Malignant tumors of oral cavity

Introduction

- Tumor is a swelling of tissue which does not imply neoplastic process.
- Neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissues.
- Benign and malignant forms are recognized.

Contents

- Definition
- Classification
- Description
- Conclusion
- ► Reference

Definition (malignant tumor)

Malignant tumor is not just one disease, but a large group of diseases, possessing characteristics of uncontrolled growth of the cells in the human body and the ability of these cells to migrate from the original site and spread to distant sites. If the spread is not controlled, malignancy can result in <u>death</u>

Classification

- Basic classification
 - carcinomas (epithelial origin)
 - sarcomas (mesenchymal origin)

Classification

- Malignant tumors of epithelial tissue origin.
- Malignant tumors of mesenchymal tissue origin.
- Malignant tumors of osseous and cartilaginous tissue origin.
- Malignant tumors of muscular tissue origin.
- Malignant tumors of nerve tissue origin.Metastatic tumors of jaws.

Malignant tumors of epithelial orig

Basal cell carcinoma (rodent ulcer

- found mostly on the upper and middle third of face.

etiology

sunlight, aging, burn, chemicals

Clinical features

- papular lesion is initially formed followed by ulceration
- borders of ulcer are rolled and rounded.
- metastasis is rare but lesion enlarges by local spread.
- slow growing.



Basal cell carcinoma

Figure 2-03: Pigmented basal cell carcinoma has features of nodular basal cell carcinoma with the addition of darker pigmentation from melanin deposition. (Courtesy of: Michael L Ramsey.)

Histological features

- Cells have deeply stained nuclei and mitotic figures are also seen.
- Peripheral palisading of malignant cells are also seen.



Basal cell carcinoma

Figure 2-04: Typical nodular appearance with peripheral palisading of cutaneous basal cell carcinoma (Courtesy of: Juan Rosai)

Types of bcc

- Adenoid basal cell carcinoma
- Cystic basal cell carcinoma.
- Keratotic basal cell carcinoma.
- Primordial basal cell carcinoma.

Differential diagnosis

- Ameloblastoma.
- Squamous cell carcinoma.
- Neoplasm of salivary glands.





- Good prognosis due to slow growth and slow metastasis.
- Surgery and radio-therapy.

Squamous cell carcinoma(epidermoid carcinoma).

- Most common oral cancer, usually affecting elderly persons.
- Lower lip is the most common site (extraorally).
- Intraorally postero-lateral part of tongue is the most common site.

Etiology

- Smoking.
- Alcohol.
- Sepsis.
- Spicy foods.
- Sharp tooth.
- Endocrinal disturbances.
- Syphilis.
- AIDS.

Clinical features

- Initially painless red speckled or white patches are form later changes into ulcerated indurated and fibrosed.
- Ulcers have heaped up borders with necrosed foul smelling base having tendency to bleed.
- Associated lymph nodes are hard and painless.



Epidermoid carcinoma Figure 2-27. Epidermoid carcinoma of the floor of the mouth. p. 158

Histological features

- Hyperorthokeratosis or hyperparakeratosis.
- Increased granular cell layer.
- Disturbed stratification.
- Increased mitotic figures.
- Pleomorphism
- Hyperchromatism.
- Loss of polarity.
- Epithelial pearl.



SQUAMOUS CELL CARCINOMA

Figure 3-31. Squamous cell carcinoma.Primary squamous cell carcinoma of salivary gland showing neoplastic squamous cells, metaplastic in origin, with varying degrees of nuclear atypia.-P - 340

Types

- Exophytic ulcerative growth of squamous cell carcinoma.
- Carcinoma of tongue(50% cases).
- Carcinoma of floor of mouth (20% cases).
- Carcinoma of buccal mucosa.
- Carcinoma of gingiva.
- Carcinoma of palate.

Treatment

- Prognosis depends upon the rate of cell differentiation. Eg. if 75% cells are well differentiated than prognosis is good.
- Surgery and radio-therapy.

Verrucous carcinoma

- Form of epidermoid carcinoma.
- Slow growing, exophytic and superficially invasive neoplasm.
- Low tendency of metastasis.
- Lymph nodes are mostly inflammatory and tender.

Etiology

Tobacco chewing.

Clinical features

- Cauliflower like whitish lesion is present.
- Occurs mostly in elderly patients (above 60 years).
- Males are usually affected.
- Common sites are alveolar mucosa, buccal mucosa, palate and gingiva.



Verrucous carcinoma

Figure 2-05: Verrucous carcinoma of the alveolar gingiva extending into the palate. Note the pebbly, granular and papillomatous surface texture of the tumor.

Histological features

- Clefts are found in epithelium covered by parakeratin lining and plugging.
- True invasion is not seen until lesion is advanced.













Verrucous carcinoma

Figure 2-06 A to G: Exophytic and pebbly white, well circumscribed tumor mass on the buccal mucosa appeared at the site of 'quid' placement. Histopathologic appearance of epithelium and associated connective tissue in verrucouscarcinoma in contradistinction to neighbouring areas of vertucous hyperplasia and simple epithelial hyperplasia. Note the bulbous and voluminous rete ridges pushing down into the corium showing features of mild dysplasia, intra epithelial cleavage, keratin pearl formation and infiltration of epithelium by chronic inflammatory cells. The subepithelial inflammatory response was intense and the basal membrane zone retained its continuity.

Differential diagnosis

- Papillary hyperplasia.
- Squamous cell carcinoma.
- Pseudoepithelomatous hyperplasia.
- Verrucous leukoplakia.

Treatment

- Prognosis is good.
- Surgery and radio-therapy.

Spindle cell carcinoma

Squamous cell carcinoma is associated with spindle cell anaplasia.

Clinical features

Non healing ulcer or exophytic growth is found.

Histological features

- Biphasic tumor (dropping of squamous or basal cells in connective tissues.)
- Connective tissues are formed of anaplastic spindle cells with giant cells.
- Tissue pattern may be of
 - fasciculated pattern
 - myxomatous pattern



Epidermoid carcinoma

Figure 2-22. Squamous cell carcinoma with spindle metaplastic features. p. 150

Treatment

- Surgery.
- ▶ Radiation.

Adenoid squamous cell carcinoma.

Found in skin and lip.

Clinical features

Appears as nodular lesion which may ulcerate.



ACINIC CELL CARCINOMA

(Acinar cell or serous cell adenoma and adenocarcinoma) Figure 3-18. Acinic cell adenocarcinoma of the palate-P- 325

Histological features

- > Dysplastic epithelium proliferates into connective tissue.
- Epithelium forms tubular duct or solid structure.
- Hyperkeratosis along with acantholysis is present.

Treatment

surgery


ADENOCARCINOMA

Figure 3-27. Adenocarcinoma.Low grade adenocarcinoma composed of a morphologically uniform population of cells showing formation of many ductal structures. Mitotic figures are rare which is typical for this group of tumor. Pg. 337

Malignant melanoma

Malignant neoplasm of epidermal melanocytes.

- Develops mostly from junctional naevi.
- Two phases are present
 - radial growth phase
 - vertical growth phase



Malignant melanoma Figure 2-34 A to C. Typical lesions involve the palate and alveolar ridge. p. 175

Radial growth phase

- ▶ 1st phase, persist for years.
- Neoplastic cells are either destroyed or shed off along with epithelium.

Vertical growth phase

- Occurs many years after radial phase.
- Neoplasm cells increase aggressively and penetrate connective tissues.
- Lesion cannot be resisted by host defense mechanism and becomes fatal soon.



Malignant melanoma Figure 2-35. Advanced OSF withhigh Ag NOR count Pg 176

Cutaneous melanoma

It is of three types

- superficial spreading melanoma. (both phases are present and tan brown admixed lesion is seen.)

- nodular melanoma. (vertical phase is present and nodular lesion is seen.)

- lentigo malignant melanoma. (both phases are present and macular lesion is seen.)

Clinical features of malignant melanoma

- Lesion is ulcerated or in form of tissue mass that is usually pigmented.
- Radial phase of lantigo malignant melanoma is formed due to sun exposure.
- This phase is absent in oral cavity because of no sun exposure.



Differential diagnosis

- Haemangioma.
- Amalgam pigmentation.
- Naevi.
- Kaposi's sarcoma.
- Hematomas.

Treatment

Prognosis is poor.

- if lesion is larger than 0.75mm.
- if present at BANS (back,arm,neck or scalp)
- surgery for lymph nodes and the lesion.
- Radiation.
- Chemotherapy.
- Cryosurgery.
 - Immunotherapy.
 - Oral melanomas surgery, jaw resection and lymph node dissection.

Malignant tumors of mesenchymal tissue origin

- Sarcomas are malignant neoplasms of mesenchymal origin.
- These metastasize through blood mainly.

Malignant neoplasm of connective tissue origin.

► Fibrosarcoma

malignant neoplasm of connective tissue fibres.

Clinical features

- > Young persons are affected mostly.
- Low potential of metastasis but local invasion is seen.
- Arises at any location in oral cavity.
- Haemorrhage, ulceration and asymmetry are the earliest symptoms.

Histological features

- Broad interlacing bands of fibroblasts are seen in streaming patterns.
- Abundant collagen is present in some lesions while some are highly cellular.
- Mitosis are also present.



Fibrosarcoma

Figure 2-66. Fibrosarcoma showing moderate degree of nuclear pleomorphism. p. 221

Differential diagnosis

- Liposarcoma.
- Rhabdomyosarcoma.
- Neurogenic sarcoma.



- Radical surgical excision.
- Prognosis is good in well differentiated neoplasm due to low metastasis rate.

Malignant neoplasms of adipose tissues.



-rare malignant tumor of mesenchymal tissue.

-lesion appears as firm, lobulated and slow growing mass.

Histological features

- Various types of lesion is seen in histological sections. These are myxoid types
 - round cell types
 - adult types
 - pleomorphic types
- Anaplastic lipoblasts and fat cells are present.



Liposarcoma

Figure 2-68. Liposarcoma. Numerous tumor giant cells and malignant cells showing features of lipoblasts. (Courtesy of Dr Juan Rosai.) p. 227



- Surgical excision.
- Radiation.

Malignant neoplasms of blood vessels

Kaposi's sarcoma

- uncommon malignant neoplasm of blood vessels (endothelial cells).

- mainly seen in HIV patients.
- mostly male homosexuals are affected who are suffering from AIDS.

- Multiple brown or purplish nodules are seen commonly.
- ▶ 1st manifestation of AIDS.
- Cervical lymph nodes are also involved.
- It has three stages
 - patch stage.
 - plaque stage.
 - nodular stage.



Kaposi's sarcoma Figure 2-71 Kaposi's sarcoma. p. 232

Histological features

- Small numerous capillaries with mono nuclear cell cuffing are seen.
- Slit shaped blood vessels with extravascular haemosiderin pigments are found.



Kaposi's sarcoma

Figure 2-72 Immunoreactivity for Factor VIII-related antigen in Kaposi's sarcoma (courtesy of: Dr Juan Rosai). p. 233

Differential diagnosis

- Pyogenic granuloma.
- ► Haemangioma.
- Angiosarcoma.



- Slow growing sarcoma, so better prognosis is there.
- X-rays and chemotherapy (chlorambucil)

Malignant lymphomas

- Can arise from any type of lymphocytes (mostly B type).
- Types may be mainly
 - non Hodgkin's lymphoma.
 - African jaw (Burkitt's)lymphoma
 - Hodgkin's disease (lymphoma)
 - Initially cervical nodes are involved followed by other lymphoid structures.

Non Hodgkin's lymphoma

- Involves lymph nodes, lymphoid tissues, extranodal tissues such as CNS, GIT, bone skin and oral cavity.
- Both nodal and extranodal involvement occurs simultaneously.

- Symptoms are
 - lymphadenopathy.
 - night sweat, fever.
 - abdominal enlargement due to hepatosplenomegaly. weight loss.

Clinical features

- Appears as swellings, which may grow and ulcerate or sometimes fungates giving foul odour.
- Causes paresthesia of lip and loosening of teeth.
- Frequently found in hard palate and posterior part of tongue.



Histological features

Two types are found

- nodular type and diffuse type.

Nodular type

- cells are arranged in clusters.
- germinal centers are not present.

- nodules of neoplastic lymphocytes in nodular arrangement.

- these are B cells origin.
- occurs in adults mostly.



Non-Hodgkin's lymphoma Figure 2-84 Follicular non-Hodgkin's lymphoma. p. 251
- Diffuse type
 - diffused or monotonous distribution of cells is present in sheets.
 - lymphocytes with large vesicular nuclei.
 - B as well as T cell origin.
 - children mostly affected.
- Treatment-

radiation and chemotherapy.

African jaw (Burkitt's) lymphoma

Etiology

- Epstein Barr virus.
- Clinical features

two forms of this disease is seen. - African form/endemic form.

- non African form/non endemic form.



Burkitt lymphoma

Figure 2-87

Burkitt lymphoma presenting as a large tumour of the jaw in an African child. (Courtesy of: WHO, World Cancer Report.2003) p. 255

African form/endemic form

- Children of 2 14 years are affected mostly.
- Involves primarily extra nodal tissues such as jaw.
- May extend to orbits and sinuses.
- Loosening of teeth may be present.

Non African form/non endemic form

- Occurs usually at the age of 10 to 12 years.
- Involves lymph nodes and lymphoid tissues. eg.- bone marrow.
- Jaw involvement is rare.

Histological features

- Monotonous arrangement of undifferentiated lymphoreticular cells (small cell lymphoma) is present.
- Macrophages are pale and scattered over darkly stained matrix in "starry sky pattern" containing cellular debris.

Treatment

Cytotoxic drugs.



Burkitt lymphoma

Figure 2-88 "Starry sky" appearance of Burkitt's lymphoma. (Courtesy of: K.W. Lee). p. 256

Hodgkin's disease (lymphoma)

Uncommon lesion of oral cavity, but cervical nodes are frequently enlarged, rubbery and non tender.

Clinical features

- Age bimodal age, young age and 5th decade.
- Pain in abdomen and back.
- Splenomegaly.
- Drenching night sweat.
- Discomfort after alcohol intake.

Pruritis.

Oral manifestations are rare but could involve mandible secondarily.

Histological features

- Multinucleated Reed Sternberg cells are the main characteristics.
- Cells have mirror image nuclei with owl eye appearance.
- Derived from B lymphocytes.
- Four patterns are found.
 - lymphocyte predominant.
 - mixed cellularity.
 - lymphocytic depleted
 - nodular sclerosis.



Hodgkin's disease

Figure 2-90. Reed-Sternberg cell.

Cells with large, pale nuclei containing purple nucleoli at the arrowheads. These are Reed-Sternberg cells that are indicative of Hodgkin's disease. Most of the cellular content of foci of Hodgkin's disease consists of reactive lymphoid cells. p. 258

Treatment

- Radiation.
- Chemotherapy.
 - eg. adreomycin, vinblastin are given.

Malignant neoplasms of plasma cel

Multiple myeloma/plasma cell myeloma.

- neoplasm of plasma cell which produces monoclonal immunoglobulins(IgG mostly).

- numerous bones are involved as multiple bony destruction areas.

Multiple myeloma



Clinical features

- Bone pain and tenderness.
- Loosening of teeth.
- Numbness.
- Macroglossia occurs due to amyloidosis (20% cases.).
- Radiologically multiple punched out radiolucent areas are present (mostly in skull.)

Mandible or maxilla may be involved.



Multiple Myeloma

Figure 2-92 D

Multiple Myeloma: The rounded "punched out" lesions of multiple myeloma appear as lucent areas with this skull radiograph. Pg 262

Histological features

- Closely packed plasma cells are seen.
- Cells have eccentrically placed nuclei with chromatic clumping in cart wheel or checkerboard pattern.
- Russel bodies may be seen.



Multiple Myeloma Figure 2-92 B

Multiple Myeloma: At medium power, the plasma cells of multiple myeloma here are very similar to normal plasma cells, but they may also be poorly differentiated. Usually, the plasma cells are differentiated enough to retain the function of immunoglobulin production. Thus, myelomas can be detected by an immunoglobulin "spike" on protein electrophoresis, or the presence of Bence-Jones proteins (light chains) in the urine. Immunoelectrophroesis characterizes the type of monoclonal immunoglobulin being produced. p. 262

Lab diagnosis

- Increased total serum protein upto 8 to 16 gm%.
- Reversed albumin : globulin ratio in serum.
- Bence Jones proteinuria.
- Anaemia.

Malignant tumors of osseous an cartilaginous tissue origin

Ewing sarcoma/round cell sarcoma.

- destructive malignant neoplasm of bone consisting of round cells.
- history of trauma may be present.
- long bones are mostly affected but jaw may be involved.

symptoms

- If jaw is involved various symptoms are
 - pain.
 - facial neuralgia.
 - lip paresthesia.
- Radiologically onion like / sunray appearance is seen over periosteum.

Histological features

- Densely packed round cells in little stroma are seen.
- Mitotic figures are seen.
- Central necrosis is present in the lesions.



Ewing's sarcoma Figure 2-73 Ewing's sarcoma is one of the "small round blue cell" tumors histologically. Note the many mitotic figures in the field. p. 234

Differential diagnosis

- ► Garre's osteomyelitis.
- Small cell osteosarcoma.
- Mesenchymal chondrosarcoma.
- ► Treatment-

radical surgical excision.

Chondrosarcoma

- Develops from pre-existing chondroma.
- Radiologically, it is a radio-opaque lesion which is due to calcification of neoplastic cartilage.

Histological features

- Large binucleated cells.
- Certain areas may show mitosis.
- Hyaline cartilage may be produced by cells and calcified.
- Bony trabeculae formation in cartilage.
- Disorganized foci of mineralization.
- May be of two types
 - clear cell chondroma
 - mesenchymal chondrosarcoma



Chondrosarcoma

Figure 2-76

This is the low power microscopic appearance of a chondrosarcoma. The tissue is recognizable as cartilage, and there are chondrocytes in clear spaces, but there is no orderly pattern. At the bottom, this neoplasm can be seen invading and destroying bone. p. 239

treatment

Surgical excision.

Osteosarcoma

- Highly malignant neoplasm of bone.
- Etiology
 - Paget's disease.
 - history of trauma.

Clinical features

- Mandible more frequently involved.
- Painful sudden growing swelling at the jaw initially.
- Asymmetry of face.
- Lower lip paresthesia.
- Toothache.



Osteosarcoma of the maxilla

Figure 2-78 Osteosarcoma of the maxilla.(courtesy of: Dr. Twinkle S. Prasad). p. 242

- Bleeding tendency of the lesion.
- Nasal obstruction may be found if present in maxilla.
- Metastasis occurs in lungs.
- Radiologically
 - sun ray appearance/radio-opaque/Codman's triangle due to sclerosis of osteolytic lesion.



Osteosarcoma

Aggressive, expansile lesion Note the 'sun ray' periosteal reaction (arrows)

Histological features

- Lesion composed of osteoblasts with anaplastic changes.
- Giant cells may be present.
- Osteoid formation is present.
- Fibroblasts are common in fibroblastic type of osteoma.
- Blood vessels predominant in telangiectatic type, while chondroblasts are found in chondroblastic type.



Osteosarcoma of the maxilla

Figure 2-80

The neoplastic spindle cells of osteosarcoma are seen to be making pink osteoid here. Osteoid production by a sarcoma is diagnostic of osteosarcoma. p. 244

Differential diagnosis

- Chondrosarcoma.
- Fibrosarcoma.
- ► Garre's osteomyelitis.
- Fractured callus.

Treatment

- Radical surgery.
- Chemotherapy.
Malignant neoplasms of muscle tissue origin



- malignant smooth muscle neoplasm.
- rare tumor of oral cavity.
- may be transformed from pre-existing leiomyoma.

Clinical features

- Cheeks , floor of mouth and jaws are affected mostly.
- Painful swelling is found at the affected site.

Histological features

- mitosis present in the lesion which resembles with leiomyoma.

- other anaplastic changes of malignancy are present.



Leiomyosarcoma Figure 2-101 D Neurofibromatosis showing spindled, wavy nuclei in fascicular form. p. 281

Treatment

- Surgical excision.
- Chemotherapy.

Rhabdomyosarcoma

Malignant neoplasm of striated muscles.

Clinical features

- age : children and young patients are affected mostly.

- soft swelling, rapidly growing in nature.

Histological features

- Four types are present
 - Pleomorphic
 - rhabdomyosarcoma
 - Alveolar
 - rhabdomyosarcoma
 - Embryonal type
 - Botryoid type

Rhabdomyosarcoma



Pleomorphic rhabdomyosarcoma

Composed of cells of various types and size as :

- Spindle cells.
- Racquet cells.
- Strap ribbon cells.

Pleomorphic rhabdomyosarcoma



Alveolar rhabdomyosarcoma

- Composed of slit like spaces (alveoli) with hanging, tear shaped, darkly stained cells.
- These cells are wall of spaces.
- Alveoli are separated by fibrous septa.

Alveolar rhabdomyosarcoma



Embryonal type

Four types of cells are present

- spindle cells.
 - round cells.
 - broad elongated cells.
 - small round cells.

Botryoid type

May present rarely.

Embryonal type



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Treatment

- Surgical excision.
- Chemotherapy.
- Radiation therapy.

Malignant tumors of nerve tissue origin

- Neurofibrosarcoma / Malignant sarcoma / Neurogenic sarcoma.
 - Tumor may arise from neurofibroma or may arise de nevo.
 - cells involved in malignancy are nerve sheath cells.

Clinical features

- Rapidly growing , painful masses are present in lip , gingiva and other parts of oral cavity and sometimes in mandible or maxilla.
- Mandibular nerve mostly involved and may cause paresthesia of lip and tongue.

Radiological features

Appears as diffuse or smooth radiolucency in mandibular canal.

Histological features

Neoplastic lesion shows spindle shaped cells with mitosis and nuclear hyperchromatism.

Neurofibrosarcoma



Differential diagnosis

- Neurofibroma.
- Fibroma.
- Leiomyoma.

Treatment

- Surgery and radiation.
- Recurrence rate is high.

Olfactory neuroblastoma

Arises from olfactory tissues in nasal cavity and nasopharynx.

Clinical features

- tumor appears as painful swelling.
- rarely metastasizing in nature.

Olfactory Neuroblastoma



Histological features

- Densely packed eosinophilic cells with rounded nuclei form the tumor.
- Rosette or Pseudorosette formation is present sometimes.

Treatment

Surgery or Radiation therapy

Metastatic tumor of jaw

- Uncommon neoplasms of jaws.
- May metastasize to jaw from primary tumor of other locations in following order
- breast > lung > kidney > thyroid > prostate > colon . Stomach > melanocarcinoma > testes > others.



Metastatic carcinoma of the lower jaw Figure 2-107 A. Metastatic carcinoma of the lower alveolus. p. 290

- Metastasis occurs in mandible > maxilla.
- Signs and symptoms are

- pain , paresthesia of lip and chin , loosening of teeth or patient may be asymptomatic.

Molar area is involved mostly due to presence of more hemopoetic tissues and metastasis occurs through vascular route.



Metastatic carcinoma of the lower jaw Figure 2-107 D. Photomicrograph of metastatic carcinoma of the alveolus. p. 290





Metastatic carcinoma of the lower jaw Figure 2-107 B. Primary from prostate. p. 290 Figure 2-107 C. An osteolytic lesion of the mandible. p. 290

Radiological features

Osteolytic or osteoblastic lesion so appears as radiolucent or radioopaque areas.

Treatment

- Prognosis is poor , as metastasis of jaw is later sign of malignancy.
- Treated by surgery , radiation and chemotherapy.

TNM staging of malignant tumo of oral cavity

- T- primary tumor
 - T_x primary tumor cannot be assessed.
 - T_0 no evidence of primary tumor.
 - T_{IS} carcinoma in situ.
 - T_1 tumor size , 2cm or less.
 - T_2 tumor size , 2 to 4 cm or less.
 - T_3 tumor size > 4 cm.
 - T₄ tumor invades adjacent structures.

N - regional lymph nodes.

- N_x regional lymph nodes cannot be assessed.
- N_0 no palpable lymph nodes clinically.
- N₁ clinically palpable homolateral lymph nodes.
- N₂ clinically palpable contralateral or bilateral lymph nodes.
- N₃ fixed clinically palpable lymph nodes.

M - Distant Metastasis.

 M_x - presence of distant metastasis cannot be assessed.

 M_0 - no distant metastasis.

 M_1 - metastasis is present.

- Stage IV : $T_1N_2M_0$
 - $T_2N_2M_0$ $T_3N_2M_0$ $T_1N_3M_0$ $T_2N_3M_0$ $T_3N_3M_0$ $T_{any}N_{any}M_1$

Conclusion (important facts)

- Malignant tumors are basically rapidly growing.
- Secondary changes occur more frequently.
- These are fixed to surrounding structures.
- Nucleo-cytoplasmic ratio is altered.
- These metastatize via blood vessels or lymphatic channels.

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Thank you