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Is quantitative salivary gland scintigraphy a mandatory examination prior to and after radioiodine therapy?

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The aim of this study was to evaluate possible deterioration of salivary gland function due to low dose radioiodine therapy using quantitative salivary gland scintigraphy (qSGS). In addition, the prevalence of salivary gland impairment (SGI) was estimated in thyroid patients. Prior to routine thyroid scintigraphy, qSGS was performed after i.v. injection of 36–126 MBq Tc-99m-pertechnetate, and the uptake was calculated as a measure of parenchymal function. 144 patients underwent qSGS prior to and 3 months after radioiodine therapy. The prevalence of SGI was estimated from qSGS in another 674 patients submitted to thyroid scintigraphy. Despite salivary gland stimulation with ascorbic acid during radioiodine therapy a significant dose related parenchymal impairment of 15–90 % could be measured after the application of 0.4–24 GBq of I-131. The prevalence of SGI was 77/674 = 11.4 % and 52/674 = 7.7 % in one/two and three/four glands, respectively. Thus, qSGS should be applied in all patients prior to and after radioiodine therapy to quantify and to document both the preexisting and the treatment induced SGI even by low dose I-131. With respect to forensic reasons qSGS might even be applied mandatory.

Key words: salivary glands – radionuclide imaging – iodine radioisotopes – adverse effects

Introduction

Radioiodine therapy using I-131 has been known to be effective for almost 50 years both to reduce hyperthyroidism or to treat differentiated thyroid carcinoma and its iodine trapping metastases. Despite an almost selective uptake of iodine in thyroid cells it can be mistaken for chlorid due to its similar atomic diameter and its comparable electrical charge. This leads to an undesired accumulation of I-131 via an energy consuming $Na^+/K^+/2Cl^-$-co-transport[1-4] in acinar cells of salivary glands as well as in gastric parietal cells. Therefore, a parenchymal impairment of salivary glands is a well-known undesired side effect of high dose radioiodine therapy as used in thyroid cancer with cumulative activities up to 40 GBq I-131.[5-7] Consequently, radioiodine therapy is performed under salivary gland stimulation using sialogoga, e.g. chewing gum or vitamin C drops in order to minimize the intraglandular transit time of I-131 and, thus, to minimize salivary gland impairment.[6-11]

However, there are only rare data on parenchymal damage in salivary glands after low dose radioiodine therapy as used for the treatment of benign thyroid diesease. This is mainly due to the lack of an easy to perform method which yields quantitative data on parenchymal function of all major salivary glands. However, recently a normal data base for quantitative salivary gland scintigraphy has been established[12, 13] on a large number of healthy subjects, and its value for the detection of mild parenchymal impairment has been demonstrated successfully in Sjögren's syndrome.[14-17]

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The aim of this study was therefore first to enlarge this normal data base in order to reduce the standard deviation of these reference values, second to quantify possible parenchymal damage in salivary glands due to low dose radioiodine therapy performed under salivary gland stimulation and third to estimate the prevalence of salivary gland impairment in patients submitted to thyroid scintigraphy.

Materials and methods

Patients

In a total of 1.130 patients quantitative salivary gland scintigraphy (qSGS) was performed prior to thyroid scintigraphy. Therefore, an additional radiation burden was omitted, and all patients gave their informed written consent. Details of patient populations investigated are given in Table 1.

In order to enlarge our nomal data base published previously[12, 13, 16] we included 312 patients without any salivary gland diseases. Inclusion and exclusion criteria were described in detail elsewhere.[12]

144 patients underwent quantitative salivary gland scintigraphy prior to and 3 months after radioiodine therapy with different cumulative activities up to 24 GBq I-131. 68 patients received radioiodine therapy for hyperthyroidism and 11 for thyroid cancer. Details of these patients are given in Table 2. Radioiodine therapy was performed under salivary stimulating conditions by peroral application of 200 mg ascorbic acid (Cebion®) three times a day during their stay in hospital.[6–11]

The prevalence of salivary gland impairment was estimated from results of quantitative salivary gland scintigrapy obtained from another 674 patients submitted for thyroid scintigraphy. Prevalence was given both for single parenchymal damage covering one or two salivary glands and for global parenchymal damage covering three or four salivary glands.

Table 2. Applied cumulative activity of I-131 in GBq and details of patient characteristics of the radioiodine therapy group.

I–131	Age			
[GBq]	range	mean ± SD	n	f/m
0.4–0.6	25–74	44.2 ± 7.4	44	34/10
0.7–1.1	36–83	56.1 ± 9.3	41	30/11
1.4–1.5	28–76	46.9±8.7	25	19/6
3.0	20–81	42.5 ± 11.3	19	14/5
6.0	19–65	43.7 ± 9.4	9	5/4
24.0	29–76	58.4 ± 10.2	6	4/2

Quantitative salivary gland scintigraphy

Quantitative salivary gland scintigraphy was performed in a standardized method as described previously[12, 16] after intravenous injection of 36–138 MBq Tc-99m-pertechnetate. For quantification one rectangular ROI over the brain, which served as a common background ROI, and four irregular ROIs over both parotid and submandibular glands were used. ROIs were copied from the study performed prior to radioiodine treatment to the study obtained after radioiodine treatment.

As a measure for parenchymal function of major salivary glands the uptake of Tc-99m-pertechnetate was calculated in percentage of the injected activity.[18–26] For compensation of noise and, thus for stabilization of data, the uptake was averaged from 12–14 min p.i. ($U_{12\text{-}14}$). Saliva excretion was stimulated by 3 ml diluted lemon juice 15 min p.i., and excretion fraction (EF) was calcultated from mean uptake at 17–19 min p.i. ($U_{17\text{-}19}$) expressed in percent of the uptake ($U_{12\text{-}14}$) measured according to equation 1.

$$EF\,[\%] = \frac{U_{12\text{-}14} - U_{17\text{-}19}}{U_{12\text{-}14}} \cdot 100 \qquad \text{(Eq. 1)}$$

Table 1. Patient characteristics of different populations investigated.

	Age			
Group	range	mean ± SD	n	f/m
Normal date base	18–82	44.2 ± 7.4	312	216/96
Radioiodine therapy	19–83	55.1 ± 12.3	144	106/38
Thyroid scintigraphy	19–83	48.7 ± 9.4	674	453/221

In order to test the reproducibility of salivary gland scintigraphy the same scintigram of a patient from the normal data base was reevaluated 10 times by 13 differently experienced technicians. Intraobserver reproducibility was expressed as variation coefficient and relative variation coefficient. To estimate the interobserver reproducibility the mean of both uptake and excretion fraction derived of all technicians was first calculated. Interobserver reproducibility was then expressed as percent deviation of each individual technician from this mean.

Statistics

Results are given as mean ± one standard deviation. Two-tailed students t-test for unpaired data were used to evaluate statistical differences, with $p < 0.05$ considered to be statistical significant.[27] Individual results of patients below the 2-sigma range of the normal data base were taken as pathological.

Results

Normal data base

The original scintigramm of a patient from the normal data base is shown in Figure 1. The mean ± one standard deviation of Tc-99m-pertechnetate uptake of all patients is given in Figure 2 for the major salivary glands. The corresponding normal values of Tc-99m-pertechnetate uptake and excretion fraction are summerized in Table 3. Tc-99m-pertechnetate uptake amounted to 0.45 ± 0.14 % and 0.39 ± 0.12 % for parotid and submandibular glands, respectively. The corresponding values for excretion fraction were 49.5 ± 10.6 % and 39.1 ± 9.2 %.

Excellent values were found for intraobserver reproducibility indicated by variation coefficients of 0.3 and relative variation coefficients of below 2 %. The deviation of the individual mean from the mean of all technicians of 1.1–5.2 % indicated an excellent interobserver reproducibility as well.

Parenchymal impairment after radioiodine

The uptake of Tc-99m-pertechnetate of parotid and submandibular glands prior to and after radioiodine therapy as well as the decrease of Tc-99m-pertechnetate uptake in percent of pretreatment values are given in Table 4 and Figure 3. A significant activity related decrease in parenchymal function could be shown in all subgroups even after as less as 0.4-0.6 GBq I-131. Parenchymal impairment increased from 0.15 % after 0.4-0.6 GBq I-131 to about 90 % after 24 GBq I-131. A patient receiving 6 GBq I-131 is shown in Figure 4.

Prevalence of parenchymal impairment

Significant parenchymal impairment was seen in 129/674 patients. Of these, one or two salivary glands were affected in 77/674 = 11.4 %, and three or four salivary glands were affected in 52/674 = 7,7 % of these patients.

In 69 of these 129 patients the etiology of parenchymal impairment could be evaluated successfully. In single salivary gland damage chronic sialolithiasis and external radiation therapy could be detected in 32 and 7 patients, respectively. In patients with global salivary gland impairment rheumatic diseases and drugs with anticholinergic side effects, i.e. neuroleptic and antidepressant drugs, were causal in 10 and 20 patients, respectively. However, in 60/129 =

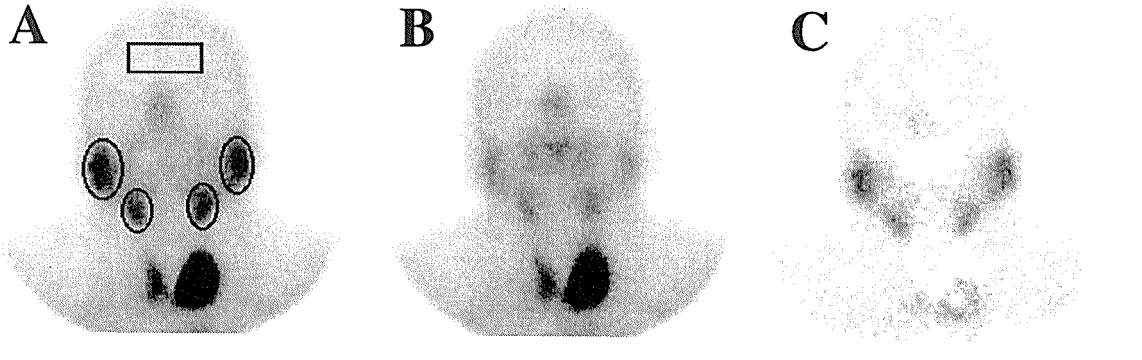

Figure 1. Sialoscintigramm of a normal patient at 13 min after injection of Tc-99m-pertechnetate prior to (A) and at 18 min p.i. after 3 ml of lemon juice p.o. as a sialogogum (B), and parametric image (C) for visualization of saliva excreted from salivary glands. ROIs used for quantification are shown in A.

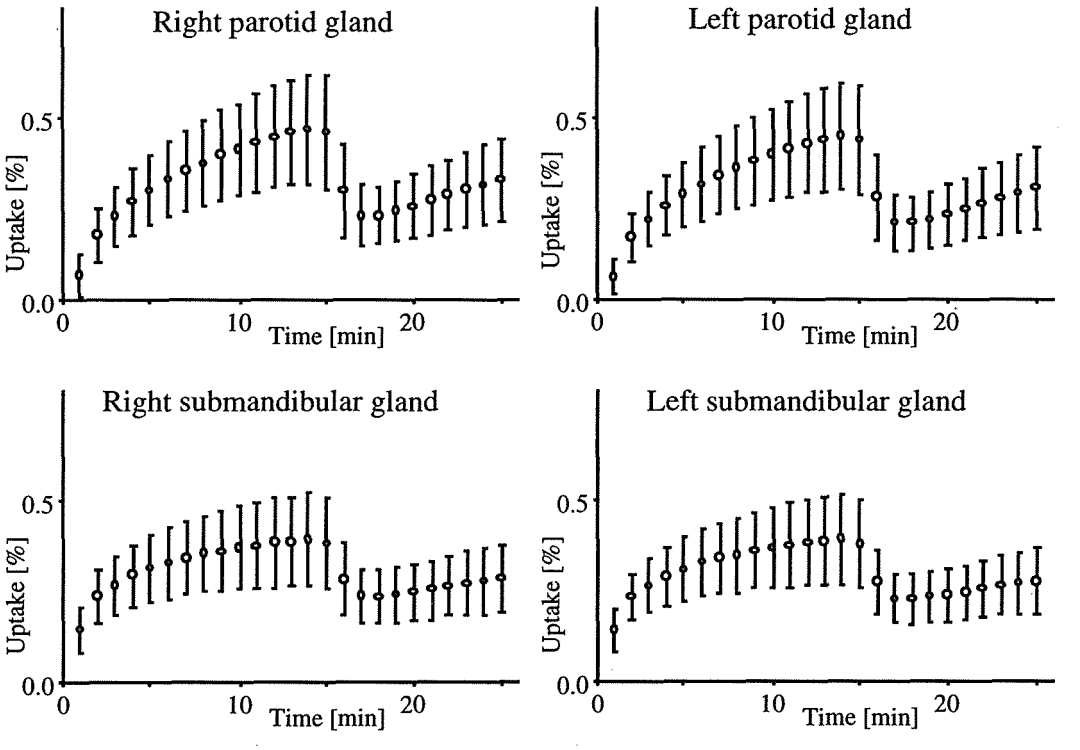

Figure 2. Time-activity-curves of Tc-99m-pertechnetate uptake in major salivary glands. Mean ± one standard deviation of 312 patients.

Table 3. Normal values of Tc-99m-pertechnetate uptake in percent of injected activity, and excretion fraction (EF) in percent of uptake. Numbers represent mean ± one standard deviation (n = 312). RPG, LPG: right, left parotid gland. RSG, LSG: right, left submandibular gland.

	RPG	LPG	RSG	LSG
Uptake [%]	0.46 ± 0.15	0.44 ± 0.14	0.39 ± 0.12	0.39 ± 0.12
EF [%]	48.2 ± 10.5	50.9 ± 10.5	38.2 ± 9.1	39.9 ± 9.2

Table 4. Mean ± one standard deviation of pertechnetate uptake in percent of injected activity in salivary glands prior to and after radioiodine therapy with different cumulative activities of I-131 in GBq, and decrease of parenchymal function in percent of pretreatment values (Δ Uptake). Note, that left and right parotid and submandibular glands were lumped together, respectively. a: decrease of parenchymal function was calculated versus normal data base since no pretreatment values were available.

Cumulative ativity I–131	n	Parotid glands			Submandibular glands		
[GBq]		prior to I–131	after I–131	Δ Uptake	prior to I–131	after I–131	Δ Uptake
0.4–0.6	44	0.42 ± 0.14	0.36 ± 0.13	14.3	0.36 ± 0.13	0.31 ± 0.11	13.9
0.7–1.1	41	0.40 ± 0.19	0.33 ± 0.13	17.5	0.35 ± 0.16	0.28 ± 0.10	20.0
1.4–1.5	25	0.38 ± 0.12	0.30 ± 0.14	21.1	0.32 ± 0.15	0.23 ± 0.14	28.1
3.0	19	0.44 ± 0.17	0.32 ± 0.16	27.3	0.37 ± 0.11	0.25 ± 0.09	32.4
6.0	9	0.46 ± 0.10	0.29 ± 0.12	34.8	0.42 ± 0.21	0.29 ± 0.19	30.9
24.0	6		0.04 ± 0.03	90.9[a]		0.05 ± 0.02	86.8[a]
Normal data base	312	0.45 ± 0.14			0.39 ± 0.12		

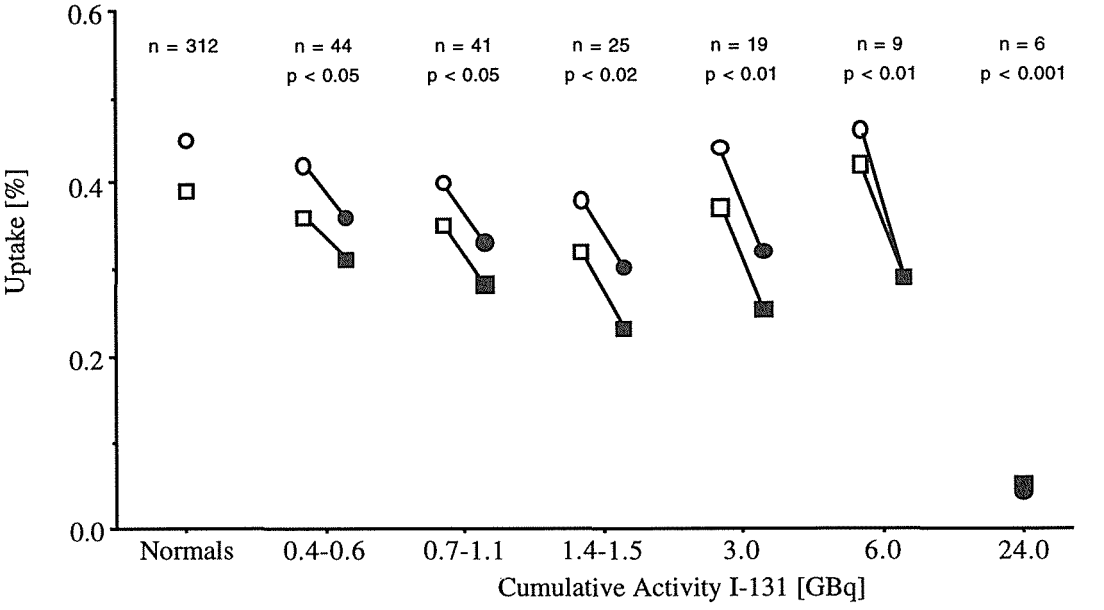

Figure 3. Mean uptake of pertechnetate in parotid (circles) and submandibular (squares) glands in normals and patients prior to (open symbols) and after (filled symbols) radioiodine treatment with increasing cumulative activities of I-131. Note, that left and right parotid and submandibular glands were lumped together, respectively. For standard deviation see table 4.

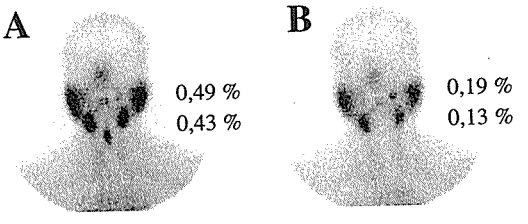

Figure 4. Sialoscintigramms 13 min after injection of Tc-99m-pertechnetate of a patient prior to (A) and and 3 months after (B) radioiodine therapy with 6 GBq-I-131 due to follicular thyroid carcinoma. Numbers denote mean uptake of Tc-99m-pertechnetate in percent of injected activity in parotid (upper) and submandibular (lower) glands, respectively. Observe the small ectopic thyroid remnant within the thyroglossal duct prior to therapy.

46.5 % of the patients with parenchymal impairment there was no reason detectable for their deminished uptake of Tc-99m-pertechnetate.

Discussion

Normal data base

A valid quantification of salivary gland function is mandatory to detect even mild or beginning parenchymal impairment.[17] Beside various semiquantitative and not routinely practical methods (for an overview see[12]) the calculation of Tc-99m-pertechnetate uptake in percent of the activity applied has been suggested[18–26] in analogy to well established state-of-the-art quantitative thyroid scintigraphy.[28] However, variable study protocols, small patient numbers and a lack of inclusion and exclusion criteria may be the main reasons for clearly different reference values and markedly enhanced standard deviations.

On the other hand, a reduction of standard deviation is desirable in order to ease the differentiation of normal and pathological parenchymal functions. This can be achieved both by enhancing the number of patients and by thoroughly selected inclusion and exclusion criteria. In our study Tc-99m-pertechnetate uptake was 0.45 ± 0.14% and 0.39 ± 0.12% for parotid and submandibular glands, and excretion fraction was 49.5 ± 10.6% and 39.1 ± 9.2%, respectively. The validity of our reference values is supported first by the similar shape of our time-activity-curves (see Fig. 2) and those reported as N(ormal)-type curves derived from qualitative salivary gland scintigraphy[29, 30] and second by successful demonstration of mild parenchymal impairment in patients suffering from ongoing Sjögren's syndrome.[17]

The excellent values measured for both intra- and interobserver reproducibility indicate a high reproducibility of salivary gland scintigraphy. Therefore, variability of Tc-99m-pertechnetate uptake of the reference values probably reflect physiological variability of parenchymal function in salivary glands.

Parenchymal impairment after radioiodine

Parenchymal impairment of salivary glands as an undesired side effect of high dose radioiodine therapy as used in thyroid cancer with cumulative activities up to 40 GBq I-131 could be shown in up to 80 % of the patients.[5–7] Consequently, radioiodine therapy is performed under salivary gland stimulation using sialogoga, e.g. chewing gum or vitamin C drops in order to minimize the intraglandular transit time of I-131 and, thus, to minimize undesired parenchymal impairment.[6–11] However, there are only limited data on parenchymal damage in salivary glands after low dose radioiodine therapy as used for treatment of benign thyroid disease.

Radioiodine therapy was performed under salivary stimulating conditions using ascorbic acid perorally three times during the patients stay in our therapeutic ward.[6–11] However, despite this commonly accepted procedure a dose related decrease of parenchymal function could be shown even after as less as 0.4-0.6 GBq I-131. This mild impairment of parenchymal function measured after radioiodine treatment did not cause any hyposialia which is in agreement to common clinical experience due to several reasons. First, a loss of function of some 15 to 33% could be demonstrated after low dose radioiodine therapy. Second, it is known from various diseases of both endocrine and exocrine glands that a loss of up to 90% of parenchyma is necessary to result in clinical symptoms, e.g. diabetes mellitus, diabetes insipidus, Sjögren's syndrome, chronic pancreatitis with exocrine insufficiency, hypopituitarism.[31] Third, patients with high dose radioiodine treatment with 24 GBq complained about hyposialia/asialia. The latter is in good agreement both with our observation that parenchymal function was impaired to about 90% and with data reported in the literature.[5, 16]

Impairment of parenchymal function was measured 3 months after radioiodine therapy. It is unclear up to now whether repair mechanisms may lead to a (partial) restoration of parenchymal function. This is suggested by a long-term follow-up in a few of our patients (unpublished data).

Quantification of parenchymal impairment with respect to forensic reasons

As to our knowledge there are no valid data in the literature concerning the prevalence of parenchymal impairment in salivary glands. Most probably this might be due to a lack of an easy to perform examination which yields valid quantitative data on salivary gland function. Using quantitative salivary gland scintigraphy we found a pathologically ecreased parenchymal function in 19.1% of 674 patients investigated. Single and global parenchymal dysfunction contributed approximately to equal amounts. Beside common reasons of global parenchymal impairment, e.g. rheumatic diseases, drugs with anticholinergic effect, i.e. neuroleptic and antidepressant drugs should be kept in mind.[32] However, we could not evaluate any reason in as much as 60/129 = 46% of these patients even though the patients history was obtained very carefully.

However, both the knowledge and extent of any kind of preexisting parenchymal damage is essential since salivary glands may be damaged even after low dose radioiodine. Consequently, clinical significant functional impairment may occur, and forensic problems may arise. Therefore, it is essential not only to inform patients with preexisting parenchymal impairment about possible occurence of hyposialia but to increase salivary gland stimulation during radioiodine therapy. Thus, quantitative salivary gland scintigraphy should be performed in all patients prior to and after radioiodine therapy in order to exclude or to quantify radioiodine induced parenchymal impairment in salivary glands.

Conclusions

Quantitative salivary gland scintigraphy is an easy to perform method with excellent intra and interobserver reproducibility which can be performed prior to thyroid scintigraphy without any additional radiation burden. It should be performed prior to radioiodine therapy in order to document salivary gland function, and it should be repeated 3 months after radioiodine therapy in order to either exclude or quantify possible radioiodine induced parenchymal impairment of salivary glands. With respect to forensic reasons quantitative salivary gland scintigraphy might even be applied mandatory.

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