# EVALUATION OF AGRESSIVENESS OF DIFFERENT HISTOLOGICAL TYPES OF AMELOBLASTOMAS USING p170 AND p300 AS A NOVEL IMMUNOHISTOCHEMICAL MARKERS

***Thesis***

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# LIST OF ABBREVIATIONS

- AB: ameloblastoma
- ABC transporters: adenosine triphosphate-dependent membrane transporters
- AMBN: Ameloblastin protein
- AP-1: promoter-bound transcription factor
- ATP: adenosine triphosphate
- CBP = CREB: cyclic-AMP responsive element binding protein
- CDK: cyclin dependent kinase
- c-jun: signal transducing transcription factor
- c-myc: nuclear transcription factor
- DNR: daunorubicin
- DOX: doxorubicin
- E1A : adenovirus E1A gene encoding for adenovirus oncoprotein
- E2F: nuclear transcription factor
- EGFR: epidermal growth factor receptor
- HIF1A : hypoxia-inducible factor 1 alpha
- htert: telomerase reverse transcripase
- ICAM-1: intercellular adhesion molecule - 1
- Ki-67: Protein expressed in all phases of cell cycle except G0, a good marker for proliferation
- MAPK: mitogen-activated protein kinase
- mdm: murine double minutes

- MDR: multiple drug resistance
- MK: Midkine
- MMPs: matrix metalloproteinases
- mRNA: messenger ribonucleic acid.
- MSD: membrane-spanning domain
- MSI+: Microsatellite instability
- myo-D: Myogenic regulatory factor- Myogenin D
- NBD: Nuclear binding domain
- p14 (ARF): Protein product induced by a variety of oncogenic signals
- PCNA: proliferating cell nuclear antigen
- PGP: P Glycoprotein
- PML : Promyelocytic oncoprotien
- POD : PML oncoprotien domain
- RA: Retinoic acid
- Ras: Rat sarcoma
- Rb: retinoblastoma
- SP1: Stimulatory protein 1
- TGF-beta: Transforming growth factor beta
- TMD: Transmembrane domain
- TNFα: Tumor necrosis factor alpha
- TRAIL: TNF-related apoptosis-inducing ligand
- VCAM-1: Vascular cell adhesion molecule -1
- VEGF: vascular endothelial growth factor
- VER: verapamil

# REVIEW OF LITERATURE

## Ameloblastoma

Ameloblastomas are with rare exceptions, benign and slow growing epithelial odontogenic neoplasms with locally infiltrative behavior (Yamada et al., 2005)[152].

**Clinical Features of Ameloblastoma:**

Ameloblastomas in general are rare in children and have an average range of age between 33-44 years in the United States (Wiseman et al., 2003)[149]. Similar age range was recorded also in the Far East (MacDonald-Jankowski et al., 2004)[88], while in West Africa the mean age showed slight variability (between 26- 40 years) (Ajayi et al., 2005)[1]. Maxillary ameloblastomas may be seen in different age mainly up to 46 years (Sugiyama et al., 2004)[131].

All ameloblastomas grow slowly and typically cause no symptoms until a swelling becomes noticeable, however pain was reported in some cases with other signs like difficulty of wearing dentures, displacement, mobility and resorption of teeth, paraethesia of the inferior dental nerve and rarely ulceration of the mucosa (Omondi et al., 2004)[106].

As the tumor grows it forms a hard, rounded swelling, the slow growth of the tumor allows reactive bone formation to keep pace with it, as a result the jaws may become grossly enlarged and distorted (Torres-Lagares et al., 2005[135], Sanchis, 2005[122]).

If the ameloblastoma is neglected, further tumor can perforate the bone and ultimately spread into soft tissue making subsequent excision difficult (Yamada et al., 2005) [152].

**Radiographic Features of Ameloblastoma:**

85% of ameloblastomas showed a rounded well defined multilocular cyst like radiolucent areas with well defined margins. The rest of radiographic pictures were variable including a honey comb, soap bubble appearance or rarely a few large radiolucent areas with small daughter cysts and the bony margins were typically scalloped (Velez and Siegel 2004)[142].

Ameloblastomas infiltrate through medullary bone often without inducing resorption. The radiographic margins are not therefore accurate indicators of the exact involvement of the lesion. Compact cortical bone mainly undergoes pressure resorption rather than invasion also the periosteum is rarely involved (Pinheiro et al., 2005)[112].

The desmoplastic ameloblastoma can resemble a fibro-osseous lesion showing radiographically an irregular radiolucent area containing fine irregular calcifications having indistinct borders others have mixed radiolucent radioopaque appearance (Hirota et al., 2005)[64].

**Microscopic Features**

The odontogenic epithelium of ameloblastoma exhibits various patterns, the two main types being follicular and plexiform. Subtypes are acanthomatous, granular-cell, basaloid, desmoplastic and clear cell. As far as is known at present, the histopathological pattern has no bearing on the clinical behavior of an ameloblastoma (Yamada et al., 2005)[152].

**a. Follicular Ameloblastoma**: follicular ameloblastomas consist of islands or trabeculae of epithelial cells in odontogenic stroma. These epithelial islands consist of a core of loosely arranged polygonal or angular cells that resemble stellate reticulum surrounded by a well organized single layer of tall columnar ameloblast like cells with nuclei away from the basement membrane (Rapidis et al., 2004)[116]. Cyst formation sometimes occurs within the epithelial islands of the follicle where it varies from small cysts within a predominantly solid tumor to a completely cystic tumor (Sugiyama et al., 2004)[130].

*Acanthomatous ameloblastomas:* acanthomatous ameloblastomas show squamous metaplasia of the central core of epithelium of the tumors follicles, which otherwise resemble the more common follicular type. Keratin formation may be prominent and the tumor may be mistaken for a squamous cell carcinoma (Britt et al., 2005)[16].

*Granular cell ameloblastomas:* are a rare subtype of follicular ameloblastoma; they usually resemble the more common follicular type, but the epithelium, particularly in the centers of the tumor islands, forms sheets of large eosinophilic granular cells resembling those of other granular cell tumors, this change may be so extensive that the peripheral columnar cells are replaced, making the tumor difficult to recognize in a small biopsy specimen. Granular cell formation was thought to be an aging or degenerative change, but can be seen in ameloblastomas in young persons (Awagu and Vigneswaran 2004)[(5)].

*Desmoplastic ameloblastomas:* Desmoplastic ameloblastomas have been reported that these tumors consist of dense collagenous fibrous tissue in which there are small, irregular islands of neoplastic epithelium (Durmus et al., 2003)[(41)]. These islands are rounded or angular, and may have slender straggling extensions. There is little or no cyst formation, and ameloblast-like cells are typically only present in small foci on the periphery of some islands of epithelium. Stellate reticulum-like tissue is also absent from the interior of the epithelial islands, which consist of densely packed spindle-shaped or polygonal cells. Squamous metaplasia or foci of keratinization may occasionally be seen centrally, and calcification in the fibrous stroma and, occasionally, bone formation is seen (Maresi et al, 2003)[(92)].

*Basal cell ameloblastoma:* consist of darkly staining cells in a predominantly trabecular pattern with little evidence of palisading at the periphery. Rare examples of extraossoeus basal cell ameloblastomas have been mistaken for basal cell carcinomas. However, the latter do not affect the oral cavity (Rozylo-Kalinowska 2002)[(120)].