Ultrasonography of the salivary glands: the role of grey-scale and colour/power Doppler

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ABSTRACT

Over the last few years the use of ultrasonography (US) in the study of salivary glands is greatly increased due to its several advantages and undoubted diagnostic potential in detecting even minimal soft tissue changes in a wide range of pathological processes. Nowadays, there is general agreement in considering US as a useful complement to other imaging techniques, such as magnetic resonance, in providing an accurate assessment of the salivary glands especially in the study of tumour pathologies. US is also useful for the evaluation of inflammatory process affecting salivary glands (e.g. Sjögren's syndrome) where its accuracy and feasibility make it a reliable method. The useful combination of the US grey-scale and the colour/power Doppler technique provides more valuable details regarding the presence and degree of soft tissues blood perfusion and may be valuable in narrowing the differential diagnosis. This review provides an overview of the main US findings observed in a wide range of pathological processes that can affect salivary glands.

Introduction

The multiplicity and the relevant diagnostic difficulties of various disorders affecting a specific anatomical structure, make it often appropriate to use different imaging techniques to obtain a definite diagnosis. The study of salivary glands represents an example due to the several pathological conditions may involve them and the overlapping of various clinical features (1, 2). The scialography was the first diagnostic imaging technique to have been introduced, followed later by direct radiological examination, telethermography, scintigraphy, ultrasonography (US), computed tomography (CT) and, more recently, by the magnetic resonance imaging (MRI) and the RM-scialography (3). Over the years, each of these imaging techniques has acquired a well-defined role in the diagnostic procedure (4, 5) and, currently, US represents the most frequently used due to its several advantages: lack of radiation, low cost, repeatability, patient friendliness, high resolution (6). The US allows detailed morphological evaluation of major salivary glands and became complementary to clinical examination for the study of the inflammatory process or expanding lesions (Fig. 1-2) (7). US allows the evaluation of the presence, number and topographical position of the lesions and, sometimes, the clarification of their nature (8). The combined use of high resolution grey-scale and power/colour Doppler (P/CD) techniques and the use of contrast agent add useful information and are valuable in narrowing the differential diagnosis (9-11). US is also widely used as guidance for interventional procedures such as aspiration and drainage of abscesses or biopsy for cytological and histological examinations. In these cases, the use of US as guidance makes the local procedure safer and minimise the risks of complications (*e.g.* transitory paralysis of the branches of the facial nerve or skin salivary fistula formation) (12).

Main diseases of the major salivary glands

Several diseases can affect the major salivary glands and includes traumatic injuries, congenital and inflammatory diseases, benign and malignant tumours and autoimmune disorders (13).

Trauma and salivary fistulas: salivary glands, especially the parotid, being superficial structures can be damaged after neck or face trauma. In this case, US allows the visualisation and the extension of fluid collection in the gland or in the surrounding tissues. US is useful in

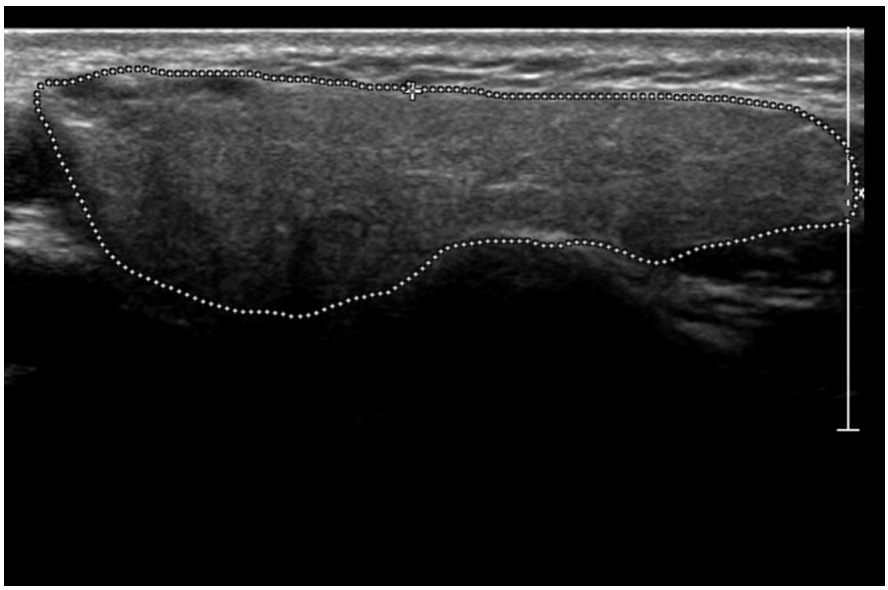

Fig. 1. US scan of parotid gland in healthy subject. To note the normal echostructure and homogenicity of parenchyma.

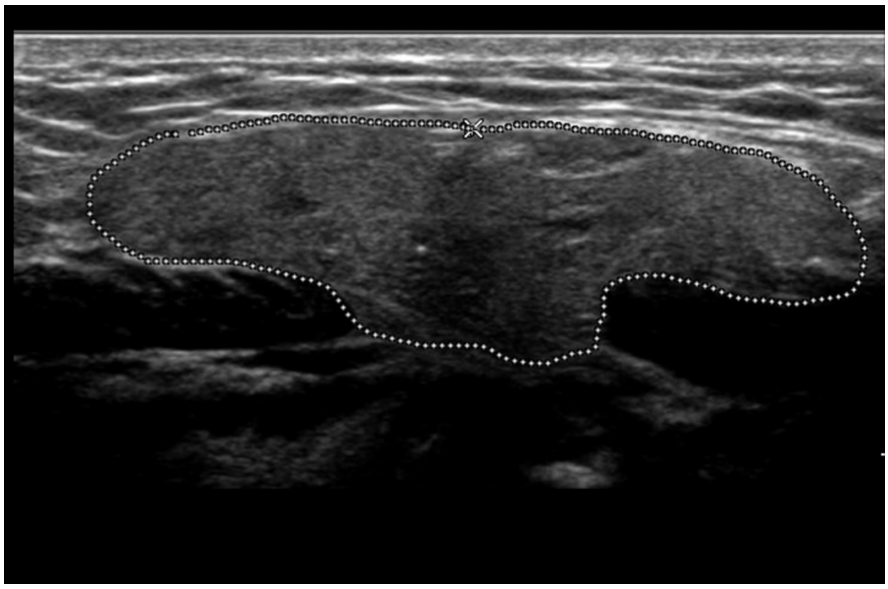

Fig. 2. US scan of submandibular gland in healthy subject. Note the normal echostructure and homogenicity of parenchyma.

the follow-up evaluation of haematoma and leakage of saliva after drainage.

Salivary cysts: primitive genetic salivary cysts are rare, whilst secondary salivary cysts are more common and, usually, the consequence of ductal diverticula (*e.g.* due to inadequate drainage). The sublingual and parotid gland are the most common involved sites (80% of cases). Parotid cysts may also results from an abscess collection or aseptic inflammation due to gland stones. On US the salivary cysts are easily recognisable as anechoic sharply well-defined lesions and are often associated with reinforce of the posterior wall and lateral acoustic shadows (14, 15).

Hypertrophy: usually painless and may be due to constitutional factors (obesity), race (people of North African, Egyptian, etc.), malnutrition, metabolic diseases (diabetes, hypo-hyperthyroidism) and chronic degenerative diseases (cirrhosis, spirochaetosis, uremic cachexia, sarcoidosis). A secondary hypertrophy can occur after surgical removal of the salivary glands (especially the sublingual). US shows an increased size of the gland with preserved margins and echogenicity (14, 15).

Pneumatocele: typical of glass blowers or trumpet, is characterised by the presence of gas in the salivary ducts and, sometimes, by the formation of diverticula. US examination allows to detect multiple hyperechoic spots or thin lines in the contest of the ducts (14, 15).

Sialolithiasis: is the most common cause of recurrent swelling or the parotid gland. The sialolithiasis affects 1–2% of the population and the salivary gland more frequently involved includes the submandibular (80–94% of cases) and the parotid (6–20%). The stones in the submandibular gland have predominantly intraductal position, while in the parotid are most frequently placed at the superficial lobe of the gland parenchyma and, rarely, at the level of Stenone's duct. The majority of calculi (90%) are radio-opaque and they are multiple in 25% of patients (16). US has a high degree of accuracy (96%) for their evaluation (17). The stone appears as hyperechoic area with characteristic posterior acoustic shadow. If the stone is located in the main duct an hypoechoic widening of upstream ducts can be observed. This finding is best appreciated by stimulating salivation of the subject with lemon juice. US allows also to visualise an hypoechoic soft edges area surrounding the stone which is a sign of an acute inflammation process. The persistence of the obstruction may lead to an abscess and, subsequently, to a pseudocyst (14, 15).

Inflammatory disease

Sialadenitis: is divided into acute and chronic process according to both the basis of pathogenesis and course of the disease. Undoubtedly, the parotid is the most involved gland by sialadenitis process (80% of cases). In acute process the use of US is recommended whilst the sialography is contraindicated for the possibility to increase the inflammation. In the acute phase of the inflammatory process the gland appear on US increased in its volume with contours not well-defined and hetero-

geneous hypoechoic pattern due to the parenchyma oedema. Sometimes the oedema is focal and makes it difficult a differential diagnosis from a nodular lesion. The evolution of an acute inflammation process to an abscess can frequently occur and is characterised by the presence of liquid or semiliquid collections with lumpy or starry contours, which tend to burrowing to the surface or into the deeper layers of the gland. A significant sign of the inflammation is the thickening of the skin overlying the gland due to an oedema of the gland wall. In acute inflammatory process an increased CD signal can be observed due to blood perfusion. All acute inflammatory process may become chronic with consequent fibrosis and narrowing or stenosis of the ducts and upstream widening ducts. In these cases CD signal can be visualised due to the increased blood perfusion. The degree of CD signal is related to the severity of the inflammatory process and can be low when an increasing oedema occurs. In the abscesses collections peripheral CD signal can be observed. Usually, in chronic inflammation process the most characteristic feature is represented by the changes of ducts calibre in the contest of the gland and the spectrum can vary from saccular or rounded appearance ("apple tree" at sialography) to wide widening ducts (as "salivary lakes"). At the level of the gland parenchyma fine punctate calcifications and lack of homogeneity can be visualised on US. In the granulomatous process (tuberculosis, syphilis, actinomicosys) the granuloma is clearly visible on US as a non-homogeneous area with well-defined edges within of an hypo-anechoic gland. Often during the exacerbation of inflammation chronic process an increasing volume of the gland and the presence of hypoechoic areas or abscess collections can be observed. In non-atrophic chronic process CD signals are more frequently seen than in normal conditions due to the presence of small vessels not visible in their entirety and surrounding widening ducts. In the phase of acute exacerbation of chronic inflammation blood vessels shows high CD signal with irregular calibre and route (9, 14-19).

Neoplastic pathology

Neoplastic disease of the salivary glands, although sometimes dramatic, is a fairly rare and represents almost 5% of the total tumours affecting the head and neck. The most involved sites includes parotid (85%), submandibular (12%) and sublingual (3%) glands (14-16). Usually the frequency of malignant tumours is greater for the submandibular glands (65–70%) (14, 15).

In the study of an expansive pathology of salivary gland US has become a priority technique imaging for its well known properties (17, 18). The recognition of a neoplastic process does not require clinic difficulties, as it is always superficial and easily palpable. The main problem is the differential diagnosis between benign and malignant tumour and the evaluation of its extension. Typically, malignant tumour assumes nodular appearance with irregularities of the margins, up to a clear infiltration of the surrounding tissues. The echotexture is inhomogeneous with hypo-anechoic or hyperchoic aspect due to necrotic-haemorrhagic or calcification areas, respectively. The presence of enlargement of regional lymphnodes is extremely important for the evaluation of a suspected malignant process. Further, the presence of metastatic-appearing lymph nodes accompanying a tumour in the salivary gland strongly suggests a malignancy. Most of the solid nodular lesions are characterised by an increased CD signal (80%). Usually, malignant tumours have greater CD signals with respect to benign tumours (83% of cases). In malignant tumours venous and arterial vessels intertwine within the lesion given the typical appearance of a vascularised nodule with several poles and the absence of a peripheral vascularisation. On CD examination malignant tumours may show multiple and irregular internal vessels, with hypervascularity and high resistance arterial flow (9, 22). Studies mainly performed on the parotid gland have shown that a resistive index (RI) of 0.8 and pulsatility index (PI) of 1.8 are suggestive for a benign lesion (23). Rarely (32% of cases), vessels in common between the nodule and surrounding parenchyma can be observed (6, 14, 15). The main limitations of US are represented by the difficulty to visualise tumours placed in the deeper region of the parotid or under the part covered by the lower jaw and to evaluate their extension to the para-retropharyngeal tract or the base of the skull. Moreover, small malignant neoplasms and metastases (less than 20 mm of diameter) and well-differentiated malignant neoplasms, sometimes, can not be easily distinguished on US from benign tumours. Therefore, in suspected neoplastic lesions is necessary to resort to other imaging techniques, such as MRI which allows the evaluation of the margins of the lesion and its extension towards the surrounding anatomical structures (24).

Benign tumours: the most common benign tumours of major salivary glands are the pleomorphic adenomas (mixed tumour), the Warthin's tumours (cystadenolymphoma) and the oncocytoma. Several typical features of these tumours can be observed on US but, sometimes, the differential diagnosis between benign and malignant tumours can be difficult (20, 21).

Pleomorphic adenoma (mixed tumour): is the most common tumour of the salivary glands and affect the parotid in 85-90% of cases. In the past it was defined as mixed tumour for the presence of both epithelial and mesenchymal component secreting mucoid, myxoid or chondroid basophilic material. Microscopically the structure of the tumour is based on nests and cords appearance, sometimes differentiated in ductal and acinar structures with few liquid component. The pleomorphic term is usually attributed to an epithelial adenoma characterised by several pathological features. Usually the pleomorphic adenoma affects females, with maximum peak incidence between 35 and 50 years old and it is described as potentially malignant tumour (4–5% of cases) with slow growth and infiltration of surrounding tissues. The pleomorphic adenoma is often bilateral or multifocal, non-adherent to the surrounding tissues and has a typical capsulated nodular structure with well-defined margins. In

the 10% of cases pleomorphic adenoma can shows uneven shapes or sinuous and irregular margins. Usually this tumour has a diameter of 2–3 cm, but if untreated can reach wider dimensions. On US the pleomorphic adenoma is easily recognisable because of its peculiar homogeneous hypoechoic echostructure (in 98% of cases) with sharp and regular margins due to the presence of a capsule and, sometimes hyperechoic areas due to calcifications. In wider adenoma the margins tend to become irregular and anechoic areas, related to necrotic process, can be observed inside the lesion (Fig. 3). In these cases US findings are consistent with those of a malignant tumour and, therefore, the presence of lateral cervical metastatic adenopathies is essential in narrowing the differential diagnosis. In the 79% of cases the pleomorphic adenoma shows colour peripheral Doppler signal and a trend that follows the outer limiting of the nodule ("basket-like" flow pattern). Inside the lesion is easy to visualise a venous or, sometimes, arterial vascular pole (Fig. 4) (15, 18, 21). US may be used to guide fine-needle aspiration biopsy (25).

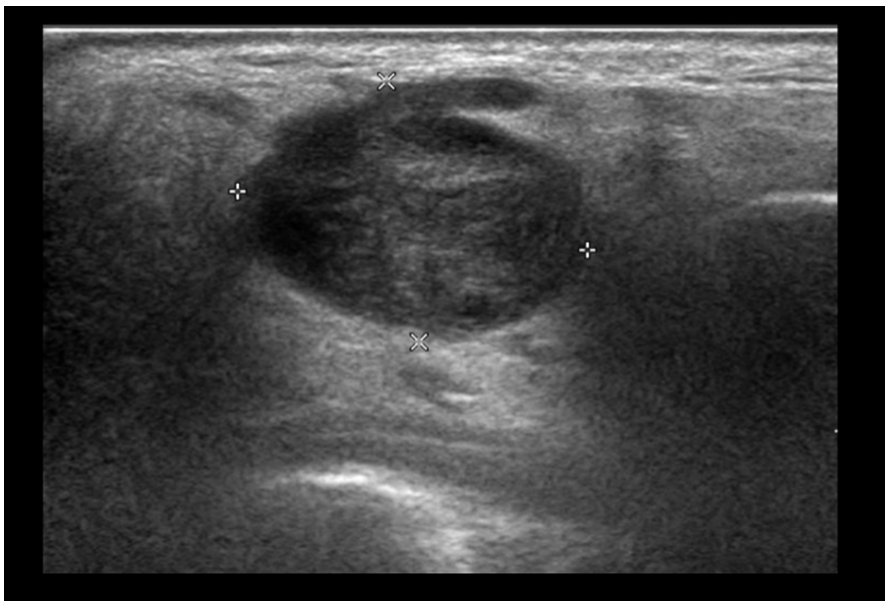

Fig. 3. The US longitudinal scan of parotid shows a pleomorphic adenoma within the gland's parenchyma. Note the lack of homogeneity and the presence of hypo-anechoic necrotic areas.

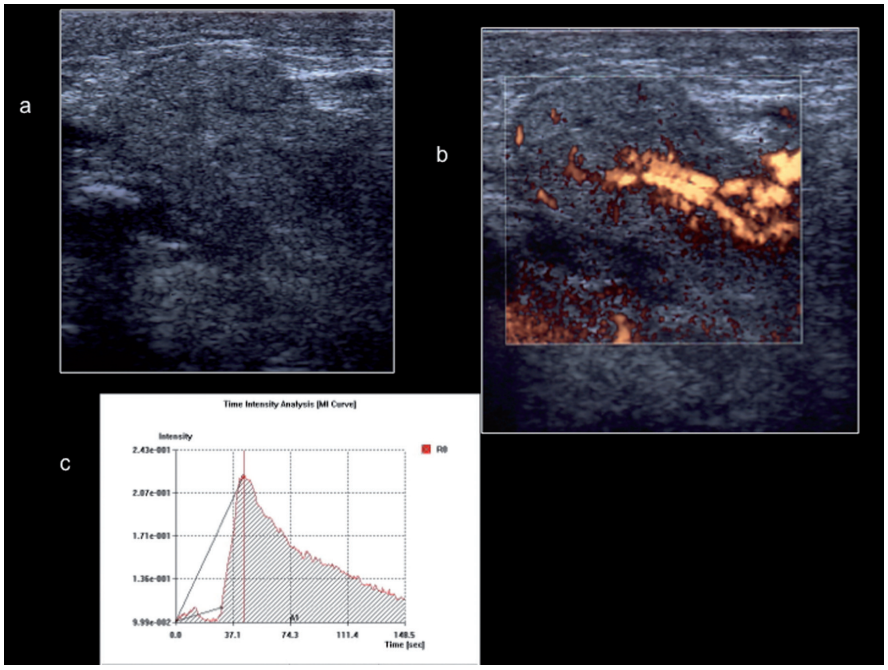

Fig. 4. US longitudinal scan of parotid gland in a patient with pleomorphic adenoma. Observe an hypo-anechoic echostructure of the gland without necrotic process or calcifications inside the lesion (**a**), the vascularisation of the tumour and the vascular pole detected by using contrast agent and PD technique (**b**) and the corresponding contrast-enhanced curve (**c**).

Warthin's tumour (*cystadenolymphoma)*: it represents 5–6% of all epithelial tumours. The monomorphic adenoma is the second most common type of benign tumour of salivary glands, and, predominantly, affects the parotid (especially the lower pole). Warthin's tumour is frequently seen in male adulthood and occurs between the fourth to seventh decades (with a peak around the age of forty). It is often bilateral, multifocal and slow-growing and it appears as well rounded or lobulated, encapsulated, cystic-aspect lesion. Lesions are multiple or bilateral in 10–15% of patients. On US Warthin's tumour has an hypo- anechoic "liquid gaps" appearance. The hypo-anechoic appearance corresponds to the histological picture characterised by large cystic spaces filled with lymphocytes, desquamated epithelium and by the cavity and the papillary lesions protruding into the lumen covered by pseudostratified cylindrical epithelium. The vascularisation is largely present at level of the echogenic areas, whilst in the liquid or semiliquid areas there is no detectable CD signal (Fig. 5) (15). *Oncocytoma*: is a rare lesion accounting for 1% of all salivary gland tumours but similar to the adenolymphoma, usually is unilateral, painless and without cystic appearance. It represents 1% of the tumours of the salivary glands and usually appears as painless lesion. Both adenolynphoma and oncocytoma, with respect to all the other tumours, are weakly positive at technetium-99m pertechnetate scintigraphy. The oncocytoma is a benign tumour that rarely relapse after surgical excision and the pattern of CD signal is similar to that one found in pleomorphic adenoma (14, 15).

Malignant tumours: the most common malignant neoplasms occurring in salivary glands are mucoepidermoid carcinoma and adenoid cystic carcinoma (cylindroma), adenocarcinoma and undifferentiated carcinoma, epidermoid or squamous cell carcinoma. Acinar cell adenocarcinoma and mesenchymal tumours (lymphomas) are less common. Less than 30% of focal lesions in the parotid gland are malignant, whereas almost 50% of focal lesions in the submandibular gland are malignant (5, 20, 21).

Mucoepidermoid carcinoma: is the most common malignant tumour of the parotid, accounting for 80–85% of cases. Mainly affects females with a peak of incidence between the fourth to fifth decade. It does not have a capsule, has a rather slow growth and can reach a size between 3 and 5 cm. Usually it is a painless lesion and difficult to differentiate from a squamous cell carcinoma (which faster invades the nearby lymphnodes) and from the adenocarcinoma (which often contains blood or fluid collections within the lesion). It accounts for 5% of all salivary gland tumours. In most cases, the tumour has parotid location but, may be found in other intraoral sites such as the palate, the alveolar process and the retromolar region. More severe malignant tumours can quickly arise, be locally infiltrative and ulcerated and causing pain and nerve paralysis of the facial nerve, with tendency to metastasise locally or distally and to relapse after surgical resection in 15% of cases (14, 15).

Adenoid cystic carcinoma (cylindroma): accounts for 20% and 5% of the submandibular and parotid tumours, respectively, with a peak incidence between the sixth to seventh decades. Usually it is unilateral and has a slow growth with tendency to infiltrate the facial nerve and to metastasise surrounding lymph nodes. Recurrence is common after surgery. On US the adenoid cystic carcinoma has a typical uneven and cribriform echostructure and, sometimes, pseudocystic appearance (14, 15). Contrast-enhanced MRI is required to demonstrate perineural extension which can not be well visualised on US (21, 24).

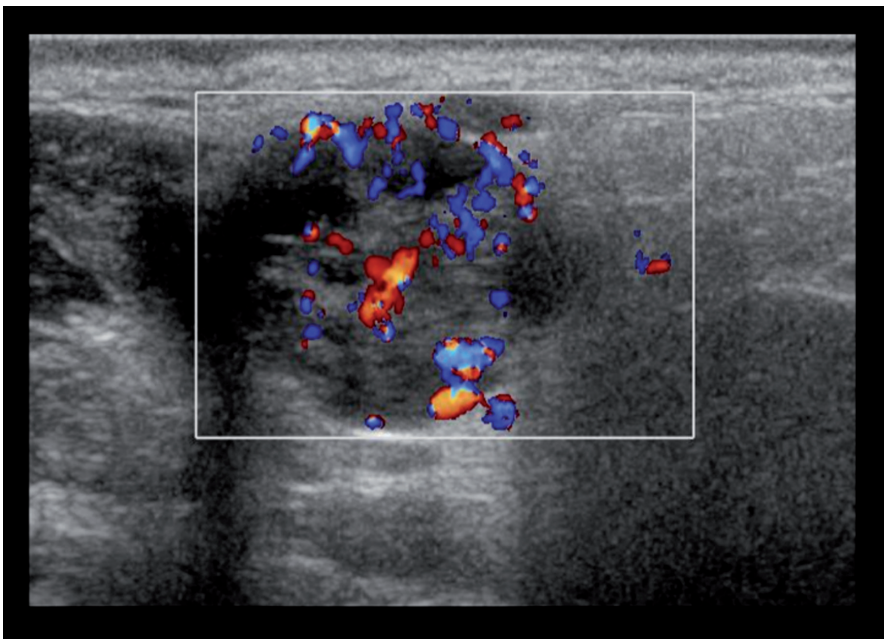

Fig. 5. US longitudinal of parotid gland in a patient with cystadenolymphoma tumour (Warthin's tumour). Note the vascularisation within the tumour detected by CD technique.

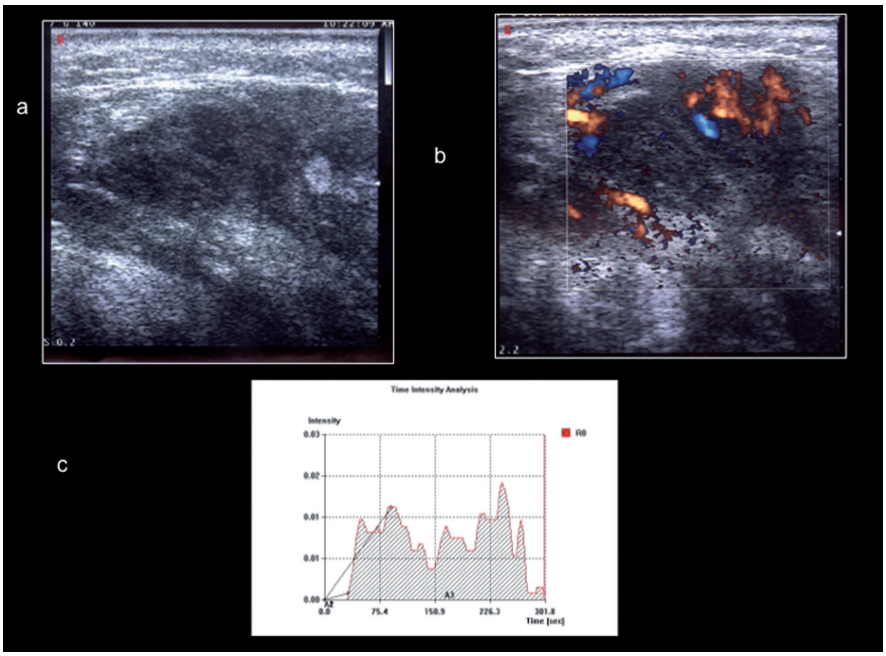

Fig. 6. US longitudinal scan of parotid gland in a patient with adenocarcinoma. Note the irregular and lack of continuity of the margins and inhomogeneity of the texture with typical hypo-anechoic pattern (**a**). Multiple and irregular vessels are well visualised after administration of contrast agent (**b**). The corresponding contrast-enhanced curve is visualised (**c**).

Adenocarcinoma and undifferentiated carcinoma: represent 27% and 35% respectively of all salivary glands malignant tumours and originate from the malignant transformation of pleomorphic adenomas which tend to degenerate in 4–5% of cases. Adenocarcinoma and undifferentiated carcinoma have rapid growth, characterised by skin ulceration and/or facial paralysis and tend to metastasise early. Both tumours are not encapsulated, their margins are irregular and often discontinues and have homogeneous hypoechoic echostructure on US (Fig. 6) and haemorrhagic necrosis, blood lakes or cystic

appearance within the lesion (14, 15, 21, 24).

Epidermoid or squamous cell carcinoma: is a rare tumour characterised by rapid growth, early local invasion and tendency to metastasise. Typical US features includes hypoechoic echotexture with lakes blood and cystic aspects, not well-defined star-shaped margins and skin retractions (14, 15).

Acinar cell adenocarcinoma: is fairly rare, almost unilateral and rarely exceeds 3 cm in diameter. Its echostructure is similar to that one of adenoma, as it is capsulated and, sometimes, with some tiny cysts inside the lesion. It does not induce marked swelling of the gland or painful symptoms and, clinically, it is similar to benign tumours. Survival after radical surgery is 25% of the cases. Histologically it is similar to the clear cell tumours of the kidney and the differential diagnosis between adenocarcinoma and acinar cell metastasis from hypernephroma is therefore difficult, except in the presence of metastases to regional lymphnodes (20% of cases) (14, 15).

Mesenchymal tumours: the lymphoid proliferation of the salivary glands can be reactive or neoplastic. Among the reactive forms of greatest interest are those represented by the sialadenitis associated with Sjögren's syndrome (SS), also known as lymphoepithelial lesion or myoepithelial sialadenitis and the one associated with chronic infection with hepatitis C virus (HCV) (5, 20, 21, 24), myastenia gravis, primary biliary cirrhosis or lymphoid hyperplasia cystic (more commonly observed in patients with chronic HIV infection). Lymphomas of the salivary glands are predominantly type B and include the B-cell lymphoma and marginal zone (MALT) lymphoma, follicular lymphoma and diffuse large B-cell lymphoma. Cystic lymphoid hyperplasia can affect both the submandibular and parotid gland and unilateral or bilateral swelling in the context of a progressive generalised lymphadenopathy can be visualised. Often the distinction between non-neoplastic lymphoproliferative disorder and MALT lymphoma is difficult and the use of histopathology must be adviced. The lymphoepithelial sialadenitis is characterised by a lymphocytic infiltrate with follicular hyperplasia which surrounds and infiltrates the salivary ducts, with disorganisation and proliferation of epithelial ductal cells and formation of lymphoepithelial lesions. Usually, the lobular gland architecture is preserved. Lymphoepithelial lesions mainly affect the parotid and submandibular glands, whilst the minor salivary and lacrimal glands may not be involved. Lymphomas account for 2–5% of tumours of the salivary glands. Almost 20% of cases are associated with SS or lymphoepithelial sialadenitis. Lymphomas involve parotid and submandibular gland in the 70% and 25% of cases, respectively, while the minor salivary glands are affected in less than 10% of cases. On US lymphomas appear as an increased gland volume, lack of homogeneities, hypoechoic focal or diffuse nodular aspect and not well-defined margins. The hypoechogenicity is due to the presence of lymphomatous proliferation that, when of severe degree, confers a cystic appearance to the lesion (Fig. 7) (2, 5, 20, 21). However, these features are not pathognomonic and, on US, lymphoma may not be reliably differentiated from other neoplastic or non-neoplastic salivary gland tumours.

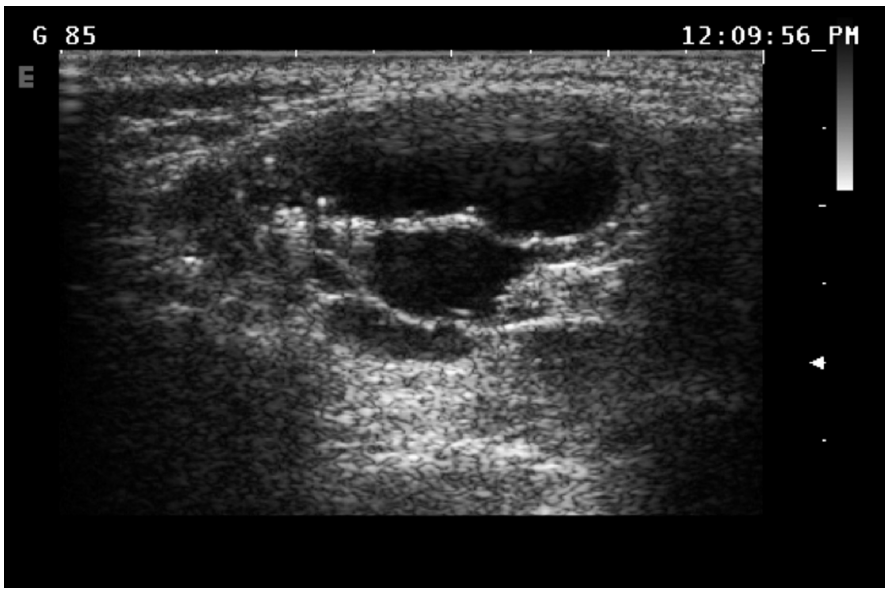

Fig. 7. US longitudinal scan of parotid gland in a patient with lymphoma. The tumour appears as an hypo-anchechoic intraglandular mass with a cystic appearance due to lymphomatous proliferation.

Metastasis in the salivary glands: uncommonly salivary glands are sites of metastases. Primary tumours metastasising to salivary glands may be located in the head and neck region, as well as in more distant parts of the body. Usually they derived from squamous cell carcinoma, malignant melanoma of the head and neck, nasopharynx carcinoma, carcinoma of the thyroid, oral cavity or renal clear cell carcinoma, carcinoma of the stomach, lung and breast. Metastatic tumours are mostly due to direct invasion by the malignancy located in immediate proximity. Metastases via blood or lymphatic system are rare and can be detected on US as focal defects of the parenchyma with a round shape and inhomogeneous hypoechoic well-defined lesions (14, 15, 26). The US features of submandibular gland metastases are not well described, although the appearances are likely to be similar to those demonstrated in parotid metastatic disease (27). Parotid metastases can vary in appearance but tend to be hypoechoic, with heterogeneous internal echotexture and poorly defined margins (27).

Primary Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disorder characterised by lymphocytic infiltrates in the lachrymal and salivary glands (28).

Dryness of the eyes (keratoconjunctivitis sicca) and mouth (xerostomia) are the main clinical features. Histology shows lymphocytic infiltration and destruction of the affected glands. pSS concerns patients who have not other connective tissue disease. For this reason, it is necessary to know if the sicca syndrome is possibly due to other pathologies (*e.g.* diabetes mellitus, hypovolemia, sarcoidosis, infection, respiratory or renal insufficiency) or conditions (*e.g.* smoking, medications). At the moment the minor salivary gland biopsy (MSGB) is considered as the gold standard for diagnosing pSS (50), but further investigations are often necessary and includes: salivary flow measurement, sialochemistry, sequential salivary scintigraphy, and sialography using liposoluble or hydrosoluble contrast material (Fig. 8). In addition, to these standard tests for assessment of salivary gland involvement, other methods have been applied such as US, MRI and CT (Fig. 9) (29). These diagnostic tools have widely replaced conventional invasive examinations in scientific research as well as in clinical practice. Among all the imaging techniques currently available for the study of salivary glands, US appears to be the most attractive one due to its several advantages and capability to detect wide echostructural abnormalities of gland parenchyma (Fig. 10-11). The main echostructural abnormalities detectable on US are represented by the parenchymal inhomogeneity, hypoanechoic or hypercheoic areas (due to multiple cysts or calcifications, respectively), increased or reduced size, irregularity of the margins and the presence of peri-intraglandular lymphnodes. The inhomogeneity of the parenchyma represents the best parameter for the pSS diagnosis (30, 31). This observation has recently been confirmed in comparison studies with MRI (30, 31). The multiple circumscribed or confluent hypoechoic areas and/or multiple cysts have a corresponding histological picture of ductal ectasia surrounded by several linfocytes or widening glandular lobules surrounding by linfocytes aggregates. The multiple hyperechoic bands observed in the later stages can be an expression of severe parenchymal subversion with replacement of connective fibrous tissue (Fig. 12). A study have shown higher sensitivity of US with respect to contrast sialography and salivary gland scintigraphy (75.3%, 72.7% and 70.1%, respectively), whereas the specificity was quite similar (83.5%, 84.9% and 82.3%, respectively) (32). These percentages are within the otherwise wide range of previous studies results showing a sensitivity of US between 43% and 90% and a specificity between 83.3 and 100% (30, 33-38). In particular, Kawamura *et al*. (35) and Salaffi *et al*. (32, 39) showed that descriptive and quantitative assessment of the salivary glands by US efficiently differentiate between pathologic and normal glands in patients with pSS.

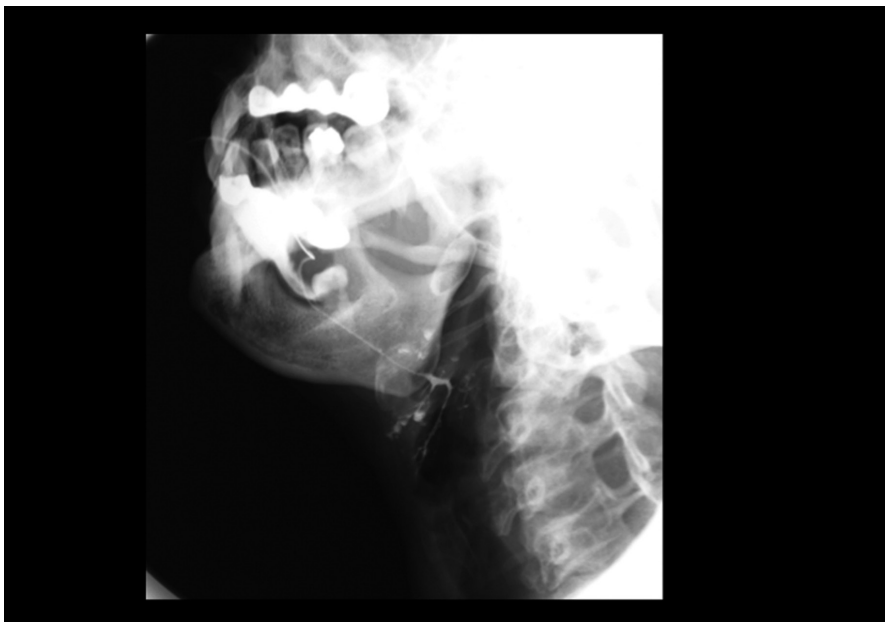

Fig. 8. The sialography in oblique view of a parotid gland in a patient with pSS shows the narrowing of the main duct, the poor representation of the main branches of the ductal gland and characteristic globular sialectasia pattern of some peripheral branching ductal.

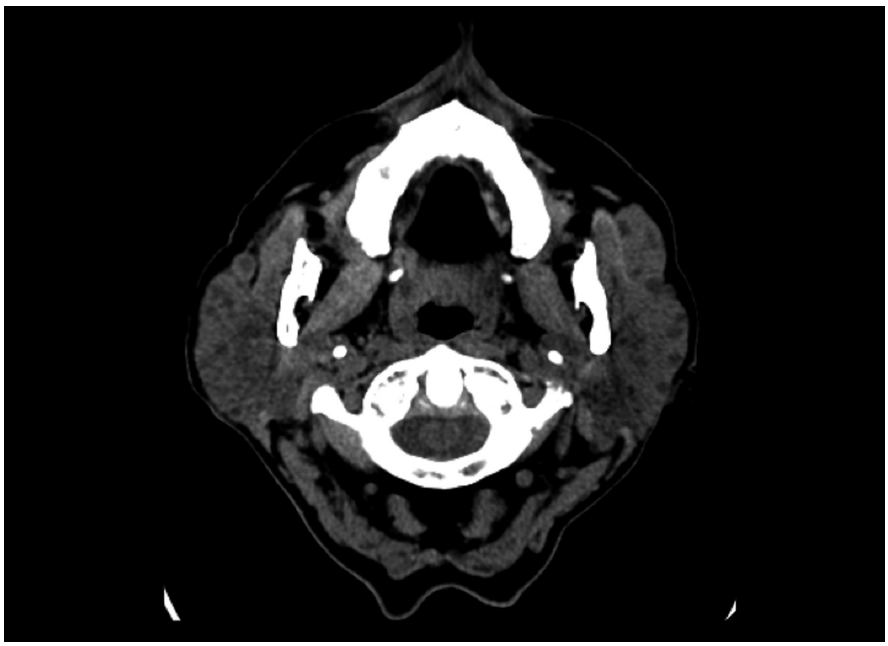

Fig. 9. The CT scan in the parenchyma of parotid glands in patient with pSS shows an increasing size, lack of homogenicity and multiple hypodense cyst-like areas.

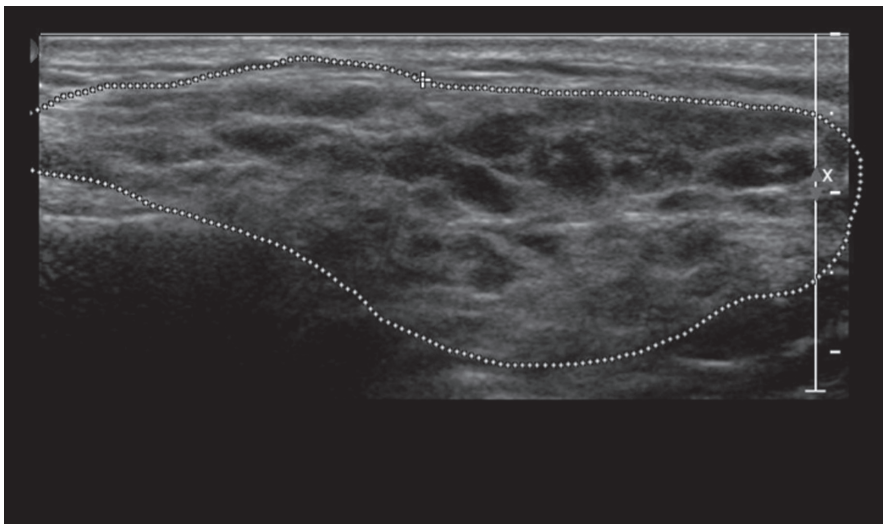

Fig. 10. US longitudinal scan of parotid gland in patient with pSS. The parenchyma is heterogeneous and characterised by multiple scattered hypoechogenic areas and echogenic bands.

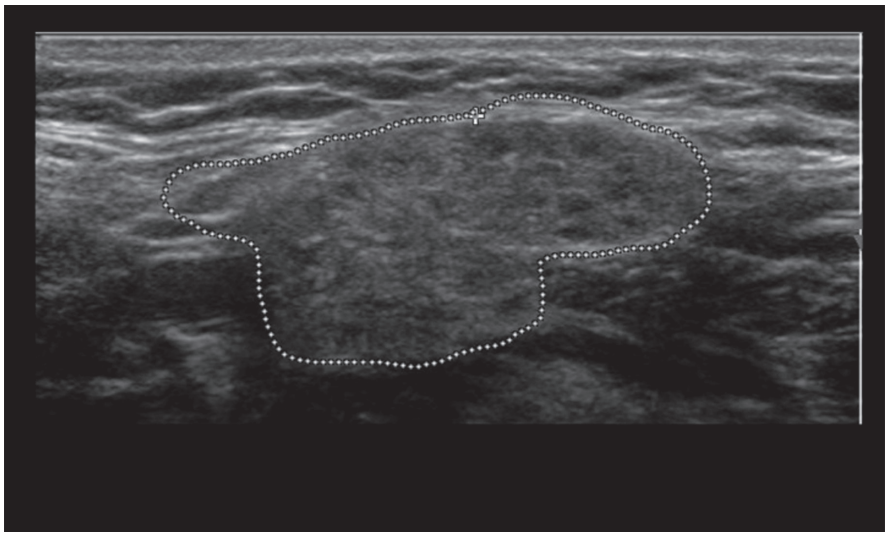

Fig. 11. US longitudinal scan of submandibular gland in a patient with pSS. The parenchyma is characterised by lack of homogenicity and multiple hypo-anechoic areas.

They have also demonstrated that US abnormalities are strongly correlated to the histological changes in minor salivary gland tissue (39) and that the proposed US score grading correlates well with sialographic gradings (39). To score the changes of the parotid gland structure several gradings and classifications have been used (33, 37). So far, the widely used grading score is the one proposed by De Vita *et al*. (33). This score is ranging from 0 to 6 and assigns points to the different degrees of glandular inhomogeneity. Score values above 0 showed a sensitivity of 88.8% in pSS and of 53.8% in secondary SS, as well as a specificity of 84.6% and of 92.2% with respect to either symptomatic or healthy subjects (33). In a published report by Takagi *et al*. (40), US of the salivary glands had a diagnostic sensitivity of 82% and specificity of 73%. Therefore, US can be considered an alternative imaging modality to sialography in the diagnosis of pSS. Milic *et al*. (41) found that the US score was positive in 129 (92%) patients with pSS and in 20 (40%) subjects from the non-pSS group. By setting the cut-off point for the US score (range 0–16) at 7, the best sensitivity/specificity ratio for pSS was achieved (91.4/94.0%, respectively). In a previous multicentre study we have reported that the optimal cut-off point of 6 for the proposed US score (total score range from 0 to 16) (Table I) had a good sensitivity/specificity ratio for pSS (75.3%/83.5%) (32). By using this threshold value the positive LR of an abnormal US was 4.58. If a threshold >8.0 was applied the test gained specificity at the cost of a serious loss of sensitivity (sensitivity 54.5%, specificity 97.5%, likelihood ratio 21.5). According to this US scoring system (32) the grade 2 corresponds to a clear parenchymal inhomogeneity, characterised by multiple scattered hypoechogenic areas of variable size (<2mm) and not uniformly distributed. As underlined by several authors (37, 38), the most relevant US sign in pSS is the parenchymal inhomogeneity which is considered to be the most relevant anatomical structural change in these patients. However, only clear evidence of lack of homogeneity, characterised by multiple scattered hypoechoic areolaes to multiple cyst-like changes, can be regarded as being of true diagnostic value for the disease. This is especially true considering that mild inhomogeneity may also be present in patients with xerostomia affected by other pathologies. In addition, with regard the presence/absence of parenchymal homogeneity, echogenicity, size of the glands and posterior glandular border the interobserver reliability assessment showed an overall agreement of 89%, 82% and 78%, respectively (k values of 0.83, 0.79 and 0.71, respectively) and the intraobserver reliability was 91%, 88% and 85%, respectively (k values of 0.85, 0.82% and 0.80%, respectively). Recently, Cornec *et al*. (42) confirmed that morphologic abnormalities of salivary glands can be detected early in the course of the disease, since US diagnostic properties did not change according to disease duration. Using a weighted score for each item and a cut-off of 5 the proposed US scoring system was slightly less specific (85.7% *vs*. 77.9%, respectively) but more sensitive (94.9% *vs*. 98.7%, respectively) than the American-European Consensus Group (AECG) criteria.

Although the salivary glands have a complex vasculature and intense hyperaemic responses associated with the se-

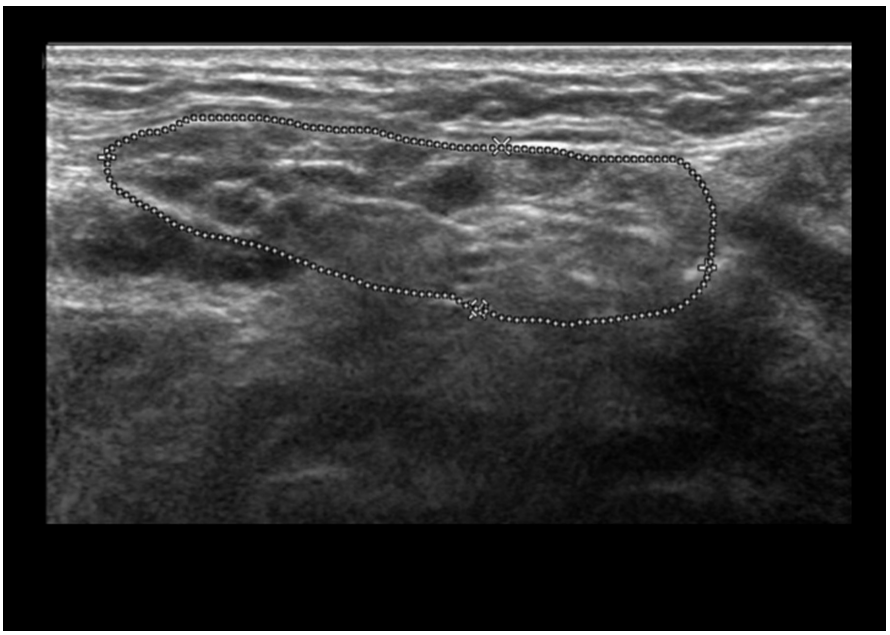

Fig. 12. US longitudinal scan of submandibular gland in a patient with pSS. Note the lack of homogenicity of the parenchyma, the not well-defined margins and the presence of hypo-anechoic areas due to replacement of fibrous connective tissue.

Table I. US grading score for the evaluation of salivay glands proposed by Salaffi F *et al*. (67).

Grade 0	Normal glands
Grade 1	Regular contour, small hypoechoic spots/areas, without echogenic bands, regular or increased glandular volume (mean values 20 + 3 mm for the parotids and 13 + 2 mm for the submandibular glands) and ill-defined posterior glandular border (definite echogenic border with respect to the neighbouring structures)
Grade 2	Regular contour, evident multiple scattered hypoechogenic areas usually of variable size (<2 mm) and not uniformly distributed, without echogenic bands, regular or increased glandular volume and ill-defined posterior glandular border
Grade 3	Irregular contour, multiple large circumscribed or confluent hypoechogenic areas (2–6 mm) and/or multiple cysts, with echogenic bands, regular or decreased glandular volume and no visible posterior glandular border
Grade 4	Irregular contour, multiple large circumscribed or confluent hypoechogenic areas (>6 mm), and/or multiple cysts or multiple calcifications, with echogenic bands, resulting in severe damage to the glandular architecture, decreased glandular volume and posterior glandular border not visible

cretion of saliva (9), poor attention has been paid to C/PDUS in this field. C/PDUS provides useful details in detecting soft tissues perfusion and measuring blood flow velocity in many pathological processes. Recently, C/PDUS has been used to evaluate the vascular anatomy of the salivary glands and to analyse either the physiological changes in blood flow that occur during salivary stimulation in normal subjects (43, 44) and the flow alterations in the diseased glands of pSS patients (9, 44). Previous physiologic studies have shown that a marked hyperaemia accompanies the secretion of saliva as shown by an increase of blood flow within the salivary glands more than five times higher than baseline (45). In our previous study (46) we have evaluated either the US features of the parotid and submandibular glands and the blood flow alterations that may occur in the salivary glands of both patients with pSS and subjects suffering from dry mouth not due to pSS (control group). Abnormal US scores were obtained in 86.6% of pSS patients and in 30% of the control group. Moreover, in pSS patients the US scores were significantly higher than in the control group (p=0.0001). The mean difference between the peak systolic velocity (PSV) values taken from parotids and submandibular glands before and during lemon juice stimulation was statistically significant (p=0.003 and p=0.01, respectively) in the healthy subjects group (46). However, no significant changes in the PSV values were found in the whole group of pSS patients. The variability of RI obtained from the salivary glands before and during lemon juice stimulation was not statistically significant from the one observed in either pSS patients or controls. US abnormalities were detected in the majority of pSS patients and their severity was significantly greater than those recorded in the control group. Among all the C/PDUS parameters only PSV was influenced by the degree of chronic inflammation, as shown by the salivary gland biopsy. These aspects have suggested that PSV may reflect the vascular changes occurring in the salivary glands during the course of an autoimmune disease such as pSS (46).

On the basis of these considerations and the results of several studies (38, 40, 42, 47, 48) there is strong evidence to support the need to replace both obsolete sialography and salivary scintigraphy with US in the AECG criteria (29, 32, 40-42, 49). In addition, we also believe that US of salivary glands should be included as an additional item in the recently proposed American College of Rheumatology (ACR) classification criteria for pSS (50, 51).

References

1. HEBERT G, OUIMET-OLIVA D, NICOLET V, BOURDON F: Imaging of the salivary glands. *Can Assoc Radiol J* 1993; 44: 342-9.
2. FISCHER T, PASCHEN CF, SLOWINSKI T *et al*.: Differentiation of parotid gland tumors with contrast-enhanced ultrasound. *Rofo* 2010; 182: 155-62.
3. KALINOWSKI M, HEVERHAGEN JT, REHBERG E, KLOSE KJ, WAGNER HJ: Comparative study of MR sialography and digital subtraction sialography for benign salivary gland disorders. *AJNR Am J Neuroradiol* 2002; 23: 1485-92.
4. BURKE CJ, THOMAS RH, HOWLETT D: Imaging the major salivary glands. *Br J Oral Maxillofac Surg* 2011; 49: 261-9.
5. HALIMI P, GARDNER M, PETIT F: Tumors of the salivary glands. *Cancer Radiother* 2005; 9: 251-60.
6. FALYAS K, LEWIS M, WILLIAMS A *et al*.: Diseases of the submandibular gland as demonstrated using high resolution ultrasound.

Br J Radiol 2005; 78: 362-9.
7. GRITZMANN N, RETTENBACHER T, HOLLERWEGER A, MACHEINER P, HUBNER E: Sonography of the salivary glands. *Eur Radiol* 2003; 13: 964-75.
8. SCHON R, DUKER J, SCHMELZEISEN R: Ultrasonographic imaging of head and neck pathology. *Atlas Oral Maxillofac Surg Clin North Am* 2002; 10: 213-41.
9. MARTINOLI C, DERCHI LE, SOLBIATI L, RIZZATTO G, SILVESTRI E, GIANNONI M: Color Doppler sonography of salivary glands. *Am J Roentgenol* 1994; 163: 933-41.
10. MANSOUR N, STOCK KF, CHAKER A, BAS M, KNOPF A: Evaluation of parotid gland lesions with standard ultrasound, color duplex sonography, sonoelastography, and acoustic radiation force impulse imaging - a pilot study. *Ultraschall Med* 2012; 33: 283-8.
11. ZENGEL P, BERGHAUS A, WEILER C, REISERM, CLEVERT DA: Intraductally applied contrast-enhanced ultrasound (IA-CEUS) for evaluating obstructive disease and secretory dysfunction of the salivary glands. *Eur Radiol* 2011; 21: 1339-48.
12. KOVACEVIĆ DO, FABIJANIĆ I: Sonographic diagnosis of parotid gland lesions: correlation with the results of sonographically guided fine-needle aspiration biopsy. *J Clin Ultrasound* 2010; 38: 294-8.
13. BIALEK EJ, JAKUBOWSKI W, ZAJKOWSKI P, SZOPINSKI KT, OSMOLSKI A: US of the major salivary glands: anatomy and spatial relationships, pathologic conditions, and pitfalls. *Radiographics* 2006; 26: 745-63.
14. GALLIPOLI A, SACCO M: Ghiandole salivari. *In*: ZIVIELLO M, BAZZOCCHI M. Gnocchi Editore. Ecografia. Napoli, 1994; 507-17.
15. CANDIANI F, RUBALTELLI L: Ghiandole salivari. *In* BAZZOCCHI M. Idelson-Gnocchi Editore. Eco-Color Doppler in Medicina Interna. Napoli, 1998; 406-16.
16. SILVERS AR, SOM PM: Salivary glands. *Radiol Clin N Am* 1998; 36: 941-66.
17. GRITZMANN N: Sonography of the salivary glands. *AJR Am J Roentgenol* 1989; 53: 161-6.
18. BRUNETON JN, MOUROU MY: Ultrasound in salivary gland disease. *ORL J Otorhinolaryngol Relat Spec* 1993; 55: 284-9.
19. TRAXLER M, SCHURAWITZKI H, ULM C, SOLAR P, BLAHOUT R: Sonography of non-neoplastic disorders of the salivary glands. *Int J Oral Maxillofac Surg* 1992; 21: 360-3.
20. LEE YYP, WONG KT, AHUJA AT: Imaging of salivary gland tumors. *Eur J Radiol*. 2008; 66: 419-36.
21. THOENY HC: Imaging of salivary gland tumors. *Cancer Imaging* 2007; 7: 52-62.
22. WEI X, LI Y, ZHANG S *et al*.: Evaluation of microvascularization in focal salivary gland lesions by contrast-enhanced ultrasonography (CEUS) and Color Doppler sonography. *Clin Hemorheol Microcirc*. 2013; 54: 259-71.
23. BRADLEY MJ, DURHAM LH, LANCER JM: The role of colour flow Doppler in the investigation of the salivary gland tumour. *Clin Radiol* 2000; 55: 759-62.
24. YOUSEUM DM, KRANT MA, CHALIAN AA: Major salivary gland imaging. *Radiology* 2000; 216: 19-29.
25. WAN YL, CHAN SC, CHEN YL *et al*.: Ultrasonography-guided core-needle biopsy of parotid gland masses. *AJNR Am J Neuroradiol* 2004; 25: 1608-12.
26. WESTERLAND O, HOWLETT D: Sonoelastography techniques in the evaluation and diagnosis of parotid neoplasms. *Eur Radiol* 2012; 22: 966-9.
27. HOWLETT DC: High-resolution ultrasound assessment of the parotid gland. *Br J Radiol* 2003;76: 271-7.
28. MOUTSOPOULOS HM: Sjögren's syndrome: autoimmune epithelitis. *Clin Immunol Immunopathol* 1994; 72: 162-5.
29. VITALI C, BOMBARDIERI S, JONSSON R *et al*.; AND THE EUROPEAN STUDY GROUP ON CLASSIFICATION CRITERIA FOR SJÖGREN'S SYNDROME: Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-8.
30. NIEMELÄ RK, TAKALO R, PÄÄKKÖ E *et al*.: Ultrasonography of salivary glands in primary Sjögren's syndrome. A comparison with magnetic resonance imaging and magnetic resonance sialography of parotid glands. *Rheumatology* 2004; 43: 875-9.
31. NIEMELÄ RK, PÄÄKKÖ E, SURAMO I, TAKALO R, HAKALA M: Magnetic resonance imaging and magnetic resonance sialography of parotid glands in primary Sjögren's syndrome. *Arthritis Rheum* 2001; 45: 512-8.
32. SALAFFI F, CAROTTI M, IAGNOCCO A *et al*.: Ultrasonography of salivary glands in primary Sjögren's syndrome: a comparison with contrast sialography and scintigraphy. *Rheumatology* (Oxford) 2008; 47: 1244-9.
33. DE VITA S, LORENZON G, ROSSI G, SABELLA M, FOSSALUZZA V: Salivary gland echography in primary and secondary Sjögren's syndrome. *Clin Exp Rheumatol* 1992; 10: 351-6.
34. ARIJI Y, OHKI M, EGUCHI K *et al*.: Texture analysis of sonographic features of the parotid gland in Sjögren's syndrome. *AJR Am J Roentgenol* 1996; 166: 935-41.
35. KAWAMURA H, TANIGUCHI N, ITOH K, KANO S: Salivary gland echography in patients with Sjögren's syndrome. *Artritis Rheum* 1990; 33: 505-10.
36. TAKASHIMA S, MORIMOTO S, TOMIYAMA N, TAKEUKI N, IKEZOE J, KOZUKA T: Sjögren's syndrome: comparison of sialography and ultrasonography. *J Clin Ultrasound* 1992; 20: 99-109.
37. HOČEVAR A, AMBROŽIČ A, ROZMAN B, KVEDER T, TOMŠIČ M: Ultrasonographic changes of major salivary glands in primary Sjögren's syndrome. Diagnostic value of a novel scoring system. *Rheumatology* 2005; 44: 768-72.
38. WERNICHE D, HESS H, GROMNICA-IHLE E, KRAUSE A, SCHMIDT W: Ultrasonography of salivary glands – A highly specific imaging procedure for diagnosis of Sjögren's syndrome. *J Rheumatol* 2008; 35: 285-93.
39. SALAFFI F, ARGALIA G, CAROTTI M, GIANNINI FB, PALOMBI C: Salivary gland ultrasonography in the evaluation of primary Sjögren's syndrome. Comparison with minor salivary gland biopsy. *J Rheumatol* 2000; 27: 1229-36.
40. TAKAGI Y, KIMURA Y, NAKAMURA H *et al*.: Salivary gland ultrasonography: can it be an alternative to sialography as an imaging modality for Sjögren's syndrome? *Ann Rheum Dis* 2010; 69: 1321-24.
41. MILIC V, PETROVIC R, BORICIC I *et al*.: Ultrasonography of major salivary glands could be an alternative tool to sialoscintigraphy in the American-European classification criteria for primary Sjögren's syndrome. *Rheumatology* (Oxford) 2012; 51: 1081-5.
42. CORNEC D, JOUSSE-JOULIN S, PERS JO *et al*.: Contribution of salivary gland ultrasonography to the diagnosis of Sjögren's syndrome: toward new diagnostic criteria? *Arthritis Rheum* 2013; 65: 216-25.
43. ARIJI Y, YUASA H, ARIJI E: High-frequency color Doppler sonography of the submandibular gland: relationship between salivary secretion and blood flow. *Oral Surg Oral Med Oral Pathol Oral Radiol Endosc* 1998; 86: 476-81.
44. CHIKUI T, YONETSU K, IZUMI M, EGUCHI K, NAKAMURA T: Abnormal blood flow to the submandibular glands of patients with Sjögren's syndrome: Doppler waveform analysis. *J Rheumatol* 2000; 27: 1222-8.
45. RINDI G, MANNI E: Fisiologia Umana, 2nd ed. Turin, Italy: Unione Tipografico-Editrice Torinese, 1982: 1149-54.
46. CAROTTI M, SALAFFI F, MANGANELLI P, ARGALIA G: Ultrasonography and colour Doppler sonography of salivary glands in primary Sjögren's syndrome. *Clin Rheumatol* 2001; 20: 213-9.
47. MAKULA E, PORKORNY G, KISS *et al*.: The place of magnetic resonance and ultrasonographic examinations of the parotid gland in the diagnosis and follow-up of primary Sjögren's syndrome. *Rheumatology* 2000; 39: 97-104.
48. YONETSU K, TAKAGI Y, SUMI M, NAKAMURA T, EGUCHI K: Sonography as a replacement for sialography for the diagnosis of salivary glands affected by Sjögren's syndrome. *Ann Rheum Dis* 2002; 61: 276-77.
49. BOOTSMA H, SPIJKERVET FKL, KROESE FGM, VISSINK A: Toward new classification criteria for Sjögren's syndrome? *Arthritis Rheum* 2013; 65: 21-3.
50. VITALI C, CAROTTI M, SALAFFI F: Is it the time to adopt salivary gland ultrasonography as an alternative diagnostic tool for the classification of patients with Sjögren's syndrome? Comment on the article by Cornec *et al*. *Arthritis Rheum* 2013; 65: 1950.
51. SHIBOSKI SC, SHIBOSKI CH, CRISWELL LA *et al*.; FOR THE SJÖGREN'S INTERNATIONAL COLLABORATIVE CLINICAL ALLIANCE (SICCA) RESEARCH GROUPS AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA FOR SJÖGREN'S SYNDROME: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort. *Arthritis Care Res* 2012; 64: 475-87.