DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS
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EPIDEMIOLOGY OF ODONTOGENIC TUMOURS IN ESTONIA. PATHOGENESIS AND CLINICAL BEHAVIOUR OF AMELOBLASTOMA

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LIST OF ORIGINAL PUBLICATIONS

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I Tamme T, Soots M, Kulla A, Karu K, Hanstein SM, Sokk A, Jõeste E, Leibur E. Odontogenic tumours, a colloborative retrospective study of 75 cases covering more than 25 years from Estonia. Journal of Cranio-Maxillofacial Surgery 2004; 32: 161–165.

II Leibur E, Tamme T, Lepp E. The ameloblastomatous potentiality of odontogenous epithelium demonstrated in tissue culture. Stomatologija, Baltic Dental and Maxillofacial Journal 2004; 6: 73–76.

III Tamme T, Leibur E, Kulla A. Mandibular ameloblastoma and maxillary adenoid cystic carcinoma: case report. ENT-Ear, Nose & Throat Journal 2003; 82: 938–940.

IV Tamme T, Soots M, Herik M, Pintson Ü, Müürsepp P, Leibur E. Ameloblastoomid ja nende kirurgilise ravi analüüs. Eesti Arst 2003; 82(2): 93–97.

ABBREVATIONS

AM	ameloblastoma
OT	odontogenic tumours
SMA	solid/multicystic ameloblastoma
UA	unicystic ameloblastoma
PA	peripherial ameloblastoma
DA	desmoplastic ameloblastoma
OKC	odontogenic keratocyst
LPC	lateral perodontal cyst
SI	stratum intermedium of the enamel organ
OPT	ortopantomogram
CT	computed tomography
MFS	maxillofacial surgery

1. INTRODUCTION

Odontogenic tumours (OT) comprise a group of lesions of the jaws, derived from primordial tooth-forming tissues and presenting in a large number of histologic patterns. Some of these lesions, particulary the odontomas, are now interpreted as developmental malformations or hamartomatous lesions rather than true neoplasms. Other lesions, such as ameloblastoma (AM), are accepted as true neoplasms and must be diagnosed and treated as such. OTs share two major characteristics, namely they arise from the tissue with the potential for differentiation into tooth or periodontal structures, and are therefore found exclusively in the mandible and the maxilla and, on rare occasions, the gingiva. Another variable but distinctive feature includes formation of tooth-related extracellular substances some of which may calcify and be visible on radiographs; they are a product of epithelial-mesenchymal interactions (Gallagher and Shklar, 2000).

The most common sites of these tumours are the mandibular molar region and the maxillary cuspid region. They are usually slow growing and asymptomatic. Certain OTs have a predilection for particular ages, gender, geographic location, and race (Sawyer *et al.*, 1985; Assael, 1992).

The AM continues to be a subject of intense interest and controversy after more than 100 years of recorded observation (Broca, 1868). But the fact is that a consensus has not been reached on the biological behaviour of this tumour (Gardner and Pecak, 1980; Gold, 1991; Martins *et al*., 1999; Becelli *et al.*, 2002; Reichart and Philipsen, 2004) and on how best to treat it (Shatkin and Hoffmeister, 1965; Sehdev *et al*., 1974; Holland and Mellor, 1981; Sampson and Porgrel, 1999; Nakamura *et al.*, 2002; Chapelle *et al*., 2004). The cellular sources of the AM have been the subject of hypotheses and numerous investigations (Orban, 1957; Eversole *et al*., 1971; Leider *et al*., 1985; Heikinheimo *et al*., 1991; Fukumashi *et al*., 2002).

There are no studies available in Estonia, dealing with odontogenic tumours. The aim of this study was therefore to examine the epidemiology of odontogenic tumours and, in particular, the histogenic origin, the biological behaviour and treatment of ameloblastomas.

2. REVIEW OF THE LITERATURE

2.1. Odontogenic tumours

Odontogenic tumours (OT) are rare, mostly benign neoplasms of dental tissue origin.

They are the lesions of the mandible and the maxilla, and on rare occasions, of the gingiva which should be considered as a differential diagnosis when analysing jaw lesions. OT constitute a group of heterogenous lesions that range from hamartomatous or non-neoplastic tissue proliferations to malignant neoplasms with metastatic capabilities. Since Broca first described an odontogenic neoplasm in 1868, various classifications have been proposed (Gabell *et al*., 1914; Thoma and Goldman, 1946; Pindborg and Clasen, 1958; Eversole *et al*., 1971; Pindborg *et al*., 1971; Gorlin 1972; Reichart and Ries, 1983; Kramer *et al.*, 1992). In the latest WHO classification, benign OT are grouped according to their putative origins into epithelial, epithelial-ectomesenchymal, and ectomesenchymal neoplasms (Table 1; Reichart and Philipsen, 2004). Malignant tumours, odontogenic carcinomas and sarcomas are extremely rare.

Table 1. Neoplasms and tumor-like lesions arising from the odontogenic apparatus (WHO, 2004)

Benign
Odontogenic epithelium with mature, fibrous stroma; odontogenic ectomesenchyme not present.
Ameloblastomas
Solid/multicystic
Extraosseous/peripheral
Desmoplastic
Unicystic
Squamous odontogenic tumour
Calcifying epithelial odontogenic tumour
Adenomatoid odontogenic tumour
Keratinizing cystic odontogenic tumour
Odontogenic epithelium with odontogenic ectomesenchyme with or without dental hard tissue formation
Ameloblastic fibroma
Ameloblastic fibrodentinoma
Ameloblastic fibro-odontoma
Complex odontoma
Compound odontoma
Odontoameloblastoma
Calcifying cystic odontogenic tumour
Dentinogenic ghost cell tumour

Mesenchyme and/or odontogenic ectomesenchyme with or without included odontogenic epithelium
Odontogenic fibroma (epithelium-poor and epithelium-rich types)
Odontogenic myxoma or fibromyxoma
Cementoblastoma
Malignant tumours (odontogenic carcinomas)
Metastasizing, malignant ameloblastoma
Ameloblastic carcinoma
(a) primary
(b) secondary (dedifferentiated), intraosseous
(c) secondary (dedifferentiated), extraosseous
Primary intraosseous squamous cell carcinoma (PIOSCC)
(a) PIOSCC solid type
(b) PIOSCC derived from odontogenic cysts
(c) PIOSCC derived keratinizing cystic odontogenic tumour
Clear cell odontogenic carcinoma
Ghost cell odontogenic carcinoma
Malignant tumours (odontogenic sarcomas)
Amleoblastic fibrosarcoma
Ameloblastic fibrodentino- and fibro-odontosarcoma

2.2. Epidemiology of odontogenic tumours

The knowledge of the basic epidemiological features, such as age, gender, geographic location and race, can be extremely valuable in development of differential diagnoses (Sawyer *et al.,* 1985; Assael, 1992; Reichart *et al.,* 2004).

Frequency
Data concerning the frequency of OT rarely appear in the literature, except the publications concerning the epidemiology of OT from Africa. Among the recorded material where the frequency of OT was taken account of, marked differences have been found in geographic variation. This is particularly notable for ameloblastomas and odontomas among African/Chinese, North American, and European countries (Fregnani *et al.*, 2002). Ameloblastoma with its different subtypes appears to be particulary frequent in Africa (Davies and Davies, 1960; Odukoya, 1995; Chidzonga *et al.,* 1996a, b; Adebiyi *et al.*, 2004;) and in some Asian populations (Chung *et al.,* 1969; Reddy, 1974; Tay, 1999, Budhy *et al.,* 2001; MacDonald-Jankowski *et al.,* 2004).

In contrast, the incidence of compound and complex odontomas was low in the series involving Oriental and African populations (Kovi and Laing, 1966; Mosadomi, 1975; Arotiba *et al.*, 1997; Lu *et al*., 1998; Laideinde *et al*., 2005).

Age

Comparison of the average age of patients with ameloblastoma in the different continents yielded following figures: United States 39.0 years; South America 13.2 years; Europe 42.3 years; Africa 30.4 years; Asia 35.2 years, and Australia 29.5 years (Reichart, 1995).

Based on the data of survey of odontomas (compound, complex) by Philipsen *et al.* (1997) the mean age at the time of diagnosis was 17.2 years for compound odontoma and 19.9 years for complex odontoma. Odontoma is clearly a lesion of childhood and adolescence.

Gender

The higher male prevalence among persons with ameloblastomas in an African study differs from the equal sex prevalence or higher female prevalence among white people (Regezi *et al.*, 1978; Shafer WG *et al.*, 1993).

In accordance with literature data regarding the male : female ratio for odontomas, a slight male predominance was found (Philipsen *et al.*, 1997).

At the same time, there is no information of the epidemiological features of these lesions among the Estonian population.

2.3. Pathogenesis of ameloblastoma

Ameloblastoma (AM) is justly considered the more unexplainable of OTs, because of its clinical and histological features, intriguingly contradictory, paradoxical and incongruent, if its benign histological aspect and its invasive and destructive clinical behaviour are considered. Histologically, the epithelium of AM resembles that of the enamel organ of the developing tooth. The peripheral cells of epithelial follicles resemble ameloblasts or preameloblasts of the tooth germ. The central cells resemble the stellate reticulum of the tooth germ (Heikinheimo, 1993; Kumamoto *et al.*, 2001; Reichart and Philipsen, 2004). Furthermore, some AMs share features with basal or squamous cell carcinomas, squamous odontogenic tumours, adamantinomas of the long bones or craniopharyngiomas of the central nervous system (Rosai, 1977; Shafer *et al.*, 1983; Paulus *et al.*, 1997; Gallager and Shklar, 2000).

Several theories have been put forward concerning the origin of the neoplastic epithelium in ameloblastoma. It has been suggested to arise directly from the enamel organ of the developing tooth, the remnants of the odontogenic epithelium, the lining of a odontogenic cyst or the basal cell layer of the oral mucosa or epidermis (Eversole *et al.*, 1971; Stoelinga, 1987; Gold 1991; El-Sissy and Rashad, 1999; Slootweg, 2004).

2.3.1. Tooth development

Tooth development involves regional and temporal patterning of the individual tooth primordia. Tooth development involves initiation, morphogenesis and cytodifferentiation, controlled by sequential and reciprocal epithelial-mesenchymal interactions (Kollar and Braid, 1970; Slavkin, 1974; Thesleff and Hurmerinta, 1981; Lumsden, 1988). The epithelial dental lamina signales to the mesenchyme during tooth initiation, and thereafter the mesenchymic cells regulate epithelial morphogenesis. Shape development is regulated by signals from the epithelial enamel knot and the dental papilla mesenchyme. The signal molecules belong to several families and four of them have been particulary intensley studied during recent years: the hedgehodges (hh), the bone morphogenic protein, the fibroblast growth factors and the Wnt-family signaling molecules (Cam *et al*., 1992; Bei and Maas, 1998; Koyama *et al*., 2001; Kumamoto *et al*., 2004).

Human odontogenesis is initiated during the sixth week of gestation (Slavkin, 1979; Ten Cate, 1998). The first sign of its initiation is local thickening of the oral epithelium. This is followed by the apperance of the dental lamina and condensation of the neural-crest-derived ectomesencymal cells. The dental lamina invaginates the underlying mesenchyme, forming buds of 10 deciduous teeth at each dental arch.

During the cap stage (Fig.1.) the dental epithelium differentiates into the enamel organ, which is composed of the inner and outer enamel epithelia, the stellate reticulum and the stratum intermedium (SI). SI consists of a few layers of squamous cells between the inner enamel epithelium and the stellate reticulum. The condensed dental mesenchyme differentiates into the dental papilla and the dental follicle, a membranous sac surrounding the tooth germ. During the cap stage, additional epithelial down-growth is initiated, giving rise to the enamel organ of the permanent tooth.

During the bell stage (Fig.1.), the enamel organ changes the morphology to reflect the anatomy of the future tooth (morphodifferentiation). The cells of the inner enamel epithelium differentiate into ameloblasts and the cells in the periphery of the dental papilla differentiate into odontoblasts (histodifferentiation). Ameloblasts undergo several differentiation processes (Fincham *et al.,* 1999): the presecretory, secretory, and maturation stages. In the presecretory stage, the basement membrane matrix separates the dental epithelium and mesenchymal preodontoblasts (Thesleff *et al.,* 1981; Adam and Watt, 1993). However, the basement membrane matrix disappears at the secretory stage, and the enamel matrix replaces the basement membrane to support and regulate the secretory ameloblast cells (Smith, 1998). In the secretory stage ameloblasts produce and secrete specific proteins in the enamel matrix that are replaced by calcium and phosphorous during the maturation stage for enamel formation. The principal component of the enamel matrix, synthesized by secretory ameloblasts, can be classified into two major categories: amelogenin, which

makes up ~ 90% of the enamel matrix, and nonamelogenins including ameloblastin, enamelin, and tuftelin (Smith, 1998). Amelogenin-null mice (Gibson *et al.*, 2001) exhibited a phenotype similar to human X-linked amelogenesis imperfecta in which ameloblast differentiation was normal but an abnormally thin enamel layer was formed. It has been suggested that amelogenins are essential for the organization of the crystal pattern and regulation of enamel thickness, and that other enamel proteins may play a role in the initial enamel formation and ameloblast differentiation (Fincham *et al.*, 1999; Moradian-Oldak, 2001). Fukumoto *et al.*, 2004 concluded, although the mechanism of ameloblastoma formation remains unclear, deregulation of ameloblast differentiation due to lack of ameloblastin is likely to be the primary cause of tumour, because no calcifications, not even dystrophic calcification are found in ameloblastoma.

During the bell stage, the dental lamina begins to disintegrate and form small islands of epithelial cell recidues (glands of Serres). This lengthy recapitulation of the activity of the embryonic oral epithelium, before initiation of the intricate inductive processes of morfodifferentiation in tooth formation, is suggested to emphasize the importance of this tissue as a source of ameloblastoma (Gold, 1991).

The apposition stage (Fig.1.) is characterized by dentin and enamel secretion. The ameloblasts first induce the odontoblasts to secrete the initial dentin matrix, which is followed by induction of the ameloblasts to secrete enamel. Dentinogenesis and amelogenesis are followed by root formation, which proceeds until the tooth is fully developed (Avery, 1992).

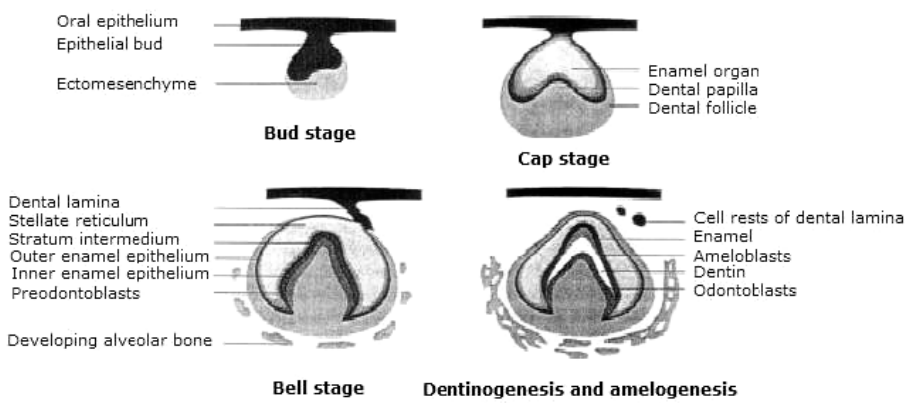

Figure 1. Tooth development.

2.3.2. The rests of Malassez and the epithelium of the follicular sac as sources of ameloblastoma

The fused extensions of the outer and inner dental epithelia of the enamel organ, called Hertwig´s epithelial root sheath, develop after the crown has been formed. As root development progresses, Hertwig´s sheath is broken up by proliferation of the connective tissue, which gives rise to the periodontal ligament. The remnants of Hertwig´s sheath persist in the periodontal ligament and alveolar bone as epithelial strands and nests — the rests of Malassez — throughout adult life and are the only odontogenic epithelial cells that remain in the periodontium after the eruption of teeth (Wentz *et al.*, 1950; Hamamoto *et al.*, 1989, Philipsen and Reichart, 2004). In pathological conditions, inflammatory stimuli and direct contact with calcified tissues seem to induce the rests to differentiate into ameloblastic cells (Hamamoto *et al.*, 1996; Hamamoto *et al.*, 1998).

After formation of the enamel crown, the epithelial organ is reduced to several layers of cuboidal cells, with the disappearance of the stellate reticulum and the no longer functioning ameloblasts. The reduced dental epithelium is attached to the crown and is surrounded by a capsular connective tissue, the follicular sac, which contains remnants of the dental lamina (Gold, 1991).

2.3.3. Developmental odontogenic cysts as potential sources of ameloblastoma

Hypothetically, developmental cystic lesions (dentigerous, odontogenic keratocyst and lateral periodontal cyst) may give rise to ameloblastoma as a secondary phenomen, as they originate from the odontogenic epithelial tissue (Gold, 1991).

Leider *et al.*, 1985 proposed a pathogenic mechanism where ameloblastoma arises in dentigerous or other types of odontogenic cysts in which the neoplastic ameloblastic epithelium is preceded temporarily by a non-neoplastic stratified squamous epithelial lining.

Numerous clinical reports have attempted to show such an association in dentigerous cysts, and some authors believe that approximately 20% of AM arise in dentigerous cysts (Bernier, 1964; McMillan and Smillie, 1981; Shear, 1994; Ayhan *et al.*, 1996; Piattelli *et al.*, 2002).

Odontogenic keratocyst (OKC) is thought to arise in place of an aborted tooth germ whose epithelial dental organ forms a cystic lesion, typically lined by a relatively thin keratinized or parakeratinized epithelium, classically arranged in corrugated folds. OKC develops from the remains of dental lamina (Lucas, 1964; Woolgar et al., 1987) or from the stellate reticulum of the enamel organ (Forssell, 1974).

Lateral periodontal cyst (LPC) is presumed to be formed of the rests of Malassez or other dental laminal residues in the periodontal ligament or adjacent alveolar bone (Standish and Shafer, 1958; Altini and Shear, 1992; Saydun *et al*., 2001).

2.3.4. Oral mucosa as a source of ameloblastoma

Central ameloblastomas that have penetrated their bony confines and grown into the overlying mucosa and peripherial ameloblastomas (PA) have been seen to appear fused with the mucosal epithelium. There are two major sources to be considered regarding the cellular origin of PA. First, they arise from the remants of the dental lamina or the Serres pearls located in the soft tissues overlying the tooth-bearing areas of the jawbones (Gardner, 1977; Zhu *et al.,* 1995). Second, tumour may arise from the surface epithelium, this attachment occurs over a relatively broad area, in alternating different areas, or in a very narrow zone (Anneroth and Johansson, 1985). The basal-cell layer in this region may be deeply staining and assume an odontogenic epithelial appearance, while the prickle cell layers become separated and form a pattern reminiscent of the stellate reticulum. This interesting observation has been made and speculated on by a number of authors (Lucas, 1976; Mehlish *et al*., 1972; Buchner and Sciubba, 1987).

Consideration of the potential sources of ameloblastoma makes it clear that the possible origins extend from the early embryologic period to well into adult life. Because of the doubt on the possible origin of AMs from cells with odontogenic potentiality, the aim of this study was to observe the development and growth pattern of the odontogenic epithelium and tooth germs in the tissue culture.

2.4. Biological behaviour of ameloblastoma

Ameloblastoma is the most common OT of epithelial origin, accounting for 1% of all tumours in the head and neck region and 11% of all OT (Regezi and Sciubba, 1993; Jackson *et al.,* 1996; Hughes *et al.,* 1999).

Ameloblastoma continues to be a subject of intense interest and controversy, even after more than 100 years of recorded observation (Broca, 1868). It is only within the last 10 years that it has become evident that a splitting up of the old ameloblastoma concept into sereval variants is appropriate.

Based on clinical and radiographic characterictics, histopathology, behavioural and prognostic aspects, the following four subtypes of ameloblastomas can presently be distinguished (Reichart and Philipsen, 2004):

– classic solid/multicystic ameloblastoma (SMA)
– unicystic ameloblastoma (UA)
– peripherial/extraosseous ameloblastoma (PA)
– desmoplastic ameloblastoma (DA).

SMA has the capacity to attain enormous size and invade adjacent structures, because neoplastic change has occurred centrally in both jaws, and there are only a few or no clinical signs in the early stages. The progression rate of swelling is slow. This tumour is often detected by chance during routine dental examination. If symptoms occur, they are usually due to the physical presence of the tumour. The most common symptoms are facial deformity (75%), pain (33%), malocclusion, loosening of teeth or ill-fitting dentures, periodontal disease or ulceration, oroantral fistula and nasal airway obstruction (Gardner and Pecak, 1980; Adekeye and Lavery, 1986). Ameloblastic involvement seems to be more common in the mandible (80–99%), particulary in the ramus or molar region (Martins *et al*., 1999; Becelli *et al.*, 2002). In the upper jaw the tumour occurs most frequently in the posterior (98%) than in the anterior region (2%): it may expand to the maxillary sinus (which provides a favourable, symptom-free location for its undisturbed growth), the pterygomaxillary fossa, the infratemporal fossa, the nasal cavity and, although infrequently, even the anterior skull base and the ethmoidal region. Maxillary bone involvement seems to be associated with higher recurrence and malignancy rates, compared with lower jaw involvement (Tsaknis and Nelson, 1980; Jackson *et al.*,1996; Williams, 1997).

Cortical bone destruction or invasion and involvement of the surrounding soft tissue are often seen in a late disease state, especially if no treatment has been provided or in tumour recurrences (D´Agostino *et al.*, 2001; Reichart and Philipsen, 2004).

Radiographically, the SMA may show considerable variation. Early radiographic investigation does not always allow to establish a positive diagnosis of ameloblastoma, the radiographic picture being often unrevealing. At a later state, however, a clear picture can be obtained, showing an ovoid or spindle-shaped area of bone rarefaction. Such radiotransparency may be small in size, well or ill-defined, sharp-edged and unilocular, or large and multilocular (Lewis, 1984). In the multilocular type the bone is replaced by a number of small well-defined radiolucent areas, giving the whole lesion a honeycomb or soap-bubble appearance. Ueno *et al*. (1986) found that among 97 cases of SMA, 47% were unilocular and 37% were multilocular; 16% had a soap-bubble or a combination of soap-bubble and multilocular appearance.

Microscopic studies indentify mainly two histological types of tumour: a follicular type consisting of the epithelial islands whose central portions are composed of a loose network resembling that of the enamel organ. The epithelium at the periphery is composed of tall columnar cells with polarized nuclei.

In the plexiform type, the epithelium is arranged in anastomosing strands and cords. The epithelial cells are closely apposed and appear basaloid or cuboidal (Gold, 1991; Regezi and Sciubba, 1993; D´Agostino, 2001).

Histologically, solid ameloblastoma consists of a two-layered area of superficial cells, an intermediate area and an inner vacuolated area whose overall appearance reminds of the structural arrangement of the enamel organ.

The literature, past and current, contains reports of ameloblastomas, well differentiated or not well differentiated, that have invaded regional tissues, implanted in the bronchiopulmonary system, or metastasized by vascular or lymphatic routes (Cranin *et al.*, 1987; Hayashi *et al.*, 1997; Okada *et al.*, 1999, Goldenberg *et al.*, 2004; Hayakawa *et al.*, 2004).

Malignant behaviour is present in about 2% of SMAs, with the diagnosis based on histological atypia and distant metastases (Houston *et al.*, 1993; Sato *et al.*, 1994).

In 1988, Ackerman et al suggested categorization of unicystic ameloblastoma (UA) into three variants: a unilocular cystic lesion in which the lining epithelium shows features of early transformation to ameloblastoma; intraluminal proliferation of ameloblastoma without penetration beyond the basement membrane into the underlying connective tissue; and the third, more aggressive subtype, intramural proliferation of ameloblastoma beyond the epithelium into the underlying connective tissue wall of the cystic lesion (Ackerman *et al.*, 1988).

Robinson and Martinez established the UA as a clinicopathologic entity on the basis of its unicystic (unilocular) radiographic appearance (UA is divided into two main patterns, unilocular and multilocular, with a clear predominance of the unilocular configuration in all studies where this feature was evaluated), patient age (lower than for SMA), relatively good response to conservative surgical treatment (contrary the response of SMA) and histologic findings (Robinson and Martinez, 1977).

The diagnosis of UA can only be made histologically and cannot be predicted preoperatively on clinical or radiographic grounds.

Peripherial ameloblastoma (PA) — also known as extraosseous ameloblastoma, or soft tissue ameloblastoma — has several of the same histologic characteristics as SMA, but it occurs in the soft tissues overlying the tooth-bearing areas of the maxilla and the mandible. PAs do not invade the underlying bone, because the cortical bone of the jaw, which represents a strong barrier to the infiltrative power of SMAs, is also an efficient barrier to invasion by PAs (Sciubba, 1991; Philipsen *et al.*, 2001). PA is a benign neoplasm (or hamartomatous lesion).

Desmoplastic ameloblastoma (DA), described by Eversole and coworkers in 1984, is considered to be a variant of SMA with some unusual clinical and microscopic features (Eversole *et al.*, 1984). It appears to favor the anterior portion of the jaw and may resemble a fibro-osseous lesion on radiographic examination (radiolucent/radiopaque). Microscopic appearance is characterized by stromal desmoplasia (Eversole *et al.*, 1984; Kawai *et al.*, 1999; Philipsen *et al.*, 2001). Unfortunately, because of the relative paucity of cases reported , it is premature to assess the biological behaviour of this particular subtype at this time.

2.5. Ameloblastoma associated with other tumours

It is not rare that multiple malignant tumours develop in more than two organs in the same human body. The incidence has been reported to be approximately 3% of all malignant tumours (Koppenfels and Thiede, 1973; Warren and Gares, 1932). In the head and neck region, Inuyama et al., reported that 23 of 1093 cases of malignant tumours developed as multiple tumours (Inuyama *et al.*, 1976). According to speciality literature, only a few cases of ameloblastoma appear to be associated with other tumours. But even when ameloblastomas do occur with other tumours, the other tumours are usually either odontogenic or osseous lesions that share a common origin or location. Ameloblastoma has been reported to occur with calcifying odontogenic cyst (Praetorius *et al.*, 1981), traumatic neuroma (Zain and Ling, 1985), aneurysmal bone cyst (Nadimi *et al*., 1986), osteogenic sarcoma (Feun *et al*., 1991), basal cell nevus syndrome (Schultz *et al*., 1987), glandular odontogenic cyst (Hisatomi *et al*., 2000), osteoblastoma (Gordon *et al*., 2001), squamous cell carcinoma (Nishimura *et al*., 2000) and latest published report described a simultaneous occurrence of ameloblastoma in the maxilla and the mandible (Miller *et al*., 2004).

Until now, only one case of both, an ameloblastoma and a salivary gland tumour has been reported occurring in the same patient at nearly the same time (Nakamura *et al*., 1988).

2.6. Treatment strategies in ameloblastoma

Management of ameloblastoma has been controversial because of the unique biological behaviour of this disease as a slow-growing, locally invasive tumour with a high rate of recurrence and possible malignant development when treated inadequately (Shatkin and Hoffmeister, 1965; Mehlisch *et al.*, 1972; Sehdev *et al.*, 1974; Tsaknis and Nelson, 1980; Pinsolle *et al.*, 1995; Rapidis *et al.*, 2004). Recurrence rates of ameloblastoma are reportedly as high as 15% to 25% after radical treatment (Shatkin and Hoffmeister; 1965; Sehdev *et al.*, 1974; Garder

and Pecak, 1980; Olasoji and Enwere, 2003) and 75% to 90% after conservative treatment (Sehdev *et al.,* 1974; Jackson *et al.,* 1996; Nakamura *et al*., 2002). Therefore, wide resection of the jaw in accordance with the treatment of malignant tumours is usually recommended for ameloblastomas.

Indeed, no radiological and histological findings, or cellular markers detectable throughout immunohistochemical analysis are reliable indicators of a tendency to recur (Bucher and Sciubba, 1987; Ong´uti *et al.,* 1999).

On the other hand, recent advancements in understanding of the biological behaviours of ameloblastoma have led to more rational surgical approaches (Gardner,1984; Müller and Slootweg, 1985; Nakamura *et al*., 1995; Nakamura *et al*., 2001; Nakamura *et al*., 2002; Chapelle *et al*., 2004).

Factors that determine the selection of surgical management are the type of tumour, its anatomical location, extent of disease, histological and radiographical characteristics as well as patient age and compliance.

Among the various types of ameloblastomas there are differences in treatment. Surgery is the mainstay of therapy for ameloblastomas today. Treatment ranges from conservative surgery to more radical procedures. The conservative surgical techniques include enucleation with bone curettage (Sampson and Porgrel, 1999; Martins *et al*., 1999) and marzupilization followed by enucleation (Nakamura *et al*., 1995; Nakamura *et al.,* 2002) as well as a combination of enucleation and Carnoy´s solution or cryosurgery (Holland and Mellor, 1981; Curi *et al.,* 1997; Lee *et al*., 2004; Chapelle *et al*., 2004).

Radical surgery as defined by Müller and Slootweg is a procedure in which the ameloblastoma is removed with a margin of "normal bone" by using segmental or marginal resection (Müller and Slootweg, 1985). There is yet no consensus on the resecting size of "normal bone". Most investigators believe in resecting at least 1 cm of the normal bone beyond the tumour margin (Gardner and Peak, 1980; Müller and Slootweg, 1985; Zwahlen RA and Grätz KW, 2002; Nakamura *et al.,* 2002), but in the literature there are also mentioned 0.5 cm (D´Agostino *et al.,* 2001) to 3 cm size of resection in the surrounding healthy tissue (Gold, 1991; Chapelle *et al*., 2004).

When planning treatment of ameloblastoma, it is important to understand its growth characteristics and to remove the full extent of the tumour, including the surrounding tissues. Recent advancements in the understanding of the biological behaviours of ameloblastoma have revealed that unicystic lesions are well localized by the fibrous capsule of the cyst, with only a few tumours broaching peripheral tissues, whereas multicystic, solid lesions are characterized by an aggressive infiltration of the adjacent tissue (Gardner, 1984; Nakamura, 1991). Gardner stated that the recommended treatment for SMA was radical treatment, whereas UA was treated by conservative methods.

According to Ackermann et al., there are three histological groups of UAs. Groups 1 and 2 (tumour confined to the epithelium of the cyst) may be treated conservately by enucleation, but lesion in Group 3 (tumour present in the

connective tissue wall of the cyst) should be treated aggressively in exactly the same manner as SMA (Ackermann *et al*., 1988; Gardner, 1984).

For the treatment strategies it is also important to evaluate the growth characteristics of ameloblastoma (clinical features, radiographic and histological findings). According to the clinical aspect, cystic lesions usually show more expansive growth than solid lesions (Nakamura, 1991). Radiographically, multilocular lesions — especially those demonstrating a soap-bubble appearance — have more invasive charateristics in which tumour cells favour infiltration of the surrounding cancellous space or the overlying mucosa rather than unilocular lesion (Müller and Slootweg, 1985). An important radiographic and clinical sign is the presence of buccal and lingual bone expansion (Gold, 1991; Williams, 1997; D´Agostino *et al*., 2001; Chapelle *et al*., 2004).

As maxillary ameloblastomas are reputed to be more aggressive having the ability to metastasize (Jackson *et al.*, 1996; Zwahlen and Grätz, 2002). Ameloblastomas of the maxilla should be treated more extensively than similar lesion in the mandible because of the proximity to vital structures and the difficulty in treating any recurrences (Gardner and Pecak, 1980; Ueda and Kaneda, 1991; Iordanidis *et al.*, 1999).

3. AIMS OF THE THESIS

The aims of the present study were:

1. to analyse retrospectively the character of odontogenic tumours in Estonia and to compare their prevalence with the figures presented in similar reports of other countries (I).
2. to study whether odontogenic epithelium of the tooth germ in tissue culture has potentiality to proliferate and differentiate in a manner similar to ameloblastoma (II).
3. to analyse retrospectively the prevalence and results of the treatment of ameloblastomas in the Southern Estonia (III, IV).

4. MATERIAL AND METHODS

4.1. Subjects

The whole study group (studies I, III, IV) consisted of 75 patients: 42 OT patients admitted to the Department of Maxillofacial Surgery (MFS) of Tartu University Clinics and 33 OT patients from the Department of Maxillofacial Surgery of Mustamäe Hospital, Tallinn. There occurred some overlapping between the study groups, as in three different studies (studies I, III, IV) 17 AM patients were included. To investigate the ameloblastomatous potentiality of the odontogenic epithelium, 14 mice molar tooth germs of 14-day-old mice embryos, consisting of the enamel organ and the dental papilla, were cultivated in a tissue culture. The material given in the four publications is presented in Table 2.

Table 2. Gerenal data about the period, institutions and goals of the study with names of the journals of publications.

Study type Period of data collection	*Institution*	*Total No of Patients or materials*	*Goals of the study*	*Name of The Journal Publications*
1. Retrospective	Multicentre study:	75	Epidemiology of OT in Estonia	J Cranio-Maxillo-facial Surg. (study I)
1977–2001	Tartu Univ. Clinics MFS	42		
1981–2001	Mustamäe Hospital MFS	33		
2. Tissue culture 1990–1991	Institute of General and Molecular Pathology, University of Tartu	14 molar tooth germs	To study amelo-blastomatous potentiality of odontogenic epithelium	Stomatologija, Baltic Dental and Maxillofacial J (study II)
3. Retrospective 1977–2001	Tartu Univ. Clinics	17	Clinical behaviour of AM and	Eesti Arst (study IV)
4. Case report	Tartu Univ. Clinics	1	treatment out-come	ENT-Ear, Nose and Throat J (study III)

4.1.1. Retrospective study of the epidemiology of OT in Estonia in 1977–2001

This collaborative retrospective study is based on the data of all OTs managed in Estonia during 1977–2001. The treatment of all OTs is concentrated at two

medical institutions with their in- and out-patient clinics: Department of Maxillofacial Surgery and Department of Pathology, Tartu University Clinics (42 cases; 1977–2001) and Departments of Maxillofacial Surgery and Department of Pathology, Mustamäe Hospital (33 cases, 1981–2001). The data from Mustamäe Hospital begins from the opening year, 1981. OTs were classified and graded histologically, according to the current World Health Organization (WHO) criteria (Kramer *et al*., 1992), on the basis of conventional hematoxylin and eosin staining of paraffin sections.

Primary data for the identification of patients were obtained from the computerised database of both hospitals according to discharge diagnosis. Further, case histories and, when needed, also the hospital´s discharge registry and logbooks of the operating theatre were studied. The following information was drawn: patient age, gender and tumour location obtained from records when available.

The diagnosis of OT was confirmed in 75 patients.

For tumour location the following scheme was used. The maxilla was divided into 6 anatomical regions, 3 on either side: anterior (from the midline to the distal surface of the canine), premolar (from the mesial aspect of the first premolar to the distal side of the second premolar), and molar (from the mesial aspect of the first molar distally). The mandible was divided into 5 anatomical regions on each side: anterior and premolar as described above, molar (from the mesial aspect of the first molar to the distal side), angle (from the distal side of the third molar to the inferior portion of the ramus, beneath the occlusal plane), and ramus (upper portion of the ramus above the occlusal plane).

4.1.2. Retrospective study evaluating the biological behaviour and treatment of ameloblastomas in Southern Estonia in 1977–2001

All 17 patients with AM, admitted to the Department of Maxillofacial Surgery, Tartu University Clinics, from a defined area of Southern Estonia between 1977 and 2001, were included in a retrospective study. Tartu University Clinics are the only medical institution which serve patients with ameloblastomas in this area. Beside gender and age, the medical records of these patients were retrieved and analysed for the anatomical distribution of the tumour, observation time, size, symptoms, type of primary operation, recurrence, average time between primary operation and secondary operation with results and complications.

4.2. Methods

4.2.1. Radiological methods

For radiological investigation, intraoral views, PA views, ortopantomograms and computer tomography were used.

4.2.2. Histological methods

Biopsy specimens were taken pre- and intraoperatively. The tissue specimens were fixed in a formalin (4% neutral buffered formaldehyde solution) and embedded in paraffin. Tumour samples were stained with haematoxylin and eosin and were reviewed to confirm or to correct a previous histologic diagnosis according to the criteria suggested in the revised World Health Organization (WHO) classification (Kramer *et al*., 1992). In problematic cases diagnosic procedure was complemented by immunohistochemistry.

The histological evaluation of the specimens was performed at the Department of Pathology, Tartu University Clinics (studies I, III, IV), and in cooperation with Department of Pathology of Mustamäe Hospital, Tallinn (study I).

The diagnosis of OT was made on clinical and radiological grounds (OPT, CT scans) and confirmed by histopathological examination.

4.2.3. Observation of the ameloblastomatous potentiality of odontogenous epithelium in tissue culture

The study was performed at the Department of General and Molecular Pathology, Tartu University.

Fourteen molar tooth germs of 14-day-old mice embryos were removed in aseptical conditions in a Hank´s solution. The explant consisted only of the enamel organ and the dental papilla. A stainless 20x20x30 mm grid was placed in a Petri dish with the medium consisting of 80% medium 199, 15% horse serum , 4 mg/ml glucose, 0.07 mg/ml ascorbic acid, 100 u per ml penicillin and streptomycin were added. Pieces of millipore filters 0.6 cm^2 with tooth germs were placed on the platform of the grid. The specimens were placed on the surface of millipore filter resting on a metal screen so that the medium filled the culture vessel to the surface of the screen. For the filter membranes, millipore membranes THWP with a porosity at 0.45μ and thickness of 25 ± 5 μ were used. All explants were gassed briefly with a mixture of 50% O_2 + CO_2 gas phase in an air-tight container and 50% N_2 and incubated at 37 ^{o} C and 100% humidity. The medium was changed after 48–72 hours. The pH was maintained at 7.6. Cultivation of the tooth germs was terminated in up to 21 days.

Microscopic observations were made daily on the living cultures. Bouin´s solution was used as the fixative. The tissues were embedded in cellulose-paraffin, serially sectioned at 8–10 μ and stained with hematoxylin-eosin.

4.3. Statistical analysis

The crosstable technique was applied for assessment the relationship of age groups and type of tumours in odontomas (compound, complex) and for ameloblastomas (uni- and multicystic) in the paper I.

The 95% confidence limits (interval) for p= 0.176 probability of recurrence were estimated with help of Fisher´s arcin transformation .

The p value was calculated using Fisher´s exact test. The distribution of age was the same, p-value was 0.4312 for compund and complex odontomas and 0.0709 for uni-and multicystic ameloblastoma.

The Statistical Analysis System (SAS) version 6.12 was used for statistical analysis of the data.

5. RESULTS

5.1. Epidemiology of OT in Estonia in 1977–2001 (publication I)

The sources of OT are given in Table 3. It shows the frequency of OT found among all biopsy specimens, including all other benign and malignant tumours of the oral and maxillofacial regions.

Table 3. Sources of odontogenic tumours

Source (years)	*Biopsies*	*Odontogenic tumours (%)*
Dept. of Maxillofacial Surgery and Dept. of Pathology, Tartu University Clinics (1977–2001)	4089	42 (1.03)
Dept. of Maxillofacial Surgery and Dept. of Pathology, Mustamäe Hospital, Tallinn (1981–2001)	6052	33 (0.55)
Total	10141	75 (0.74)

The distribution of the histological types and frequency of OT is presented in Table 4. There were altogether 75 OT. Of these, 74 (98.6%) were benign, and 1 (1.3%) was malignant. The most frequent beningn tumour was odontoma (compound, complex; 34.3%), followed by ameloblastoma with different subtypes (25.3%), ameloblastic fibroma (16%), odontogenic myxoma (12%) and benign cementoblastoma (8%). The other, less common types were calcifying epithelial odontogenic tumour and adenomatoid odontogenic tumour, accounting for 1.3% each.

Table 4. Histologic types and frequency of odontogenic tumours

Tumour type	*No of tumour*	*Percentage*
BENIGN		
1. Odontoma	26	34.6
compound	12	16
complex	14	18.6
2. Ameloblastoma	19	25.3
multicystic	13	17.3
unicystic	6	8
3. Ameloblastic fibroma	12	16
4. Odontogenic myxoma	9	12
5. Benign cementoblastoma	6	8
6. Calcifying epithelial odontogenic tumour	1	1.3
7. Adenomatoid odontogenic tumour	1	1.3
MALIGNANT		
9. Primary intra-osseous carcinoma	1	1.3
TOTAL	75	100

The nineteen AMs were subdivided into 2 biological — microscopic subtypes: 13 solid, multicystic and 6 unicystic ameloblastomas.

The 75 OTs were found in 28 males and in 47 females. The overall male to female ratio was 1:1.7. The gender distribution is listed in Table 5 and the age distribution in Table 6. It shows that there was no significant statistical differences (p=0.4312) in case of odontomas and ameloblastomas (p=0.0709).

Table 5. Gender distribution of odontogenic tumour cases

Type of tumour	*Number*	*Male*	*Female*	*Male:female ratio*
Odontoma:	26	8	18	1.0 : 2.3
compound	12	3	9	1.0 : 3.0
complex	14	5	9	1.0 : 1.8
Ameloblastoma:	19	10	9	1.1 : 1.0
multicystic	13	7	6	1.0 : 1.0
unicystic	6	3	3	1.0 : 1.0
Ameloblastic fibroma	12	5	7	1.0 : 1.4
Odontogenic myxoma	9	4	5	1.0 :1.3
Benign cementoblastoma	6	1	5	1.0 : 5.0
Calcifying epithelial odontogenic tumour	1	0	1	NA
Adenomatoid odontogenic tumour	1	0	1	NA
Primary intra-osseous carcinoma	1	0	1	NA
TOTAL	75	28	47	1 : 1.7

NA, not applicable

Table 6. Age distribution of odontogenic tumour cases

Type of tumour	Number of cases	Age (years)								Mean
		0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	
Odontoma:	26	4	8	8	4	–	1	1	–	23.7
compound	12	3	4	3	1	–	–	1	–	21.8
complex	14	1	4	5	3	–	1	–	–	25.4
Ameloblastoma:	19	1	3	2	2	–	7	2	2	44.7
multicystic	13	–	1	1	1	–	6	2	2	48.7
unicystic	6	1	2	1	1	–	1	–	–	38.5
Ameloblastic fibroma	12	–	2	1	1	7	–	1	–	39.2
Odontogenic myxoma	9	4	–	3	1	1	–	–	–	18.0
Benign cemento-blastoma	6	–	2	–	1	1	2	–	–	36.6
Calcifying epithe-lial odontogenic tumour	1	–	–	–	–	–	1	–	–	(51.0)
Adenomatoid odontog. tumour	1	–	–	–	1	–	–	–	–	(38.0)
Primary intra-osseous carcinoma	1	–	–	–	–	–	1	–	–	(58.0)
TOTAL	75	9	15	14	10	9	12	4	2	32.5

No statistical differences in the distribution of ages (p=0.4312) in cases of odontomas and ameloblastomas (p=0.0709)

Fifty-one tumoures (68%) were found in the second, third and fourth decades but also in the sixth decade of life. The members in the sixth decade can be attributed mainly to the high prevalence of SMAs in elderly people.

The site distribution is summarized in Table 7. In general, more frequent were mandibular tumours (mandibular to maxillary ratio 1.6:1), which was particularly evident for AMs (mandible to maxilla ratio 2.8:1). The most frequently affected areas were the premolar (20%) and the molar regions (21.3) in the mandible and the most common location in the maxilla was the premolar region (17.3%).

Table 7. Distribution of odontogenic tumours by location

Type of tumour	*Number*	*Maxilla*				*Mandible*						*Maxilla : Mandible*
		Anterior	Premolar	Molar	Total	Anterior	Premolar	Molar	Angle	Ramus	Total	
Odontoma:	26	7	5	1	13	4	6	2	1	–	13	1.0 : 1.0
compound	12	3	3	1	7	2	2	–	1	–	5	1.0 : 0.7
complex	14	4	2	–	6	2	4	2	–	–	8	1.0 : 1.3
Ameloblastoma:	19	1	1	3	5	1	1	6	4	2	14	1.0 : 2.8
multicystic	13	1	1	2	4	1	–	4	3	1	9	1.0 : 2.0
unicystic	6	–	–	1	1	–	1	2	1	1	5	1.0 : 3.0
Ameloblastic fibroma	12	–	2	1	3	–	3	5	1	–	9	1.0 : 3.0
Odontogenic myxoma	9	–	3	1	4	1	2	1	1	–	5	1.0 : 1.3
Benign cementoblastoma	6	–	1	1	2	–	1	2	1	–	4	1.0 : 2.0
Calcifying epithelial odontogenic tumour	1	–	1	–	1	–	–	–	–	–	–	–
Adenomatoid odontogenic tumour	1	–	–	–	–	–	1	–	–	–	1	–
Primary intraosseous carcinoma	1	–	–	–	–	–	1	–	–	–	1	–
TOTAL	75	8	13	7	28	6	15	16	8	2	45	1.0 : 1. 6

5.2. The ameloblastomatous potentiality of the odontogenous epithelium demonstrated on a tissue culture (publication II)

After 2 days of cultivation, visible initiation of the enamel outgrowth of the mouse molar tooth germ enamel organ was observed (Figure 1 in publication II, Stomatologija, Baltic Dental and Maxillofacial J, 2004; 6: page 74). After 4 days of cultivation continuation of epithelial outgrowth of the enamel organ along the millipore filter was observed. Its structure resembled the pattern of the dental lamina often seen in ameloblastomas of the jaw. The nuclei were round or oval with some distinct nucleoli and uniformly distributed fine granular chromatins (Figure 2 in publication II, Stomatologija, Baltic Dental and Maxillofacial J, 2004; 6: page 74). After 9 days of in vitro cultivation of a tooth germ, the epithelium of the outer layer of the enamel organ exhibited laterally disposed outgrowth buds (Figures 3; 4 in publication II, Stomatologija, Baltic Dental and Maxillofacial J, 2004; 6: page 74). A 12-day cultivation of the mouse tooth germ growth with the formation of microcysts in the stellate reticulum continued. The areas which at first presented the stellate reticulum-like appearance (Figure 5 in publication II, Stomatologija, Baltic Dental and Maxillofacial J, 2004; 6: page 74) later become microcysts (Figure 6 in publication II, Stomatologija, Baltic Dental and Maxillofacial J, 2004; 6: page 74). The reduced dental epithelium is surrounded by a capsular connective tissue, the follicular sac, which contains the remanants of the dental lamina. A histologic section of a 15-day specimen showed that the outer epithelium of the enamel organ has differentiated into a lamellar-like structure resembling the pattern of the ameloblastoma. Formation of microcysts and continued formation of epithelial buds was observed. A layer of cuboidal to columnar cells formed the outline of the parenchyma. The cuboidal to columnar cells resembled the internal dental epithelium (preameloblasts) and the polyhedral, or spindle-shaped, cells resembled the stellate reticulum of the enamel organ (Figure 7 in publication II, Stomatologija, Baltic Dental and Maxillofacial J, 2004; 6: page 74). After 21 days the formation of microcysts and the penetration of epithelial sheets continued (Figure 8 in publication II, Stomatologija, Baltic Dental and Maxillofacial J, 2004; 6: page 74). Well defined polygonal or round squamous cells with cyanophilic cytoplasm and lamellar growth and microcyst formation were seen (Figure 9 in publication II, Stomatologija, Dental and Maxillofacial J, 2004; 6: page 74).

5.3. Evaluation of biological behaviours and treatment of ameloblastomas in Southern Estonia (publications III; IV)

The data for these reports (publication III, including a case report) were gathered from 17 cases of AM. The age of the patients at the onset of lesions ranged from 7 years to 74 years, with a median of 45.2 years and the male/ female ratio was 0.9:1. On the basis of the cases histories it became evident that the dominant symptom was facial deformity. Odontogenic problems as malocclusion, loosening of teeth, or ill-filling dentures, periodontal disease, etc. were the second most frequent symptoms. Three ameloblastoma cases were discovered incidentaly at dental radiographic examination. In this series, 14 tumours were mandibulary, accounting for 82%, and 3 cases were maxillary, accounting for 18%. Analysis of the radiographic changes on OPT and CT scans revealed that in 4 cases AM were unicystic and in 13 cases AM were multicystic. When the size of the lesions was analysed the followings results were obtained: in 3 cases the diameter was until 3 cm, in 5 cases it was 3 to 6 cm and in 9 cases it was larger than 6 cm.

The treatment used in the 17 patients is shown in Table 8.

Table 8. The type of primary operations.

Type of surgery	*Patients No.*	*%*
Enucleation with bone curettage	9	52.9
Resection of tumour with preservation of lower border of mandible	4	23.5
Partial maxillary resection	1	5.8
Full-thickness resection of the mandible	3	17.6
TOTAL	17	99.8

Enucleation with bone curettage, complete removal of the epithelial lining of the lesion after adequate surgical exposure, was performed in 9 (52.9%) patients. Among them, there were 2 maxillary cases. Radical approach, re-section with preservation of lower border of the mandible was the surgical procedure in 4 (23.5%) patients. Full-thickness resection of the diseased mandible was done in 3 (17.6%) patients. Partial maxillary resection was done in one (5.8%) patient.

The patients were followed-up for periods ranging from 1 year to 21 years. During this time 3 recurrences appeared. All three patients were managed by enucleation and showed evidence of recurrence after 5, 10 and 12 months, respectively. The avarage time interval between the primary operation and the second procedure was 9 months.

6. DISCUSSION

6.1. Epidemiology of OT in Estonia in 1977–2001

Odontogenic tumours are relatively uncommon lesions. The present study comprised all OT managed in Estonia during 1977–2001. The treatment of all OT cases is concentrated at two medical institutions with their in- and out-patient clinics. The study period (1977–2001) involved profund changes in the political situation in Estonia, while the organization of the treatment of OT was not altered. The frequency of OT among all oral and maxillofacial biopsy specimens was 0.74%, ranging from 0.55% at Mustamäe Hospital to 1.03% at Tartu University Clinics. The frequency 0.74%, is the lowest ever reported in the literature, being as high as 30% in a Nigerian study (Arotiba *et al.,* 1997) and as low as 1.1% in a Finnish study (Happonen *et al.,* 1982) and in a Canadian study (Daley *et al.,* 1994).

The most frequent tumours in the present study were compound and complex odontomas (34.3%), the result being similar to that of a Mexican study (Mosqueda-Taylor *et al.,* 1997; Santos *et al.,* 2001). The prevalence for the Estonian population was almost twice as high as that recorded for the Turkish (18%) population (Günham *et al.,* 1990). In most other series from Canada, Finland, North America and Germany, the results showed that odontoma was the lesion most commonly diagnosed among OT (Regezi *et al.,* 1978; Happonen *et al.,* 1982; Mothes *et al.* 1991; Daley *et al.,* 1994).

In contrast, the incidence of compound and complex odontomas was low in the series involving Chinese (6.2%) and Nigerian polulations (Wu and Chan, 1985; Arotiba *et al.,* 1997; Lu *et al.,* 1998; Ladeinde *et al.,* 2005).

It is difficult to perform a comparative analysis of the frequency of odontomas, because these tumours are interpreted as developmental malformations or hamartomas rather than true neoplasms (Gallagher and Shklar, 2000; Assael, 1992; Reichart and Philipsen, 2004). This lesion is usually discovered on routine radiographic examination and it does not cause pain; treatment is generally provided by dentists or oral surgeons in the Western countries. Only problematic odontomas commonly require hospital management. In our case, the treatment of all OT cases is concentrated at two institutions and it is documented in their databases, which is related to tradition (referral by dentists) and to the small population.

Hence, the institutional background and the specific features of the country appear essential in assessment of compound and complex odontomas.

The mean age of the patients with compound odontomas was 21.8 years, and the mean age of those with complex odontomas was 25.4 years, which is higher compared with other reports (Minderjahn, 1979; Santos *et al.,* 2001). A predilection for females was observed in this study, which is in accordance with

the data from Mexico and North America (Mosqueda-Taylor *et al.*, 1997; Santos *et al.*, 2001; Regezi *et al.* 1978).

Lesions that present aggressive biological behaviour, such as ameloblastomas, represent a considerable number the OT (Arotiba *et al.*, 1996; Ladeinde *et al.*, 2005; Budhy *et al.*, 2001; MacDonald-Jankowski *et al.*, 2004; Adebiyi *et al.*, 2004). In our survey, they comprised 25.3% of all OTs, which indicates a frequency comparable to that found by Mothes et al. (1991) in Germany. We compared our data to those from Finland and Poland, where the respective data were 8.8% and 36.6% (Happonen *et al.*, 1982; Stypulkowska, 1998).

In the present study, the age distribution of ameloblastoma was higher (mean age 44.7 years) than that reported by other researchers, yet it is consistent with the results of Reichart et al. (1995) who compared 3677 ameloblastomas in a metaanalysis from different continents and found that the patients mean age, 42.3 years, was considerably higher in European countries than in the other continents. Also the gender distribution among men and women (n = 19) in our study, men 52.6 % and women 47.4 % (ratio 1.1 : 1) is similar to the result of Reichart et al.

When comparing the age distribution for the two subtypes of ameloblastomas in this study, an obvious contrast between the multicystic and unicystic ameloblastomas was found. The mean age of the patients with unicystic ameloblastoma (23.3 years) was much lower than that of the patients with multicystic ameloblastomas (49.3 years). The avarage age of the patients with unicystic ameloblastoma was similar to that reported by Ackermann et al. (1988; 23.8 years).

Another point for discussion is use of considering the age distribution covering nearly 10 decades of life, the absolute numbers entered in our tables, can only give a rough approximation, if one considers that the age reported by many authors is calculated arithmetically, and the characteristic Gaussian distribution can be missed. For the sake of clarification, we quantified additionally, for each single form of tumour, the decades of life in which they occur most often, and presented the upper and lower maxima of the age known at present.

In summary, this collaborative rertospective study, which involved the entire Estonian population, demonstrates that OTs are relatively rare in Estonia compared with other countries. There were differences in the prevalence of certain OT in comparison with data from other countries.

6.2. The ameloblastomatous potentiality of the odontogenous epithelium demonstrated on a tissue culture

The processes playing a role in normal odontogenesis may also occur in development of AM. Study of odontogenesis may shed new light on the pathogenesis of AMs and study of OTs may improve the understanding of normal odontogenesis.

Regarding AM, it is necessary to analyze step by step, the circumstances and the time points in the odontogenic process where local or temporal errors could occur which might determine the biological impossibility for the ameloblastomatous tissues to produce calcified dental tissues in tumour mass.

The nutritional medium, which has proved successful for normal growth and development for tooth germs in a tissue culture, provides verification of the concept that AMs arise from the epithelium possessing the potentiality for enamel formation (Matthiessen *et al.*, 1980; Stenman *et al*., 1985; Dong WJ, 1990; Snead *et al*., 1992). Our previous studies have also shown that tooth germs continued development in a tissue culture with formation of dental tissues (Leibur, 1978).

In this study (Leibur *et al.*, 2004), observation of the growth pattern of the enamel organ cultured in vitro, establishes the potentiality of the tissue to form AMs. Our results support earlier studies (Robinson and Lefkowitz, 1958) that a normal odontogenic epithelium in vitro has the potentiality to proliferate and differentiate in a manner similar to that seen in static histologic sections of AM.

Microscopically, ameloblastoma possesses the following characteristics 1) hyperchromatism of the basal cell nuclei, 2) palisading of the basal cells, which are typically columnar and perpendicular to the basement membrane, 3) cytoplasmic vacuolation of these cells and 4) polarization of the nuclei of the basal cells to the distal ends of the cells, i.e., away from the basement membrane. This last feature is referred to as reverse polarization (Hoffman *et al.*, 1987; Gardner,1992). Of great importance also is the nature of polarization; in ameloblasts, secretion of the matrix occurs toward the connective tissue, with the nuclei polarized away from the connective tissue, an orientation that is almost unique to this cell type. As there occurs little or no inductive effect in AM, one can see neither mesenchymal differentiation nor matrix production by the tumour cells (Stenman *et al*., 1985; Dong, 1990). In normal tooth formation, one cannot speak of “ameloblast” until actual enamel matrix formation is initiated; columnar cells with palisaded, polarized nuclei that are not yet producing the matrix are most properly called “pre-ameloblast” (Gallagher and Shklar, 2000).

However, if these neoplastic cells are similar to differentiated ameloblasts, why are they unable to form a recognizable enamel matrix? They lack some detail which transforms them to histologically active ameloblasts. This functional detail is probably the absence of a stratum intermedium (SI) adjacent

to the ameloblastic layer. For some reason, there is no SI in the ameloblastoma (Stenman *et al*., 1985; Dong, 1990; Yasuda *et al*., 1991). In normal odontogenesis, when polarization of the nuclei occurs and the epithelium passes from the inductive to the secretory phase, there occur differentiating into active ameloblasts and profound modifications in the stellate reticulum and in the outer epithelium of the enamel organ (Ten Cate, 1998). As demonstrated in the present study, atrophies of the stellate reticulum, driving the outer epithelium to approximate SI, form the reduced epithelium of the enamel organ. At the same time, the outer epithelium acquires a meshed aspect, becoming permeable to nutritive elements from the blood capillaries of the dental sac, which are then closer to the reduced epithelium, protruding to the stellate reticulum (Cerri *et al.*, 2004). All this facilitates arrival of nutritional elements to SI where they will be pre-metabolized, reaching later the ameloblasts (Gartner et al., 1978; Wakita and Hinrichsen, 1980). The evidence that pre-ameloblasts in the enamel-free areas of the mouse molars cannot differentiate into secretory ameloblasts without the support of SI (Sakakura *et al.,* 1989) suggests that cell-cell communication and /or interaction is essential for differentiation of ameloblasts (Nakamura *et al.,* 1995; Nakamura and Ozawa, 1997).

SI layer is apparently essential for enamel formation.

Although forming an ameloblastic layer, ameloblastoma is not able to elaborate the enamel matrix, because it lacks SI. The explanation for the lack of the SI layer is absence of the outer epithelium in the neoplastic islands, which could hinder formation of the reduced epithelium. Histological examination of ameloblastoma verifies that the neoplastic epithelial islands are surrounded by a peripherial cellular layer resembling the inner epithelium of the enamel organ, either in the pre-ameloblastic or in the ameloblastic phase (Stenman *et al*., 1985; Yasuda *et al*., 1991). There is no simultaneous occurrence of the cellular layers which could be called the inner and the outer epithelia, present in the same neoplastic island, or formation of the reduced epithelium of the enamel organ.

The stellate reticulum with nests and cords of columnar epithelium tends to undergo degeneration, forming microscopic cysts, as was shown in the mouse molar tooth germ explant after 21 days of cultivation in our study. Microcysts then expand to form large cystic spaces within the tumour and give to AM its multi-cystic gross and radiologic apperance. This nutritive competition can cause metabolic deficiencies for the cells of the stellate reticulum, which can explain the degeneration of central cells of the island and the consequent formation of cystic cavities in its interior.

Although the above studies demonstrate the ameloblastomatous potentiality of the odontogenic epithelium, they do not preclude the origin of ameloblastomas from the basal cells of the oral mucosa, the epithelium remnants of the dental lamina or the sheath of Hertwig`s rests as well as directly from the epithelium of the enamel organ.

This study presents additional experimental evidence that ameloblastomas orginate from an epithelium possessing odontogenic potentiality. The ameloblastoma arises from the preameloblasts before they are transformed ameloblasts in the stage of dental proliferation (bell stage, morphodifferentiation).

6.3. Comparison of biological behaviours in ameloblastoma patients treated in Southern Estonia with other published data

The neoplastic classification of ameloblastoma has been subject of dispute since the first description of the lesion published in 1827 by Cusak (Cusak, 1827). Deviations from the expected behaviour of a "benign" lesion have been presumed to be atypical occurrences. However, actually, an individual ameloblastoma behaves depending on biological determinants.

Several reports deal with the behaviour of ameloblastoma (Robinson, 1937; Smith, 1968; Daramola, 1975; Raubenheimer *et al.* 1994; Junquera, 2003). According to several studies, ameloblastoma occurs with equal frequency in men and in women (Menhisch *et al.*, 1978; Pinstolle *et al.*, 1995), as was also noted in the present study, where the male/female ratio was 0.9 : 1.

The age distribution is usually from the first to the seventh decade of life with mean age in the fourth decade. In the present study the age ranged from 7 to 74 years with a mean age of 45.2, which is a finding made in several other reports (Podtar, 1969; Mehlish *et al.*, 1978; Kameyama *et al*., 1987; Hatada K *et al.*, 2001; Zwahlen and Grätz, 2002).

In the present series, 18% of ameloblastomas occurred in the maxilla, a figure comparable to the corresponding data from America (16% to 22%) and Turkey (18.8%) (Regezi *et al*. 1978; Günham *et al*., 1990; Philipsen *et al*., 1991). In contrast, 2% to 8% of ameloblastomas were maxillary in Asian and African countries (Odukoya, 1995; Kayana, 1982; Ueno *et al.*, 1986). This may suggest another geographic difference.

Ameloblastoma is often asymptomatic, as was shown also in our earlier and present studies (Leibur *et al*., 1996; Tamme *et al*., 2003). There may occur a facial deformity (64%) and an incidental finding on radiographic examination, or an odondogenic problem (malocclusion, loosening of teeth, or ill-fitting dentures, periodontal disease etc.), the last two acconting for 18% each.

Analysis of the size of radiographic changes on OTP and CT scans shows that its range is 2 to 6 cm. These results showed a longer delay in the presentation of the studied patients compared with similar cases reported from Italy, the Netherland and Greece (D´Agostino *et al.*, 2001; Chapelle *et al*. 2004; Rapidis *et al.*, 2004).

Tumour initiation probably begins as a field of neoplastic change permitting neoplastic growth centres to arise and spread centripetally. Invasion of tumour into the cancellous bone interstices makes its recognition by radiographic means

impossible until a tumour mass is formed. The tumour freely invades the medullary spaces between the cancellous bone trabeculae, at first without notable bone resorption. As the tumour mass increases, extensions reach deeper into the medullary spaces in a three-dimensional fashion. The tumour stroma abuts the cancellous trabeculae, and as resoption proceeds, the ameloblastic epithelium may be seen directly surrounding the resorbing bone. Concurrent macrocyst formation and pressure due to fluid accumulation contribute to cancellous bone resorption. With continued tumour mass build-up or cystic formation, the lamellar (cortical) bone begins to be resorbed as the tumour lies adjecent to it. Pockets of the tumour may lie within the cupped-out areas of the lamellae ahead of the main tumour mass (Kramer, 1963).

In summary, it can be said that ameloblastoma is asymptomatic; this study also demonstrated that quite often the diagnosis of ameloblastoma was delayed. This probably reflects the level of dental care, when routine radiographs (OPT) are not taken at regular intervals, allowing patients to refer promptly when early lesions are first detected.

6.4. Mandibular ameloblastoma and maxillary adenoid cystic carcinoma

Because ameloblastoma and adenoid cystic carcinoma are not related in terms of histogenesis, they are not very likely to occur in the same patient at nearly the same time. While ameloblastoma arises from the odontogenic epithelium, adenoid cystic carcinoma is believed to orginate in the intercalated duct reserve cell or the terminal tubule complex (Regezi and Sciubba, 1996).

Until now, a case similar to ours (Tamme *et al*., 2003) has been reported when an ameloblastoma and a salivary gland tumour occurred in the same patient at nearly the same time (Nakamura *et al*., 1988). We can suggest two explanations for the lack analogous of reports in the literature. Firstly, the overall incidence of both tumours is relatively low. According to statistical reports on jaw tumours, AM is relatively rare, while adenoid cystic carcinoma of the salivary glands is not so uncommon, especially in the minor salivary glands (Regezi and Sciubba, 1993; Khan *et al.*, 2001). And secondly, both tumours affect different age groups. Ameloblastoma occurs primarily in patients between 30 and 50 years (Regezi and Sciubba, 1993). At 74 years of age, the patient studied by us was much older than the average ameloblastoma patient.

Most patients with adenoid cystic carcinoma are aged between 40 and 70 years (Regezi and Sciubba, 1993; Khan *et al*., 2001). When ameloblastoma and a concomitant tumour of the head and neck develop, it is difficult to identify the nature of the latter tumour on clinical grounds, because the biological behaviour of ameloblastoma varies considerably. Final diagnosis must be based on

histologic investigation. In the patient studied by us, it is difficult to prove that the AM and the adenoid cystic carcinoma involved both the mandible and the maxillary region at the same time, because when the AM appeared, there were no signs of any neoplastic changes in the palate, i.e. there was neither clinical nor radiological evidence of the adenoid cystic carcinoma. When two histologically unrelated tumours appear at different anatomic locations almost simultaneously, differential diagnosis is of invaluable help in providing the patient with the best possible treatment that is targeted to minimizing tumour recurrence while maximizing functional and aesthetic results.

6.5. Comparison of Southern Estonian patients with the figures presented in similar reports from other countries: treatment and outcome

Optimum management of patients with ameloblastoma is still a matter of discussion.

The results of our study show that the treatment of ameloblastoma must be as radical as possible. According to the data obtained both from our own surgical series and from review of the literature, the most appropriate therapeutic approach appears to be marginal or segmental resections which are effective in eradicating SMA, whereby osteotomic lines are placed in healthy tissues (Small and Waldron, 1955; Sehdev *et al.,* 1974; Forssell *et al.,* 1974; Maclntosh 1991; Marx *et al.,* 1993; Reichart *et al*., 1995; D´Agostino *et al*., 2001; Chapelle *et al*., 2004). Due to our results we recommend to perform at least 1.5 cm resection of healthy tissues around the ameloblastic lesion, in order to avoid recurrences. Conservative surgical treatment should be considered only in UA, when extraosseous spread has not yet occurred (Stoelinga and Bronkhorst, 1988; Ackerman *et al.,* 1988; Williams 1997; Rapidis *et al*., 2004; Chapelle *et al*., 2004).

Clinical and radiographic presentation only did not suggest the diagnosis of ameloblastoma. Final diagnosis should be based on histologic investigation.

The results of the treatment of the studied patients showed that the radical operation of ameloblastomas was effective. Three of the ameloblastomas treated primarily conservatively recurred in the first year after surgery. Management of recurrence must be more aggressive than the first surgical step, because recurrence seems to be more aggressive than primary lesion and it multifocal by nature (D´Agostino *et al*., 2001; Hatada *et al*., 2001; Olasoji and Enwere, 2003). The recurrence rate in our study was as high as 17.6% for conservatively treated patients and 0% in the case of radical treatment. A radical approach is particularly indicated in upper jaw ameloblastoma, as maxillary bony configuration is delicately intricate and borders on many vitally important stuctures.

Follow-up of patients with ameloblastoma should be carried out regulary. As most recurrences present within the first 5 years, yearly follow-up during this period is advisable (Stoelinga and Bronkhorst, 1988; Reichart *et al*., 1995, Olasaji and Enwere, 2003). Thereafter, follow-up at every 2 years seems appropriate but it should cover at least 25 years as recurrences may appear after a long time (Hayward, 1973; Demeulemeester *et al*., 1988; Martins and Favaro, 2004).

In summary, conseravtive treatment should be used only in the treatment of UA, while the radical approach should be the first choice in treatment in SMA.

7. CONCLUSIONS

1. The present collaborative retrospective study (1977–2001) which involved the entire Estonian population, demonstrates that odontogenic tumours are relatively rare in Estonia compared with other countries. The frequency 0.74% is the lowest ever reported in the literature. (I)
2. This study shows differences in the prevalence of certain odontogenic tumours in comparison with the data from other countries. The most frequent tumours in the present study were compound odontoma and complex odontoma, accounting for 34.3%, followed by uni- and multicystic ameloblastoma, 25.3%. (I)
3. In our study, the age distribution for the two subtypes of ameloblastomas, an obvious contrast between the multicystic and unicystic ameloblastomas was found. The mean age of the patients with unicystic ameloblastoma (23.3 years) was much lower than that of patients with multicystic ameloblastomas (49.3 years). (I)
4. Tissue culture studies of mouse embryo tooth germs and the enamel organ demonstrated epithelial proliferation from the borders of the odontogenic epithelium and the formation of a lamellar-like structure observed in ameloblastoma. This study provides additional experimental evidence that ameloblastomas originate from the epithelium with odontogenic potentiality. (II)
5. It is possible that an ameloblastoma and a salivary gland tumour involved two different anatomic locations in the same patient at nearly the same time. (III)
6. The results showed that treatment of ameloblastomas must be radical. Conservative treatment should only be used for unicystic ameloblastomas, while the radical approach should be the first choice treatment in solid, multicystic ameloblastomas.(III; IV)

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SUMMARY IN ESTONIAN

Odontogeensed kasvajad Eestis: epidemioloogia, patogenees ja kliinilised iseärasused

Odontogeensed kasvajad (OT) on lõualuude kasvajad, mis võivad tekkida hambaalgme formeerumise häirest. Võttes arvesse, et hammas on bidermaalne organ, kuuluvad OT erineva koegeneesiga moodustiste hulka. Nad võivad lähtuda hambaalgme epiteliaalset päriltolu emaliorganist, mesenhümaalset päriltolu hamba papillist või mõlemast.

Nende kasvajate gruppi kuuluvad nii odontoomid, mida tänapäeval interpreteeritakse kui arengulist malformatsiooni, kui ka ameloblastoomid, mida iseloomustab asümptomaatiline kulg, lokaalselt invasiivne kasv ning kalduvus retsidiividele.

Sageli leitakse need kasvajad hambaravi käigus röntgenuuringuid tehes. Eelislokalisatsiooniks on alalõuas molaaride ja ülalõuas kaniinide piirkond.

Lähtuvalt eri maade epidemioloogiliste uuringute tulemustest on leitud kindlate odontogeensete kasvajate ealist, soolist, rassilist ning geograafilist korrelatsiooni. Samuti on esinemissagedus erinev eri maade, kontinentide vahel, eriti odontoomide ja ameloblastoomide osas.

Ameloblastoomi (AM) kirjeldas esmakordselt Broca juba 1868 aastal. Vaatamata sellele on kirjanduses erinevad seisukohad nii tuumori patogeneesi, omaduste kui ka ühtsete ravi meetodite kohta.

Uurimistöö eesmärgid ja ülesanded

Arvestades asjaolu, et varem pole Eestis uuritud odontogeenseid kasvajaid, püstitati antud uurimistöös järgmised eesmärgid:

1. Analüüsida retrospektiivselt odontogeensete kasvajate levimusnäitajaid Eestis ja võrrelda neid teiste maade sarnaste epidemioloogiliste uuringutega (I).
2. Välja selgitada, kas hambaalgme emailiorgani rakkudel on võime prolifereeruda ja diferentseeruda koekultuuri tingimustes sarnaselt ameloblastoomi histoloogilisele struktuurile (II).
3. Analüüsida tagasivaatavalt ameloblastoomide levimusnäitajaid ja ravi tulemusi Lõuna-Eesti elanikkonnas (III; IV).

Uuritav materjal ja meetodid

Antud uuringus (uuring I, II, IV) kaasati 75 patsienti: 42 OT juhtu oli diagnoositud TÜ Kliinikumi stomatoloogiakliiniku näo-lõualuudekirurgia osakonnas ja 33 OT juhtu Tallinna Mustamäe Haigla näo-lõualuudekirurgia osakonnas.

Uuring hõlmas ajavahemikku 1977–2001. Erinevate uuringute puhul esines uurimisgruppide kattumine, kuna eelpool mainitud ajavahemikus viidi läbi erineva eesmärgiga uuringud.

Retrospektiivses uuringus (uuring I), mis käsitles OT epidemioloogiat Eestis tervikuna, aastatel 1977–2001, uuriti algmaterjalina läbi nimetatud perioodi haiguslood ning vajadusel ka operatsiooniraamatud ja haigete hospitaliseerimise registreerimisraamatud. Kõik 75 odontogeense kasvaja juhtu diagnoositi histoloogilise leiu alusel ning klassifitseeriti vastavalt kehtivale Maailma Terviseorganisatsiooni (WHO) kriteeriumitele.

Teises retrospektiivses uuringus (uuring IV) käsitleti Lõuna-Eesti elanikkonna haigestumust ameloblastoomi ja hinnati ravitulemusi.

Lisaks neile uuringutele jälgiti embrüonaalse odontogeense epiteeli arengut (uuring II). Uuringumaterjaliks kasutati 14 hiire embrüo hambaalget, mis koosnesid emaliorganist ja hambapapillist.

Uurimistööst tulenevad järeldused

1. Läbiviidud retrospektiivne uuring (1977–2001), mis hõlmas kogu Eesti elanikkonda näitas, et odontogeensed kasvajad on harva esinevad lõualuude kasvajad Eestis. Uuringu tulemusena saadud esinemissagedus 0.74% on üks madalamaid esinemissagedusi kirjanduses.
2. Käesolev uuring näitas kindlate odontogeensete kasvajate osas levimusnäitajate erinevusi võrreldes teiste maade epidemioloogiliste uuringute andmetega. Kõige sagedasem odontogeenne kasvaja uuringu tulemuste alusel oli kompleksne ja liitodontoom (34.3%), teisel kohal ühe-ja mitmekambriline ameloblastoom (25.3%).
3. Antud uuringu tulemused näitasid, et haigestumus ühe-ja mitmekambrilise ameloblastoomi erines vanuseliselt oluliselt. Patsiendi keskmine vanus ühekambrilise ameloblastoomi korral (23.3 aastat) oli oluliselt madalam kui mitmekambrilise ameloblastoomi haigetel (49.3 aastat).
4. Läbiviidud morfoloogiline uuring hiire embrüonaalse hambaalgme arengust koekultuuris näitas, et odontogeenne epiteel omab võimet prolifereeruda ja moodustada lamellaar-rakulisi struktuure, mis sarnanevad ameloblastoomi histoloogilisele leiule, milles polariseeritud ameloblastid ümbritsevad tähekujulise võrgustiku sarnast epiteliaalset südamikku. Eksperimendist ilmnes, et ameloblastoom pärineb odontogeensest epiteelist.
5. On võimalik, et kaks erineva anatoomilise lokalisatsiooniga kasvajat, ameloblastoom ja süljenäärme kasvaja ilmneda samal patsiendil üheaegselt.
6. Ameloblastoomide ravi peab olema radikaalne. Kolde ekskohleatsiooni võib kasutada ainult ühekambriliste ameloblastoomide puhul. Radikaalne ravi peab olema kõigi mitmekambriliste ameloblastoomide puhul esmaseks ravi meetodiks.

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Teadustegevus

Peamiseks uurimisvaldkonnaks on odontogeensete kasvajate epidemioloogia, ameloblastoomide patogenees ja kliinilised omadused.

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