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Cover Letter

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Dear Sir/Madam,

Please find submitted a review of the changes in the 4th edition of the WHO Classification of Head and Neck Tumours that are of most relevance to the oral and maxillofacial surgeon. The review should be of great interest to your readership and help to increase awareness of the newly defined and reclassified tumours.

Yours faithfully,

Dr Robert Kennedy.

4/11/17

Conflicts of interest: None

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Author contribution

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Please provide details in the table below of each author(s) contribution to the submitted manuscript

AUTHORS	Conception and design of study/review/case series	Acquisition of data: laboratory or clinical/literature search	Analysis and interpretation of data collected	Drafting of article and/or critical revision	Final approval and guarantor of manuscript
Robert Kennedy	Entire conception and design of review	Entire literature search	Both analysis and interpretation of literature	Full authorship of article	Yes

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WHO's in and WHO's out of the mouth, salivary glands and jaws in the 4th edition of WHO Classification of Head and Neck tumours.

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WHO's in and WHO's out of the mouth, salivary glands and jaws in the 4th edition of WHO Classification of Head and Neck tumours

Abstract

Changes in the 4th edition of the WHO Classification of Head and Neck Tumours are reviewed focusing on their impact on the surgical care of diseases affecting the salivary glands, jaws and oral cavity. Updates to the salivary chapter include the addition of secretory carcinoma and sclerosing polycystic adenosis. The odontogenic cysts are back and the odontogenic keratocyst is listed among them, having lost its brief and confusing designation as a neoplasm. The newly defined sclerosing odontogenic carcinoma and primordial odontogenic tumour are added. Oropharyngeal tumours have been separated from the oral cavity tumours, reflecting the great importance of HPV in carcinoma of the tonsils. The problems of grading oral epithelial dysplasia persist.

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Introduction

The WHO text (1) is a classification of tumours with an emphasis on neoplasms and aims to achieve consistent nomenclature and diagnosis of tumours across the globe. This should facilitate epidemiological research with accurate comparisons of incidence between countries as well as effective transfer of treatments and diagnostic tests. In its 4th edition, the WHO Classification of Head and Neck Tumours contains new additions, updates and reclassifications. The changes reflect an improved understanding of the morphological and behavioural range of head and neck tumours. There is much greater detail on the molecular drivers of neoplasia and it is hoped this will facilitate greater use of targeted therapies in the future.

Odontogenic and maxillofacial bone tumours

This chapter is expanded to include the odontogenic cysts [omitted in the previous edition (2)] as well as benign and malignant tumours of bone and cartilage. There have been changes in the nomenclature for odontogenic tumours, some providing a helpful simplification but others having the potential to cause confusion.

Malignant odontogenic tumours

The classification of malignant odontogenic tumours has been simplified. There is now only one ameloblastic carcinoma, one primary intraosseous carcinoma and one odontogenic sarcoma. Odontogenic carcinosarcoma, eliminated in the previous edition, has been included with a small number of well-defined cases referenced. Metastasising ameloblastoma has been moved from the malignant section to the benign bringing it into line with the benign metastasizing pleomorphic adenoma. Metastasising ameloblastoma does show a benign microscopic appearance at both the primary and metastatic sites. The most common sites of metastasis are the lungs followed by cervical lymph nodes. The overall mean 5-year survival is just 44%. Cases with cervical lymph node metastases only and managed by surgery do appear to have a better survival, although data are very limited (3).

The only newly defined malignant odontogenic tumour included is the rare and recently described sclerosing odontogenic carcinoma (4-9). Reported cases have been in men and women between 40-70 years of age. Presentation is as an expansile masses sometimes with nerve signs. There is a relatively even distribution between the maxilla and mandible with variable cortical destruction and tooth resorption (4-8). The cytological features are bland but an aggressive pattern of infiltration into muscle and nerve is seen. The carcinoma extends beyond what appear at surgery to be clear margins (3) and the tumour recurs after curettage alone (5). Resection with a 5mm margin has been recommended (8). Neck dissection, chemotherapy and radiotherapy have also been used (4-5). However, no metastases nor disease related deaths have been reported and the need for adjunctive

therapies is not clear. It is important to recognise this entity, so that its aggressive histological appearance does not lead to overtreatment.

Benign odontogenic tumours

Ameloblastic fibro-dentinoma and ameloblastic fibro-odontoma are now considered by most authorities to be developing odontomas and have been removed. The odontoameloblastoma was previously described as a distinct entity combining the features of an ameloblastoma with those of an odontoma. It still has a brief mention in the section on ameloblastomas as it is now considered to be an ameloblastoma that has grown around, or originated in, the follicle of an odontoma or developing tooth. Ossifying fibroma is given a section amongst the benign odontogenic tumours under the term cemento-ossifying fibroma. This better reflects its odontogenic origin but has no implications for its management.

The classification of ameloblastomas remains contentious especially regarding unicystic types. The term ameloblastoma, solid/multicystic type has been replaced by ameloblastoma without further qualification which may cause some confusion. Many pathologists are likely to continue using the term solid/multicystic to differentiate the conventional ameloblastoma from unicystic and other variants. Ameloblastoma, unicystic type retains its full and descriptive name. The unicystic ameloblastoma without invasion of its wall can probably be managed more conservatively than the solid/multicystic type (10-11) but there is a lack of follow up studies and unicystic ameloblastomas do appear to recur, albeit less frequently than solid/multicystic types. Clear differentiation between types of ameloblastoma would therefore seem essential, although diagnosis of a unicystic ameloblastoma without mural invasion can only be confirmed on examination of the entire excision specimen. It remains to be seen to what extent this new classification will be accepted and it would seem likely that the growing understanding of the mutational drivers of ameloblastomas will assist in predicting behaviour and allow for more targeted therapies (12). A significant proportion of ameloblastomas carry a mutation of BRAF (13), as in some melanomas and thyroid

carcinomas. There is emerging evidence that ameloblastomas carrying this BRAF mutation follow a more aggressive course (14).

The only newly defined benign odontogenic tumour added is the primordial odontogenic tumour described in a series of six patients (15) all in the first two decades of life with an even gender distribution. All presented with an asymptomatic swelling in the posterior mandible (5 cases) or the posterior maxilla (1 case). Imaging showed well-defined radiolucencies (35-90 mm in maximum dimension) associated with unerupted variably resorbed or displaced teeth in an apparent pericoronal relationship. The tumours were solid and well circumscribed comprising loose fibrous tissue with tissue similar to the dental papilla and a characteristic complete peripheral lining of cuboidal to columnar epithelium. The lesions were easily enucleated and no recurrences reported with up to 20 years of follow up.

Odontogenic cysts

The odontogenic cysts were a notable omission from the previous edition. This caused difficulties both because there is overlap between the histological appearances of cysts and odontogenic and salivary neoplasms and because of changes in terminology made at the same time. In the previous edition, the odontogenic keratocyst (OKC) and calcifying odontogenic cyst (COC) were listed as keratocystic odontogenic tumour and calcifying cystic odontogenic tumour, respectively. This led to much confusion and the nomenclature was not widely accepted. The propensity for recurrence together with association with PTCH gene mutations (16) had been taken as supportive of a neoplastic designation for the OKC. However, not all OKCs possess identifiable PTCH mutations (17) and it was not clear whether the neoplastic designation was meant to apply to all OKCs or just a subset, as cysts were omitted. The 2017 WHO panel did not believe there was sufficient evidence to justify classification as a neoplasm and the designations OKC and COC are back as the preferred terms, though the 2005 terms remain acceptable synonyms.

Maxillofacial bone tumours

Benign and malignant tumours of bone and cartilage are now described in the same chapter as the odontogenic tumours allowing for features specific to the gnathic bones to be emphasised. In terms of patient care, this is most relevant for osteosarcoma, which has a lower propensity for metastasis when arsing in the gnathic bones compared to the other skeletal sites. Indeed, resection with clear margins is the most important prognostic factor for osteosarcoma of the jaws, with the role of (neo)adjuvant therapy remaining controversial (18).

Key points

- Sclerosing odontogenic carcinoma is a recently described entity that despite its aggressive microscopic appearance carries a good prognosis. No metastatic spread nor disease related deaths have been reported.
- Metastasising ameloblastoma is now defined as benign, despite carrying a significant mortality rate.
- Ameloblastic fibro-dentinoma and ameloblastic fibro-odontoma are considered to be stages in developing odontomas and may be treated by enucleation.
- Primordial odontogenic tumour is an emerging entity seen in young people and appears to be adequately managed by enucleation.
- Odontogenic keratocyst is reinstated as the preferred term for keratocystic odontogenic tumour, reflecting its probable non-neoplastic nature.

Tumours of the Salivary Glands

A multitude of different epithelial tumours arise in the salivary glands with many subtypes suggested. Only well documented epithelial neoplasms are included often with supporting genetic data. The soft tissue section of the chapter has been expanded and a section on non-neoplastic epithelial lesions added.

Benign salivary tumours

There have been no recently recognised entities added to this section. Metastasising pleomorphic adenoma was previously listed as a distinct entity in the malignant tumours section. It now occupies a subcategory of pleomorphic adenoma within the benign tumours section. Metastasising pleomorphic adenoma cannot be distinguished histologically from a typical pleomorphic adenoma and is only diagnosed on detection of metastases usually following multiple local recurrences. In a well-documented series of 11 cases, 2 patients died as a direct result of metastatic tumour (19). But recognition of the lesion as a benign entity may allow more aggressive metastastecomy as a treatment, particularly when metastases are few.

Non-neoplastic epithelial lesions

The new additions of nodular oncocytic hyperplasia, intercalated duct hyperplasia and sclerosing polycystic adenosis are included in this new section. Nodular oncocytic hyperplasia is a benign non-neoplastic nodular proliferation occurring in the parotid gland. Intercalated duct hyperplasia is similarly rare and usually an incidental finding in excisions made for other salivary tumours.

Sclerosing polycystic adenosis (Figure 1) was described in the 1990s (20) named for its resemblance to fibrocystic change and sclerosing adenosis of the breast. It appears as a painless slow growing mass most commonly in the parotid gland and less frequently the submandibular gland and even more rarely in the minor glands. (20-21). Men and women are affected over a wide age range (20-21). The lesion comprises a lobular well circumscribed proliferation of ducts and acini. Cytological atypia can be present (21-22) and there is evidence that this may be a neoplastic rather than reactive process (23). A single case of malignant transformation is described following multiple recurrences (24). Treatment is by complete surgical excision with good margins but a recurrence rate of 19% is reported (25).

Malignant tumours

The only recently defined entity added to this chapter is secretory carcinoma (Figure 2). This was previously described in most publications under the term mammary analogue secretory carcinoma (MASC) owing to the morphological similarity to secretory carcinoma of breast which is caused by the same ETV6-NTRK3 translocation. The tumour arises in the major and minor glands over a wide age range and without significant gender bias (26-27). Presentation is usually as a painless mass (26-28) with a well circumscribed but unencapsulated periphery. The carcinoma appears cytologically low grade (26-27) but has a 20% incidence of metastases (28). Prognosis is generally good but worse with increasing stage, high grade transformation and possibly atypical fusion transcripts (26,29-30). Previous to its definition, cases would likely have been diagnosed as acinic cell carcinoma (31). The higher metastatic rate and possibility of targeted therapies taking advantage of the known translocation (32), make correct diagnosis essential.

Intraductal carcinoma is included as a section encompassing entities previous described as low grade cribriform cystadenocarcinoma or low grade salivary duct carcinoma. These rare carcinomas show what is described as an intraductal growth pattern and are considered to be non-invasive/in situ. Presentation is usually as an asymptomatic swelling most frequently in the parotid gland and rarely in the submandibular or minor glands (33-36). Ages of patients in the largest series ranged from 32 to 94 years without significant gender bias (33-35). The designation of “intraductal” is based on the well circumscribed architecture and the presence of an intact periphery of myoepithelial cells surrounding an intraluminal proliferation of ductal cells. The cytological features are usually low grade. The view that an intact layer of surrounding myoepithelial cells indicates that the proliferation is an intraductal one would seem to assume that the myoepithelial cells are not themselves neoplastic. The justification of this assumption is not clear. Management is by parotidectomy and no recurrences nor metastatic disease have been reported in cases with the usual low grade features (34-35). High grade cytology has been associated with multiple recurrences and

high grade transformation to widely invasive high grade adenosquamous carcinoma with metastatic disease has also been described (33, 37).

Polymorphous low grade adenocarcinoma has been renamed polymorphous adenocarcinoma (PAC). The low grade descriptive term has now been dropped as, whilst most are low grade, more aggressive forms are included within the spectrum of this diagnosis and high grade transformation is described (38). Management is usually by wide local excision (39-40) and there is an overall excellent prognosis with a 10 year disease specific survival of 96.4% (40). The incidence of lymph node metastases ranges from to 0% to 17% (41-44), and this behaviour often seemed at odds with the low grade designation. More aggressive behaviour is associated with a base of tongue location and a papillary or cribriform architecture (43-44). These features are seen in tumours described under the term cribriform adenocarcinoma of tongue and subsequently cribriform adenocarcinoma of minor salivary gland (CAMSG) (45-46). CAMSG has a metastatic rate of 70-100% (45-46) exceeding that of PAC. The microscopic features of CAMSG can overlap with those of PAC (44) and CAMSG is regarded by the WHO as an emerging entity and is not separated from PAC. CAMSG is however recognised as a distinct entity by many pathologists who will likely continue to report it as a distinct tumour and clinicians need to be aware of its more aggressive course.

The WHO emphasises that appropriate management of carcinoma ex-pleomorphic adenoma is determined by the extent of invasion and the type of carcinoma. The authors of the Royal College of Pathologists dataset for salivary carcinomas further emphasise that “the prognosis of the carcinomatous component is poorer than that of comparable carcinomas developing de novo” (47). It is generally accepted that an intracapsular carcinoma ex-pleomorphic adenoma follows an essentially benign course after conservative surgical management (48-49). Minimal invasion is also associated with a relatively favourable prognosis (49). However, the cut off for what constitutes minimally invasive is not clear. The

WHO (1) cites a range of 4-6mm and the Royal College of Pathologists (47) a range of 5–6 mm, both acknowledging the need for further validation. The issue as to the correct cut off is compounded by difficulties in its measurement that can be caused by multifocality, multinodular growth or an incomplete capsule. Furthermore, the importance of extent of invasion can be superseded by grade of carcinoma. For example, Griffith et al. (50) described 3 cases of salivary duct carcinoma ex-pleomorphic adenoma (a high grade carcinoma) with less than 2mm extracapsular invasion. Despite this "minimal invasion", 2 cases gave rise to metastatic disease and one patient had died from their disease after 16 months. Determination of the prognosis and correct management for carcinoma ex-pleomorphic adenoma requires careful clinico-pathological correlation. Factors including extent of invasion, carcinoma grade and stage need to be assessed together. It would seem incorrect to base treatment solely on the extent of invasion.

Key points

- Sclerosing polycystic adenosis is listed as a non -neoplastic epithelial lesion but there is some evidence that it may be a neoplasm and carries a significant recurrence rate.
- Secretory carcinoma has a higher metastatic rate than acinic cell carcinoma and has potential for targeted therapy, making correct identification of this new entity essential.
- Intraductal carcinoma with the usual low grade appearances can be managed effectively by parotidectomy.
- Polymorphous adenocarcinoma is the new designation for polymorphous low grade adenocarcinoma, recognising a wider spectrum of behaviour.

Tumours of the oral cavity and mobile tongue.

Tumours of the oral cavity and mobile tongue have been separated from those of the oropharynx reflecting the importance of HPV in carcinoma of the tonsils and oropharynx (51). HPV associated oral epithelial dysplasia is described as lesions occurring mostly in adult men on the ventral or lateral tongue lesion (52). Microscopy shows full-thickness

dysplasia with frequent apoptosis. However, the risk of malignant transformation is unknown.

The WHO group was unable to produce a unified dysplasia grading that could be applied to all aerodigestive tract sites. Separate dysplasia grading systems are kept for larynx and oral cavity, reflecting the differences in aetiology and the very different normal structure of the epithelium at these sites. Some have felt that one unified system would promote reproducible grading but this has so far proved impossible to define. Perhaps it will be an objective for the next edition.

Conflict of Interest

There are no conflicts of interest.

Ethics statement/confirmation of patient permission

There is no ethical approval required. There is no patient identifying information included.

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Figure Legends

Figure 1. Slerosing polycystic adenosis arising in the parotid gland

The photomicrographs show slerosing polycystic adenosis arising in the parotid gland. There is a typically circumscribed lobular proliferation of ducts and acini within a sclerotic stroma (A) (H&E x2.5). Distinctive brightly eosinophilic granules are seen in some cells (B) (H&E x10).

Figure 2. Secretory carcinoma in the parotid gland

The photomicrographs show a secretory carcinoma in the parotid gland. The neoplasm has microcystic surface and abundant secretory material (2A) (H&E x5). There is a monophasic cell population showing abundant bubbly cytoplasm (2B) (H&E x10).

WHO is in and WHO is out of the mouth, salivary glands, and jaws sections of the 4th edition of the WHO classification of head and neck tumours

Abstract

This review of changes to the 4th edition of the *WHO classification of head and neck tumours* focuses on their impact on the surgical care of diseases that affect the salivary glands, jaws, and oral cavity. Updates to the chapter on the salivary glands include the addition of secretory carcinoma and sclerosing polycystic adenosis. The odontogenic cysts are back, and the odontogenic keratocyst is listed among them, as it has now lost its brief and confusing designation as a neoplasm. The newly-defined sclerosing odontogenic carcinoma and primordial odontogenic tumour have been added. Oropharyngeal tumours have been separated from those of the oral cavity, which reflects the importance of HPV in carcinoma of the tonsils. The problems of grading oral epithelial dysplasia persist.

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Introduction

The WHO text[1] is a classification of tumours with an emphasis on neoplasms, and it aims to achieve consistent nomenclature and diagnosis of tumours across the globe. This should facilitate epidemiological research with accurate comparisons of incidence among countries as well as effective transfer of treatments and diagnostic tests. In its 4th edition, the WHO *classification of head and neck tumours* contains new additions, updates, and

reclassifications.[1] The changes reflect an improved understanding of the morphological and behavioural range of head and neck tumours. There is much greater detail on the molecular drivers of neoplasia, and it is hoped that this will facilitate greater use of targeted treatments in the future.

Odontogenic and maxillofacial bone tumours

This chapter has been expanded to include odontogenic cysts (omitted from the previous edition[2]) as well as benign and malignant tumours of bone and cartilage. There have been changes in the nomenclature of odontogenic tumours, some of which provide a helpful simplification, but others that have the potential to cause confusion.

Malignant odontogenic tumours

The classification of malignant odontogenic tumours has been simplified. There is now only one ameloblastic carcinoma, one primary intraosseous carcinoma, and one odontogenic sarcoma. Odontogenic carcinosarcoma (eliminated from the previous edition) has been included, with reference to a small number of well-defined cases. Metastasising ameloblastoma has been moved from the malignant to the benign section, which brings it into line with the benign metastasising pleomorphic adenoma, as it does show a benign microscopic appearance at both the primary and metastatic sites. The most common sites of metastases are the lungs, followed by the cervical lymph nodes. The overall mean 5-year survival is just 44%. Patients with cervical lymph node metastases alone who are managed by resection seem to survive better, although data are limited.[3]

The only newly-defined malignant odontogenic tumour included is the rare, and recently described, sclerosing odontogenic carcinoma.[4-9] Reported cases have been in men and women between 40-70 years of age. It presents as an expansile mass, sometimes with nerve signs. There is a relatively even distribution between the maxilla and mandible, with variable cortical destruction and tooth resorption. [4-8] The cytological features are bland but there is an aggressive pattern of infiltration into muscles and nerves. The carcinoma extends beyond what seem at operation to be clear margins,[3] and the tumour recurs after curettage alone.[5] Resection with a 5 mm margin has been recommended.[8] Neck dissection, chemotherapy, and radiotherapy have also been used.[4,5] However, no metastases or disease-related deaths have been reported, and the need for adjunctive treatment is not clear. It is important to recognise this entity, so that its aggressive histological appearance does not lead to overtreatment.

Benign odontogenic tumours

Ameloblastic fibrodentinoma and ameloblastic fibro-odontoma are now considered by most authorities to be developing odontomas, and have been removed. The odontoameloblastoma was previously described as a distinct entity that combined the features of an ameloblastoma with those of an odontoma. It still has a brief mention in the section on ameloblastomas, as it is now considered to be an ameloblastoma that has grown around, or originated in, the follicle of an odontoma or developing tooth. The ossifying fibroma is given a section among the benign odontogenic tumours under the term cemento-ossifying fibroma, which better reflects its odontogenic origin but has no implications for its management.

The classification of ameloblastomas remains contentious, particularly regarding unicystic types. The term ameloblastoma, solid/multicystic type, has been replaced by ameloblastoma without further qualification, which may cause some confusion. Many pathologists are likely to continue using the term solid/multicystic to differentiate the conventional ameloblastoma from unicystic and other variants. The ameloblastoma, unicystic type, retains its full and descriptive name. The unicystic ameloblastoma without invasion of its wall can probably be managed more conservatively than the solid/multicystic type, [10, 11] but there is a lack of follow-up studies and unicystic ameloblastomas do seem to recur, albeit less often than solid/multicystic types. Clear differentiation between types of ameloblastoma therefore seems essential, although diagnosis of a unicystic ameloblastoma without mural invasion can be confirmed only on examination of the entire excised specimen.

It remains to be seen to what extent this new classification will be accepted, and it seems likely that the growing understanding of the mutational drivers of ameloblastomas will assist in the prediction of their behaviour and allow for more targeted treatments.[12] A considerable proportion of ameloblastomas carry a mutation of BRAF, [13] as do some melanomas and thyroid carcinomas, and there is emerging evidence that ameloblastomas that carry this BRAF mutation follow a more aggressive course.[14]

The only newly-defined benign odontogenic tumour that has been added is the primordial odontogenic tumour, which has been described in a series of six patients, [15] all in the first two decades of life, with an even distribution between the sexes. All presented with an asymptomatic swelling in the posterior mandible (n=5) or the posterior maxilla (n=1). Images showed well-defined radiolucencies (35-90 mm in maximum dimension) associated with unerupted, variably-resorbed or displaced teeth in apparent pericoronal relations. The

tumours were solid and well-circumscribed, and comprised loose fibrous tissue with tissue similar to the dental papilla and a characteristic complete peripheral lining of cuboidal to columnar epithelium. The lesions were easily enucleated and no recurrences reported with up to 20 years' follow up.

Odontogenic cysts

Odontogenic cysts were a notable omission from the previous edition, which caused difficulties both because there is overlap between the histological appearances of cysts and odontogenic and salivary neoplasms, and because of changes in terminology made at the same time. In the previous edition, odontogenic keratocysts (OKC) and calcifying odontogenic cysts (COC) were listed as keratocystic odontogenic tumours and calcifying cystic odontogenic tumours, respectively. This led to confusion, and the nomenclature was not widely accepted. The propensity for recurrence, together with association with mutations of the Drosophila segment polarity gene Patched (PTCH) gene,[16] had been taken as supportive of a neoplastic designation for the OKC. However, not all OKC possess identifiable PTCH mutations [17] and it was not clear whether the neoplastic designation was meant to apply to all OKC or just a subset, as cysts were omitted. The 2017 WHO panel did not think there was sufficient evidence to justify its classification as a neoplasm, and the designations OKC and COC are back as the preferred terms, though the 2005 terms remain acceptable synonyms.

Maxillofacial bone tumours

Benign and malignant tumours of bone and cartilage are now described in the same chapter as the odontogenic tumours, which allows for features specific to the gnathic bones to be emphasised. In terms of care of patients this is most relevant for osteosarcoma, which has less propensity to metastasise when it arises in the gnathic bones than in other skeletal sites. Indeed, resection with clear margins is the most important prognostic factor for osteosarcoma of the jaws, and the role of (neo)adjuvant treatment remains controversial.[18]

Key points

- Sclerosing odontogenic carcinoma is a recently-described entity that, despite its aggressive microscopic appearance, carries a good prognosis. No metastatic spread or disease-related deaths have so far been reported.
- Metastasising ameloblastoma is now defined as benign, despite its appreciable mortality.
- Ameloblastic fibrodentinoma and ameloblastic fibro-odontoma are considered to be stages in the development of odontomas and may be treated by enucleation.
- Primordial odontogenic tumour is an emerging entity that is seen in young people and seems to be adequately managed by enucleation.
- "Odontogenic keratocyst" has been reinstated as the preferred term for a keratocystic odontogenic tumour, which reflects its probable non-neoplastic nature.

Tumours of the salivary glands

Many different epithelial tumours arise in the salivary glands, and many subtypes have been suggested. Only well-documented epithelial neoplasms are included, often with supporting

genetic data. The soft tissue section of the chapter has been expanded and a section on non-neoplastic epithelial lesions added.

Benign salivary tumours

No recently recognised tumours have been added to this section. Metastasising pleomorphic adenoma was previously listed as a distinct entity in the section on malignant tumours, and it now occupies a subcategory of pleomorphic adenoma within the section on benign tumours. Metastasising pleomorphic adenoma cannot be distinguished histologically from a typical pleomorphic adenoma and is diagnosed only on detection of metastases, usually after many local recurrences. In a well-documented series of 11 patients, two died as a direct result of metastatic tumours. [19] However, recognition of the lesion as a benign entity may allow excision of more aggressive metastases, particularly when there are few of them.

Non-neoplastic epithelial lesions

The new additions of nodular oncocytic hyperplasia, intercalated ductal hyperplasia, and sclerosing polycystic adenosis are included in this section. Nodular oncocytic hyperplasia is a benign non-neoplastic nodular proliferation that occurs in the parotid gland. Intercalated duct hyperplasia is similarly rare, and usually an incidental finding in excisions of other salivary tumours.

Sclerosing polycystic adenosis (Fig. 1) was described in the 1990s [20] and named for its resemblance to fibrocystic change and sclerosing adenosis of the breast. It presents as a painless, slow-growing mass usually in the parotid gland, less often in the submandibular

gland, and even more rarely in the minor glands.[20, 21] Both men and women are affected, over a wide age range.[20, 21] The lesion comprises a lobular, well-circumscribed proliferation of ducts and acini. Cytological atypia can be present [20, 23] and there is evidence that this may be a neoplastic rather than reactive process. [23] A single case of malignant transformation has been described after multiple recurrences.[24] Treatment is by complete excision with good margins, but a recurrence rate of 19% has been reported.[25]

Malignant tumours

The only recently defined tumour that has been added to this chapter is secretory carcinoma (Fig. 2). This was previously described in most publications as "mammary analogue secretory carcinoma (MASC)" because of its morphological similarity to secretory carcinoma of breast, which is caused by the same ETV6-NTRK3 translocation. The tumour arises in the major and minor glands over a wide age range and without particular sex bias. [26, 27] It usually presents as a painless mass [26, 28] with a well-circumscribed but unencapsulated periphery. The carcinoma looks cytologically low grade [26, 27] but has a 20% incidence of metastases.[28] Prognosis is generally good but worsens with increasing stage, high grade transformation, and possibly atypical fusion transcripts.[26, 29, 30] Before its definition, cases would probably have been diagnosed as acinic cell carcinoma. [31] The higher metastatic rate and possibility of targeted treatments, which take advantage of the known translocation, [32] make correct diagnosis essential.

Intraductal carcinoma is included as a section that encompasses entities previously described as low grade cribriform cystadenocarcinoma or low grade salivary duct carcinoma. These rare carcinomas have what is described as an intraductal growth pattern, and are

considered to be non-invasive/in situ. They usually present as a symptomless swelling, usually in the parotid gland, and rarely in the submandibular or minor glands. [33-36] Ages of patients in the largest series ranged from 32 to 94 years without particular sex bias.[33-35] The designation "intraductal" is based on the well-circumscribed architecture and the presence of an intact periphery of myoepithelial cells that surround an intraluminal proliferation of ductal cells. The cytological features are usually low grade. The view that an intact layer of surrounding myoepithelial cells indicates that the proliferation is an intraductal one seems to assume that the myoepithelial cells are not themselves neoplastic, but the justification for this assumption is not clear. Management is by parotidectomy and no recurrences or metastatic disease have been reported in cases with the usual low grade features.[34,35] High grade cytology has been associated with multiple recurrences, and high-grade transformation to widely invasive high-grade adenosquamous carcinoma with metastatic disease has also been described.[33, 37]

Polymorphous low grade adenocarcinoma has been renamed polymorphous adenocarcinoma (PAC). The low grade descriptive term has now been dropped as, while most are low grade, more aggressive forms are included within the range of this diagnosis and high grade transformation has been described.[38] Management is usually by wide local excision[39, 40] and an overall excellent prognosis with a 10-year disease-specific survival of 96.4% has been reported.[40] The incidence of lymph node metastases ranges from 0 to 17% ,[41-44] and this behaviour often seemed at odds with the low grade designation. More aggressive behaviour is associated with it when is situated at the base of the tongue and has papillary or cribriform architecture.[43,44] These features are seen in tumours described under the term "cribriform adenocarcinoma of tongue" and subsequently "cribriform adenocarcinoma of minor salivary gland" (CAMSG).[45, 46] CAMSG has a metastatic rate of 70%-100%, which exceeds that of PAC.[45, 46] The microscopic features of CAMSG can overlap with those of PAC, [44] and CAMSG is regarded by the WHO as an emerging entity and is not separated from PAC. CAMSG is, however, recognised as a distinct entity by many pathologists who

will probably continue to report it as a distinct tumour, and clinicians need to be aware of its more aggressive course.

The WHO emphasises that appropriate management of carcinoma ex-pleomorphic adenoma is governed by the extent of invasion and the type of carcinoma. The authors of the Royal College of Pathologists dataset for salivary carcinomas further emphasise that "the prognosis of the carcinomatous component is poorer than that of comparable carcinomas developing de novo".[47] It is generally accepted that an intracapsular carcinoma ex-pleomorphic adenoma follows an essentially benign course after conservative surgical management.[48,49] Minimal invasion is also associated with a relatively favourable prognosis.[49] However, the cut-off point for what constitutes minimally invasive is not clear. The WHO[1] cites a range of 4-6 mm and the Royal College of Pathologists [47] a range of 5–6 mm, but both acknowledge the need for further validation. The issue of the correct cut-off point is compounded by difficulties in its measurement that can be caused by its multifocal and multinodular growth, or an incomplete capsule. The importance of extent of invasion can also be superseded by the grade of carcinoma. For example, Griffith et al [50] described three cases of salivary duct carcinoma ex-pleomorphic adenoma (a high grade carcinoma) with less than 2 mm extracapsular invasion. Despite this "minimal invasion", two of them developed metastatic disease, and one died of the disease after 16 months. Establishment of the prognosis, and correct management of carcinoma ex-pleomorphic adenoma, require careful clinicopathological correlation. Factors to consider include extent of invasion, grade of carcinoma, and stage, and these must be assessed together. It seems wrong to base treatment solely on the extent of invasion.

Key points

- Sclerosing polycystic adenosis is listed as a non -neoplastic epithelial lesion, but there is some evidence that it may be a neoplasm and it carries an appreciable rate of recurrence.
- Secretory carcinoma has a higher metastatic rate than acinic cell carcinoma, and has potential for targeted treatment, which makes correct identification of this new entity essential.
- Intraductal carcinoma with the usual low grade appearances can be managed effectively by parotidectomy.
- Polymorphous adenocarcinoma is the new designation for polymorphous low grade adenocarcinoma, and this includes a wider range of behaviour.

Tumours of the oral cavity and mobile tongue

Tumours of the oral cavity and mobile tongue have been separated from those of the oropharynx, which reflects the importance of HPV in carcinoma of the tonsils and oropharynx.[51] HPV-associated oral epithelial dysplasia is described as a lesion that presents mostly in adult men, and on the ventral or lateral tongue. [52] Microscopy shows full-thickness dysplasia with frequent apoptosis. However, the risk of malignant transformation is unknown.

The WHO group was unable to produce a unified grading of dysplasia that could be applied to all sites in the aerodigestive tract. Separate systems for grading dysplasia are kept for the larynx and oral cavity, which reflects the differences in aetiology and the different structure of the normal epithelium at these sites. Some have thought that one unified system would promote reproducible grading, but this has so far proved impossible to define. Perhaps it will be an objective for the next edition.

Conflict of Interest

I have no conflicts of interest.

Ethics statement/confirmation of patients' permission

No ethics approval was required, and no identifying information was included.

QUERIES FOR AUTHOR:

Throughout: the journal uses the word "significant(ly)" only in a statistical sense, so where it has been used adjectivally it has been changed.

Throughout: the journal prefers "think" to "believe", as "think" implies rational deduction, whereas "believe" implies an act of faith.

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Legends to Figures

Figure 1. Photomicrographs showing sclerosing polycystic adenosis arising in the parotid gland. **(A)**There is a typically circumscribed lobular proliferation of ducts and acini within a sclerotic stroma (haematoxylin and eosin, original magnification x 2.5). (B) Distinctive brightly eosinophilic granules are seen in some cells (haematoxylin and eosin, original magnification x 10).

Figure 2. Photomicrographs showing secretory carcinoma in the parotid gland. (A)The neoplasm has a microcystic surface and abundant secretory material (haematoxylin and eosin, original magnification x 5). (B) There is a monophasic cell population showing abundant bubbly cytoplasm (haematoxylin and eosin, original magnification x 10).

Figure 1a

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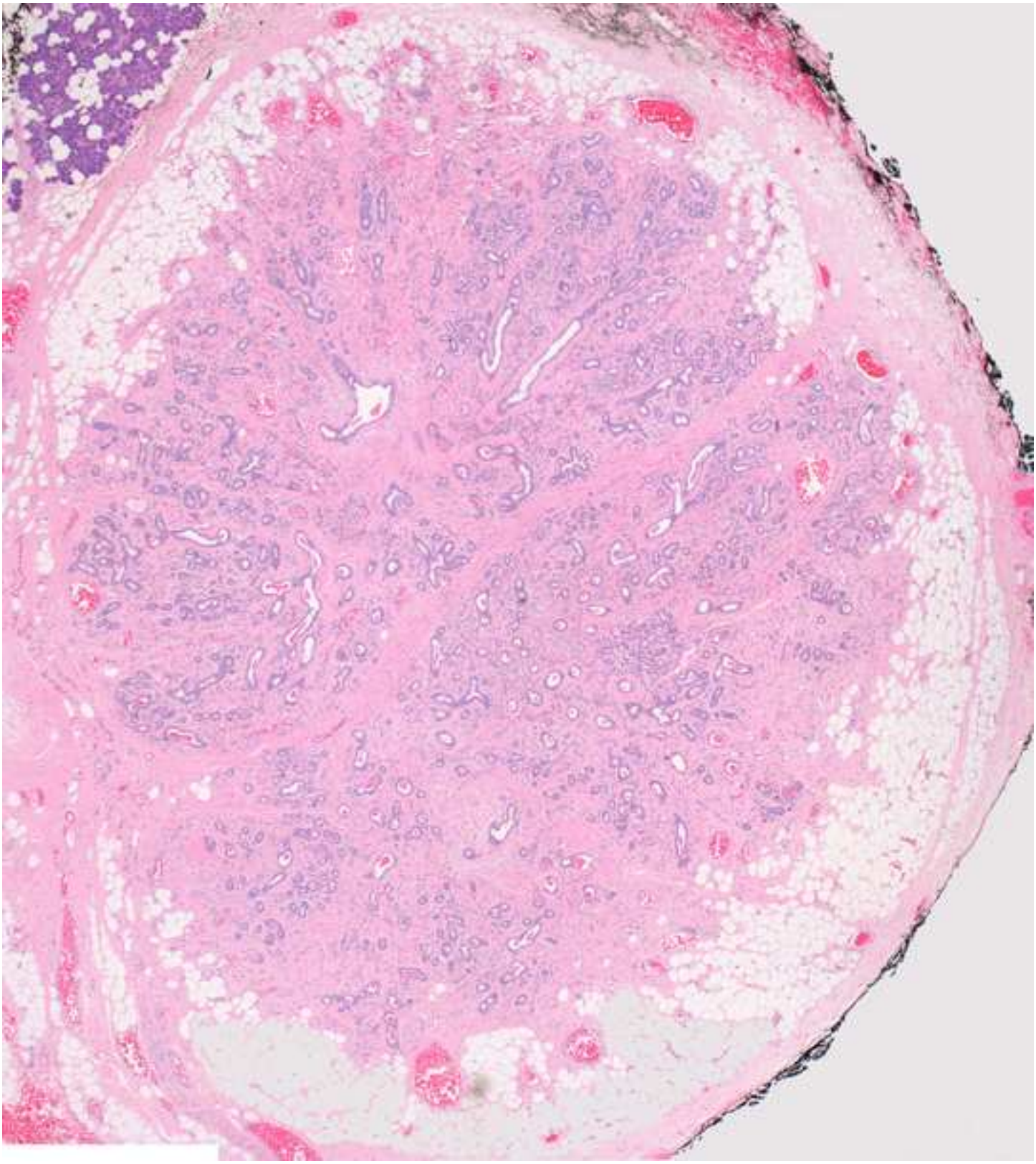

Figure 1b

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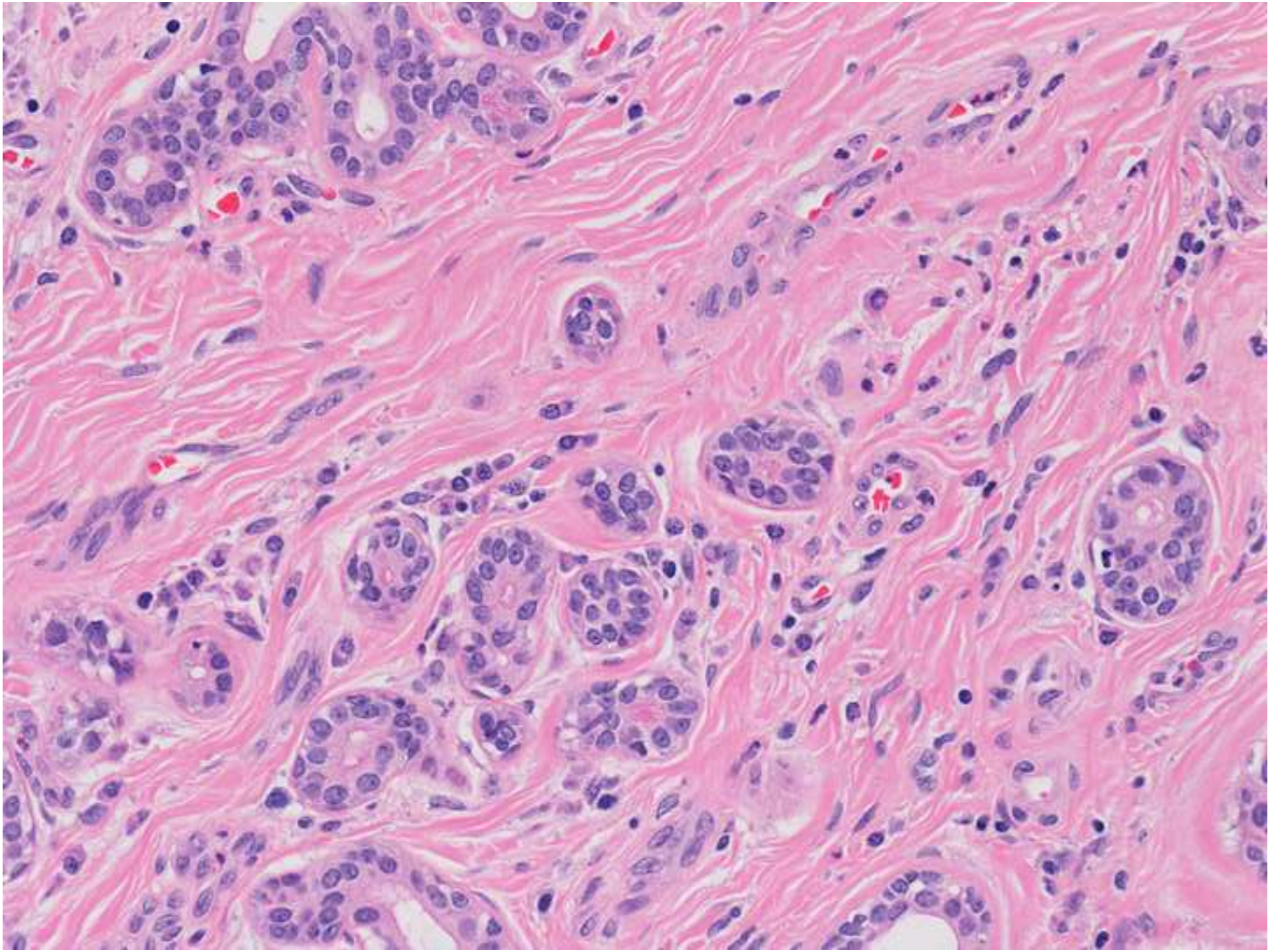

Figure 2a

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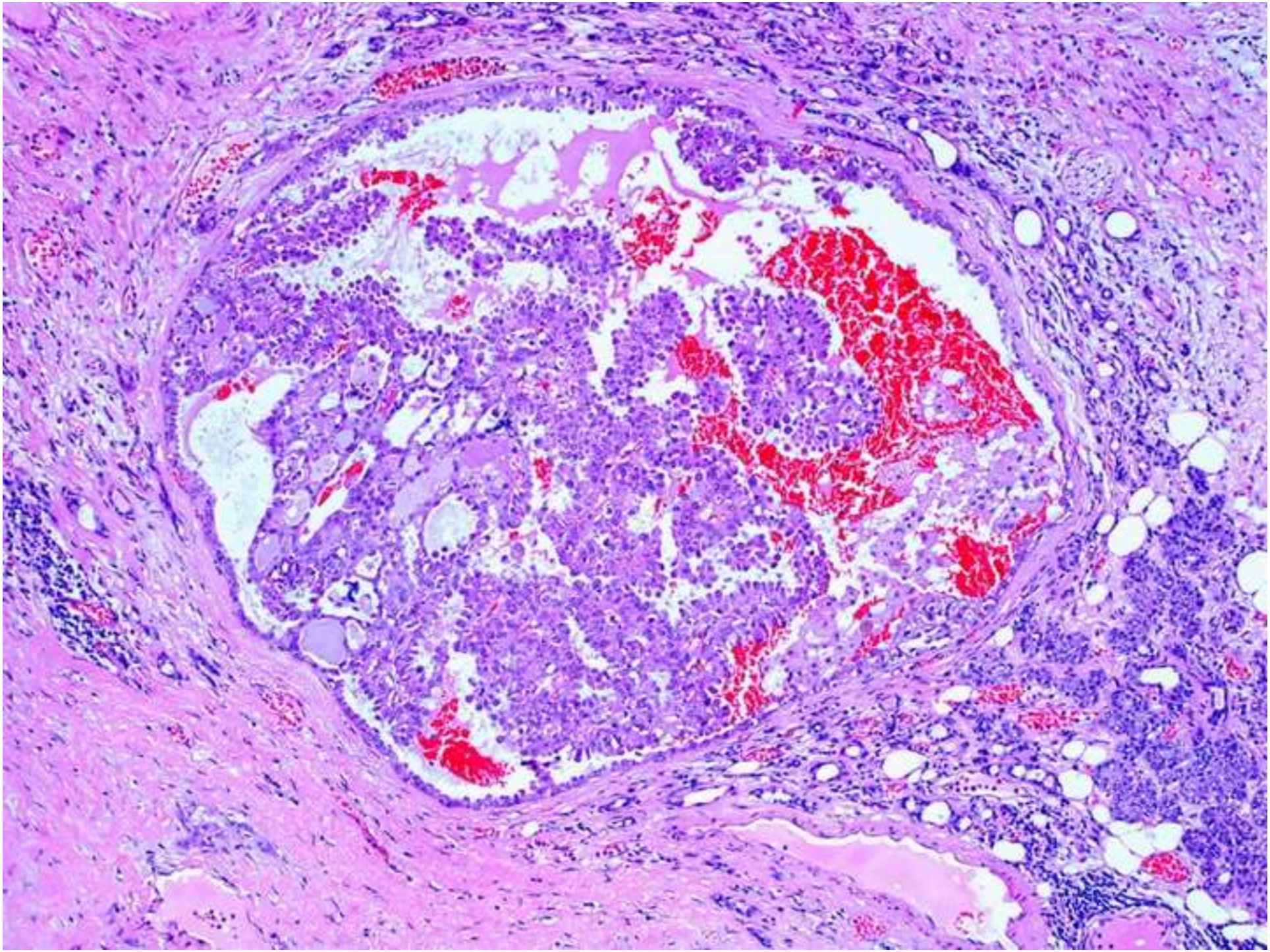

Figure 2b

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