterally on the images, the parotid glands are visible as oval-shaped regions of activity. Caudally and medially from the parotid glands, the submandibular glands appear more circular or kidney-shaped; they are most distinct at 10 minutes but can barely be distinguished from the surrounding blood activity at 60 minutes. The oral activity, whose origin and location will be discussed in detail in Chapter 4, is faintly visible at 10 minutes and increases throughout the study, eventually becoming the most intense region of activity.

Schall et al.(1971) evaluated the normal and abnormal pattern of pertechnetate uptake and excretion, as seen on sequential images, and proposed a classification of salivary gland function based on the following criteria:

Class 1. Normal results, with rapid uptake of $^{99m}$Tc-pertechnetate by the salivary glands within the first 10 minutes, progressive increase in concentration, and prompt excretion into the oral cavity by 20 to 30 minutes. At the end of the study (at 60 to 80 minutes), the oral activity is higher than activity in the glands.
Class 2. Mild to moderate dysfunction, with relatively normal salivary dynamics, but reduced absolute level of concentration; or with normal uptake, but a delay in the entire time sequence. Oral activity is less than normal and approximately equals glandular uptake at the end of the study.

Class 3. Severe dysfunction, with markedly delayed and diminished concentration and excretion of $^{99m}$Tc-pertechnetate. Oral activity may not be obvious even at the end of the study.

Class 4. Very severe dysfunction, with complete absence of active concentration. Glandular activity is no more than background, and the oral cavity may even appear as a negative defect.

This qualitative classification, sometimes with slightly modified criteria, was adopted by several authors as a useful screening method to visually separate normal uptake and excretion of $^{99m}$Tc-pertechnetate from various stages of salivary dysfunction (Simon et al., 1976; Katz et al., 1980; Janin-Mercier et al., 1982).

Daniels et al. (1979) devised a semi-quantitative scintigraphy score by allotting grades to 5 factors observed on sequential scintigraphic images: the time at which pertechnetate appears in 1. parotid glands, 2. submandibular glands, and 3. the oral region; and the concentration of pertechnetate in 4. parotid glands and 5. submandibular glands. Grades used were: 0 (normal), 1 (delayed or reduced pertechnetate accumulation), and 2 (marked delay or reduction of pertechnetate accumulation). The timing of pertechnetate appearance was based on the following ranges: in parotid and submandibular glands, normal = less than 4 minutes, delayed = 4-20 minutes, and marked delay = greater than 40 minutes to absent; in the oral region, normal = up to 20 minutes, delayed = 20 - 40 minutes, and marked delay = greater than 40 minutes to absent. Adding the grades for
Fig. 2. Normal shape of parotid and submandibular gland time-activity curves.

each of the 5 factors gives a scintigraphy score on a scale of 0 (=normal) to 10 (=total absence of salivary gland function).

Time-activity curves graphically display the variation in radioactivity in regions of interest over a period of time. Glandular curves represent a summation of active uptake, secretion and excretion of pertechnetate by the salivary glands and as such reflect various aspects of glandular function. The shapes of the parotid and submandibular gland time-activity curves vary between normal subjects, although their basic pattern remains the same (Fig.2). The initial sharp rise is explained by arterial supply in the gland proper and by active uptake of pertechnetate by the glandular parenchyma, which already takes place in the first minute (Schall et al., 1972; Fox et al., 1986). The curves then continue to rise gradually and, after attaining a maximum, decrease as a result of excretion of pertechnetate into the oral cavity. In normal subjects, the rate of the resting salivary secretion is probably the major factor influencing the shape of the curve in that a high resting secretion will result in a relatively low and early maximum, whereas in the case of a low resting secretion the reverse will occur (Hug, 1973; Tainmont, 1982). In a series of 17 normal subjects, Busemann-Sokole and van den Akker(1977) found that the time-activity curves of right and left glands were generally symmetric, both in amplitude
and time of maximum uptake. The parotid gland curves mostly reached a plateau and had a broad peak extending over several minutes, whereas the submandibular gland curves exhibited a sharper peak followed by a rather rapid decline (Fig. 2). The time of maximum pertechnetate uptake varied between subjects, but in each subject the submandibular glands reached their maximum uptake earlier than the parotid glands. The mean time for the submandibular glands was 9 minutes (range 4-24 minutes) and for the parotid glands 28 minutes (range 13-48 minutes). In 70% of the subjects, the submandibular glands had already reached maximum uptake by 10 minutes after pertechnetate injection (Table 1).

Table 1. Time of maximum $^{99m}$Tc-pertechnetate uptake in a series of 17 normal subjects.

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<td>6</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Submandibular</td>
<td>12</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Assuming that the oral activity represents pertechnetate uptake in the minor salivary glands, several authors have reported the following sequence in the time of maximum glandular uptake: parotid glands, submandibular glands, sublingual glands and palatine glands (Börner et al., 1965; Kessler et al., 1969; Lafaye et al., 1973). From this they concluded that serous glands concentrate pertechnetate faster than either mixed glands or mucous glands. However, two observations are in direct contradiction with this conclusion. Firstly, as already mentioned above, submandibular glands consistently reach their maximum uptake earlier than the parotid glands. Secondly, it has been demonstrated that the oral activity does not represent pertechnetate uptake in the sublingual and minor salivary glands of the oral cavity, but instead is due entirely to radioactive saliva excreted by the parotid and submandibular glands (Chapter 4). Since, under resting conditions, the flow rate of the submandibular glands is two to three times greater than that of the parotid glands (Schneyer and Levin, 1955), the available data once more suggest that the shape of the time-activity curve and the time of maximum uptake are related to the flow rate rather than to the histologic type of the gland.

In the literature on salivary gland scintigraphy there is a consensus to evaluate pertechnetate secretion and excretion under reproducible
stimulated conditions in order to fully assess the functional capacity of the glands. Stimulation of the salivary flow will not only accentuate the differences between normal and abnormal glandular function with respect to pertechnetate, but will also result in a much shorter examination time without forfeiting information (Schall and DiChiro, 1972; Busemann-Sokole et al., 1977; Greyson and Noyek, 1982). However, opinions differ on the mode of stimulation — gustatory or parasympathomimetic — and the time of administration of the stimulant after pertechnetate injection. Many authors have recommended subcutaneous injection of carbachol (carbamylcholine chloride), a parasympathomimetic agent, at approximately 20 minutes after pertechnetate injection (Zum Winkel et al., 1973; Albegger et al., 1973; Albrecht and Creutzig, 1976; Jung and Meyzis, 1976; Busemann-Sokole et al., 1977; De Rossi and Focacci, 1980). This agent acts directly on the glands via the circulation and therefore has the disadvantage of potential cholinergic side-effects in patients with bronchial asthma, coronary disease and peptic ulcer. For this reason, others prefer some form of gustatory stimulation, i.e. oral administration of citric acid, ascorbic acid or commercially available lemon juice, which, moreover, acts on the glands in a more physiological manner via receptors and reflex arcs (Hug, 1973; Parret and Peyrin, 1979; Schneider et al., 1984; Tsujii, 1985). However, since the glandular response to gustatory stimulation is dependent on the presence of normal taste buds and intact reflex arcs, partial or complete interruption of the nervous transmission will result in a decreased or even absent salivary flow that is not directly related to the secretory ability of the glands per se. Abnormal gustatory stimulated flow rates must therefore be anticipated in patients with a decreased taste acuity (hypogeusia) due to marked degenerative changes in the taste receptors or reflex arcs. Such changes have been reported, for instance, in patients with Sjögren's syndrome, diabetes mellitus, facial paralysis, or after radiation to the head and neck area (Henkin et al., 1972; Guerrier and Uziel, 1979; Yamashita et al., 1985; Tsujii, 1985). A modified taste sensation may also be present in smokers, patients with colds, or denture wearers (Henkin and Christiansen, 1967).

Another factor which may affect the glandular response to gustatory stimulation is the distribution of the stimulating solution in the mouth. Enfors (1962) pointed out that an even distribution is essential for a balanced stimulated secretion from the right and left glands. In an experiment in subjects holding their heads in different positions while a citric acid solution was administered, he showed that the salivary flow was higher from the gland on the downward-turned side of the face. Even when the position of the head in the sagittal plane was carefully checked, considerable differences were sometimes found between the quantity of
Table 2. Percent uptake of $^{99m}$Tc-pertechnetate by normal functioning parotid and submandibular glands (mean ± 1SD).

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>time p.i. (min)</th>
<th>parotid gland</th>
<th>submand. gland</th>
<th>parotid gland uncorrected for BG</th>
<th>submand. gland uncorrected for BG</th>
<th>parotid gland corrected for BG</th>
<th>submand. gland corrected for BG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schall et al., 1972</td>
<td>10</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>0.78 ± 0.23</td>
<td>0.47 ± 0.20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hug, 1973</td>
<td>41</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>0.79 ± 0.15</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>van den Akker &amp; Busemann-Sokole, 1977</td>
<td>17</td>
<td>28</td>
<td>9</td>
<td>0.81 ± 0.26</td>
<td>0.45 ± 0.24</td>
<td>0.44 ± 0.15</td>
<td>0.24 ± 0.11</td>
<td></td>
</tr>
<tr>
<td>Noodt et al., 1985</td>
<td>45</td>
<td>-</td>
<td>-</td>
<td>0.50 ± 0.20</td>
<td>-</td>
<td>0.54 ± 0.18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = number of subjects

BG = background activity
secretion from the right and left glands, even though previous parasympathomimetic stimulation had elicited a similar output bilaterally. These observations were confirmed by Ericson (1969) who found in a large series of normal subjects that the correlation coefficient for the stimulated secretion from the right and left parotid glands was 0.80 after citric acid stimulation but not less than 0.95 after parasympathomimetic stimulation.

A specific disadvantage of gustatory stimulation in sequential salivary gland scintigraphy is that it involves opening of the mouth and manipulating under the gamma camera to administer the stimulant, which may result in movement of the head, and hence a change in position of the salivary glands relative to the detector. It is apparent that such a change in position may influence the number of counts in regions of interest centred over the salivary glands, which makes the registration of quantitative data less reliable. Nevertheless, the present trend is towards using gustatory instead of parasympathomimetic stimulation.

Quantitation of \(^{99m}\text{Tc}\)-pertechnetate uptake and excretion by the major salivary glands.

Quantitation of pertechnetate uptake by the salivary glands of normal subjects was first attempted by Harden et al. (1967). On dot scans obtained by rectilinear scanning 30-35 minutes after pertechnetate injection, the uptake was calculated by drawing circles around the glands and comparing the number of enclosed dots with the dot values obtained from scanning a phantom containing a known amount of pertechnetate. A correction for background activity was made by drawing circles of the same diameter in adjacent areas and subtracting the dots in these circles from the dots over the glands. In this manner, Harden et al. (1967) measured a mean parotid gland uptake of 0.35% of the administered dose, with a slightly lower uptake by the submandibular glands. However, using a gamma camera and a data processing or computer system, subsequent authors consistently found a higher parotid gland uptake (Table 2). Maximum submandibular gland uptake was more variable but always considerably lower than parotid gland uptake.

Several authors have proposed the use of function parameters for a semi-quantitative analysis of the time-activity curves. Parameters recommended for characterizing glandular accumulation of pertechnetate include the time to reach maximum uptake (Albrecht and Creutzig, 1976; De Rossi and Focacci, 1980; Peyrin, 1983), the rate of accumulation measured from the slope of the ascending part of the curve (De Rossi and Focacci, 1980; Schneider et al., 1984) and uptake ratios calculated directly from the measured counting rate. The most frequently used uptake ratios are:
in which \( \text{Max} \) = the number of counts at the maximum of the curve and \( \text{BG} \) = the number of counts in a background region measured at the same time. Normal values of the latter ratio are presented in Chapter 5 (Table 2) and closely agree with the values reported by Häusler et al. (1977). The times of maximum pertechnetate uptake observed by various authors are shown in Table 3. The usefulness of this parameter is limited, however, considering its dependence on the resting salivary flow which shows a large interindividual variation (Mason and Chisholm, 1975).

### Table 3. Time of maximum \(^{99m}\)Tc-pertechnetate uptake in parotid and submandibular glands of normal subjects (mean ± 1SD).

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of subjects</th>
<th>Parotid gland</th>
<th>Submandibular gland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hug, 1973</td>
<td>41</td>
<td>29.7 ± 15.8</td>
<td></td>
</tr>
<tr>
<td>Albrecht &amp; Creutzig, 1976</td>
<td>16</td>
<td>20.5 ± 6.5</td>
<td>12.3 ± 6.9</td>
</tr>
<tr>
<td>Busemann-Sokole &amp; van den Akker, 1977</td>
<td>17</td>
<td>28 ± 11</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>De Rossi &amp; Focacci, 1980</td>
<td>32</td>
<td>19 ± 3</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>Peyrin, 1983</td>
<td>50</td>
<td>23 ± 1.4*</td>
<td>13 ± 1.3*</td>
</tr>
</tbody>
</table>

*SEM

The amount of pertechnetate excreted in response to a stimulus is considered by many the most reliable parameter to distinguish between normal and abnormal glandular function (Havlik et al., 1976; Albrecht and Creutzig, 1976; Glanzmann et al., 1978; Schneider et al., 1984). Relative and absolute excretory values have been recommended which are expressed, respectively, as a percentage of the maximum glandular uptake and as a percentage of the injected activity (Table 4). Distinct advantages of the relative values are on the one hand their independence of the height of maximum uptake, and on the other hand the fact that they can be obtained directly from the measured counting rate without calculation of
Table 4. Values of different excretory parameters measured in normal subjects (mean ± 1SD).

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Max - Min</th>
<th>Max - Min</th>
<th>Max* - Min*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Max - BG</td>
<td>x 100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max - BG</td>
<td>x 100%</td>
<td></td>
</tr>
<tr>
<td>Hug, 1973</td>
<td>41</td>
<td>53 ± 11</td>
<td>41 ± 10</td>
<td>0.35 ± 0.14</td>
</tr>
<tr>
<td>Havlik et al., 1976</td>
<td>11</td>
<td>53 ± 7</td>
<td>41 ± 9</td>
<td>0.26 ± 0.17</td>
</tr>
<tr>
<td>Albrecht &amp; Creutzig, 1976</td>
<td>16</td>
<td>53 ± 11</td>
<td>41 ± 10</td>
<td></td>
</tr>
<tr>
<td>van den Akker &amp; Busemann-Sokole, 1977</td>
<td>17</td>
<td>53 ± 7</td>
<td>41 ± 9</td>
<td></td>
</tr>
<tr>
<td>Tainmont, 1982</td>
<td>49</td>
<td>63 ± 10</td>
<td>72 ± 10</td>
<td></td>
</tr>
<tr>
<td>Bornemann &amp; Creutzig, 1983</td>
<td>102</td>
<td>62 ± 11</td>
<td>48 ± 9</td>
<td></td>
</tr>
<tr>
<td>Peyrin, 1983</td>
<td>50</td>
<td>73 ± 1.5**</td>
<td>53 ± 1.3**</td>
<td></td>
</tr>
<tr>
<td>Noodt et al., 1985</td>
<td>45</td>
<td>81 ± 15</td>
<td>72 ± 18</td>
<td>0.40 ± 0.18</td>
</tr>
</tbody>
</table>

n = number of subjects
Max = maximum glandular counts
Min = minimum glandular counts
BG = background counts
* calculated as % injected dose
** SEM
the percentage injected activity. These advantages also apply to the maximum/minimum excretory ratio advocated by Busemann-Sokole et al. (1977) and Yamashita et al. (1985), the normal values of which are presented in Chapter 5 (Table 2).

As shown in Table 4, relative excretory values have been calculated in two ways, the difference being whether or not background activity is subtracted from the maximum counts in the denominator of the fraction. It is apparent that subtraction of background activity results in a higher percentage of excretion. Furthermore, the considerable differences between authors in the way background activity is measured also have a large influence on the calculated percentages. Tainmont (1982), for instance, assumes that background activity in the submandibular gland area is twice that in the parotid gland area. This explains why he, in contrast with all other authors, finds a higher percentage of excretion in the submandibular gland than in the parotid gland.

Recently, Blue and Jackson (1985) introduced a method to determine the stimulated salivary clearance of pertechnetate. In contrast with the semi-quantitative parameters mentioned above, this stimulated salivary clearance is independent of patient size (volume of distribution) and of gastric or thyroid function with respect to pertechnetate. Using commercial lemon juice as a stimulant, the authors collected whole saliva for 10 minutes and a single blood sample at the exact midpoint of the collection period. Serum and saliva samples were counted after which a pertechnetate clearance value, expressed as ml/min, was calculated. A comparison of the salivary clearance values from a group of normal subjects with the values obtained in a group of patients with known salivary dysfunction (Sjögren’s syndrome; status after radiotherapy) showed that all normal values were greater than 15.0 ml/min, whereas all of the abnormal patients’ clearances were less than 10.6 ml/min. These results seem to indicate that stimulated salivary clearance of pertechnetate clearly separates normal subjects from patients with salivary dysfunction. However, the patients in this study all had advanced sicca symptoms, and it is likely that an overlap of values with a subsequent decrease in sensitivity will occur when the method is used in patients with less advanced disease. Furthermore, a distinct limitation of the method is that it can only be used in patients with multiglandular involvement.

Even though many of the above mentioned authors have recommended the routine use of quantitative parameters, it remains questionable whether this is really necessary in everyday clinical practice. It seems reasonable to suggest that in the majority of clinical situations sufficient information on glandular function can be obtained by gross visual assessment of the scintigraphic images and time-activity curves. For
research purposes, however, and sequential monitoring of patients with specific diseases, a quantitative approach certainly provides a more objective means of long-term follow-up. This is exemplified by the study presented in Chapter 7, in which quantitative parameters have been used to evaluate the effectiveness of a particular surgical procedure.

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Chapter 4

THE ORAL ACTIVITY

I. ORIGIN AND LOCATION OF THE ORAL ACTIVITY IN SEQUENTIAL SALIVARY GLAND SCINTIGRAPHY WITH $^{99m}$Tc-PERTECHNETATE.*

II. THE INFLUENCE OF DENTAL RESTORATIONS ON SALIVARY GLAND SCINTIGRAPHY WITH $^{99m}$Tc-PERTECHNETATE.**

ORIGIN AND LOCATION OF THE ORAL ACTIVITY IN SEQUENTIAL SALIVARY GLAND SCINTIGRAPHY WITH $^{99m}$Tc-PERTECHNETATE.

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University of Amsterdam, Amsterdam, The Netherlands

Abstract

Conflicting views exist regarding the origin and location of the oral radioactivity seen in salivary gland scintigraphy with $^{99m}$Tc-pertechnetate. The normal accumulation of oral activity was studied in a series of healthy subjects by sequential scintigraphy (anterior and lateral views) after intravenous injection of 74 MBq of $^{99m}$Tc-pertechnetate. Ligation of the parotid ducts and/or cannulation of the submandibular ducts, which prevented their secretions from reaching the oral cavity, established that the oral activity was due entirely to radioactive saliva secreted by the parotid and submandibular glands. Pertechnetate mouthwash studies confirmed that radioactive saliva is adsorbed to oral mucosa and that adsorption to the lingual mucosa is the major contributor to the oral activity. Pertechnetate uptake in sublingual and minor salivary glands of the oral cavity was not visualized, thereby invalidating scintigraphy in the study of these glands. In the diagnosis of salivary gland disorders, oral activity is a useful indicator of major salivary gland function.

Introduction

Scintigraphy of the salivary glands using $^{99m}$Tc-pertechnetate was introduced into clinical practice by Börner et al. in 1965\(^1\). During the ensuing 10 years both static and dynamic scintigraphy have become increasingly popular as noninvasive means of investigating salivary gland disorders, even though the diagnostic limitations have not yet been fully established. A major difficulty with these scintigraphic studies is the disagreement regarding the origin of the "oral activity", the radioactivity seen to accumulate in the oral region. This activity has been attributed by some to pertechnetate uptake in the sublingual and minor salivary glands\(^1-5\) and by others to radioactive saliva secreted by the parotid and submandibular glands\(^6,7\). To further complicate the matter, many investigators have accepted both sources, but without reference to their relative contributions\(^8-16\).

In the present study, the exact origin and location of the oral activity were investigated in a series of volunteers in order to establish the significance of this activity in salivary gland scintigraphy.
Materials and Methods

Sequential scintigraphy was performed in 18 healthy volunteers, none having a history of salivary gland disorder, to study the accumulation of $^{99m}$Tc-pertechnetate in the region of the oral cavity. Informed consent was obtained from each subject before his participation. A Searle Radiographics Pho/Gamma III HP scintillation camera and a low-energy high-resolution parallel-hole collimator were used, together with a 4096-channel analyzer and magnetic tape data-processing system. In all subjects sequential studies were carried out in the frontal view, with the subject in the supine position and with the head slightly extended. Immediately after intravenous injection of 74 MBq of $^{99m}$Tc-pertechnetate, consecutive 2-minute scintiscans were made up to 10 minutes, followed by 5-minute scintiscans every 10 minutes up to 65 minutes after injection. The digitized data were stored on magnetic tape at 2-minute intervals and later replayed to obtain time-activity curves for selected regions over the right and left parotid and submandibular glands ($4 \text{ cm}^2$) and different parts of the oral activity ($2.5 \text{ cm}^2$).

Positional changes resulting from opening the mouth were investigated after completion of the sequential series: scintiscans in frontal and lateral views were obtained with the mouth closed and with the mouth held maximally open with a bite block. In four subjects the position of the palate was established in frontal and lateral views by an acrylic palatal plate containing a small $^{99m}$Tc marker in the midline. In two subjects, lateral sequential studies up to 65 minutes after injection were carried out to follow the accumulation of oral activity in this projection.

The effects of radioactive saliva secreted by the major salivary glands were studied in eight subjects. In five subjects saliva from these glands was prevented from reaching the mouth by ligation of both parotid ducts and cannulation of both submandibular ducts, after which the sequential study was started. The individual contributions of these glands were studied in three subjects in whom, respectively, one parotid duct was ligated, both parotid ducts were ligated, and both submandibular ducts were cannulated. In each subject, the sequential study was continued up to 55 minutes after injection of $^{99m}$Tc-pertechnetate and compared with a normal study performed 1 week previously. Ligation merely involved tying a suture around the parotid duct under local anesthesia. The temporary obstruction caused no adverse effects throughout a 1-year followup.

In two subjects, a submandibular duct was located by inserting a polyethylene catheter cut to the length of the duct and containing a small $^{99m}$Tc source at each end. Before introducing the catheter into the submandibular duct, the lingual nerve was anesthetized with a 2%
lidocaine solution. This also blocked the secretory-motor fibers to the submandibular gland, thereby preventing obstructive symptoms from developing. In two other subjects the orifice of the parotid duct was located on the scintiscans using only the tip of a catheter containing a small $^{99m}$Tc marker.

Frontal and lateral scintiscans were obtained in three subjects after a saline mouthwash containing 20 MBq of $^{99m}$Tc-pertechnetate had been held in the mouth for 10 minutes. Scintiscans were then repeated twice, each time after thoroughly rinsing the mouth with saline solution for 10 minutes. The data were stored on magnetic tape and replayed to calculate the percentage of activity retained in the oral cavity after each rinse.

**Results**

In all normal frontal and lateral sequential studies, radioactivity became visible in the oral region during the first 10 minutes after the intravenous injection of $^{99m}$Tc-pertechnetate. As early as 4 minutes after injection, the frontal images showed weak diffuse bands of activity extending cranially from the submandibular glands to the midline. These bands were followed by distinct activity in the midline ("lower activity"), which in lateral studies corresponded to activity ventrally in the oral region (Fig. 1). Activity in the upper part of the mouth ("central activity") became

![Fig. 1. Normal sequential images in frontal (top) and left lateral (bottom) views after intravenous injection of $^{99m}$Tc-pertechnetate. Diagrams show locations of parotid gland (P), submandibular gland (S), central activity (C), lower activity (O), lateral activity (L), nasal activity (N), and thyroid gland (T).]
Fig. 2. Relative shapes and magnitudes of time-activity curves from 2.5 cm² regions in oral activity after intravenous injection of 74 MBq of $^{99m}$Tc-pertechnetate. Curves are averaged from 10 normal subjects and are uncorrected for background activity because of its variable magnitude in different oral regions.

Fig. 3. Oral activity seen frontally (A) and laterally (B) in normal study is absent after ligation of both parotid ducts and cannulation of both submandibular ducts (C,D). Radioactive saliva in submandibular duct catheters is visible on frontal image in midline, particularly where catheters run briefly toward detector after emerging from mouth (C, arrow). Haze over thyroid region (C,D) is due to leakage from catheters onto absorbent paper. Ligation of parotid ducts (without submandibular cannulation) suppresses lateral oral activity, both for bilateral ligation (E) and for right ligation only (F). Note retention of activity in obstructed glands (C,E,F). Images obtained 50-65 min after injection.
Fig. 4. Time-activity curves from subject shown in Figs. 3A-D. (A) Normal study and (B) after ligation of both parotid ducts and cannulation of both submandibular ducts. All regions of interest are 4 cm$^2$.

Fig. 5. Frontal images with mouth closed (A) and open (B) show downward displacement of oral activity and separation of nasal and central oral activity when mouth is opened. Note triangular configuration of oral activity when mouth is open. Lateral images with mouth closed (C) and open (D) further elucidate changes (see text). (E) Frontal mouth-open image; (F) repeat with pinhole collimator. Note almost circular configuration of oral activity and central area of diminished radioactivity.
discernible by 10 minutes and increased until it became the predominant feature, surpassing submandibular gland activity within 20 minutes and parotid gland activity within 40 minutes after injection. In the lateral projection the central activity was seen to be crescent-shaped and nonuniform (Fig. 1), with its most intense part situated posteriorly. The lower activity gradually seemed to merge with the increasing central activity, subsequently becoming less distinct. Activity laterally in the oral cavity ("lateral activity") appeared at the same time as, or slightly later than the central activity and accumulated to form either separate collections of activity or lateral extensions of the central activity (Fig. 1). As with the lower activity, the central and lateral activities were preceded by the appearance of weak diffuse bands extending from the parotid glands to the oral region.

Time-activity curves of the central, lower, and lateral activities generally showed consistent shapes (Fig. 2). The central activity continuously increased, whereas the lower activity either increased gradually to a plateau or decreased after reaching a maximum at 10-20 minutes. The two lateral activities were usually equal and tended to increase gradually. In 8 of the 18 subjects, sudden decreases were observed in glandular curves. Such a decrease in submandibular gland activity always correlated with a concurrent peak or increase in lower activity; similarly, a sudden decrease in parotid gland activity always correlated with a concurrent sharp increase in lateral activity.

In sequential studies after ligation of both parotid ducts and cannulation of both submandibular ducts, no accumulation of oral activity was observed (Figs. 3 and 4). Only ligation of parotid duct(s) resulted in absence or slight accumulation of lateral activity (Figs. 3E and 3F). As seen in lateral views, only cannulation of submandibular ducts resulted in absence of lower activity. This effect was obscured in frontal views by radioactive saliva in the cannulas (see cannula artifact in Fig. 3C).

The scintiscans obtained with the mouth closed and open showed a striking difference both in the configuration and in the position of the oral activity (Fig. 5). In frontal views with the mouth open, the oral activity as a whole was displaced downwards; in addition, the central and lower activities were separated, leaving an area of diminished activity between them, and the lateral activities lengthened in a downward and medial direction. On lateral images, the oral activity shifted in a ventrocaudal direction when the mouth was opened with the most intense posterior part changing from a dorsocaudal to a horizontal or even a ventrocaudal direction. Radioactive markers established the location of the palate, the submandibular duct, and the parotid duct orifice and related these structures to the oral activity (Fig. 6).
Radioactivity was retained in the mouth after a $^{99m}$Tc-pertechnetate mouthwash. Figure 7 shows that this retained oral activity closely resembles the oral activity seen after intravenous injection not only in configuration, but also in displacement when the mouth is opened. After the mouth was thoroughly rinsed with saline solution, the distribution of
Fig. 7. Retained pertechnetate mouthwash activity viewed frontally (A,B) and laterally (C,D) with mouth closed (A,C) and open (B,D). Markers are on bridge of nose (arrow 1) and on palate (arrow 2). Note configuration and displacement of retained activity on opening mouth and separate location of palatal marker. Mouthwash activity (C,D) closely resembles oral activity after intravenous injection of pertechnetate, viewed laterally with mouth closed (E) and open (F).

the oral radioactivity remained the same, although the total activity decreased on the average by 25% after the first rinse (range, 10-37%) and a further 7% after the second rinse (range, 4-10%).

Discussion

Within 2-4 minutes after intravenous injection of 99mTc-pertechnetate in normal subjects, areas of increased activity in the salivary gland region were recognized and could be identified with the parotid and submandibular glands. Increased activity in the region of the oral cavity appeared during the initial 10 minutes after injection, but its correspondence with anatomic structures could not be so readily ascertained. Moreover, this oral activity became greater than either parotid or submandibular gland uptake and usually was still increasing at 1 hour after injection, whereas the parotid and submandibular glands reached their
maximum uptake considerably earlier\textsuperscript{17}. In the literature, two unrelated explanations for the oral activity are presented. Several authors\textsuperscript{1-5} attribute the oral activity solely to uptake in the sublingual and the minor salivary glands, particularly the palatine glands. They suggest that scintigraphy provides the only method of investigating minor salivary gland function, and therefore diminished or absent oral activity is interpreted as conclusive evidence of minor salivary gland involvement in systemic glandular disorders, such as Sjögren's disease. On the other hand, Harden et al.\textsuperscript{6} suggest that the oral activity is mainly due to saliva from the major salivary glands; they conclude that adsorption of pertechnetate to the oral mucosa takes place, since the small volume of radioactive saliva in the mouth would not account for the oral activity seen. While they do not rule out the minor salivary glands altogether, they consider adsorption to be the more important factor. Most authors accept both these explanations for the oral activity\textsuperscript{8-16}. However, without a clear indication as to the relative contributions of radioactive saliva and minor gland uptake, the oral activity cannot be properly interpreted.

Our ligation and cannulation studies clearly show that the oral activity visualized during the normal sequential studies was entirely dependent on radioactive saliva secreted by the parotid and submandibular glands. It follows that scintigraphy cannot be used to investigate the function of minor salivary glands. However, since pertechnetate concentration in minor salivary gland tissue does occur\textsuperscript{18}, our observations show that uptake in these glands does not become visible above background.

Although we have shown that oral activity is due to radioactive saliva, the continuous increase and considerable magnitude of this oral activity cannot be accounted for solely by saliva circulating in the oral cavity. Adsorption of pertechnetate to the oral mucosa, as suggested by Harden et al.\textsuperscript{6}, must therefore be considered. Our pertechnetate mouthwash studies support Harden’s thesis, since the radioactivity was not only partially retained in the oral cavity after the mouthwash, but it maintained the same activity distribution. The similarity in activity distributions from mouthwash and intravenous pertechnetate further indicates mucosal adsorption of pertechnetate from radioactive saliva.

Valuable insight into the location of the oral activity was gained from the views obtained when the mouth was open. The downward displacement of the central activity, resulting in distinct separation from the palatal marker, ruled out the palate as the location of this activity. Particularly in the lateral view, the configuration and displacement of central activity suggests its location on the tongue. This might be explained by the numerous lingual papillae which provide a large surface area for mucosal adsorption of pertechnetate.
The lateral activity originated mainly from parotid secretions, since this activity did not accumulate when salivary flow from the parotid gland was obstructed. The diffuse bands of activity often seen between the parotid glands and the mouth represented radioactive saliva in the parotid ducts. Lateral activity appeared to be situated in the region of the buccal mucosa near the parotid duct orifice, as suggested by Grove and Di Chiro and Sorsdahl et al.\textsuperscript{9}. When seen in frontal images, the lengthening of the lateral activity in a downward direction corresponds to the stretching of the buccal mucosa that occurs when the mouth is opened. Activity in the horseshoe-shaped mandibular sulcus now also became discernible due to the change in the angle between the mandible and the detector.

Markers placed at each end of a submandibular duct not only located the length and course of the duct on the scintiscans, but also defined the position of the sublingual gland, whose medial surface is in close contact with the duct. In our series, no accumulation of pertechnetate was observed in the sublingual glands. Furthermore, in a patient, we were able to measure the concentration of pertechnetate in a histologically normal sublingual gland, removed during surgery in the floor of the mouth at 1 hour after intravenous injection of 74 MBq of \textsuperscript{99m}Tc-pertechnetate. Plasma samples obtained at the time of excision were also measured, and a gland-to-plasma (G/P) concentration ratio of 0.69 was found \([G/P = (\text{percent dose/gm gland})/(\text{percent dose/ml plasma})]\). By comparison, also at 1 hour after injection of pertechnetate, Lazarus et al.\textsuperscript{19} found a mean G/P ratio of 2.50 \((n = 6)\) for excised parotid tissue. For rat muscle, Papadopoulos et al.\textsuperscript{20} found a tissue-to-plasma ratio of 0.21 ± 0.010 (mean ± s.e.m., \(n = 6\)). Assuming typical weights of 30 gm for the parotid gland and 5 gm for the sublingual gland, we calculated that total pertechnetate uptake of the parotid should be about 20 times that of the sublingual gland. From these data it is understandable that sublingual gland uptake is not visualized on scintiscans. The submandibular duct markers showed definitely that the lower activity could not be attributed to uptake in the sublingual glands, as suggested by zum Winkel et al.\textsuperscript{15}. In agreement with Sorsdahl et al.\textsuperscript{9}, we consider the lower activity to represent radioactive saliva in the floor of the mouth near the orifices of the submandibular ducts. Radioactive saliva in the duct itself is usually seen early during the study as a weak diffuse band of activity. The relation between submandibular gland saliva and the lower activity was also supported by the time-activity curves that showed peaks or sharp increases in the lower activity concurrent with sudden decreases in submandibular gland activity.

In clinical practice, oral activity is not due to pertechnetate uptake in sublingual and minor salivary glands and should only be regarded as a useful indicator of major salivary gland function.
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THE INFLUENCE OF DENTAL RESTORATIONS ON SALIVARY GLAND SCINTIGRAPHY WITH $^{99m}$Tc-PERTECHNETATE

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Abstract

During sequential salivary gland scintigraphy with $^{99m}$Tc-pertechnetate, circumscript "cold" areas with less than background activity are sometimes seen in the region of the oral cavity. This phenomenon is due to the presence of extensive dental restorations and should not be misinterpreted in terms of deficient $^{99m}$Tc-pertechnetate uptake in the minor salivary glands of the oral cavity.

Introduction

Since its introduction into clinical practice, salivary gland scintigraphy has gained widespread acceptance as a useful diagnostic procedure for evaluating salivary gland disorders. Following intravenous injection of $^{99m}$Tc-pertechnetate radioactivity accumulates not only in the major salivary glands but also in the region of the oral cavity (oral activity). In the past, this oral activity has generally been attributed to pertechnetate uptake in the sublingual and minor salivary glands of the oral cavity\textsuperscript{1-4}. However, we have recently shown the oral activity to be entirely due to radioactive saliva excreted by the parotid and submandibular glands\textsuperscript{5-7}, which implies that diminished accumulation of oral activity is only indicative of parotid and submandibular gland dysfunction. In extreme cases of xerostomia, therefore, oral activity is entirely absent and only background activity is seen throughout the oral region. Occasionally, however, a circumscript cold area with even less than background activity is observed within the oral region, a phenomenon which cannot be explained solely by the absence of radioactive saliva in the mouth.

The purpose of the present article is to clarify this by means of a case presentation.
A 58-year-old man was referred to the Department of Oral and Maxillofacial Surgery, University of Amsterdam, for evaluation of a progressive xerostomia of 18 months' duration. On physical examination, the oral mucous membranes were dry with loss of the papillary structure of the tongue. Massage of the major salivary glands failed to produce saliva. The dentition was in good repair with an extensive, removable partial denture in the upper jaw connected to the remaining teeth by precision attachment (Fig. 1). There was no enlargement of the major salivary glands. Routine laboratory tests, parotid gland sialography, and ophthalmologic examination did not reveal apparent abnormalities. A parotid gland biopsy showed only slight inflammatory changes. Sequential salivary gland scintigraphy was then performed in the frontal view using the following protocol: After intravenous injection of 74 MBq of $^{99m}$Tc-pertechnetate, consecutive 5-minute scintiphotographs were made up to 20 minutes. Without moving the subject, 0.25 mg carbachol was then injected subcutaneously to stimulate salivary excretion and the study was continued for a further 20 minutes. The data were simultaneously digitized, stored on magnetic tape, and later replayed to obtain time-activity curves for selected regions over the salivary glands.

The images and time-activity curves of the scintigraphic study showed normal uptake of pertechnetate in the major salivary glands. However, oral activity did not accumulate and the parotid and submandibular glands failed to empty after stimulation with carbachol, indicating a disturbance of the excretory function of these glands. Throughout the study the images showed a sharply defined cold area transversing the region of the oral cavity (Fig. 2, left).

In order to investigate whether the cold area observed could be due to the presence of the partial denture, this appliance was later removed from the patient's mouth and
Fig. 2. Left, frontal scintiphotograph after intravenous injection of 74 MBq of $^{99m}$Tc-pertechnetate showing distinct "cold" area transversing the region of the oral cavity (arrow). Right, scintifotograph of uniform source of $^{99m}$Tc showing the cold area produced by the removable partial denture.

placed on a uniform source of $^{99m}$Tc at an angle resembling that of the dental arch during the preceding scintigraphic study. On the image obtained from this setup, the partial denture was visible as a cold area identical to that seen on the salivary gland images (Fig. 2, right).

Discussion

A previous study in normal subjects has shown that, after intravenous injection of pertechnetate, a uniform background activity is present throughout the oral region when radioactive saliva from the parotid and submandibular glands is prevented from reaching the oral cavity. This observation indicates that pertechnetate concentration in minor salivary glands of the oral cavity, as reported by Stephen and associates, cannot be distinguished from the background activity in the oral region. Theoretically, it is possible that diminished pertechnetate uptake in the minor salivary glands produces an area with less than background activity within the oral region. In the literature Schall and colleagues have used this hypothesis to explain "negative oral defects" on scintiphotographs of patients with severe xerostomia. The present report provides a different explanation for this phenomenon. The cold area observed on the images was so distinct and well-defined that it suggested the presence of a radiation-absorbing medium with an atomic number higher than that of the normal surrounding tissues (bone, soft tissue, and, if present, teeth). The subject, indeed, had an extensive precision partial denture containing alloys of chromium, cobalt, and gold, the latter having a high atomic
number. When removed from the mouth and placed on a uniform source of $^{99m}$Tc, this denture produced a cold area identical to that seen during salivary gland scintigraphy. This clearly demonstrated that the cold area on the salivary gland images did not indicate minor salivary gland dysfunction with regard to $^{99m}$Tc-pertechnetate uptake but merely represented absorption of radiation in the materials, particularly the gold alloys, used in the partial denture construction.

In conclusion, the presence of extensive dental restorations may result in more or less distinct cold areas in the oral region during scintigraphic studies of the salivary glands. Especially in patients with severe xerostomia, when superposing oral activity is absent, one should be careful not to misinterpret these artifacts in terms of deficient $^{99m}$Tc-pertechnetate uptake in the minor salivary glands of the oral cavity.

References

Chapter 5

SEQUENTIAL SALIVARY GLAND SCINTIGRAPHY USING TECHNETIUM-99m AND CARBACHOL: A CLINICAL TEST

Published in Medical Radionuclide Imaging, Vol II, Vienna, 1977, International Atomic Energy Agency, pp. 363-369
SEQUENTIAL SALIVARY GLAND SCINTIGRAPHY USING TECHNETIUM-99m AND CARBACHOL: A CLINICAL TEST

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Abstract

Sequential scintigraphy of the major salivary glands after intravenous injection of $^{99m}$Tc-pertechnetate and stimulation of salivary excretion by subcutaneous injection of carbachol has become a valuable method in the diagnosis of salivary gland disorders. Usually, carbachol is administered 20 minutes after pertechnetate injection and studies are continued up to 90 minutes. Here, the comparative usefulness of carbachol stimulation at 10 minutes and 20 minutes is investigated in two groups of 10 normal subjects. Analogue images and time-activity curves for major salivary glands, skull and oral regions were obtained. Two ratios indicating glandular function were calculated for each subject: maximum glandular activity/background activity and maximum glandular activity/minimum glandular activity after carbachol. Skull activity multiplied by a factor 1.4 was used as a reliable measure of background activity in the glandular regions. The submandibular glands in the series consistently reached maximum uptake early, frequently by 10 minutes, so that postponement of carbachol injection to 20 minutes is unnecessary. Furthermore, the parotid gland curves after carbachol stimulation at 10 minutes continued to increase for several minutes. This brought the maximum/background and maximum/minimum ratios close to the values obtained after carbachol stimulation at 20 minutes. Carbachol stimulation at 10 minutes is therefore considered suitable for evaluating not only submandibular but also parotid gland function. Moreover, since the minimum of the carbachol-induced drop in activity is reached within 10 - 12 minutes and a continuation of the study does not provide additional data, a total examination time of 30 minutes is sufficient for obtaining all necessary information. Sequential salivary gland scintigraphy therefore becomes a more practical procedure.

Introduction

A sequential scintigraphic study of the salivary glands using $^{99m}$Tc-pertechnetate reflects glandular concentration and excretion of pertechnetate. However, only parotid and submandibular gland function can be studied since pertechnetate uptake in sublingual and minor salivary glands is not visualized: radioactivity appearing in the oral region is entirely due to the salivary excretion from the parotid and submandibular
glands. In a previous study on 17 normal subjects, we found consistently that submandibular glands reached maximum pertechnetate uptake earlier than parotid glands, the mean time of maximum uptake being, respectively, 9 minutes (range 4 - 24 minutes) and 28 minutes (range 14 - 48 minutes) after injection. The scintigraphic study therefore has to extend up to one hour or longer after injection before glandular excretion can be properly evaluated. Application of a stimulant, such as carbachol (carbamylcholine chloride), a parasympathomimetic agent, accelerates excretion so that the scintigraphic study can by shortened to a more acceptable time without forfeiting information. It also provides a rapid way of investigating the patency of the major excretory ducts. Carbachol is usually administered 20 minutes or later after intravenous injection of pertechnetate, and studies are continued up to 70 or 90 minutes. However, the early maximum uptake consistently found in submandibular glands suggests that earlier carbachol administration might be preferable, particularly when evaluating disorders of the submandibular glands.

In the present study we have investigated the effect of carbachol stimulation at 10 minutes and at 20 minutes after pertechnetate injection in two groups of 10 normal subjects in order to establish a shorter and, therefore, more practical clinical test for major salivary function.

Material and methods

Sequential scintigraphy was performed in the frontal view with a Nuclear Chicago HPIII scintillation camera and low-energy, high-resolution, parallel-hole collimator together with a 4096-channel analyser and magnetic tape storage system. With the subject supine and with the head slightly extended, 74 MBq of $^{99m}$Tc-pertechnetate was administered intravenously. Starting immediately, two 2-minute then consecutive 5-minute scintiphotos were made, and digitized data were stored at 2-minute intervals. Without moving the subject, 0.25 mg of carbachol was injected subcutaneously between 10 - 11 minutes in 10 subjects and between 20 - 21 minutes in the other 10 subjects, after which the study was continued for at least 20 minutes. Time-activity curves were later obtained for selected regions of 4 cm$^2$ over the parotid and submandibular glands and skull (above the parotid gland near the transverse sinus), and of 2.5 cm$^2$ over lower and lateral oral activity. Activity was calculated as percentage of $^{99m}$Tc-pertechnetate administered by measuring a standard activity in a Perspex phantom constructed to the dimensions of the head. Non-uniformity of the scintillation camera was taken into consideration.

To compare the glandular response to carbachol stimulation at 10 and 20 minutes, two ratios were calculated: maximum glandular activity/
background activity and maximum glandular activity/minimum glandular activity. The maximum of the time-activity curve was taken whether attained already before, at or after carbachol administration, and the minimum was taken at 10 minutes after activity started to drop following carbachol administration. To estimate the percentage background activity in the major salivary gland regions, 800 mg of perchlorate was administered orally in 6 subjects at the end of the sequential study with carbachol stimulation, and further 5-minute data were obtained in the frontal view after 30 minutes. Also, sequential studies were performed in 6 subjects in whom a major salivary gland had been removed. A comparison was made between the skull activity and the activity measured over glands after perchlorate administration and over empty glandular regions.

Fig. 1. $^{99m}$Tc-pertechnetate time-activity curves and sequential images of major salivary glands from a normal subject showing the effect of carbachol stimulation at 10.5 min (arrow). Note steep increase in parotid gland activity before rapid drop in activity at 14 min.
Results

In the 20 normal subjects, response to carbachol stimulation was determined by examining the pertechnetate time-activity curves of parotid and submandibular glands before and after carbachol stimulation.

Preceding stimulation at 20 minutes, submandibular gland activity was already decreasing in all 10 subjects (the maximum having been reached by 10 minutes in 7 subjects), whereas parotid gland activity was decreasing in 5 subjects and still increasing in the other 5 subjects. Preceding stimulation at 10 minutes, submandibular gland activity was already decreasing in 3 subjects, approaching a plateau in 2 subjects and still increasing in 5 subjects, whereas parotid gland activity was still increasing in all 10 subjects.

Following stimulation, a rapid drop in activity was observed, in most subjects immediately but occasionally after a short delay of 2 - 3 minutes. In parotid gland activity following stimulation at 10 minutes, a longer delay of up to 7 minutes was observed in 9 out of 10 subjects; in 5 of these

![Graph of 99mTc-pertechnetate time-activity curves](image)

Fig. 2. $^{99m}$Tc-pertechnetate time-activity curves of major salivary glands with subcutaneous injection of carbachol at 21 min (arrow) from a normal subject. Submandibular gland activity reached maximum uptake at 6 min and only a small effect of carbachol injection is seen at 24 min.
Table 1. Comparison of percentage injected $^{99m}$Tc-pertechnetate activity between 10-20 min after injection in 4 cm$^2$ regions over skull and major salivary glands.

<table>
<thead>
<tr>
<th></th>
<th>No. of Subjects</th>
<th>% Injected activity mean ± 1SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull region</td>
<td>20</td>
<td>0.10 ± 0.01 (0.07-0.12)</td>
</tr>
<tr>
<td>Empty glandular region:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parotid gland</td>
<td>2</td>
<td>0.15 , 0.13</td>
</tr>
<tr>
<td>Submandibular gland</td>
<td>4</td>
<td>0.14 ± 0.03 (0.12-0.18)</td>
</tr>
<tr>
<td>Glandular region after perchlorate:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parotid gland</td>
<td>6</td>
<td>0.14 ± 0.03 (0.12-0.20)</td>
</tr>
<tr>
<td>Submandibular gland</td>
<td>6</td>
<td>0.15 ± 0.02 (0.12-0.18)</td>
</tr>
</tbody>
</table>

Ratio "gland"/skull activity mean ± 1SD (range)

|                                      |                 |                                         |
| Empty glandular region:              |                 |                                         |
| Parotid gland                        | 2               | 1.35 , 1.29                             |
| Submandibular gland                  | 4               | 1.40 ± 0.11 (1.34-1.56)                 |
| Glandular region after perchlorate:  |                 |                                         |
| Parotid gland                        | 6               | 1.34 ± 0.30 (1.04-2.14)                 |
| Submandibular gland                  | 6               | 1.51 ± 0.21 (1.18-1.86)                 |

Table 2. Pertechnetate activity ratios obtained in normal subjects after carbachol administration at 10-11 min (n = 10) and at 20-21 min (n = 10).

<table>
<thead>
<tr>
<th></th>
<th>Maximum/Background mean ± 1SD (range)</th>
<th>Maximum/Minimum mean ± 1SD (range)</th>
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<tbody>
<tr>
<td>Carbachol injection</td>
<td>10-11 min 20-21 min</td>
<td>10-11 min 20-21 min</td>
</tr>
<tr>
<td>Parotid gland</td>
<td>2.34 ± 0.56 (1.38-3.37)</td>
<td>2.11 ± 0.33 (1.58-2.75)</td>
</tr>
<tr>
<td>Submandibular gland</td>
<td>2.21 ± 0.59 (1.46-3.90)</td>
<td>1.72 ± 0.28 (1.44-2.53)</td>
</tr>
</tbody>
</table>
Fig. 3. $^{99m}$Tc-pertechnetate time-activity curves and sequential images of major salivary glands and oral activity from a normal subject showing the effect of carbachol stimulation at 10.5 min (arrows). Sharp decrease in submandibular gland activity correlates with sharp increase in lower oral activity; similarly, decrease in parotid gland activity correlates with increase in corresponding lateral oral activity.

an even steeper increase in activity was seen during the delay (Fig. 1). In 5 out of 10 subjects following stimulation at 20 minutes, a drop in submandibular gland activity was hardly recognizable or was even completely obscured by the already decreasing time-activity curve (Fig. 2).

The drop in activity following stimulation always occurred at the same
time bilaterally and a minimum approaching the background was reached within 10 - 12 minutes regardless of what time carbachol was administered. From a comparison of skull activity with activity over glands after perchlorate administration and over empty glandular regions, background activity for the major salivary glands was estimated to be skull activity multiplied by a factor 1.4 (Table 1). The normal values for the ratios maximum/background and maximum/minimum shown in Table 2 were found to be similar for carbachol stimulation at 10 minutes and at 20 minutes.

Comparison of glandular and oral activity curves showed a consistent correlation between the rapid drop in parotid and submandibular gland activity after stimulation and a sharp rise in, respectively, lateral and lower oral activity (Fig. 3).

**Discussion**

To be useful as a routine function test, the time duration of sequential salivary gland scintigraphy should be as short as feasible but should still provide the necessary information. A stimulant is administered ideally at

![Fig. 4. 99mTc-pertechnetate time-activity curves from a patient with chronic sialoadenitis of the left parotid gland showing the effects of carbachol stimulation at 11 min and at 21 min (arrows). Note that both studies provide essentially the same information.](image)
the maximum of the pertechnetate time-activity curve. For submandibular
glands this maximum activity is frequently attained by 10 minutes after
pertechnetate injection, so that postponing carbachol administration until
20 minutes is not necessary. On the other hand, parotid gland activity
reaches a maximum later and carbachol stimulation at 20 minutes is
normally used. However, in nearly all our normal subjects, parotid gland
activity continued to increase after carbachol stimulation at 10 minutes
which brought the maximum/background and maximum/minimum
ratios calculated for carbachol stimulation at 10 minutes very close to the
ratios obtained at 20 minutes (Table 2). We therefore consider carbachol
stimulation at 10 minutes suitable for evaluating not only submandibular
but also parotid gland function. This is exemplified by Fig. 4, which shows
similar results in a patient when carbachol was administered at 10 minutes
and at 20 minutes. The continued activity increase after carbachol
stimulation is possibly due to radioactive saliva filling the ductal dead
space before being massively excreted into the mouth.

In estimating pertechnetate background activity in the major salivary
gland regions, the skull activity showed consistent and reproducible values
and a quite consistent relation with activity measured over empty
glandular regions and over glands after administration of carbachol
followed by perchlorate. Skull activity multiplied by a factor 1.4 can
therefore be reliably used for background activity.

In evaluating glandular function, the ratio maximum/background
provides a measure of the concentrating ability while the ratio maximum/
minimum provides a measure of the excretory capacity (maximum/
minimum ratio: >1 indicates a decrease; = 1 indicates a plateau; <1
indicates continued increase). An additional advantage of these ratios is
that they can be obtained directly from the measured counting rate without
calculation of the percentage injected pertechnetate activity. In two groups
of patients, 7 with long-standing submandibular sialolithiasis and 8 with
chronic parotid sialoadenitis, we found that the combination of the two
ratios distinguished well between the pathological condition and normal
function. For the group with sialolithiasis, we found a mean maximum/
background ratio of 1.59 ± 0.49 SD (range 1.16 - 2.59) and a mean
maximum/minimum ratio of 1.09 ± 0.14 SD (range 0.96 - 1.36); for the
group with chronic sialoadenitis these ratios were, respectively, 1.98 ± 0.42
SD (range 1.61 - 2.58) and 1.07 ± 0.26 SD (range 0.88 - 1.68).

The correlation between parotid and submandibular saliva and,
respectively, lateral and lower oral activity was accentuated by injection of
carbachol, and corroborated our previous findings that oral activity is
solely due to radioactive saliva and can only be used as an additional
indicator of major salivary gland function.
By administering carbachol at 10 minutes after pertechnetate injection, the total examination time necessary for evaluating major salivary gland function is brought back to 30 minutes, so that sequential salivary gland scintigraphy becomes a more practical procedure.

References


Chapter 6

DIAGNOSTIC IMAGING IN SALIVARY GLAND DISEASE

Accepted for publication in Oral Surgery, Oral Medicine, Oral Pathology.
DIAGNOSTIC IMAGING IN SALIVARY GLAND DISEASE

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Abstract

A review of the current status of salivary gland imaging is presented. The potentials and limitations of sialography, scintigraphy, ultrasound, computed tomography and magnetic resonance imaging are discussed so that a rational approach to their use can be adopted.

Introduction

Are imaging procedures usually necessary in the diagnostic work-up of salivary gland diseases and if so, what are the indications for the various methods? The marked increase in imaging procedures in the last decade has made these questions even more relevant today than they were in the past.

Clinical signs and symptoms of diseases of the salivary glands generally tend to be non-specific. However, the superficial location of these glands easily permits inspection and palpation so that a thorough physical examination, combined with a detailed history, often provides sufficient information for a clinical diagnosis. Nevertheless, confirmation of this diagnosis and further evaluation are frequently necessary and imaging procedures play an important role in this respect. When further investigations have to be conducted, it is apparent that the clinician should not only have a knowledge of what methods are available, but should also appreciate the potential value and limitations of each method so that he can make a rational choice.

The purpose of this article is therefore to discuss the current status of the various imaging procedures and to present a survey of their application in salivary gland disease (Table 1).
Table 1. Usefulness of imaging procedures in salivary gland disease.

<table>
<thead>
<tr>
<th>Imaging procedure</th>
<th>Tumors and cysts</th>
<th>Sialoadenitis</th>
<th>Sjögren's syndrome</th>
<th>Sialolithiasis and obstructive disorders</th>
<th>Sialosis</th>
<th>Congenital anomalies and traumatic disorders</th>
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<td>Sialography</td>
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<td>Scintigraphy</td>
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<td>Ultrasound</td>
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<td>Computed tomography</td>
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<td>Magnetic resonance imaging</td>
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<td>Plain radiography</td>
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++ may provide useful information.
+ useful in selected cases only.
* if necessary in combination with sialography or i.v. contrast infusion.
Sialography

Sialography still is the most widely used radiographic method for examination of the salivary glands. Nevertheless, Holt once characterized sialography as the neglected stepchild of roentgendiagnosis, because throughout the years this diagnostic procedure has remained controversial, being considered worthless by some authors and indispensable by others\textsuperscript{1}. However, the question whether or not sialography is useful cannot be answered in the absolute sense, since the answer largely depends on the type of salivary gland disorder under investigation. Overrating the diagnostic information that can be obtained may lead to indiscriminate use of sialography and subsequently to disappointing results, particularly in tumor diagnosis, and this is probably the main reason why many clinicians are dissatisfied with the method. Furthermore, since negative experiences may reflect unfavourably on sialography as a whole, the danger exists that its use will be discarded altogether, even in cases in which useful information can be obtained. It is therefore extremely important to fully appreciate the true indications for sialography, so that unrewarding examinations can be avoided as much as possible.

Most authors nowadays agree that sialography is of limited use in tumor diagnosis\textsuperscript{2-4}. Space-occupying lesions are only indirectly visualized by displacement or disruption of the ductal system and even though more than 80 percent of tumors can be detected by a refined sialographic technique, lesions less than 1 centimeter in diameter usually are not demonstrated\textsuperscript{5,6}. Furthermore, differentiating between an intrinsic and extrinsic location and predicting the benign or malignant nature of a tumor are not reliably possible\textsuperscript{7,8}. Nevertheless, sialography still retained some popularity as a method for evaluating space-occupying lesions, until the introduction of computed tomography, and more recently magnetic resonance imaging, finally made the question of its usefulness as a sole procedure irrelevant (vide infra).

The main indications for sialography are inflammatory and non-neoplastic diseases, which generally show changes in the ductal system itself. These disorders form a heterogeneous group consisting of the various types of sialoadenitis, including Sjögren's syndrome, granulomatous diseases, obstructive disorders such as sialolithiasis and strictures, sialosis, as well as traumatic lesions and developmental anomalies. In many instances their clinical picture is similar with only a limited number of nonspecific signs and symptoms, such as pain, persistent or recurrent diffuse swelling or diminished function. However, in contrast to this, their sialographic images exhibit a wide variety of ductal changes, that are often sufficiently characteristic for the clinician to differentiate one disease from
the other\textsuperscript{9}. For instance, both Sjögren's syndrome and sialosis may present with painless, often bilateral and persistent parotid enlargement and xerostomia, so that clinically the differential diagnosis may be difficult. In Sjögren's syndrome, however, sialography will generally show sialectasias

![Parotid sialogram of a patient with Sjögren's syndrome showing globular collections of contrast material evenly distributed throughout the gland.](image1)

![The scintigraphic image reveals decreased and asymmetrical pertechnetate uptake in the parotid glands and absence of uptake in the submandibular glands.](image2)

![Parotid sialogram of a patient with sialosis. The ducts are thin and slightly separated but otherwise normal.](image3)

![The scintigraphic image reveals markedly increased pertechnetate uptake in the enlarged parotid and submandibular glands.](image4)

Fig. 1. A, Parotid sialogram of a patient with Sjögren's syndrome showing globular collections of contrast material evenly distributed throughout the gland. B, The scintigraphic image reveals decreased and asymmetrical pertechnetate uptake in the parotid glands and absence of uptake in the submandibular glands. C, Parotid sialogram of a patient with sialosis. The ducts are thin and slightly separated but otherwise normal. D, The scintigraphic image reveals markedly increased pertechnetate uptake in the enlarged parotid and submandibular glands.
distributed throughout the parotid gland with or without dilation of the main ducts, whereas in the case of sialosis the ductal system of the enlarged gland appears essentially normal, even though the sparse peripheral branches are more separated and narrower than usual due to compression by the hypertrophied serous acinar cells. If a contraindication for sialography exists, differentiation between Sjögren’s syndrome and sialosis is also possible by performing scintigraphy with $^{99m}$Tc-pertechnetate which may show a decreased isotope uptake in Sjögren’s syndrome or a characteristic increased isotope concentration in sialosis\textsuperscript{10} (Fig. 1).

Clinical signs and symptoms of salivary gland obstruction are often pathognomonic, but nevertheless further evaluation frequently requires a sialographic examination. Although radiopaque calculi can usually be detected on preliminary plain radiographs, approximately 20 percent of submandibular and 40 to 70 percent of parotid calculi are reported to be poorly calcified and therefore cannot be demonstrated by plain radiography\textsuperscript{11,12}. However, on a sialogram these radiolucent stones may be visualized as a filling defect or, more rarely, as an area of narrowing of the duct with proximal dilatation (Fig. 2). Whether these stones are truly radiolucent, or in fact radiopaque but merely difficult to visualize with plain radiography remains the question. The latter view is supported by Suleiman and Hobsley, who, by using lateral, anteroposterior and intrabuccal plain radiographs, were able to demonstrate more than 70 percent of parotid calculi\textsuperscript{13}. Sialography is normally not indicated when a
radiopaque stone is situated in the distal part of the duct, because manipulation with the catheter or pressure during injection of the contrast medium may displace it deeper into the duct, possibly even to a location inaccessible from the mouth. However, this objection does not apply to deeply situated stones. In these cases sialography provides valuable information on the location of the stone, which determines the choice of operative procedure necessary for its removal. When a stone turns out to be situated in the intraglandular part of the duct, glandular excision or removal of the stone via a parotidectomy approach is indicated, whereas in the case of an extraglandular location transoral removal is the treatment of choice. The extent of glandular damage, as seen on a sialogram, is not the decisive factor in the question whether a gland should be excised or left in situ, considering the remarkable capacity for functional recovery once the obstruction is removed.

Occasionally confusion may be caused by the presence of phleboliths, calcified lymph nodes or other paraoral pathologic calcifications. These radiopaque structures are normally readily distinguishable from salivary calculi, but in case of doubt a sialographic study will demonstrate their location outside the ductal system.

Finally, as a morphologic study, sialography is also useful for detecting and evaluating strictures, salivary fistulae, sialoceles and developmental anomalies, but for technical reasons the procedure cannot always be carried out. The alternative is then to perform salivary gland scintigraphy with $^{99m}$Tc-pertechnetate.

**Scintigraphy with $^{99m}$Tc-pertechnetate**

In contrast with other imaging procedures, scintigraphy is primarily a function test, although the method also provides some information on the morphology and topography of the major salivary glands. The examination is carried out with a gamma camera after intravenous injection of 74 MBq $^{99m}$Tc-pertechnetate, which is selectively concentrated and secreted by the salivary glands. Sequential analogue images are usually made during a period of 60 to 90 minutes, permitting a continuous visual monitoring of the salivary dynamics with respect to pertechnetate. However, acceleration of pertechnetate excretion by oral administration of citric acid or subcutaneous injection of 0.25 mg of the parasympathomimetic agent carbachol (carbamylcholine chloride) at 10 or 20 minutes after pertechnetate injection shortens the examination time to a more acceptable 30 or 40 minutes and, moreover, provides a rapid means of investigating ductal patency. Data may be simultaneously digitized with an on-line computer system and later replayed to obtain time-activity curves from
regions of interest placed over the salivary glands and background areas over the skull. Ratios calculated from these curves or absolute uptake measurements are useful to quantitate glandular function in selected cases\textsuperscript{21,22}.

In the diagnosis of salivary gland tumors the results of scintigraphy have been disappointing\textsuperscript{23-25}. The resolution of the imaging system is such that only tumors exceeding 1.5 cm in diameter are visualized. Furthermore, differentiation between benign and malignant masses is not possible, since both types generally do not concentrate pertechnetate, resulting in “cold spots” on the scintigraphic images. The only exceptions are Warthin’s tumor and oncocytoma, which generally take up more pertechnetate than the surrounding normal glandular tissue, thereby appearing as “hot spots” (Fig. 3). In the wider area of head and neck oncology, scintigraphy has successfully been used to study the effect of radiation on salivary gland function\textsuperscript{26}, and to detect subclinical salivary leakage after extensive neck surgery as a major cause of postoperative wound infection\textsuperscript{27}.

Scintigraphic results in salivary gland infections depend on the activity of the inflammatory process. Acute sialoadenitis usually shows diffusely increased pertechnetate concentration in the enlarged gland as a result of hyperaemia and delayed or absent isotope excretion due to compression of the ductal system by inflammatory oedema. Chronic sialoadenitis, on the other hand, frequently results in a loss of ability to concentrate pertechnetate, reflecting the parenchymal damage and interstitial fibrosis. Pertechnetate uptake in the diseased gland may range from almost normal to absent, depending on the severity and duration of the inflammatory process. However, most salivary gland infections can easily be diagnosed on the basis of the history and clinical observations, so that scintigraphy is generally not necessary for the diagnosis per se. Scintigraphy at a later stage may be useful, especially in the case of recurrent infection, to assess the rate of recovery as a guideline for further surgical or medical
Several authors suggest that in patients with sialolithiasis scintigraphy can be used as a preoperative test to determine the type of treatment: markedly decreased or absent pertechnetate uptake in the involved gland would indicate the necessity for glandular excision, whereas in the case of normal or only slightly decreased pertechnetate uptake surgical removal of the stone should be attempted, leaving the gland in situ. However, recent observations have shown that markedly decreased or absent pertechnetate uptake preoperatively does not necessarily rule out the possibility of functional recovery after stone removal (Fig. 4). The predictive value of scintigraphy in these cases is therefore limited, which makes the method unsuitable as a routine test in the preoperative workup.

As a noninvasive procedure, scintigraphy is particularly useful in the diagnosis and follow-up of patients with Sjögren’s syndrome or other systemic diseases involving the salivary glands (Fig. 1). The main advantage of scintigraphy in these instances is the possibility to examine all major salivary glands simultaneously and continuously over a period of time, so that the full extent of glandular dysfunction can objectively be demonstrated. In Sjögren’s syndrome the results of scintigraphy correlate well with the patients subjective symptoms of xerostomia, as well as with the results of other diagnostic methods, such as sialography, sialometry and minor salivary gland biopsy. For this reason, some authors nowadays do not perform sialography or sialometry, but instead use scintigraphy, together with a parotid- or labial salivary gland biopsy, to
diagnose and quantitate the oral component of Sjögren’s syndrome.

An absolute indication for scintigraphy exists when the ductal orifice of a major salivary gland cannot be found or cannot be cannulated. This problem occurs when, for no obvious reason, one or several ductal orifices are not present in their usual location, suggesting the possibility of glandular aplasia. It may also be due to the presence of scar tissue or an inflammatory infiltrate in the vicinity of an excretory duct, resulting in transposition or stenosis of the distal part of the duct with or without a fistulous redirection of the salivary flow. Furthermore, the main excretory duct is usually not accessible anymore after surgical procedures such as glandular excision, ductal ligation or ductal repositioning towards the oropharynx as treatment for drooling. Signs or symptoms may persist or develop after these operations, requiring further evaluation, or it may be considered of interest to objectively document the effect of a clinically successful ductal ligation or repositioning on the glandular function. Finally, in some patients an attempt at sialography may fail, because it proves to be technically impossible to probe and cannulate an excretory duct, particularly the submandibular duct, even though the orifice is patent and in its normal position. It is apparent that in all these instances salivary gland scintigraphy is the only diagnostic procedure available to confirm the clinical diagnosis and to assess glandular function, if present, including the residual patency of the main excretory duct.

An application of salivary gland scintigraphy not related to primary glandular pathology is the use of the procedure for determining the early prognosis of Bell’s palsy as an alternative for the submandibular salivary flow test. A scintigraphic examination performed within 10 days after symptomatic onset and, if necessary, repeated 3 weeks later will show whether the stimulated excretion of pertechnetate from the submandibular gland on the affected side is normal, decreased or even absent in comparison with the healthy side. A recent study indicates that this parameter reliably predicts the prognosis of facial nerve paralysis and thus provides the information necessary for a choice of further treatment.

**Ultrasound**

Diagnostic utilization of ultrasound is based on the transmission of an ultrasonic beam into the area to be scanned and the reflection or echo of the sound waves, which occurs when these waves reach an interface between tissues of different density or impedance. The potential of ultrasonographic procedures in various fields of medicine is generally acknowledged, but the value of the method in detecting salivary gland pathology often appears to be overlooked, even though the first reports on
the use of ultrasound in parotid disorders were published a decade ago\textsuperscript{36,37}. In comparison with other imaging procedures such as sialography and computed tomography, ultrasound has some distinct advantages: it is inexpensive, widely available, easy to perform, painless and, most important, noninvasive without any known harmful effects on the patient. Furthermore, the tomographic plane can be easily manipulated at the time of imaging, which may increase the diagnostic information obtained.

The main application of ultrasound in the diagnosis of major salivary gland disease is the differentiation of cystic or fluid-containing lesions from solid masses\textsuperscript{38}. Cystic lesions generally contain no tissue interfaces producing internal echoes and therefore appear as echofree areas with the typical sign of posterior wall enhancement. This latter phenomenon is due to the fact that fluid is a good transmitter of ultrasound waves, so that the interface with the solid posterior wall produces a strong echo behind the cyst. Solid tumors larger than 5 millimeter are readily visualized by ultrasound, since they are less echogenic than the surrounding normal salivary parenchyma (Fig. 5). The sensitivity of the method in detecting superficial lobe parotid masses approaches 100 percent, and intraparotid tumors can generally be differentiated from superficially located extra-glandular lesions\textsuperscript{39}. However, since bone reflects rather than transmits sound, tumors in the deep lobe of the parotid are mostly obscured by the mandible and the mastoid process\textsuperscript{38}. Therefore, computed tomography remains the method of choice for evaluating deep lobe parotid masses and parapharyngeal space lesions. Several authors have reported ultrasound to be helpful for differentiating benign from malignant tumors, the best

\begin{figure}
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\includegraphics[width=0.5\textwidth]{ultrasound_image.png}
\caption{Ultrasonographic image of Warthin's tumor showing sharply defined lateral and posterior margins and some internal echoes. There is echo enhancement behind the tumor.}
\end{figure}
sonographic criteria being the margins and the echostructure of the examined lesions\textsuperscript{39,42}. Benign tumors usually are weakly echogenic with homogeneous echo strength and density and, most important, sharply defined, sometimes lobulated margins. Malignant tumors, on the other hand show a nonhomogeneous echopattern and irregular ill-defined margins, although well-defined margins have also been reported, particularly in muco-epidermoid tumors\textsuperscript{42,43}. On the basis of these criteria Wittich and colleagues\textsuperscript{39} and Bruneton and co-authors\textsuperscript{40} were able to assess the benign or malignant nature of a lesion in 87, respectively 80 percent of their patients. However, it should be realized that, even though the sonographic pattern is sometimes sufficiently characteristic to suggest a specific tumor type, ultrasound is not capable of providing a definite diagnosis. Therefore, aspiration cytology or excisional biopsy is always necessary to establish the histology of a lesion.

The role of ultrasound in inflammatory and obstructive diseases is limited, sialography usually being more informative in these cases. However, it may be difficult to clinically differentiate acute suppurative parotitis from an acute abscess and, for obvious reasons, sialography is not indicated in these conditions. Therefore, in case of doubt, ultrasound can be used to determine whether an abscess exists, since diffuse inflammation will show an enlarged gland without a focal mass, whereas an abscess will produce a discrete, fluid-filled, echofree area that is well demarcated from adjacent glandular tissue\textsuperscript{38,39,43,44}. Scattered internal echoes may also be visible, reflecting the presence of semi-solid necrotic material within the abscess cavity\textsuperscript{43,45}. If the presence of pus is established, ultrasound can

Fig. 6. Sialolithiasis of right parotid gland. On the ultrasonographic image the calculus is visible as an echodense spot (arrow) casting an acoustic shadow. The parotid duct was not accessible anymore after several attempts to remove the calculus via an intraoral approach.
guide aspiration for the purpose of draining the abscess and obtaining material for culture. Furthermore, since the method is quick and easily reproducible, it can also be used to monitor response to therapy.

Pickrell and associates were the first to use ultrasound for preoperative localization of a parotid gland calculus. Recent studies indicate that ultrasound is a fairly reliable method for demonstrating salivary calculi, since more than 90 percent of stones larger than 2 millimeter can be detected as echodense spots casting a characteristic acoustic shadow. To some extent, distinguishing between an intraglandular and intraductal location is also possible with this procedure. Nevertheless, plain radiography and sialography remain the methods of choice for evaluating salivary calculi, because they are on the whole more accurate, both for detection and precise localization of calculi. The use of diagnostic ultrasound should therefore be restricted to selected cases, for instance patients with signs and symptoms of calculous obstruction in whom a salivary duct cannot be cannulated. (Fig. 6).

**Computed tomography**

Computed tomography (CT) of the salivary glands was introduced as a new diagnostic technique in 1978, and subsequent experiences have firmly established the procedure as the method of choice for evaluating space-occupying lesions in and around the major salivary glands. CT findings in inflammatory and nonneoplastic diseases have also been reported, but most authors agree that the results are generally nonspecific and may sometimes be confused with malignancy. Therefore, if radiologic examination is indicated in these cases, plain radiography and sialography remain the investigations of choice.

The major advantages of CT are its ability to directly visualize soft and hard tissues and to demonstrate small differences in soft tissue density. Axial and coronal planes can be used to visualize the parotid and submandibular glands, but in most cases the straight axial projection provides excellent anatomic detail obviating the need for an additional coronal view. In parotid imaging, however, it may be necessary to slightly change the angle of the axial projection to avoid artifacts from dental restorations.

On CT scans the normal parotid gland is readily discernible, being more radiodense than adjacent fat but less dense than surrounding muscles because of its high fat content and high concentration of saliva. However, parotid density is variable, the parotids being less dense in older and heavier individuals whose glands are more infiltrated with fat. The submandibular gland contains less fat than the parotid gland so that its...
density is similar to adjacent muscles. However, this gland is mostly easily identified due to its characteristic shape and location (Fig. 10).

On plain CT images most intraparotid benign tumors appear as sharply marginated masses. As a rule, these tumors are hyperdense in comparison with the surrounding parenchyma, but, less frequently, hypodense lesions
Fig. 9. Lipoma of left cheek. A, Well-defined mass with density characteristic of fat anterior to the masseter muscle (arrows). B and C, Sialography reveals anterolateral displacement of Stensen's duct (arrows). Note opacified parotid gland (P).

can also be observed (Fig. 8). In contrast to benign tumors, malignant lesions are reported to have poorly defined margins\textsuperscript{50,52}. They may also extend beyond the gland, obliterating adjacent fat and fascial planes\textsuperscript{54,56}. However, several authors have observed some malignant tumors to be well-defined and marginated\textsuperscript{54,61}, so that in fact differentiation between benign and malignant masses is not always reliably possible by means of CT, let alone that tumor histology can be predicted\textsuperscript{53,62}. Exceptions are fat-containing tumors, such as lipomas and liposarcomas, showing CT densities characteristic of fat\textsuperscript{51,53,55,57} (Fig. 9), and vascular lesions, such as hemangiomas and chemodectomas, which strikingly enhance following intravenous contrast infusion\textsuperscript{51,55}. The submandibular gland has a higher

Fig. 10. Axial CT scan showing a pleomorphic adenoma of the left submandibular gland (arrows). The gland is markedly enlarged in comparison with the normal right submandibular gland (S).
density than the parotid gland, so that a submandibular gland tumor may have nearly the same density as the gland itself and therefore may be difficult to identify. However, comparison with the contralateral normal gland will generally show a difference in size and/or contour, indicating the presence of a space-occupying lesion (Fig. 10). Nevertheless, a combination of CT and sialography may sometimes be necessary to clearly outline a submandibular gland tumor.

Because of the slight density difference between a tumor and the surrounding normal salivary tissue, most early authors recommended a combination of CT and sialography, rather than plain CT, to improve localization of a mass and to better define its margins. Furthermore, sialographic delineation of the glandular borders was considered essential to differentiate intrinsic from extrinsic lesions, particularly deep-lobe parotid tumors from parapharyngeal masses. Others, however, have shown that with the newer generation, high-resolution CT scanners intraductal contrast is generally not necessary, unless plain CT provides insufficient information or a specific anatomic structure, such as Stensen's duct, must be visualized. If sialography is performed, watersoluble contrast medium is preferable since oily contrast material is denser than necessary and may obscure anatomic detail or even create artifacts. A combination of CT and intravenous contrast infusion has also been advocated because most salivary gland tumors, and certainly a hemangioma, will enhance with contrast medium. However, this combined procedure is primarily indicated in the case of an extrasalivary tumor, particularly a parapharyngeal mass, to distinguish between a vascular lesion, such as a chemodectoma, and other types of tumor occurring in this region. Also, in selected cases, enhancement of the major regional vessels, i.e. the carotid arteries and the retromandibular and internal jugular veins, may be helpful by demonstrating their relationship to an intradinal regardless lesion.

Probable the most important indication for CT is the clinical situation in which it cannot be established whether a mass is intrinsic or extrinsic to the gland. This is particularly true for a deep-seated lesion, jammed between the mandible and the mastoid, whose origin may be either in the deep lobe of the parotid or in the parapharyngeal tissues. The surgical approaches to the two locations differ in that removal of a deep-lobe parotid tumor requires a transparotid approach involving complete dissection and retraction of the facial nerve, whereas in the case of an extrinsic parapharyngeal mass a transcervical approach can be utilized. Therefore, CT findings in these instances may be extremely useful, not only for treatment planning but also for preoperative patient counseling with regard to expected morbidity.
The anatomic structure most related to postoperative morbidity after parotid gland surgery is the facial nerve, whose path through the glandular parenchyma arbitrarily divides the gland into a superficial and a deep part. The nerve itself is not visible on axial CT scans, but theoretically the course of the nerve through the gland can be inferred from its spatial relationship to visualized landmarks such as the styloid process and the retro-mandibular vein, both structures being directly medial to the facial nerve. Some authors claim that in this way the position of the nerve in relation to a tumor can be accurately determined in 75 percent or more of the patients\textsuperscript{52,54,55,60}. However, as noted by Wiesenfeld and colleagues\textsuperscript{61}, these landmarks are only visible on scans of the superior part of the parotid gland and, moreover, may be variable or distorted due to the tumor. Furthermore, the retromandibular vein cannot always be identified on plain CT scans, so that intravenous contrast infusion or concomitant sialography may be necessary to clearly visualize this vessel. Nevertheless, it is apparent that CT may be of some help in determining whether a tumor lies medial or lateral to the facial nerve. However, expectations should not run too high, since in many cases it will not be possible to predict the position of the nerve with any certainty\textsuperscript{56}.

**Magnetic resonance imaging**

Magnetic resonance imaging (MRI) is an exciting new imaging technique based on the phenomenon of nuclear magnetic resonance (NMR). The method is capable of producing high-quality tomographic images of certain parts of the body, including the salivary glands, without the use of ionizing radiation (Fig. 11).

In short, the technique involves placing the patient in a strong magnetic field so that nuclei of certain elements will align themselves along the axis of this field. The patient is then exposed to a second, perpendicularly orientated, magnetic field in the radio-frequency (RF) region of the electromagnetic spectrum, which causes the nuclei in the subject to resonate about their equilibrium position. After switching off the RF pulse, the nuclei return to their original equilibrium position while emitting a RF wave, which can be detected as an NMR signal. There are a number of nuclei whose properties enable them to be measured by NMR, but it is the combined sensitivity and abundance of hydrogen which makes MRI possible. The procedure, therefore, essentially provides information on the water content of various tissues. As the hydrogen nucleus contains a single proton, the term proton density is used to describe the distribution of resonating nuclei within the patient\textsuperscript{63}. The relaxation process of the nuclei after removal of the RF pulse is characterized by the time constants
Fig. 11. A. Axial MR scan (spin-echo image; TR = 700 ms; TE = 30 ms) of a patient with an adenoid cystic carcinoma in the tail of the left parotid gland (white arrow). The tumor is well separated from the internal carotid artery and internal jugular vein (black arrows). B. Coronal MR scan (spin-echo image; TR = 600 ms; TE = 30 ms) showing medial displacement of the internal jugular vein by the tumor (arrow).

T1 and T2 and the choice and timing of the pulse sequences determine the amount of T1 or T2 information in the signal. This information together with the proton density of the examined tissue are the data from which an image can be constructed. The sensitivity of MRI is such that small differences in water content are sufficient to distinguish between normal and pathologic tissue, and in this respect the procedure is superior to CT. However, as far as diagnostic specificity is concerned, both techniques are somewhat disappointing since tissue characterization still remains very difficult. Recent studies indicate that in the diagnosis of parotid masses MRI offers several advantages over CT. In a preliminary comparative evaluation of 12 parotid masses, Schaefer and colleagues assessed five clinically important imaging parameters, including conspicuity of the lesion, marginal appearance, internal architecture, regional extension and artifact degradation. They concluded that for all these parameters MRI was equal or superior to CT. Similarly, Lloyd and Phelps found MRI to be superior to CT for demonstration of parapharyngeal space tumors. Particularly in this location, the greater soft-tissue contrast resolution of MRI and the possibility of obtaining direct, three-dimensional projections without repositioning the patient result in a better delineation of the tumor from
surrounding soft-tissue structures. Furthermore, flowing blood in MRI will not produce a signal, because the activated protons have moved away from the imaging plane before their emitted signal is detected. The major vessels in the parotid gland and the parapharyngeal space are therefore clearly recognizable without the use of contrast agents, so that their relationship to the mass can easily be appreciated (Fig. 11). The absence of streak artifacts due to bone related X-ray scattering and dental restorations (amalgam and gold) is another important advantage of MRI over CT in the investigation of salivary gland pathology. However, ferromagnetic stainless steel in dentures and orthodontic braces will produce extensive artifacts in MRI and, if possible, these appliances should be removed prior to imaging.

A disadvantage of MRI is the slow patient throughput due to the long sequence acquisition time. Furthermore, the procedure is contraindicated in patients with cardiac pacemakers and in patients with ferromagnetic hemostatic clips in whom a risk of dislodgement with resulting hemorrhage or of injury of sensitive adjacent structures, such as the brain, exists. A recent study indicates that with stapedectomy prostheses there is no danger of displacement, but further research is required before patients with other types of metal implants can safely be exposed to MRI.

Discussion

For more than 50 years sialography and plain radiography were the only modalities available for salivary gland imaging. In the last decades scintigraphy, ultrasound, CT and, very recently, MRI have been introduced for this purpose and there is no doubt that these procedures have considerably widened the diagnostic scope. However, the marked increase in imaging techniques has also introduced the need of selecting the appropriate procedure in the individual patient. Furthermore, a danger of overutilization exists and it should be realized that not every clinical situation automatically requires an imaging procedure. CT scanning, for instance, is not necessary when a tumor has been diagnosed as a pleomorphic adenoma by cytology and is clinically palpable in the superficial lobe of the parotid gland.

The relative abundance of imaging techniques presently available makes a full appreciation of their diagnostic value absolutely essential for a well-considered choice. Sialography provides detailed information on ductal morphology, which is not otherwise obtainable. It remains, therefore, the method of choice in cases of sialoadenitis, sialosis and obstruction, but, as a sole procedure, has become obsolete in tumor diagnosis since the advent of CT scanning. Scintigraphy with $^{99m}$Tc-
Pertechnetate is primarily a function test and has the advantage that all major salivary glands can be examined simultaneously and continuously over a period of time. The method is particularly useful in systemic diseases involving the salivary glands, such as Sjögren's syndrome, because it objectively demonstrates the full extent of glandular dysfunction. Its value in tumor diagnosis and in infections and obstructive disorders is limited, but nevertheless the procedure may provide significant information in selected cases. A special indication for scintigraphy exists when the ductal orifice of a major salivary gland cannot be found or cannot be cannulated. This problem may occur in a variety of clinical conditions and makes scintigraphy the only diagnostic procedure available to confirm the diagnosis and to assess the remaining glandular function. The potential of ultrasound for detecting salivary gland pathology often appears to be overlooked. In certain clinical situations the method is competitive with CT and, considering its advantages, should be used more often as an initial screening procedure, for instance to distinguish between a diffuse inflammatory process and a mass lesion or between a cyst and a solid tumor. Furthermore, ultrasound is an accurate procedure to define the presence and extent of abscess formation in acute suppurative sialoadenitis. The principal advantage of CT is the ability to directly visualize the salivary glands and neighbouring structures, so that the location and extent of mass lesions can be accurately demonstrated. For this reason the procedure is particularly useful to establish whether a tumor is intrinsic or extrinsic to a gland. It should be remembered, however, that CT scanning is not capable of providing a specific diagnosis, except for typical cases such as lipoma or cyst, and that in most instances the method does not reliably distinguish between benign and malignant masses. The newest technique is MRI, which accurately images the major salivary glands and adjacent soft tissues without the use of ionizing radiation. The main indication for MRI is evaluation of mass lesions, particularly parapharyngeal space tumors, and preliminary studies indicate that in this respect the procedure is superior to CT-scanning. Advantages of MRI over CT include better contrast resolution, absence of artifact degradation from dental restorations, visualization of major vessels without intravenous contrast injection and direct, three-plane imaging without patient repositioning. These advantages result in a better delineation of the tumor and it appears, therefore, that MRI may very well replace CT for salivary gland imaging in the near future.

In conclusion, this review of the present state of salivary gland imaging shows that the introduction of new techniques has had a strong impact in that the role of older procedures has considerably diminished and new diagnostic possibilities have become available, particularly in tumor
diagnosis. However, as before, the diagnostic work-up in each patient should be individually tailored, which requires a critical attitude towards the actual value of the various methods in each particular case.

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Chapter 7

SUBMANDIBULAR GLAND FUNCTION FOLLOWING TRANSORAL SIALOLITECTOMY

Published in Oral Surgery, Oral Medicine, Oral Pathology 56: 351-356, 1983.
SUBMANDIBULAR GLAND FUNCTION FOLLOWING TRANSORAL SIALOLITHECTOMY

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Abstract

Conflicting views exist with regard to surgical treatment of a salivary stone in the knee of the submandibular duct, the options being excision of the submandibular gland and transoral removal of the stone. The key question in this dispute is whether or not a gland with a stone in this position has suffered irreparable functional damage. To determine the extent of glandular recovery after transoral sialolithectomy, a clinical and scintigraphic study has been carried out in a consecutive series of twenty-one patients. The results show a return to normal function in the vast majority of these patients, which indicates that transoral removal of the stone is the treatment of choice.

Introduction

Does the presence of a stone at the knee of the submandibular duct warrant excision of the submandibular gland? Even today this question is the subject of lively debate, and a search of the literature reveals widely diverging views. Most authors recommend excision of the submandibular gland when a stone is located at the knee of the submandibular duct, that is, in the region of the sharp turn where the duct curves around the posterior border of the mylohyoid muscle. On the other hand, some authors claim that nearly all submandibular stones, including those at the knee of the duct, can successfully be removed transorally. This latter view is corroborated by the results of the present study, in which submandibular gland function was evaluated clinically and scintigraphically in a series of patients at least 1 year after transoral removal of a stone from the knee of the submandibular duct.

Material and methods

From January, 1974, to December, 1979, seventy-four patients with submandibular sialolithiasis were seen in the Department of Oral and
Maxillofacial Surgery of the University of Amsterdam. In forty patients the stone was located in the anterior part (anterior and middle thirds) of the submandibular duct, that is, anterior to a line joining the mesial surfaces of the second mandibular molars. In thirty-four patients the stone was situated in or in the vicinity of the knee of the submandibular duct. The age and sex distribution of the patients in the latter group is shown in Fig. 1. In agreement with the literature a mean age of 39.7 years and a male-female ratio of 2:1 were found. With the aid of general anesthesia, transoral removal of the stone was attempted in thirty of the thirty-four patients. The operative procedure described by Seward was used. Four patients declined surgical intervention in the absence of clinical symptoms. The results of transoral removal could be evaluated in twenty-one patients. The remaining nine patients were not included in the study for the following reasons: three patients did not respond to a request for a follow-up examination; in four patients stones were removed bilaterally, so that an intraindividual comparison of the function of the surgically treated gland with that of the contralateral normal gland was not possible; and in two patients the stone could not be removed transorally, necessitating submandibular gland excision during the same operative session.

The twenty-one patients were examined clinically and radiographically
(orthopantomogram and a posterior oblique occlusal radiograph) at least 1 year after transoral removal of the stone from the knee of the submandibular duct. At the same time, sequential salivary gland scintigraphy was performed to examine the function of both the treated gland and the contralateral normal gland. At the follow-up visit the patients were asked whether there had been any obstructive or inflammatory symptoms after the operation, and a clinical and radiographic search was made for recurrent stones. Furthermore, a superficial clinical impression of the glandular function was obtained by milking both the normal and the treated submandibular glands and comparing the quantity and quality of the saliva expressed from the ducts. The age of the patients at the time of surgery and the duration of symptoms preoperatively were recorded in order that we might investigate whether these factors had any influence on the functional recovery of the gland.

The scintigraphic procedure has been described in detail elsewhere\textsuperscript{17} and will be only briefly summarized here. A scintillation camera (Siemens Gammasonics HP) with a standard field of view and a low-energy high-resolution collimator were used, together with an on-line computer system (DEC Gamma-11). The patient was placed in a supine position under the scintillation camera, with the head slightly extended. After intravenous injection of 74 MBq $^{99m}$Tc-pertechnetate consecutive 5-minute images were made during a period of 30 minutes to visualize the uptake and excretion of pertechnetate by the major salivary glands. Without moving the subject, 0.25 mg carbachol was injected subcutaneously 10 minutes after the pertechnetate injection to stimulate salivary excretion, after which the study was continued for another 20 minutes. The data were simultaneously digitized and stored at 1-minute intervals and later replayed to obtain time-activity curves from regions of interest over both submandibular glands and from background regions over the skull (Fig. 2). From the curves, two ratios are then calculated: the maximum glandular activity/background activity (Max/BG) ratio, which gives a measure of the concentrating ability of the gland, and the maximum glandular activity/minimum glandular activity (Max/Min) ratio, which gives a measure of the excretory ability of the gland. The maximum of the time-activity curve is taken, whether attained before, at, or after carbachol administration, and the minimum is taken at 10 minutes after activity starts to drop following carbachol administration. Background activity in the glandular region is estimated to be skull activity multiplied by a factor of 1.4.

To investigate whether symmetry of glandular function normally exists, sequential salivary gland scintigraphy was also performed in twenty subjects without evidence of salivary gland disease. The same data-acquisition and analysis procedure as described above was used, and
Fig. 2. Scintigraphic study of a patient 18 months after transoral removal of a stone from the knee of the right submandibular duct. A, B, and C: Analogue images taken 5 to 10 minutes, 10 to 15 minutes, and 20 to 25 minutes after pertechnetate injection. D: Computer-derived image showing the regions of interest over both submandibular glands and over the background regions. Subcutaneous injection of carbachol at 10 minutes (arrow) produces a rapid excretion of pertechnetate from both submandibular glands. The function curves and the ratios show that the surgically treated gland accumulates more pertechnetate than the contralateral normal gland, which may be due to a slightly lower resting salivary flow rate from the treated gland.

Max/BG and Max/Min ratios were calculated and were compared for the right and left submandibular gland by means of Wilcoxon's signed rank test. Furthermore, for each individual normal subject, the difference between the ratios from the right and left submandibular glands was calculated and expressed as a percentage. In the group of twenty-one patients, these percentages were used to determine whether the differences
maximum glandular activity ratio
minimum glandular activity ratio

Fig. 3. Correlation between right and left submandibular gland function in twenty subjects with no evidence of salivary gland disease.

Fig. 4. Comparison of “pathologic” and contralateral normal submandibular gland function in twenty-one patients after removal of a stone from the knee of the submandibular duct. The broken line is the line of identity.
between the ratios from the surgically treated and the contralateral normal glands were within the normal range or whether they should be considered abnormal.

Results

In the group of normal subjects, there was no significant difference between the Max/BG ratios and between the Max/Min ratios from the right and left submandibular glands (as tested by Wilcoxon's signed rank test). A highly significant correlation was found between the Max/BG ratios (r=0.88, p<0.001) and between the Max/Min ratios (r=0.92, p<0.001) from the right and left submandibular glands of these subjects (Fig. 3). From the group of normal subjects it was calculated that the difference between the right and left submandibular glands was maximally 25 percent for the Max/BG ratio and 15 percent for the Max/Min ratio. For the group of twenty-one patients the function of the treated gland is compared with the function of the contralateral normal gland in Fig. 4. In sixteen of the twenty-one patients the treated submandibular gland showed a similar function, for both the concentration (Max/BG ratio) and excretion (Max/Min ratio) of $^{99m}$Tc-pertechnetate when compared to the contralateral normal gland.

Clinically and radiographically, there were no signs or symptoms of obstruction and, in comparison with the contralateral normal gland, a normal quantity of clear saliva could be expressed from the duct of the treated gland. In the remaining five patients either one or both ratios from the treated gland were decreased when compared with the ratios from the contralateral normal gland. Yet, even these patients were free of symptoms and massage of the treated submandibular gland produced at least some normal, clear saliva. In only one patient a small stone was found in the intraglandular part of the submandibular duct. However, reexamination of the preoperative radiographs showed that this stone had been overlooked at the time of operation.

In the group of sixteen patients with normal scintigraphic ratios from the treated gland, the mean age at the time of operation was 33 years (range: 18 to 53 years) and the mean duration of symptoms before surgery was 6.6 years (range: 1 week to 15 years). For the five patients with decreased scintigraphic ratios from the treated gland the mean age at the time of operation was 52 years (range: 43 to 62 years), with a mean duration of symptoms before surgery of 5.3 years (range: 1 month to 16 years).
Discussion

When a stone is present in the submandibular duct, the choice of treatment is based mostly on the following criteria: duration and severity of obstructive or inflammatory symptoms, age and sex of the patient, and the location of the stone in the duct. The changes in the ductal system, as seen on a sialogram, can also be taken into consideration. However, sialography is not normally recommended when the stone is located anteriorly in the duct, since this procedure may dislodge the calculus and carry it further into the duct.

There is general agreement that stones in the anterior and middle thirds of the submandibular duct are best removed via an intraoral approach\textsuperscript{13}. However, Rauch\textsuperscript{1} and Schultz\textsuperscript{18} report that, respectively, 35 and 54 percent of all stones are found in the region of the sharp curve (knee) of the duct and considerable controversy exists about the surgical treatment of these stones. This is illustrated by Table 1, which presents a survey of the literature from the past 30 years on surgical treatment of submandibular sialolithiasis. Most authors believe that when a stone is situated in the knee of the duct and there are, or have been, obstructive or inflammatory signs or symptoms, the gland has suffered irreparable damage and should be excised\textsuperscript{1-8}. On the other hand, Dechaume and coauthors,\textsuperscript{9} Seldin and associates,\textsuperscript{10} Whinery,\textsuperscript{11} and Laudenbach and colleagues\textsuperscript{12} are of the opinion that the submandibular gland has a remarkable capacity for functional recovery, once the obstruction is removed, and subsequently

<table>
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<th>Author</th>
<th>No. of patients</th>
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<th>Submandibular gland extirpation*</th>
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<td>108 (51%)</td>
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*Including secondary extirpation.
recommend transoral removal of all stones, even if they are situated deep in the submandibular duct. With due reservation concerning the extrapolation of results from animal experiments to the human situation, this view seems to be supported by the results of experimental studies, which show extensive regeneration of glandular parenchyma after prolonged ligation of the excretory duct.\textsuperscript{24-27}

The disadvantages of submandibular gland excision are obvious: it not only creates a submandibular scar but also involves some risk of damage to the lingual nerve, the hypoglossal nerve, and, most notably, the mandibular branch of the facial nerve. That the latter complication occurs more frequently than is generally appreciated is evident from the reports by Kenefick\textsuperscript{22} and Goudal and Bertrand,\textsuperscript{23} who find permanent damage of the mandibular branch of the facial nerve in, respectively, 9 and 6 percent of their patients. However, those who favour submandibular gland excision point out that histopathologic examination of the excised gland often shows degenerative and inflammatory changes which, in their opinion, justify their decision. The fact that these changes are, to a greater or lesser extent, almost always seen is, in itself, not sufficient evidence that the gland could not have functioned satisfactorily if it had been left in situ after removal of the obstruction. Therefore, in clinical practice, the key question seems to be whether there is irreparable functional damage in a gland with a stone situated in the knee of the duct. It would be ideal if this could be established preoperatively, but unfortunately there is no accurate method available today to predict the chance of functional recovery. As a consequence, this question can be answered only by a retrospective study. Surprisingly, however, long-term results of transoral sialolithotomy are virtually lacking in the literature. Only Beetke\textsuperscript{20} and Esser and Zecha\textsuperscript{28} specifically mention a postoperative follow-up after several years, but in their studies the state of the gland is assessed solely by clinical criteria.

An objective evaluation of submandibular gland function after transoral removal of a stone can be achieved by quantitative measurement of the salivary flow (sialometry), preferably, for comparison, from both submandibular glands or by sequential salivary gland scintigraphy. Sialometry has the disadvantage that it is invasive, since it requires cannulation of both submandibular ducts which, moreover, is not always technically possible. Sequential salivary gland scintigraphy is a relatively noninvasive procedure, is well tolerated by the patient, and is eminently suitable for evaluation of salivary gland function.\textsuperscript{17,29} Furthermore, it has the advantage that all major salivary glands can be examined simultaneously; for that reason, we have chosen this method for our retrospective study.

Our results have clearly shown that 75 percent of the glands function normally after removal of a stone from the knee of the duct, and
apparently a functional restitutio ad integrum has taken place in these cases. In the remaining patients one or both of the scintigraphic ratios were abnormal and, on clinical inspection, the salivary flow from the treated gland was less than the flow from the contralateral normal gland. Nevertheless, these patients were free of symptoms and, with the exception of one patient, no clinical or radiographic signs of recurrent stone formation were found. Even though the numbers are small, the pronounced difference in mean age between the two groups of patients indicates that the capacity for full functional recovery is to some extent dependent on age. On the other hand, the duration of symptoms before surgery was similar in both groups, which suggests that this factor has no influence in this respect. This observation is in keeping with the results of Isacsson, Ahlner, and Lundquist,30 who find no statistical evidence of correlation between the duration of symptoms and the degree of histologic changes in a series of 108 submandibular glands with a clinical diagnosis of chronic sialoadenitis.

In conclusion, our findings strongly corroborate the view of Dechaume and co-authors,9 Seldin and colleagues,10 Whinery,11 and Laudenbach and associates12 that the presence of a stone at the knee of the submandibular duct does not necessarily warrant excision of the submandibular gland. Instead, transoral removal of the stone is recommended as the treatment of choice, since this procedure not only leaves the submandibular gland intact as a functioning organ but also obviates the risk of the above-mentioned surgical complications.

References

Chapter 8

ABSOLUTE INDICATIONS FOR SALIVARY GLAND SCINTIGRAPHY
WITH $^{99m}$Tc-PERTECHNETATE

ABSOLUTE INDICATIONS FOR SALIVARY GLAND SCINTIGRAPHY WITH $^{99m}$Tc-PERTECHNETATE

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Abstract

In recent years salivary gland scintigraphy has gained widespread acceptance as a useful means for evaluating salivary gland disorders. An absolute indication for this procedure exists when the ductal orifice of one or several major salivary glands cannot be found or cannot be cannulated. Clinical conditions in which this problem occurs include technical failure to probe and cannulate the duct, developmental anomalies, obstructive disorders, traumatic lesions and fistulae and the need of postsurgical information after glandular excision or after ligation or repositioning of a major excretory duct. The clinical value of scintigraphy in these conditions is demonstrated by means of case presentations.

Introduction

A detailed history and a thorough physical examination still are the most important diagnostic tools in the evaluation of salivary gland disorders. Nevertheless, confirmation of the clinical impression is frequently necessary and for that purpose several diagnostic methods are available, including sialography, sialometry, sialochemistry, microbiology, scintigraphy, computerized tomography, ultrasound, and fine-needle, incisional, or excisional biopsy. Sialography, sialometry, sialochemistry, and microbiology require the presence and patency of the ductal orifice, either to inject contrast medium to visualize the ductal system or to collect saliva for microbial, quantitative, or qualitative analysis. However, in some patients the ductal orifice is not accessible or cannot be found, and in these instances salivary gland scintigraphy provides the sole means to evaluate both the functional and morphologic status of the affected gland.

The purpose of this article is to present a survey of the clinical conditions in which salivary gland scintigraphy is essential to establish a diagnosis.
Scintigraphic method

Sequential scintigraphy was performed in the frontal view by means of a scintillation camera with a small field of view and a low-energy, high-resolution, parallel-hole collimator. Data were simultaneously digitized with an on-line computer system. The patient was placed in a supine position under the scintillation camera, with the head slightly extended. Immediately after intravenous injection of 74 MBq $^{99m}$Tc-pertechnetate, consecutive 5-minute analogue images were made during a period of 30 or 40 minutes to visualize the uptake and excretion of pertechnetate by the major salivary glands. The stimulant carbachol (carbamylcholine chloride), a parasympathomimetic agent, was regularly used to accelerate excretion. Stimulation not only shortens the scintigraphic study to a more acceptable time without forfeiting information but also provides a rapid way of investigating the patency of the major excretory ducts. When stimulation was used, 0.25 mg carbachol was administered subcutaneously at 20 minutes or, more recently, at 10 minutes after intravenous injection of pertechnetate, and the study was then continued for a further 20 minutes. The digitized data were collected at 1-minute intervals and were later replayed to obtain time-activity curves from regions of interest placed over right and left major salivary glands and background regions over the skull. Two ratios were calculated from the curves: (1) the ratio of maximum glandular activity to background activity, which gives a measure of the concentrating ability of the gland, and (2) the ratio of maximum glandular activity to minimum glandular activity, which gives a measure of the excretory ability of the gland. The maximum of the time-activity curve was taken, whether attained before, at, or after carbachol administration, and the minimum was taken 10 minutes after activity started to drop following carbachol administration. These ratios are particularly useful in repeat studies to quantitate the effect of treatment on salivary gland function.

Case reports

Case 1

A 19-year-old woman had obstructive symptoms, related to mealtimes, in the left submandibular fossa. Sialography of the left submandibular gland was attempted but resulted in extravasation of the contrast medium into the floor of the mouth. Some months later a second attempt was made, but this time the duct could not be cannulated. During a third attempt, after surgical exposure of the submandibular duct with the aid of local anesthesia, the catheter could not be introduced, probably because of a stricture proximally from the point of insertion. Because the complaints persisted, extirpation of the left submandibular gland was considered. However, it was decided that salivary
Fig. 1. Obstructive symptoms in the left submandibular gland. Technical failure to probe and cannulate the left submandibular duct. The scintigraphic study shows normal uptake of pertechnetate in the left submandibular gland, as well as in the other major salivary glands. Maximum uptake in the submandibular glands is reached by 10 minutes, and carbachol stimulation at 20 minutes (arrow) has only little effect. The accumulated pertechnetate is completely excreted, indicating an undisturbed passage of saliva through the ducts. On the basis of this study, the planned excision of the left submandibular gland was abandoned.
gland scintigraphy should be performed first in order to evaluate the functional status of the gland. Surprisingly, the uptake of pertechnetate in and the excretion of pertechnetate from the left submandibular gland were found to be normal (Fig. 1). On the basis of the scintigraphic study, the floor of the mouth was again carefully inspected and a salivary fistula was found in the scar of the previous incision, approximately 2 cm behind the submandibular duct orifice. A sialogram made through the fistula showed a normal architecture of the left submandibular gland. However, since the fistulous entrance was very narrow, it was dilated, after which a catheter was introduced and kept in place for 10 days. The patient has remained free of symptoms since that time. In this case the scintigraphic examination prevented excision of a normal submandibular gland.

Case 2

A 28-year-old woman was referred by her dentist for removal of third molars. On routine intraoral examination, the orifices of the left parotid and left and right submandibular ducts were seen to be present and a normal quantity of saliva could be expressed from these ducts. However, the right parotid duct orifice could not be found. There was no history of right parotid gland disease; nor were there any signs or symptoms of xerostomia. The dentition was in good repair, with no evidence of excessive dental caries. A preliminary diagnosis of aplasia of the right parotid gland was made. Salivary gland scintigraphy showed normal uptake of pertechnetate in the left parotid and left and right submandibular glands. However, in the region of the right parotid gland there was complete absence of pertechnetate uptake, which confirmed the clinical diagnosis of aplasia of the right parotid gland (Fig. 2).

Case 3

A 69-year-old man was referred for evaluation of a swelling in the left submandibular fossa. Approximately 1 year previously the patient had complained of a swelling in the anterior part of the floor of the mouth, which was painful when he wore his lower denture. He was referred to a plastic surgery service in another hospital, where the swelling was excised. According to the discharge report, the genioglossus muscle was partially divided and the mucosal edge was sutured to the periosteum on a lower level to deepen the lingual sulcus. Microscopic examination of the excised tissue showed fibrous
Fig. 3. Obstruction and complete functional atrophy of the left submandibular gland due to iatrogenic trauma to the submandibular duct. The scintigraphic study shows total absence of pertechnetate uptake in the left submandibular gland.

tissue and salivary gland tissue with chronic inflammatory changes. After this operation the patient experienced episodes of pain and swelling in the left submandibular fossa, especially at mealtimes. During the following months these symptoms gradually subsided, but a persistent swelling developed in the left submandibular fossa. On examination, a firm, painless swelling was found in the left submandibular fossa. Occasionally there was still some pain during and after eating, but this was less severe than before. Intraorally, a firm ridge of scar tissue was found anteriorly in the left side of the floor of the mouth. The orifice of the left submandibular duct could not be located. To evaluate left submandibular gland function, salivary gland scintigraphy was
performed. Whereas normal uptake and excretion of pertechnetate were observed in the right and left parotid and right submandibular glands, there was no discernible uptake in the left submandibular gland (Fig. 3). On the basis of the history and the clinical and scintigraphic examination findings, a diagnosis of functional atrophy of the left submandibular gland after surgical trauma to the submandibular duct was made. In retrospect, it seems likely that the original condition was an irritation fibroma in the floor of the mouth due to an ill-fitting denture. The scintigraphic examination objectively ascertained the destruction of functional parenchyma and confirmed the clinical diagnosis.

Fig. 4. Obstruction and functional atrophy of the left parotid gland due to transpositioning and stenosis of the parotid duct. A: Preoperative scintigraphic study showing decreased pertechnetate uptake in the left parotid gland. After carbachol stimulation at 11 minutes (arrow) there is complete retention of activity within the gland. B: Postoperative study showing improvement in pertechnetate uptake in the left parotid gland. After carbachol stimulation at 11 minutes, excretion of pertechnetate is now normal, though slightly delayed. Note visualization of repositioned left parotid duct on 15-20 minutes scintigraphic image (arrow).
Case 4

A 28-year-old woman was referred for evaluation of recurrent pain and swelling in the left preauricular area, related to mealtimes. The symptoms had been present for approximately 3 months. On examination, a slight, painless swelling was found in the region of the left parotid gland. Intraoral inspection revealed a band of fibrous tissue in the left cheek running vertically toward the upper alveolar ridge, where it was firmly attached in the region of the first molar. In this band, near the alveolar ridge, there was a fistula producing a purulent discharge, but the left parotid duct orifice could not be found. On questioning, the patient said that there had been recurrent inflammatory episodes in this region for the past 10 years. A dental radiograph showed a periapical granuloma of the left first maxillary molar. Sequential salivary gland scintigraphy showed that pertechnetate uptake in the left parotid gland was decreased in comparison to the normal right parotid gland. After stimulation of salivary excretion by carbachol, the right parotid and both submandibular glands excreted the accumulated pertechnetate. However, no excretion of pertechnetate from the left parotid gland was observed (Fig. 4, A). On the basis of the history and the clinical and scintigraphic examinations, it was assumed that recurrent inflammation in this area, with subsequent fibrosis, had resulted in gradual transpositioning and stenosis of the left parotid duct. With the patient under general anesthesia, the parotid duct was located near the alveolar ridge and freed from the fibrous tissue. Repositioning was achieved by submucous tunneling. After resection of the stenosed distal end, the duct was cannulated and reinserted in its normal position with Mersilene sutures. Already during the operation and in the postoperative period, clear saliva flowed from the cannula, which was kept in place for 10 days. At a later stage, with the area under local anesthesia, an apicoectomy of the left first maxillary molar was performed. The patient has remained free of symptoms since that time. A repeat scintigraphic study 1 year postoperatively showed that, in comparison with the preoperative study, pertechnetate uptake in the left parotid gland was increased. Although somewhat delayed, excretion of pertechnetate after carbachol stimulation was complete, which confirmed the clinical impression of an undisturbed passage of saliva through the repositioned parotid duct (Fig. 4, B).

Case 5

A 59-year-old man was referred with a complaint of pain and swelling in the right submandibular and sublingual regions of 2 weeks duration. There was a history of removal of several stones from the right submandibular gland 15 years previously and of excision of the right submandibular gland for recurrent pain and swelling 18 months before the present referral. Clinical examination revealed a right submandibular scar and a painful, nonfluctuant swelling in the right submandibular fossa. Intraorally, the right sublingual plica was swollen and hyperaemic; no saliva could be expressed from the right submandibular duct. A panoramic radiograph showed a 1-cm radiopaque structure superimposed on the right lower border of the mandible in the region of the antegonial notch, presumably a salivary stone. To establish whether residual salivary gland tissue was present, sialography was attempted. However, this procedure could not be carried out because cannulation of the right submandibular duct proved to be technically impossible. Salivary gland scintigraphy was then performed and showed a normal pattern of pertechnetate uptake and excretion in the right and left parotid and left submandibular glands but also a small, distinct pertechnetate accumulation in the
Fig. 5. Sialolithiasis and chronic sialoadenitis of the right submandibular gland which had allegedly been excised 18 months previously. The scintigraphic study shows a small but distinct accumulation of pertechnetate in the region of the right submandibular gland (arrow), indicating that only part of the gland has been removed. After carbachol stimulation at 10 minutes, there is retention of activity due to obstruction of the salivary flow.

region of the allegedly removed right submandibular gland. This indicated the presence of some remaining functioning salivary gland tissue, so that apparently only part of the right submandibular gland had been removed during the previous operation (Fig. 5). Confirmation was obtained by surgical intervention, during which the deep part of the right submandibular gland was removed, together with a stone in the knee of the submandibular duct.
Fig. 6. Ligation of the left parotid duct during excision of a squamous cell carcinoma from the cheek. Postoperative scintigraphic studies show gradual functional atrophy of the left parotid gland. A: Directly postoperatively there is diffuse uptake of pertechnetate throughout the entire left parotid gland. Concentration of pertechnetate within the gland due to salivary flow toward the main excretory duct, as seen in the normal right parotid gland, does not occur. B: Three months after surgery there is still residual uptake of pertechnetate in the left parotid gland, although considerably less than in the normal right parotid gland. C: One year after surgery there is no discernible uptake of pertechnetate in the left parotid gland.

Case 6

A 40-year-old man was referred for treatment of an ulcer in the left cheek. In the past 2 years there had been occasional slight complaints, but the patient could not remember when he had first noticed the ulcer. On intraoral examination, an area of leukoplakia was seen in the left cheek on the occlusal line, with a small 4-mm ulcer just behind the parotid duct orifice. There was no cervical lymphadenopathy, and further physical examination findings were noncontributory. A biopsy showed the lesion to be a well-differentiated squamous cell carcinoma. With the patient under general anesthesia, a wide local excision was carried out. On the lateral aspect of the buccinator muscle the parotid duct was identified, divided, and doubly ligated. The defect was then covered with a free skin graft by the bolus tie-over technique for immobilization of the graft.
Postoperatively, the patient was given 0.25 mg of atropine intramuscularly three times daily for 10 days to suppress salivary excretion. Swelling of the obstructed gland was not observed immediately postoperatively or during the follow-up period.

To evaluate the functional status of the gland, sequential scintigraphic studies were performed immediately postoperatively and 3 months and 1 year after the operation. These studies showed a gradual decrease of pertechnetate uptake in the left parotid gland. One year postoperatively there was no discernible uptake, which confirmed the functional atrophy of the gland after ligation of the main excretory duct (Fig. 6).

Discussion

Nearly two decades ago Börner and co-authors introduced salivary gland scintigraphy with $^{99m}$Tc-pertechnetate into clinical practice. Since then numerous articles on the subject have been published and the method is now firmly established as a useful means of investigating salivary gland disorders. The principal advantage of scintigraphy is that the salivary gland dynamics can be visualized and quantitated by following the uptake and excretion of pertechnetate by the glandular parenchyma, which provides valuable information on the functional and, to a lesser extent, also on the morphologic and topographic status of the gland or glands involved in a disease process. However, scintigraphy by itself is rarely diagnostic and the results should always be interpreted in the context of data provided by the history, the physical examination, and, if necessary, other diagnostic procedures.

The nature of the scintigraphic procedure implies that functional disorders, such as sialolithiasis and the various types of sialoadenitis and sialosis, are most profitably investigated by this method. The information obtained can be helpful in the diagnosis and differential diagnosis, as well as in the posttreatment evaluation, of diffuse inflammatory and non-inflammatory salivary gland swelling. For instance, the presenting signs and symptoms of patients with Sjögren's syndrome and patients with various types of sialosis are often very similar, but scintigraphy generally shows decreased glandular uptake of pertechnetate in Sjögren's syndrome and markedly increased uptake in sialosis. It follows that scintigraphy may serve as a simple routine test for initial differentiation between these two disorders, so that unnecessary clinical and laboratory investigations can be avoided.

In mass lesions in the region of the major salivary glands a distinction should be made between a mass adjacent to, but not involving, the salivary gland and a salivary gland tumor per se. In case of doubt, the morphologic and topographic information provided by scintigraphy may be helpful to establish the extrasalivary nature of a swelling. In the diagnosis of salivary gland tumors, however, scintigraphy with $^{99m}$Tc-pertechnetate has not
lived up to expectations. On the one hand, this is due to the fact that the spatial resolution of the imaging system presently available is 1 to 2 cm, so that only tumors that are already amenable to clinical inspection and palpation are visualized. On the other hand, increased experience with scintigraphy in tumor diagnosis has shown a lack of specificity, since both benign and malignant tumors fail to concentrate pertechnetate, resulting in "cold" areas on the salivary gland images. The only exceptions are the papillary cystadenoma lymphomatosum, or Warthin's tumor, and oncocytoyoma. These tumors tend to concentrate more pertechnetate than the surrounding normal glandular tissue and, therefore, appear as "hot" areas on the scintigraphic images.

In the literature on salivary gland scintigraphy attention has been focused mainly on the well-defined disease entities mentioned above. However, there is another group of patients that has received relatively little attention. These patients do not represent a specific type of salivary gland disease but are grouped together because they have in common the fact that the ductal orifice cannot be found or cannot be cannulated. Also included are those patients in whom, for some reason, only part of the main excretory duct can be visualized sialographically. It is apparent that this severely limits the diagnostic possibilities. As a consequence, salivary gland scintigraphy becomes the major diagnostic procedure to confirm the clinical diagnosis and to assess the extent of glandular dysfunction. Within the spectrum of salivary gland disorders, a number of clinical conditions fall into this category and can be subdivided into the following groups:

Technical failure. A suspicion of salivary gland disease in patients in whom it proves to be technically impossible to probe and cannulate a main excretory duct, even though the ductal orifice is patent and in its normal position. This problem occurs mainly in the submandibular gland and is due mostly to such factors as the inability to open the mouth widely, the presence of lower incisors in linguoversion, or hypertrophy and extreme mobility of the papilla. According to the literature, this technical problem arises in 10 to 20% of the patients in whom sialography is attempted.5,6

Developmental anomalies. Aplasia or agenesis (the congenital absence of one or several major salivary glands) may occur alone7,8 or in combination with other congenital abnormalities, mostly defects of the lacrimal apparatus.9-11 A familial pattern has been reported8,10 indicating that heredity is an etiologic factor. The main symptoms of aplasia are xerostomia, difficulty in eating, and excessive dental caries. A provisional diagnosis can be made when the orifice of one or several major salivary glands cannot be found on intraoral inspection. The condition is rare, but it is conceivable that in some patients aplasia of one or even two major salivary glands will go unnoticed, unless detected by chance, because the
remaining glands produce sufficient saliva to mask the salivary deficiency and to prevent the subjective feeling of xerostomia. When aplasia is suspected, salivary gland scintigraphy is the only method available to demonstrate objectively the absence of functioning glandular parenchyma. Furthermore, scintigraphy has the added advantage that all major salivary glands can be examined simultaneously. Atresia (the congenital absence of the ductal orifice or part of the duct itself) is extremely rare and is usually detected in early infancy by the presence of a ranula-like swelling in the floor of the mouth. If necessary, the clinical diagnosis can be confirmed by scintigraphic demonstration of retention of pertechnetate in the affected gland due to complete obstruction of the salivary flow.

**Obstructive disorders.** Seward distinguishes between papillary and ductal obstruction. Acute and chronic papillary obstructions are usually due to a bite trauma, an ulcer, or chronic irritation with subsequent fibrosis, and they rarely cause diagnostic problems. Apart from sialolithiasis and mucous plugs, ductal obstruction may be caused by traumatic injury to the duct or, indirectly, by a tumorous or inflammatory process outside the ductal wall. When sialography proves to be impossible, scintigraphy becomes the major diagnostic method to confirm the clinical diagnosis and to evaluate the functional status of the gland as well as the residual patency of the main excretory duct. It is apparent that these findings largely determine the choice of treatment in the individual patient.

**Traumatic lesions and fistulae.** A persistent fistula or a sialocele of a major salivary gland may be the result of sharp or blunt trauma to the soft tissues of the face or may occur as a complication after operations in the region of the salivary glands or their main excretory ducts. As in the case of congenital fistula, sialography or fistulography should be attempted, but these procedures are not always successful. Scintigraphy and, in case of doubt, counting of radioactivity in the fistular fluid may confirm the diagnosis and provide useful information on the functional status of the gland as a guideline for therapy. In the early phase after reconstruction of the duct or conversion of an external fistula into an internal one, ductal patency should be checked by scintigraphy rather than by sialography to avoid the potential risk of secondary injury.

**Status after surgical treatment.** Subtotal or total extirpation of a major salivary gland and ligation of a parotid duct to induce glandular atrophy are procedures that are frequently used in the management of tumorous or inflammatory disorders of the salivary glands. Furthermore, repositioning of the parotid ducts into the oropharynx is a well-accepted method for treatment of persistent drooling. Symptoms may persist or develop after these procedures, requiring further evaluation, or it may be considered of
interest to objectively document the effect of a clinically successful ligation or repositioning of a parotid duct on the glandular function. Since, for obvious reasons, sialography is no longer possible, the presence of residual functioning glandular tissue as a possible source of complaints or, in the case of ligation or repositioning of a parotid duct, the functional status of the whole gland can then be assessed only by a scintigraphic study.\textsuperscript{19,25}

In summary, we have presented a survey of the clinical conditions in which salivary gland scintigraphy is essential to establish a diagnosis. These conditions do not form a separate type of salivary gland disease but merely share the problem that a ductal orifice is either not accessible or cannot be found. Each disorder is exemplified by a case presentation to illustrate that only scintigraphy provided the information necessary for a definite diagnosis.

References

Summary

Salivary gland scintigraphy with $^{99m}$Tc-pertechnetate was introduced into clinical practice in 1965 and initially enjoyed considerable popularity at a time when, from a practical point of view, only plain radiography and sialography were available to complement the history and physical examination in the diagnosis and follow-up of salivary gland disorders. However, over the ensuing years the interest in the procedure gradually subsided, despite its obvious usefulness for evaluating the functional status of the major salivary glands. In the present thesis, therefore, an attempt has been made to promote a balanced use of salivary gland scintigraphy by providing answers to some questions directly related to its clinical application. These questions have been formulated in Chapter 1.

In Chapter 2, the physical characteristics of technetium-99m, as well as the distribution and excretion of $^{99m}$Tc-pertechnetate in man, are briefly described. Also, the available data on the handling of iodide and pertechnetate by the salivary glands are reviewed, leading to the following conclusions: from animal experiments, there are strong indications that iodide and pertechnetate are transported into saliva by cells of the ductal system, even though there is also some evidence for an additional role of the acinar cells. In the human salivary glands, pertechnetate and iodide are probably transported by the same mechanism, but the exact site or sites of this transfer system are as yet not identified.

In Chapter 3, an outline of the normal pattern of $^{99m}$Tc-pertechnetate uptake and excretion by the major salivary glands is presented, followed by a brief description of the criteria used in qualitative and semi-quantitative classifications based on a visual interpretation of sequential scintigraphic images. The advantages of stimulating pertechnetate excretion at some point during the scintigraphic examination are emphasized, as are the relative merits and pitfalls of gustatory and parasympathomimetic stimulants used to produce this effect. The normal shapes of parotid and submandibular gland time-activity curves and their quantitative analysis by means of various function parameters are also discussed.

In the first part of Chapter 4, various aspects of the radioactivity appearing in the region of the oral cavity after intravenous injection of
$^{99m}$Tc-pertechnetate were investigated. To study the normal accumulation of this oral activity, sequential scintigraphy in the anterior or lateral view was performed in a series of 20 healthy subjects. It was observed that the oral activity is not a single entity, but instead consists of 4 different parts showing a distinct sequence in their time of appearance and a specific relation with fluctuations in parotid or submandibular gland activity.

In 8 subjects, the origin of the oral activity was examined by repeating the scintigraphic study after ligation of the parotid ducts and/or cannulation of the submandibular ducts, which prevented saliva from entering the oral cavity. The results clearly demonstrated that the activity normally accumulating in the oral region is due entirely to radioactive saliva excreted by the parotid and submandibular glands.

To establish the location of the oral activity, frontal and lateral scintigraphic images with the mouth closed and opened were obtained at the end of the normal studies to investigate whether opening of the mouth resulted in a positional change of this activity. Also, in 8 subjects, radioactive markers were applied to the palate, or inserted into the submandibular duct or the parotid duct orifice, in order to relate the position of these anatomic landmarks to the oral activity. The configuration and the downward displacement of the oral activity on opening the mouth, resulting in distinct separation from the palatal marker, not only ruled out the palate as the location of this activity but also strongly suggested that it represents accumulation of pertechnetate in the region of the tongue. Pertechnetate mouthwash studies in 3 subjects confirmed that radioactive saliva is adsorbed to oral mucosa and that adsorption to the lingual mucosa is the major contributor to the oral activity. A possible contribution to this activity from pertechnetate uptake in the sublingual glands could be discarded, since the markers situated at both ends of the submandibular duct defined the position of the sublingual gland and no pertechnetate accumulation was observed between these markers.

From these observations, it was concluded that pertechnetate uptake in the sublingual and minor salivary glands of the oral cavity is not visualized on scintigraphic images, so that scintigraphy cannot be used to evaluate the function of these glands. However, since the oral activity proved to be entirely dependent on radioactive saliva excreted by the parotid and submandibular glands, this activity is a useful indicator of major salivary gland function.

In the second part of Chapter 4, attention is focused on the circumspect "cold" areas with less than background activity that are sometimes seen in the region of the oral cavity during salivary gland scintigraphy with $^{99m}$Tc-pertechnetate. Evidence is presented that this phenomenon is not
due to deficient pertechnetate uptake in the minor salivary glands of the oral cavity, but instead represents absorption of radiation in extensive dental restorations.

Chapter 5 deals with the feasibility of reducing the scintigraphic examination time from the usually recommended 60 minutes or longer to 30 minutes. Such a reduction can be achieved by administering a salivary stimulant, e.g. carbachol, at 10 minutes instead of at 20 minutes after pertechnetate injection, and by terminating the scintigraphic study 20 minutes after stimulation. To investigate whether this change in procedure is possible without forfeiting information, sequential salivary gland scintigraphy was performed in two groups of 10 normal subjects. In these subjects, the glandular response to carbachol stimulation at 10 and 20 minutes was evaluated by calculating two semi-quantitative function parameters from the time-activity curves, i.e. the ratio maximum glandular activity/background activity (Max/BG), indicating the concentrating ability of the glands, and the ratio maximum glandular activity/minimum glandular activity (Max/Min), indicating their excretory capacity. To estimate the background activity in the major salivary glands, a comparison was made between the activity in background regions over the skull and the activity measured over glands after perchlorate administration and over "empty" glandular regions. It appeared that skull activity multiplied by a factor 1.4 provides a reliable measure for glandular background activity.

The results showed that the values of the function parameters after carbachol stimulation at 10 minutes corresponded with the values obtained after stimulation at 20 minutes. Carbachol stimulation at 10 minutes could therefore safely be recommended for evaluating parotid and submandibular gland function. Moreover, since the minimum of glandular activity following carbachol stimulation was reached within 10 to 12 minutes and continuation of the study did not provide additional data, a total examination time of 30 minutes sufficed for obtaining all necessary information. As a result, sequential salivary gland scintigraphy with $^{99m}$Tc-pertechnetate has become a more practical procedure.

In Chapter 6, a review of the current status of diagnostic imaging in salivary gland disease is presented. The potentials and limitations of sialography, scintigraphy with $^{99m}$Tc-pertechnetate, ultrasound, computed tomography and magnetic resonance imaging are discussed and a rational approach to their use is recommended. The review clearly shows that the introduction of new techniques has had a strong impact in that the role of older procedures has considerably diminished as new diagnostic pos-
sibilities have become available, particularly in tumor diagnosis. It is emphasized, however, that a diagnostic work-up should be individually tailored, which requires a critical attitude towards the actual value of the various imaging procedures in each particular case.

In Chapter 7, salivary gland scintigraphy with $^{99m}$Tc-pertechnetate was not used in its capacity as a diagnostic procedure, but instead served as a function test to evaluate the effect of transoral sialolithectomy on submandibular gland function. A study involving 21 patients in whom a stone was removed from the knee of the submandibular duct at least 1 year before scintigraphic examination showed that in the vast majority of these patients submandibular gland function returned to normal after the transoral surgical procedure. It was concluded, therefore, that the presence of a stone in the knee of the submandibular duct does not necessarily warrant excision of the submandibular gland and that transoral removal is the treatment of choice for a stone in this location.

In Chapter 8, a survey is presented of the salivary gland disorders in which scintigraphy with $^{99m}$Tc-pertechnetate proved to be essential for establishing a diagnosis. The patients involved did not represent a specific type of salivary gland disease, but merely shared the problem that a ductal orifice was either not accessible or could not be found, so that scintigraphy provided the sole means to evaluate both the functional and morphologic status of the affected gland. Clinical conditions in which this problem occurred included technical failure to probe and cannulate a duct, developmental anomalies, obstructive disorders, traumatic lesions and fistulae, and the need of postsurgical information after glandular excision or after ligation or repositioning of a major excretory duct. The clinical value of scintigraphy in these conditions is discussed and exemplified by means of case presentations.
Samenvatting

Speekselklierscintigrafie met $^{99m}$Tc-pertechnetaat werd in 1965 in de kliniek geïntroduceerd en werd aanvankelijk met veel enthousiasme begroet, omdat voordien bij de diagnostiek van speekselklierafwijkingen eigenlijk alleen "blanco" röntgenonderzoek en sialografie beschikbaar waren als aanvulling op de anamnese en het fysisch onderzoek. Echter, ondanks de duidelijke waarde van de methode voor de beoordeling van de speekselklierfunctie, nam de belangstelling ervoor in de daarop volgende jaren geleidelijk af. In dit proefschrift wordt derhalve een poging gedaan om een evenwichtig gebruik van speekselklierscintigrafie te bevorderen door enkele vragen met betrekking tot de klinische toepassing ervan te beantwoorden. Deze vragen zijn geformuleerd in Hoofdstuk 1.

In Hoofdstuk 2 worden de fysische eigenschappen van technetium-$^{99m}$ en de lichaamsverdeling en uitscheiding van $^{99m}$Tc-pertechnetaat na toediening bij de mens kort beschreven. Tevens wordt een overzicht gepresenteerd van uit de literatuur beschikbare gegevens over de verwerking van jodide en pertechnetaat door de speekselklieren, waaruit de volgende conclusies kunnen worden getrokken: op grond van dierexperimenteel onderzoek bestaan er sterke aanwijzingen, dat uitscheiding van jodide en pertechnetaat naar het speeksel plaatsvindt via de cellen van het gangssysteem. Recent onderzoek heeft echter aangetoond, dat ook de acini in dit opzicht een rol kunnen spelen. In de speekselklieren van de mens worden jodide en pertechnetaat waarschijnlijk door hetzelfde mechanisme getransporteerd, maar de exacte locatie van dit overdrachtsysteem is tot op heden niet geïdentificeerd.

In Hoofdstuk 3 wordt het normale patroon van $^{99m}$Tc-pertechnetaat opname en uitscheiding door de grote speekselklieren in het kort besproken. Vervolgens wordt een overzicht gegeven van de criteria, die worden gebruikt bij de kwalitatieve en semi-quantitatieve classificaties gebaseerd op een visuele interpretatie van in serie vervaardigde scintifoto's. De voordelen van het stimuleren van pertechnetaat excretie tijdens het scintigrafisch onderzoek worden benadrukt, evenals de relatieve voor- en nadelen van gustatore en parasympathomimetische stimulantia, die worden gebruikt om dit effect te bewerkstelligen. De normale vorm van funktiecurven van de glandula parotis en submandibularis, alsmede de
semi-kwantitatieve analyse ervan middels diverse functie-parameters, worden eveneens besproken.

In het eerste gedeelte van Hoofdstuk 4 worden diverse aspecten van de, na intraveneuze injectie van $^{99m}$Tc-pertechnetaat, in de regio van de mondholte verschijzende radioactiviteit onderzocht. Om de normale accumulatie van deze mondactiviteit te bestuderen werd bij 20 gezonde proefpersonen serie-scintigrafisch onderzoek in frontale en laterale richting uitgevoerd. Hierbij werd waargenomen, dat de mondactiviteit niet een enkelvoudig fenomeen vertegenwoordigt, maar is opgebouwd uit 4 onderdelen, die een duidelijke volgorde vertonen in hun tijd van verschijnen en bovendien een specifieke relatie blijken te hebben met activiteitsfluctuaties in de glandula parotis of submandibularis.

De herkomst van de mondactiviteit werd nagegaan door bij 8 personen het scintigrafisch onderzoek te herhalen na ligaren van de ductus parotideus en/of canuleren van de ductus submandibularis, waardoor verhinderd werd dat speeksel de mondholte bereikte. De resultaten toonden duidelijk aan, dat de zich normaliter in de regio van de mondholte ophopende activiteit geheel veroorzaakt wordt door radioactief speeksel uitgescheiden door de glandulae parotides en submandibulares.

Om de lokatie van de mondactiviteit vast te stellen werden aansluitend op het normale scintigrafisch onderzoek frontale en laterale scintifoto's met open en gesloten mond vervaardigd, teneinde te onderzoeken of het openen van de mond resulteerde in een standsverandering van deze activiteit. Tevens werden bij 8 personen het palatum, de ductus submandibularis of het orificium van de ductus parotideus gemanueerd met behulp van radioactieve puntbronnen om de positie van deze anatomische structuren ten opzichte van de mondactiviteit vast te leggen. De configuratie en de benedenwaartse verplaatsing van de mondactiviteit bij het openen van de mond, waardoor een duidelijke scheiding ontstond tussen de mondactiviteit en de markeringsbron op het palatum, sloten niet alleen het palatum als lokatie van deze activiteit uit, maar waren tevens sterk suggestief voor een stapeling in de regio van de tong. Scintigrafisch onderzoek verricht bij 3 personen na een pertechnetaat mondspoeling bevestigde, dat radioactief speeksel wordt geadsorbeerd aan de mondmucosa en dat adsorptie aan de tongmucosa de grootste bijdrage levert aan de mondactiviteit. Een mogelijke bijdrage vanuit pertechnetaat opname in de glandula sublingualis kon worden uitgesloten, aangezien de positie van deze klier werd afgebakend door radioactieve puntbronnen gesitueerd aan beide einden van de ductus submandibularis en er tussen deze markeringspunten geen stapeling van pertechnetaat werd waargenomen.

De uiteindelijke conclusie luidt, dat pertechnetaat opname in de
glandula sublingualis en in de kleine speekselklieren van de mondholte niet op scintifoto's wordt afgebeeld, zodat scintigrafie niet kan worden gebruikt om de functie van deze klieren te beoordelen. Echter, aangezien de accumulatie van mondactiviteit geheel afhankelijk bleek te zijn van door de glandulae parotides en submandibulares uitgescheiden radioactief speksel, kan deze activiteit zinvol worden benut als een maat voor de functie van de grote speekselklieren.

In het tweede gedeelte van Hoofdstuk 4 wordt aandacht besteed aan de circumscripte, minder dan achtergrond-activiteit bevattende "cold areas", die soms tijdens speekselkrierscintigrafie met $^{99m}$Tc-pertechnetaat worden gezien in het gebied van de mondholte. Er kon worden aangetoond, dat dit fenomeen niet berust op verminderde pertechnetaat opname in de kleine speekselklieren van de mondholte, maar wordt veroorzaakt door absorptie van straling in uitgebreide tandheelkundige restauraties.

Hoofdstuk 5 handelt over de vraag of het mogelijk is om de veelal aanbevolen scintigrafische onderzoekstijd van 60 minuten of langer te bekorten tot 30 minuten. Een dergelijke reductie kan worden bereikt door een stimulans, b.v. carbachol, 10 in plaats van 20 minuten na pertechnetaat injectie toe te dienen en door het scintigrafisch onderzoek 20 minuten na stimulatie te beëindigen. Teneinde na te gaan of deze procedurele verandering zonder verlies aan informatie kon worden doorgevoerd, werd serie-scintigrafisch onderzoek verricht bij 2 groepen van 10 normale proefpersonen. De respons van de speekselklieren op carbachol stimulatie na 10 en 20 minuten werd bij deze personen geëvalueerd door uit de funktiecurven 2 semi-kwantitatieve funktie-parameters te berekenen, te weten de verhouding maximum activiteit in de klier/"background" activiteit (Max/BG), als maat voor de opnamecapaciteit van de klieren, en de verhouding maximum activiteit in de klier/minimum activiteit in de klier (Max/Min), als maat voor hun excretievermogen. Om de hoeveelheid "background" activiteit in de grote speekselklieren bij benadering vast te stellen werd de activiteit in "background" regio's op de schedel vergelijk met de activiteit in klierregio's na toediening van perchlorataat en met de activiteit in "lege" klierregio's bij patiënten, bij wie een speekselklier was geëxtirpeerd. Het bleek, dat vermenigvuldiging van de activiteit in een regio op de schedel met een faktor 1.4 een betrouwbare maat opleverde voor de "background" activiteit in de klieren.

De resultaten toonden aan, dat de waarden van de funktie-parameters bij carbachol stimulatie na 10 minuten overeenkwamen met de waarden bij stimulatie na 20 minuten. Carbachol stimulatie na 10 minuten kon derhalve zeker worden aanbevolen om de functie van de glandula parotis
en submandibularis te beoordelen. Aangezien bovendien het minimum van de door carbachol veroorzaakte activiteitsdaling binnen 10 tot 12 minuten werd bereikt, en een voortzetting van het onderzoek geen verdere gegevens opleverde, was een totale onderzoeksduur van 30 minuten voldoende om alle noodzakelijk geachte informatie te verkrijgen. Serie-scintigrafisch onderzoek met $^{99m}$Tc-pertechnetaat is hierdoor een meer praktische procedure geworden.

In Hoofdstuk 6 wordt een overzicht gegeven van de huidige stand van zaken bij de beeldvormende diagnostiek van speekselklierandoeningen. De mogelijkheden en beperkingen van sialografie, scintigrafie met $^{99m}$Tc-pertechnetaat, echografie, computertomografie en kernspinresonantietomografie worden besproken en een rationele benadering bij het gebruik van deze onderzoekmethoden wordt aanbevolen. Het overzicht toont duidelijk aan, dat de introductie van nieuwe technieken een grote invloed heeft gehad, in zoverre dat het belang van oudere methoden aanzienlijk is afgenomen en nieuwe diagnostische mogelijkheden beschikbaar zijn gekomen, in het bijzonder bij de diagnostiek van tumoren. Er wordt echter benadrukt, dat de diagnostische procedure op het individu behoort te worden afgestemd, hetgeen in elk afzonderlijk geval een kritische instelling vereist ten opzichte van de werkelijke waarde van de diverse beeldvormende technieken.

In Hoofdstuk 7 werd speekselklierscintigrafie met $^{99m}$Tc-pertechnetaat in plaats van als diagnostische methode gebruikt als funktietest om het effect van transorale sialolithectomie op de functie van de glandula submandibularis te beoordelen. Uit een onderzoek bij 21 patiënten, bij wie tenminste 1 jaar tevoren een steen was verwijderd uit de hilus van de ductus submandibularis, bleek, dat de klierfunktie na de transorale chirurgische ingreep bij het merendeel van deze patiënten weer op een normaal niveau was teruggekeerd. Hieruit werd geconcludeerd, dat de aanwezigheid van een steen in de hilus van de ductus submandibularis een extirpatie van de glandula submandibularis niet per se noodzakelijk maakt en dat transorale verwijdering van een dergelijke steen de voorkeur verdient.

In Hoofdstuk 8 wordt een overzicht gegeven van de speekselklierafwijkingen, waarbij scintigrafisch onderzoek met $^{99m}$Tc-pertechnetaat essentieel bleek te zijn om tot een diagnose te komen. De betrokken patiënten behoorden niet tot één specifiek ziektebeeld, maar hadden slechts gemeen dat een orificium van een uitvoergang hetzij niet toegankelijk was of niet kon worden gevonden, zodat de functionele en morfologische toestand van de klier alleen met behulp van scintigrafie kon
worden beoordeeld. Dit probleem deed zich voor bij de volgende klinische situaties: het technisch mislukken van sonderen en canuleren van een uitvoergang, ontwikkelingstoornissen, obstructieve afwijkingen, traumatische lesies en fistels, en de behoefte aan postchirurgische informatie na klierextirpatie of na ligeren of repositioneren van een hoofduitvoergang. Het nut van scintigrafie bij deze klinische situaties wordt besproken en toegelicht met enkele ziektegeschiedenissen.
STELLINGEN

I
De mondactiviteit bij speekselklierscintigrafie met $^{99m}$Tc-pertechnetaat wordt veroorzaakt door radioactief speeksel uitgescheiden door de glandulae parotides en submandibulares.

II
Bij de chirurgische behandeling van een diep in de ductus submandibularis gelegen speekselsteen verdient transorale verwijdering van de steen de voorkeur boven extirpatie van de glandula submandibularis.

III
Voor de diagnostiek van speekselkliertumoren is conventionele sialografie obsoleet.

IV
Parotischirurgie kan zowel voor de patiënt als voor de operateur een "zenuwslopende" bezigheid zijn.

V
Het niet onderkennen van het fenomeen, dat een ranula gepaard kan gaan met een zwelling in de hals kan leiden tot onnodig mutilerende chirurgie.

VI
Bij de behandeling van een arterio-veneuze malformatie in onder- of bovenkaak moet aan het mogelijk curatieve effekt van embolisatie het voordeel van de twijfel worden gegund.

VII
In de afweging tussen conservatief en operatief behandelen van onderkaaksfracturen wordt vaak ten onrechte op voorhand operatief behandelen als ingrijpender beschouwd.
VIII
Het gebruik van de aanduiding hoofd-halschirurg werkt verwarrend en dient derhalve vermeden te worden.

IX
De recente negatieve publiciteit rond het beroep van leraar is wetenschappelijk onvoldoende gefundeerd en doet onrecht aan het overgrote deel van deze beroepsgroep, dat zijn taak met inzet en enthousiasme vervuld.

X
Het plaatsen naast de wandelroute van het metrostation naar het AMC van een 3 bij 4 meter grote advertentie van NRC-Handelsblad, met een afbeelding van een onder een operatielamp opgesteld, agressief ogend operatieteam, voorzien van de tekst “Uw geld of Uw leven”, zal de gemoedsrust van de (nog) lopende patiënt niet ten goede zijn gekomen.

H.P. van den Akker
Amsterdam, 21 januari 1988