

Pomen patologije v otorinolaringologiji (patologija glave in vratu)

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Vsebina predavanj

- Tumorji in prekanceroze v področju glave in vratu
- Pomen okužbe s HPV
- Tehnika zaledenelega reza

Tumorji v področju glave in vratu

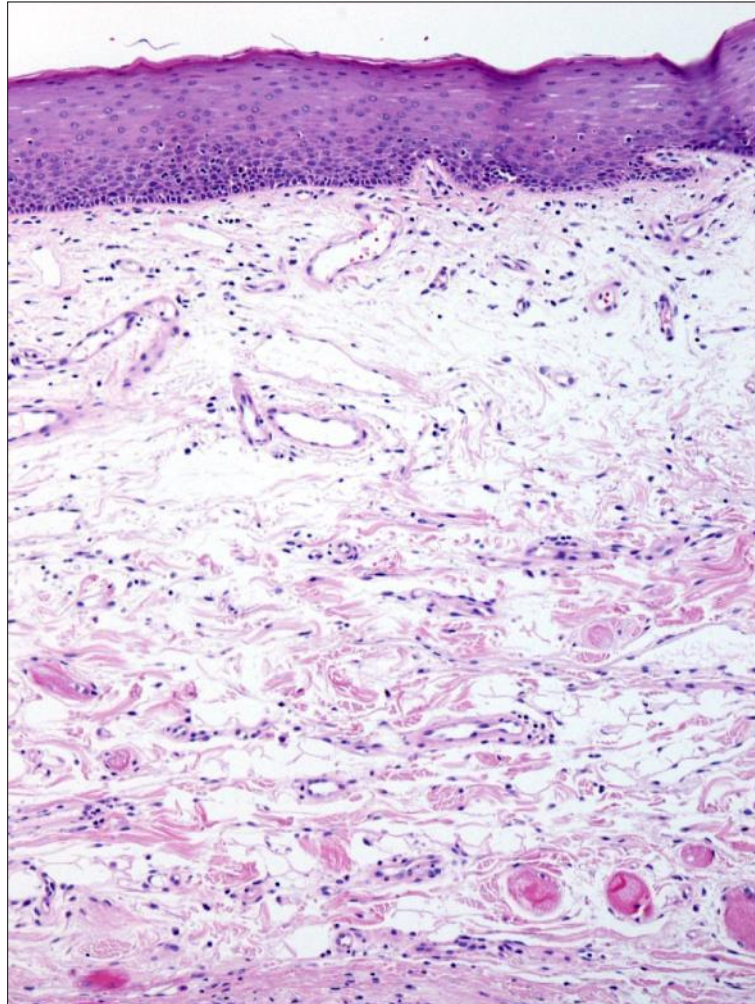


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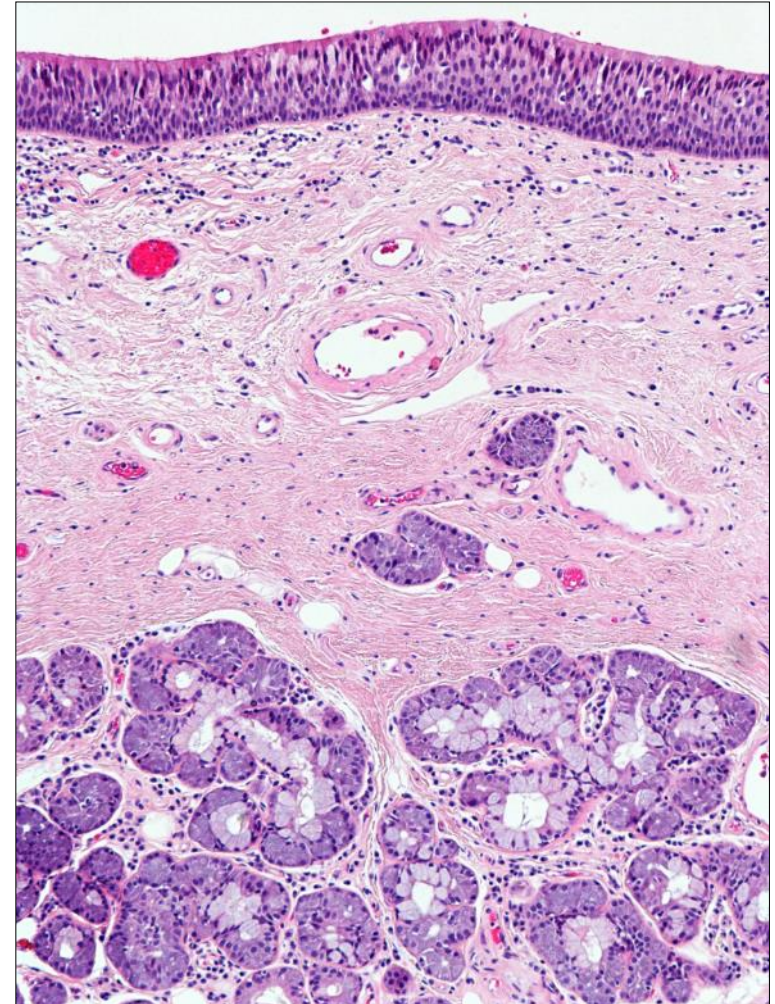
UNIVERSITY OF LJUBLJANA ♦ FACULTY OF MEDICINE

Normalna sluznica

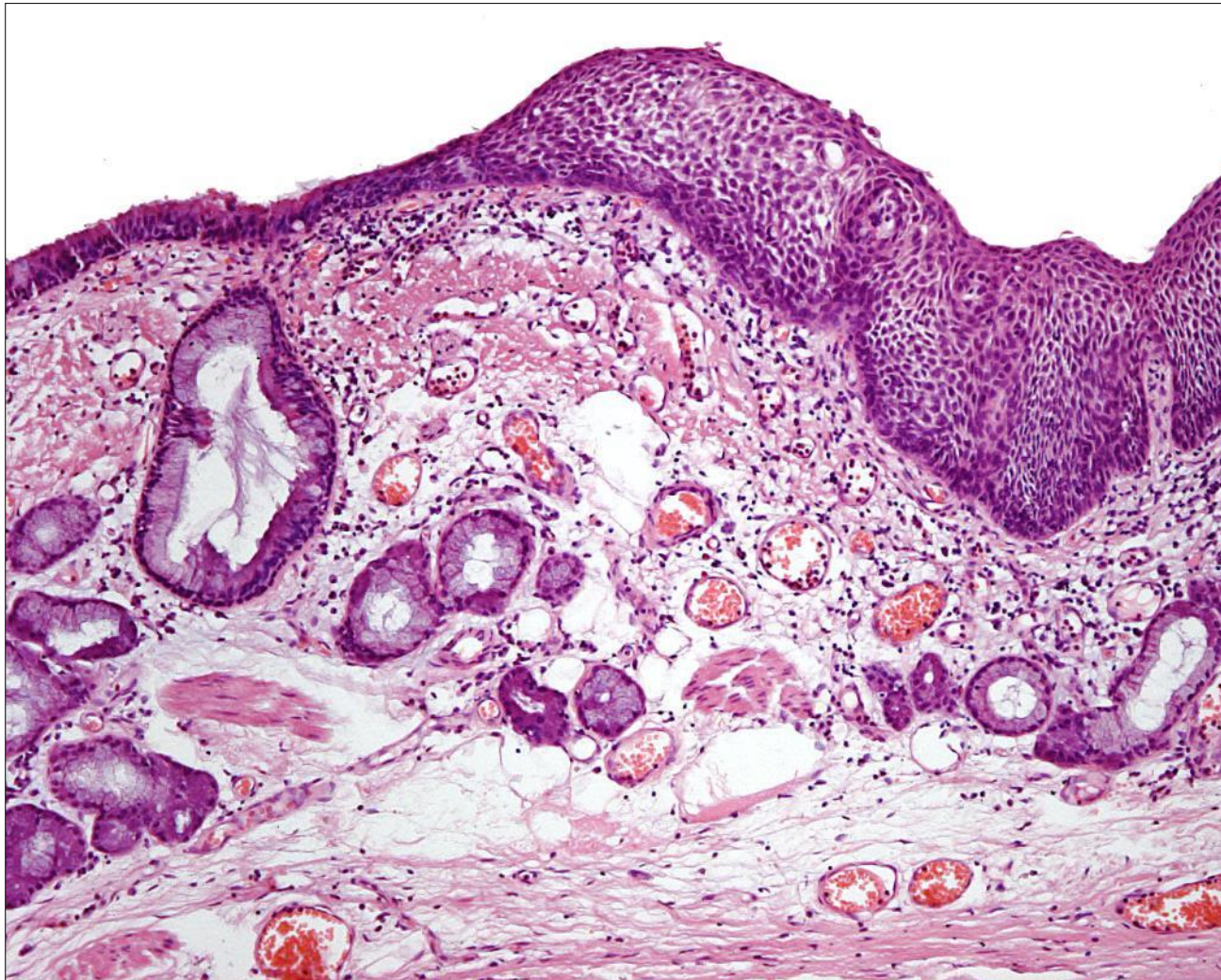
ustne votline



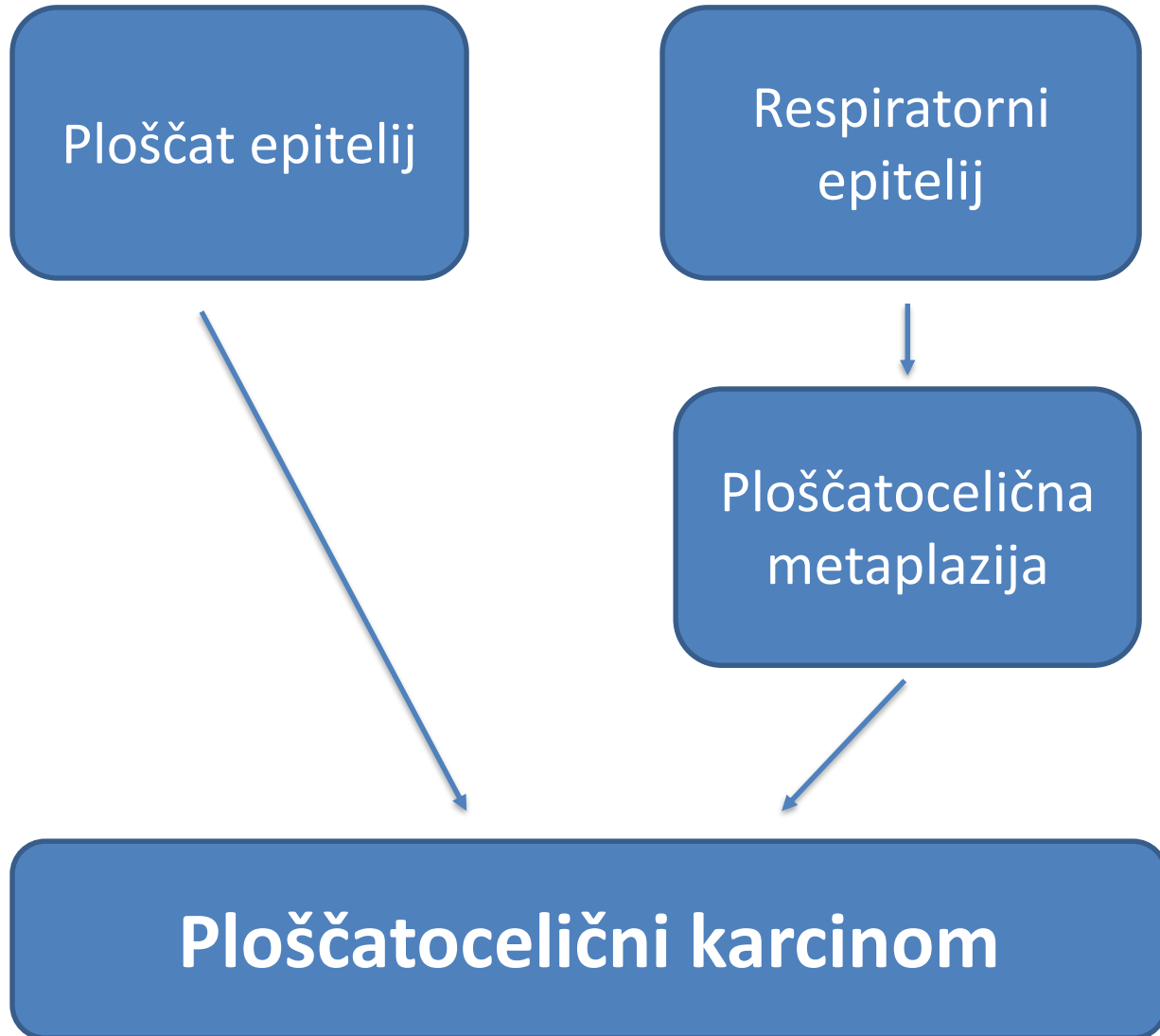
grla



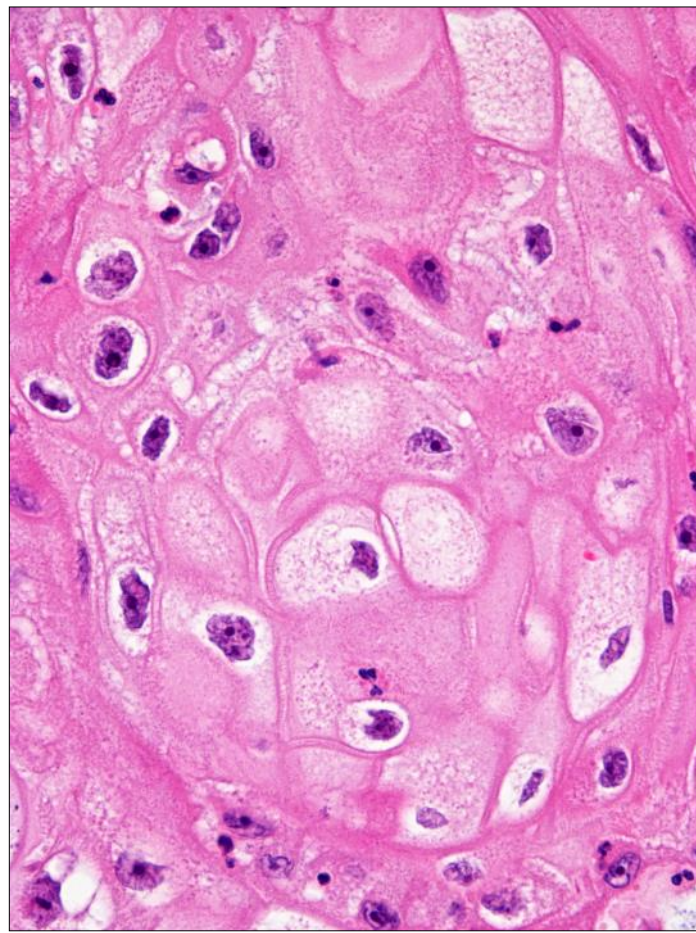
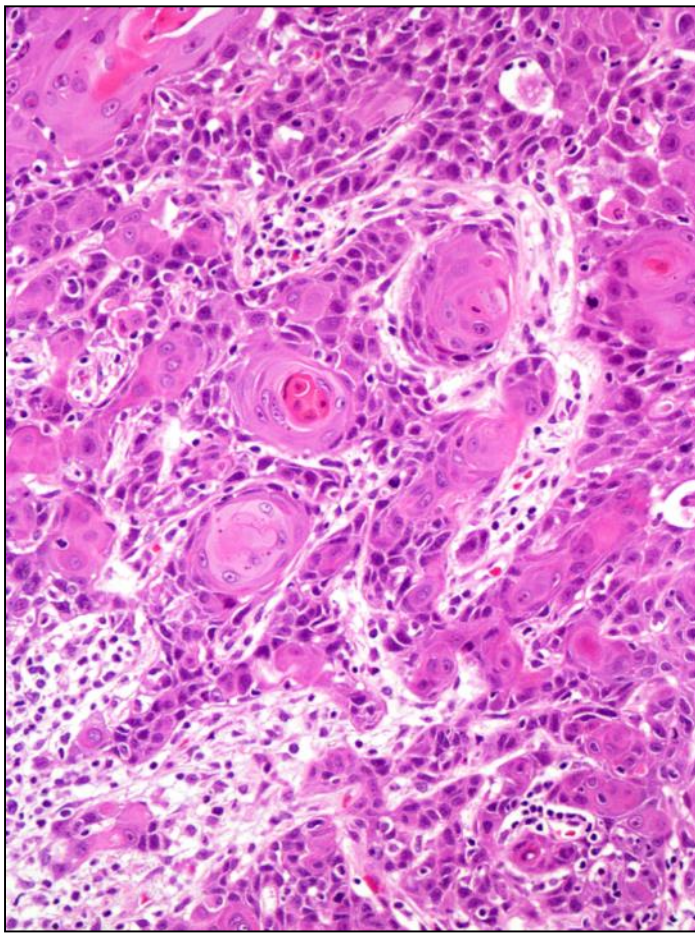
Ploščatocelična metaplazija



Sluznice v področju glave in vratu



Ploščatocelični (skvamozni) karcinom: keratinizacija in/ali dezmosomi



Ploščatocelični (skvamozni) karcinom

- Ustna votlina
- Žrelo
- Grlo
- Nosna votlina
- Obnosni sinusi
- Žleze slinavke
- Koža
- Požiralnik
- Analna in genitalna sluznica in koža
- Maternični vrat
- Pljuča

Etiologija ploščatoceličnega karcinoma glave in vratu

- Kajenje
- Alkohol
- HPV (oropharynx, obnosni sinusi)
- EBV (nasopharynx)
- Ostalo: reflux (GERB)
- Neznano pri nekaterih bolnikih

Uporabnost v diagnostiki: zasevki v bezgavkah neznanega izvora (origo ignota)

EBV poz.



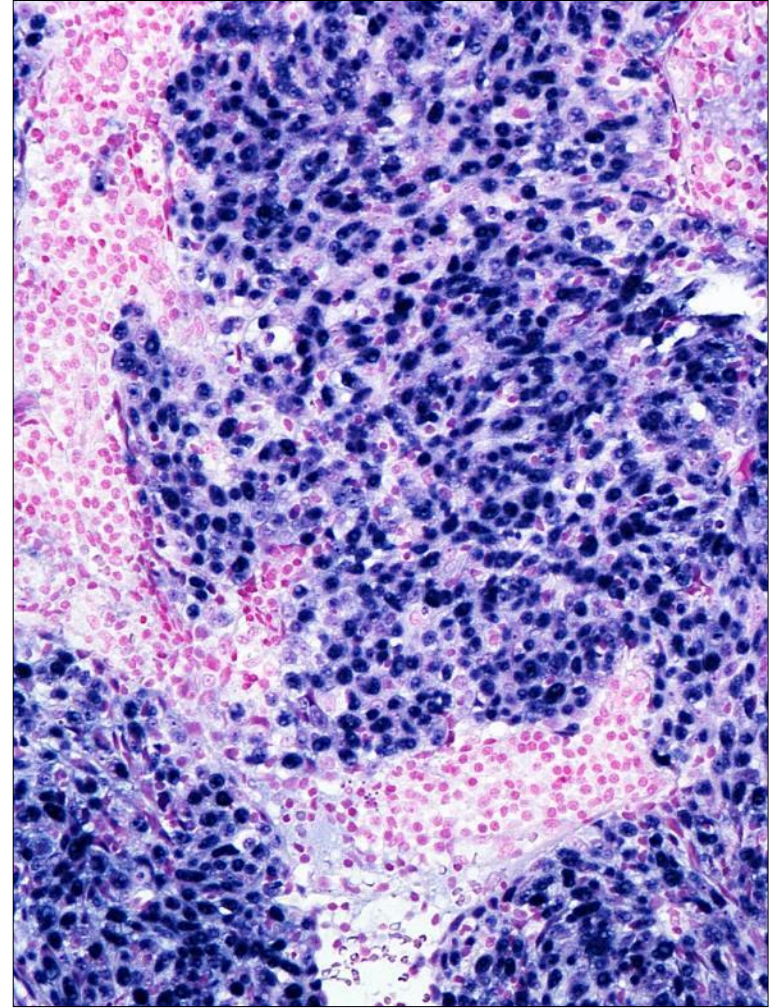
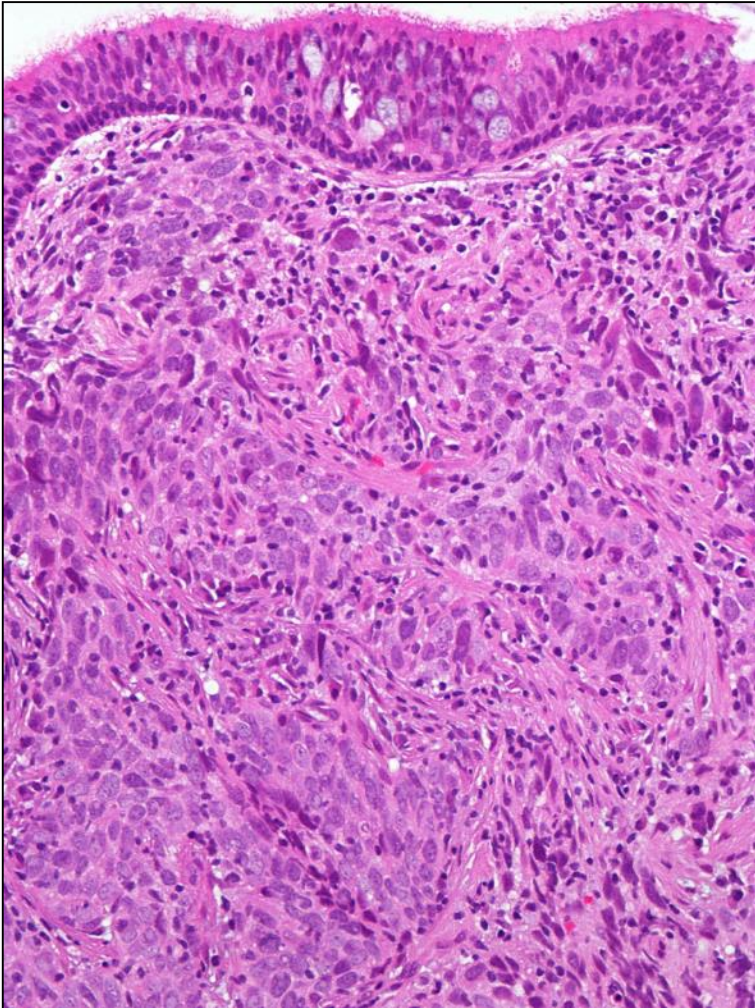
Nasopharynx

HPV poz.



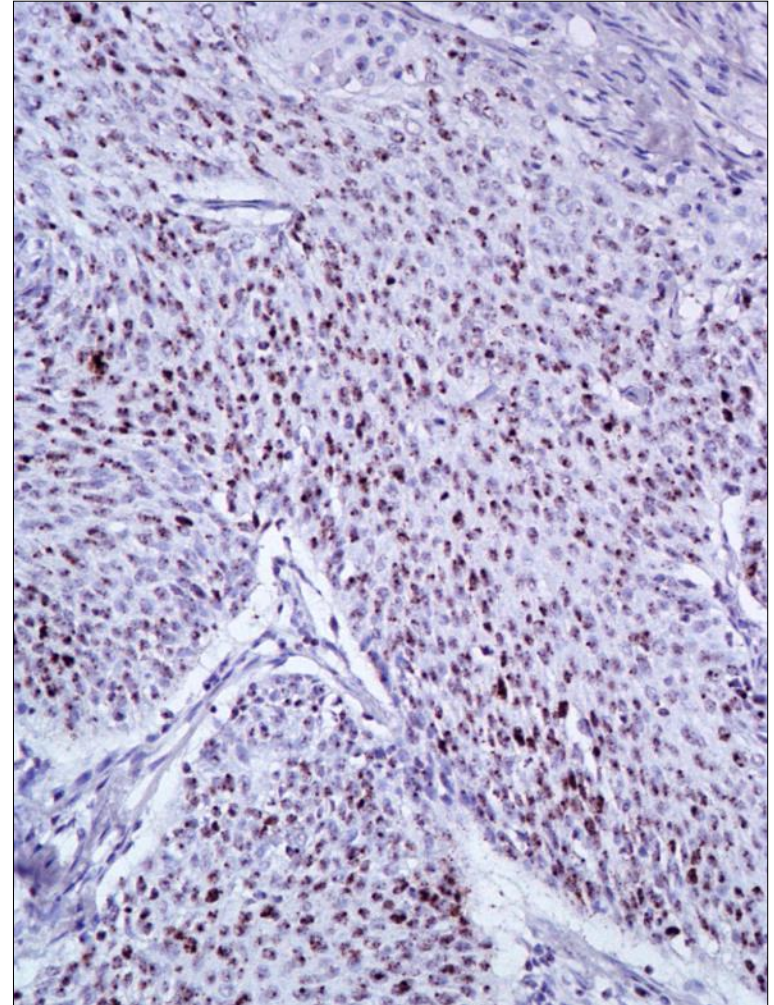
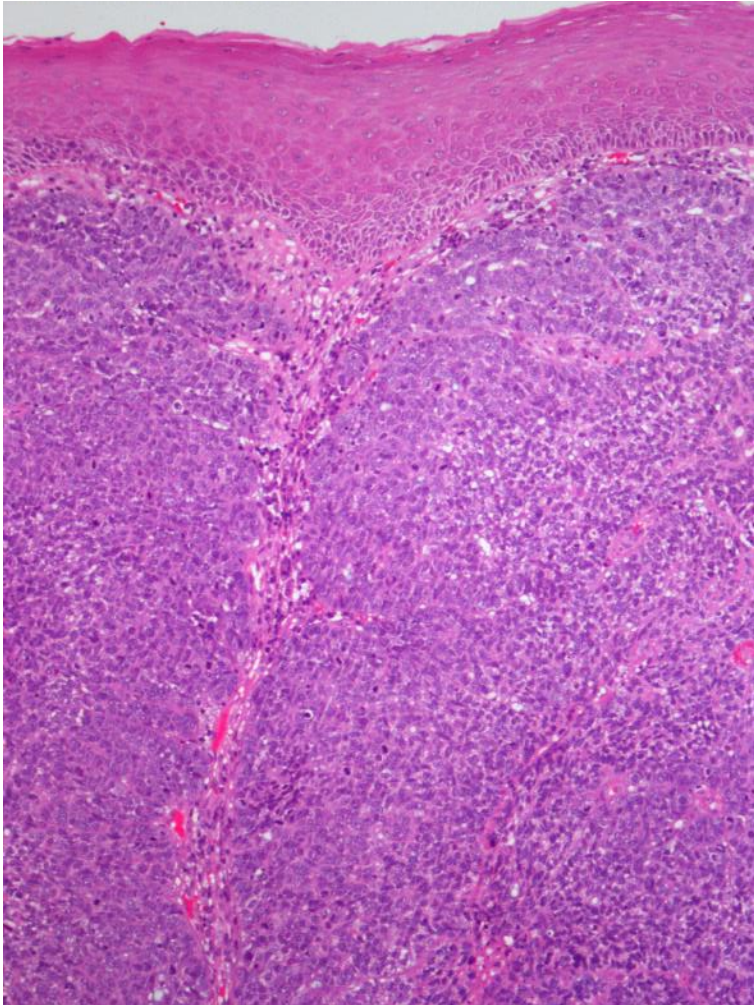
Oropharynx
(palatinalna ali
lingvalna tonzila)

Karcinom nosnega žrela



Epstein-Barr virus

Karcinom ustnega žrela



HPV

Prekanceroze glave in vratu



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Prekanceroze

Definicija: Epitelij sluznic z morfološkimi spremembami, ki so posledica genetskih sprememb, s povečanim tveganjem za razvoj ploščatoceličnega karcinoma

Sinonimi:

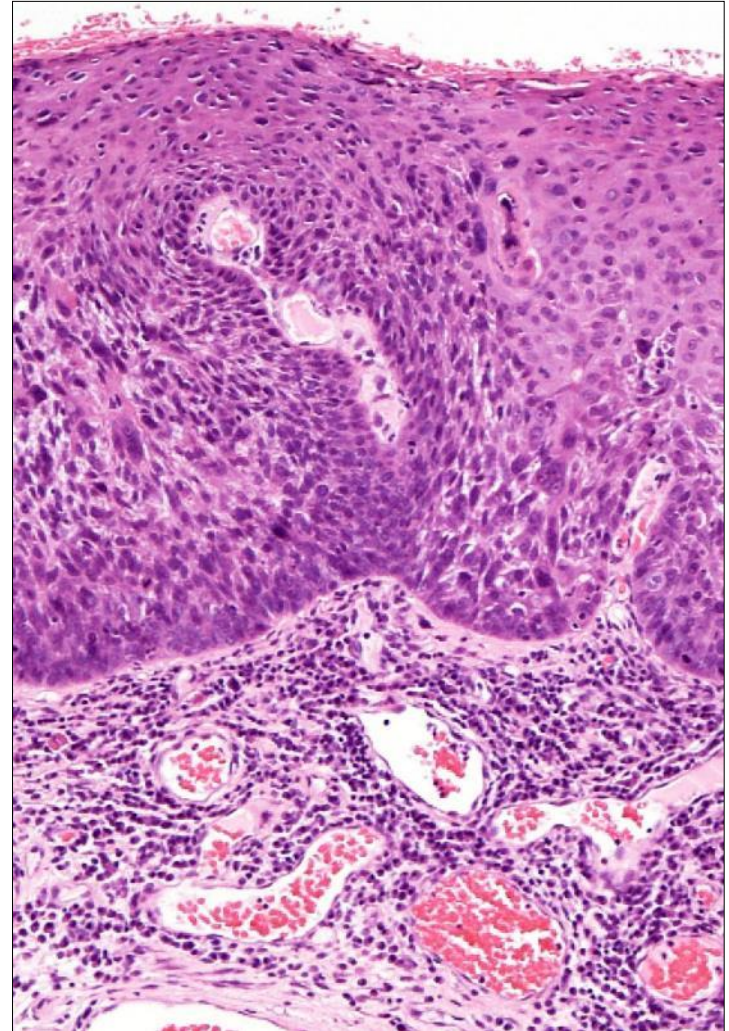
- displazija
- skvamozna intraepitelijska neoplazija (SIN)
- skvamozna intraepitelijska lezija (SILs)

Prekanceroze

- Terminologija: Ljubljanska klasifikacija, WHO klasifikacija ...
- Etiologija: alkohol, tobak, HPV ?
- Klinična slika neznačilna (eritroplakija, levkoplakija ...)
- Usoda: spontana regresija, progres, ponovitev
- “Field cancerization”

Prekanceroze: grading

- Celični in jedrni polimorfizem (različne oblike in velikosti)
- Atipije
- Povečano razmerje jedro : citoplasma
- Povečani nukleoli
- Mitoze
- Molekularni markerji ???



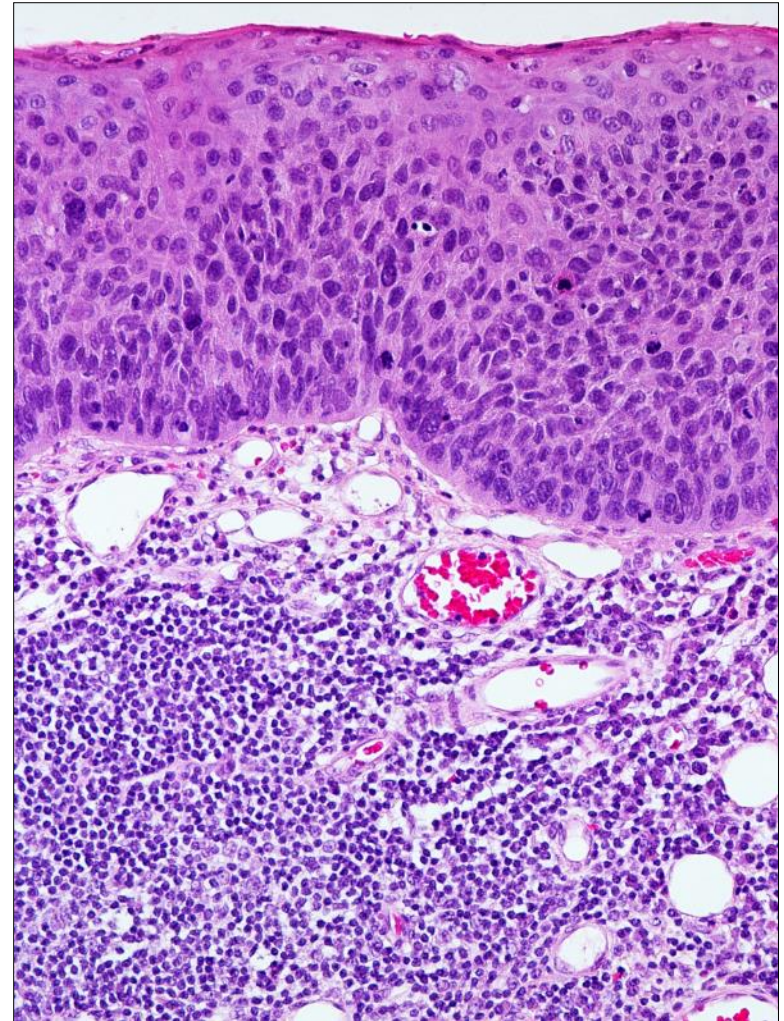
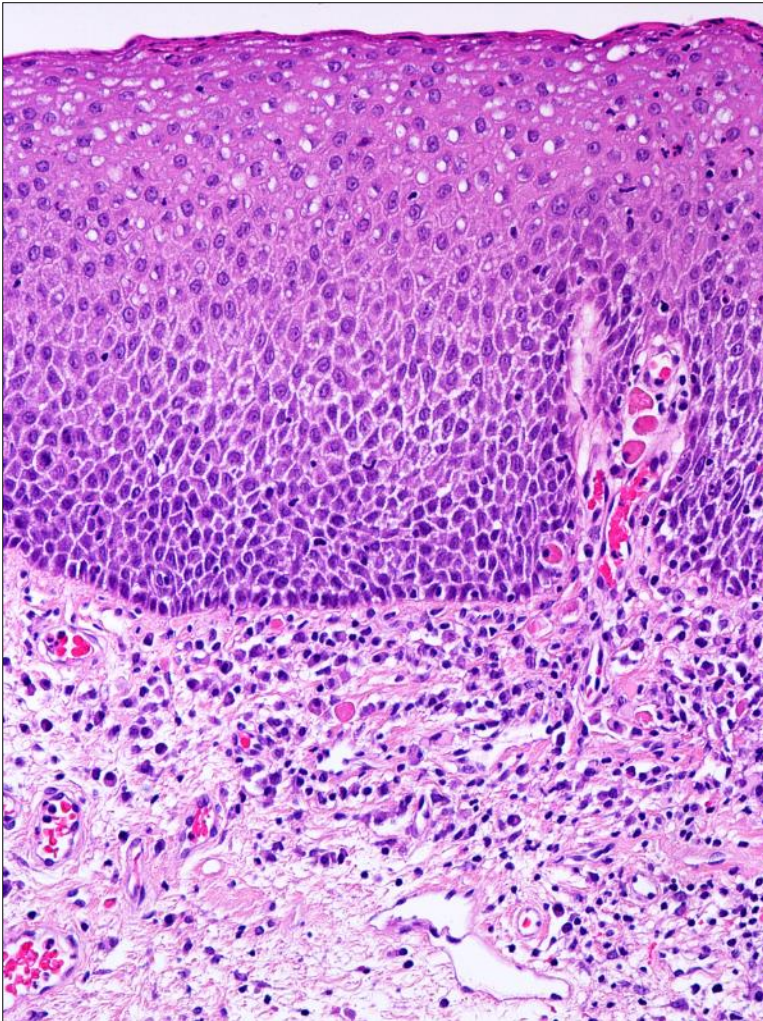
Skvamozne intraepitelijske lezije (displazija)

- 1. Nizke stopnje:** razvoj karcinoma v 2% pac.
- 2. Visoke stopnje:** razvoj karcinoma v 13% pac.
- 3. Carcinoma in situ (intraepitelijski karcinom):** citološko karcinom, vendar ne sega preko bazalne membrane in zato ne zaseva

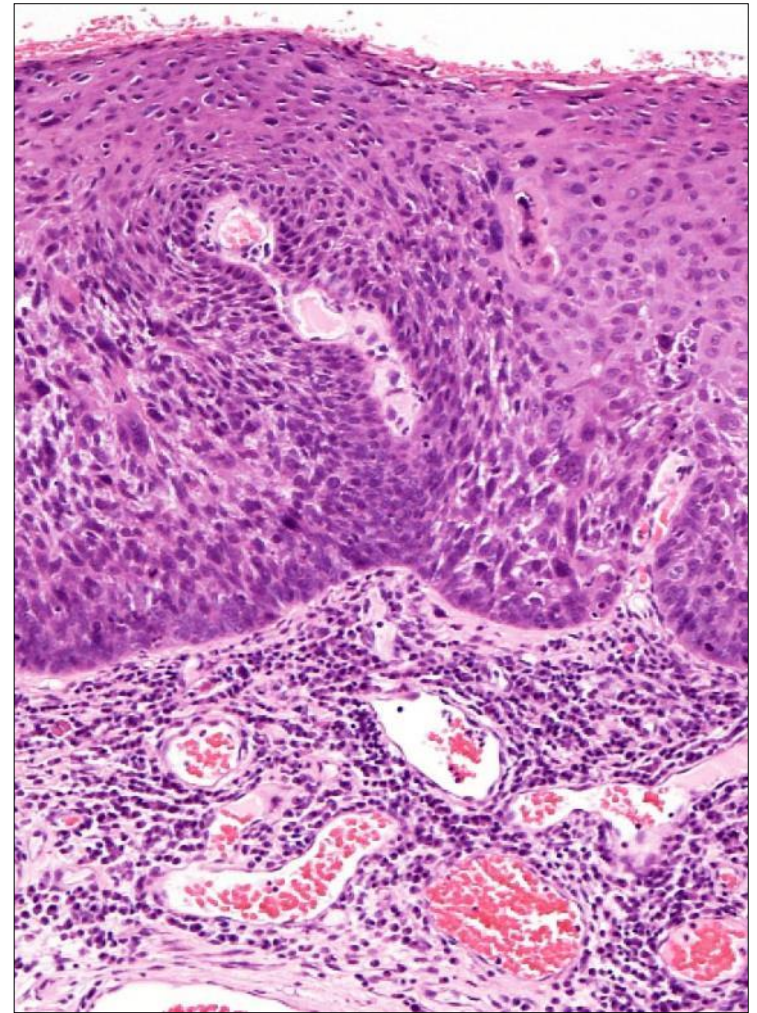
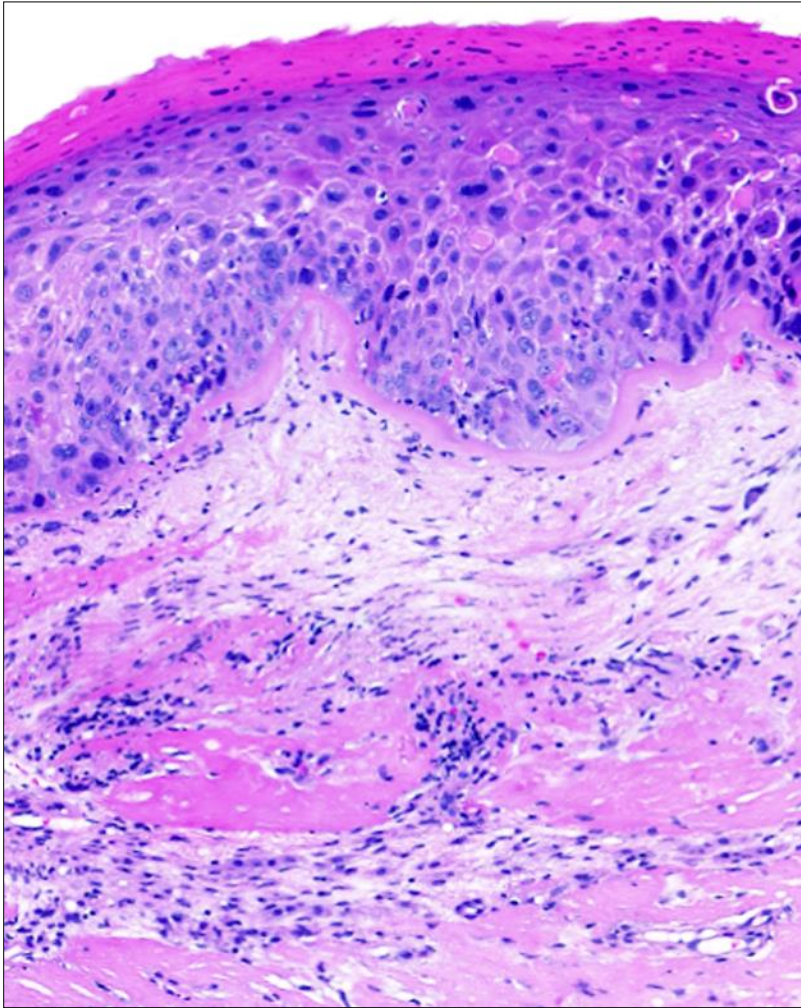
Displazija

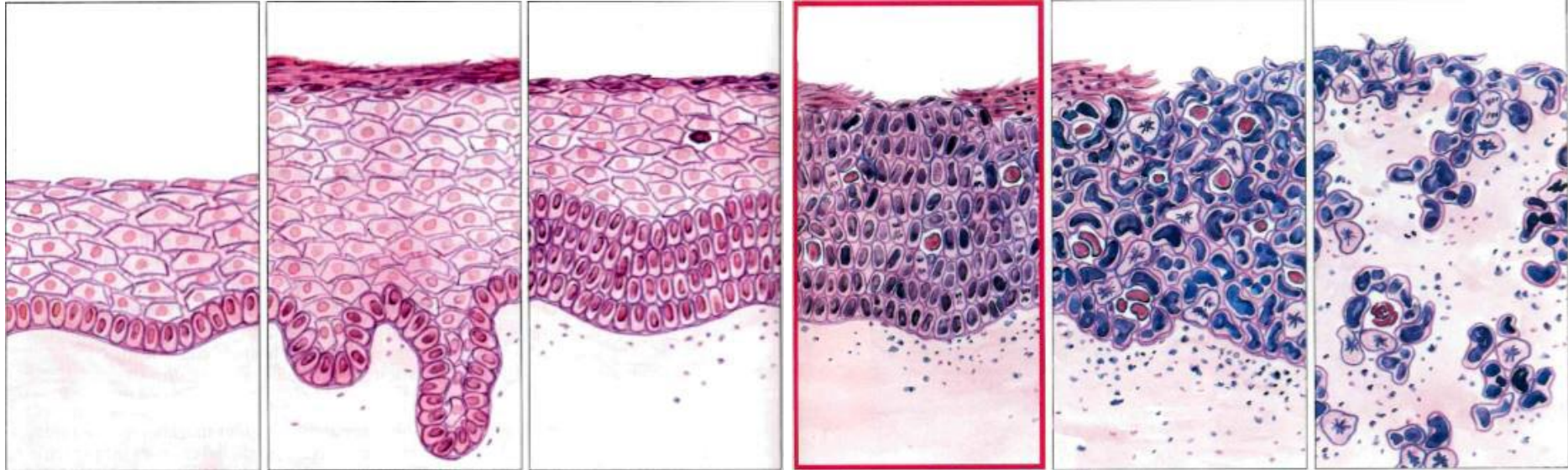
nizke stopnje

visoke stopnje



Carcinoma in situ





Normalna
sluznica

Hiperplazija

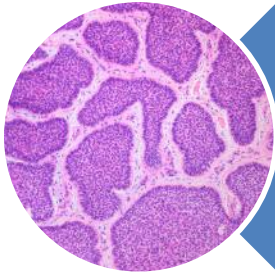
Displazija

Ca in situ

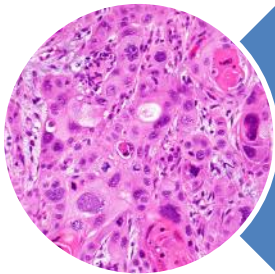
Invazivni ca

*Kambič V and Gale N. Epithelial hyperplastic lesions
of the larynx. Elsevier 1995*

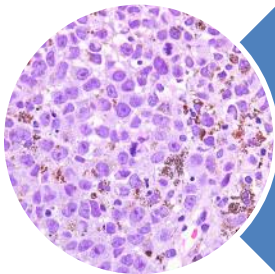
Koža



Bazalnocelični karcinom



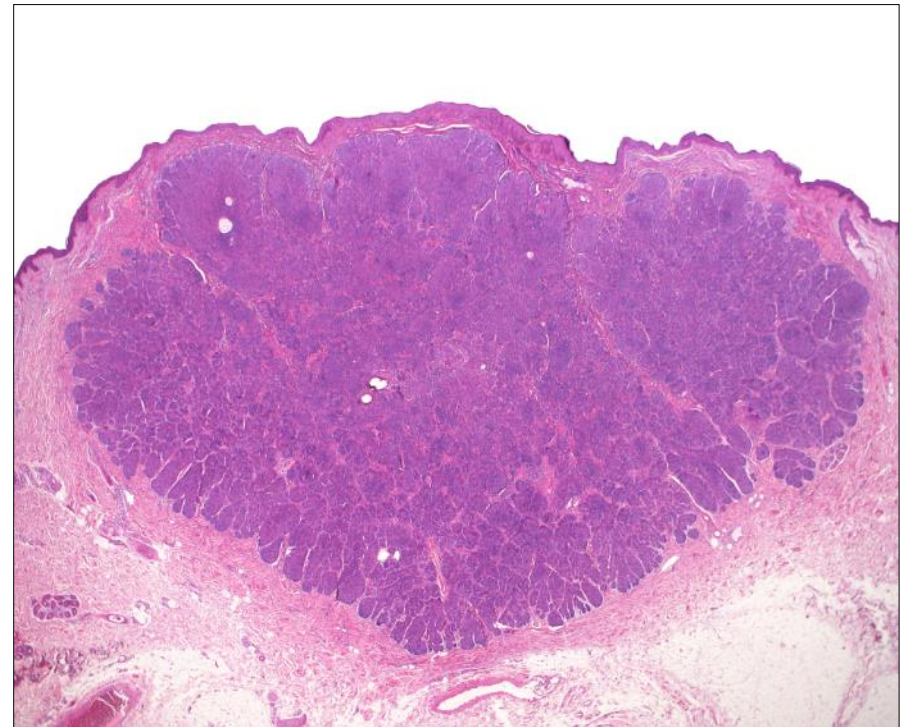
Ploščatocelični karcinom



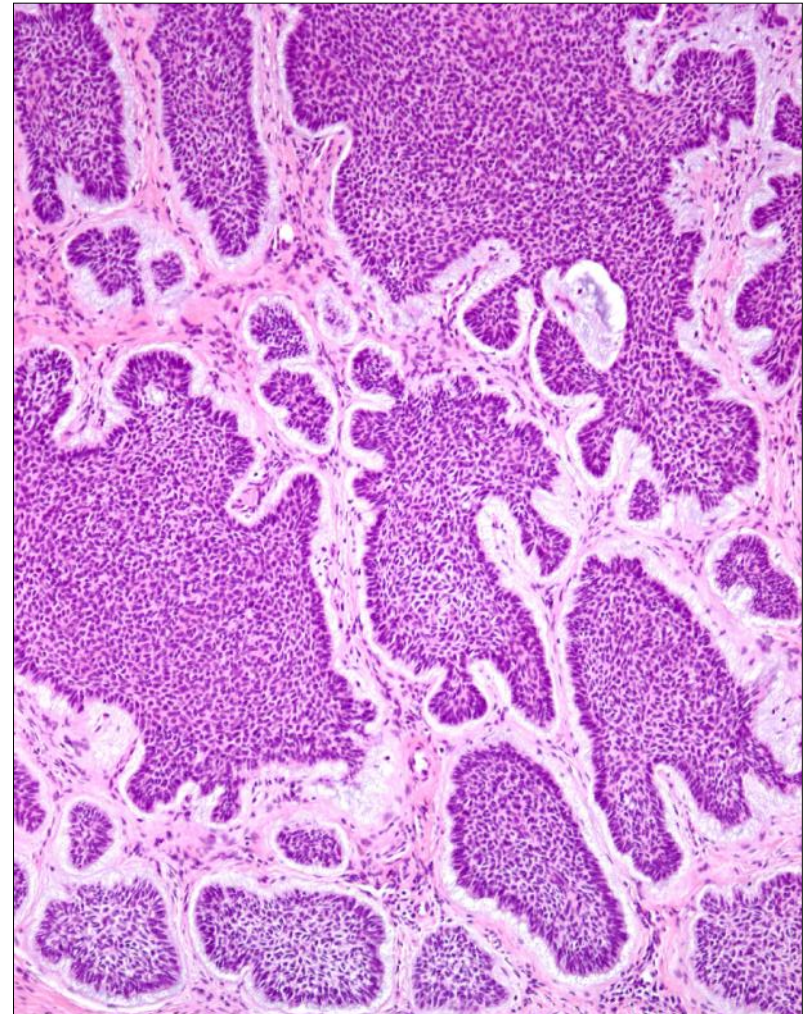
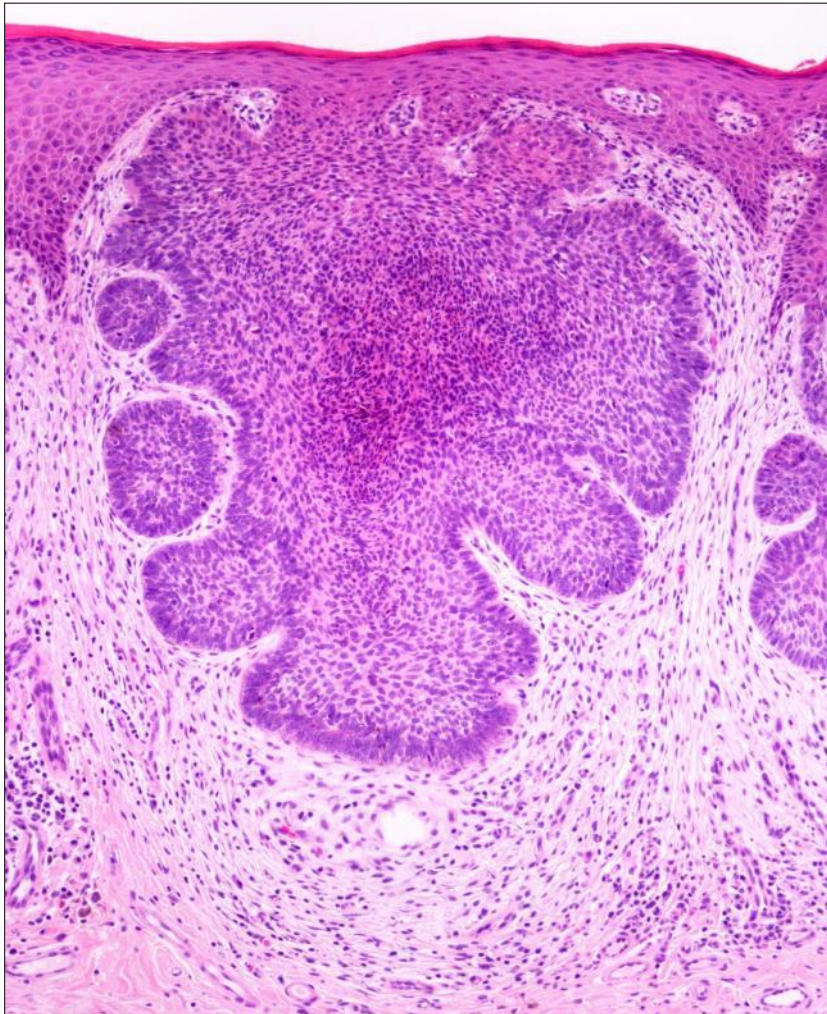
Melanom

Bazalnocelični karcinom

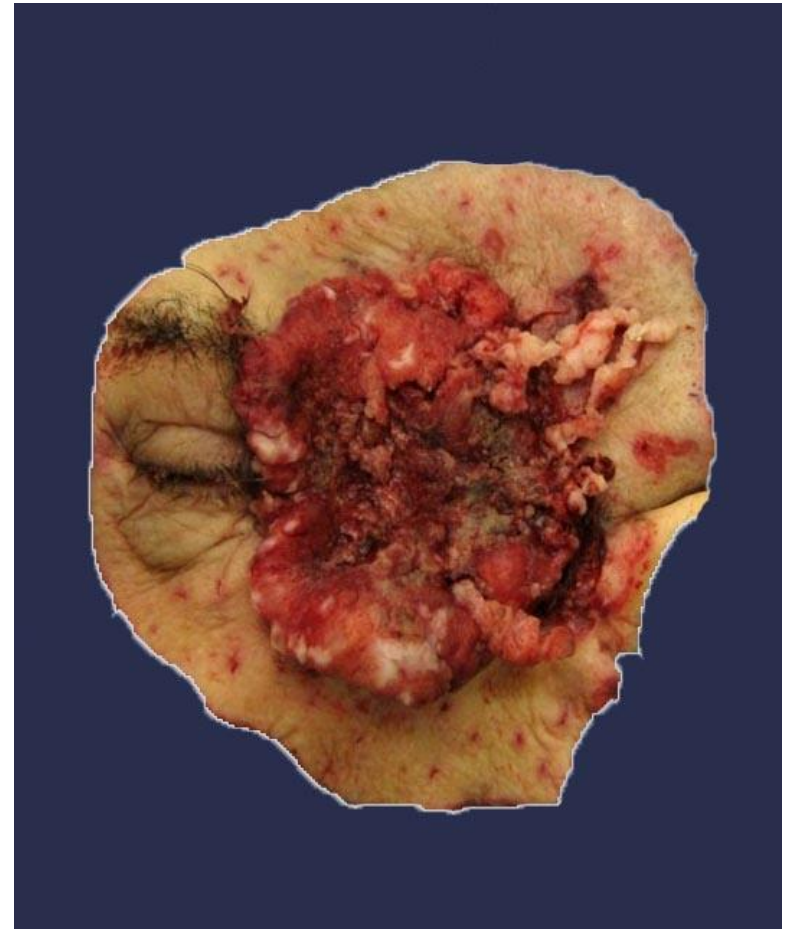
- Najpogostejši mlg tumor pri človeku
- Na soncu izpostavljeni koži
- Počasna rast
- **Destrukcija tkiva!**
- Zaseva izjemno redko
- Th: ekscizija (v celoti!)



Bazalnocelični karcinom



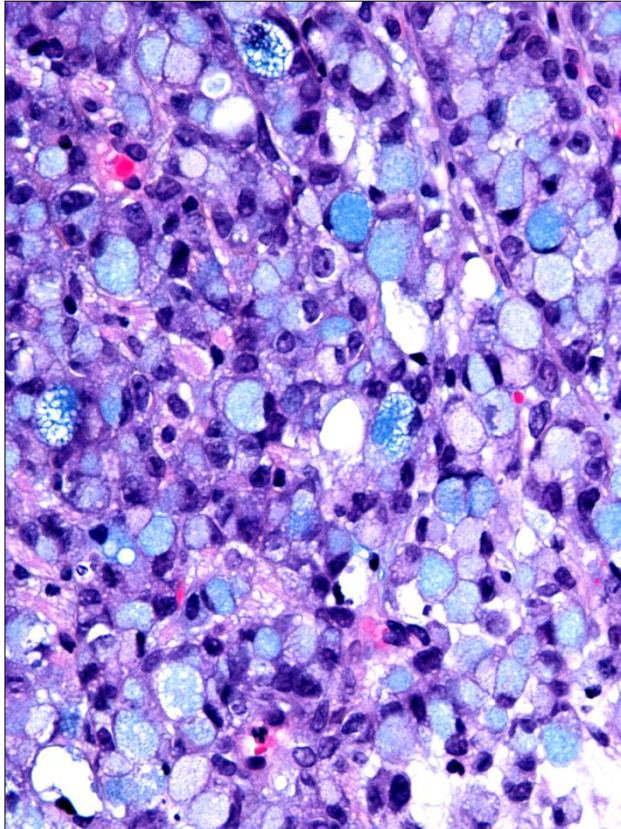
Bazalnocelični karcinom



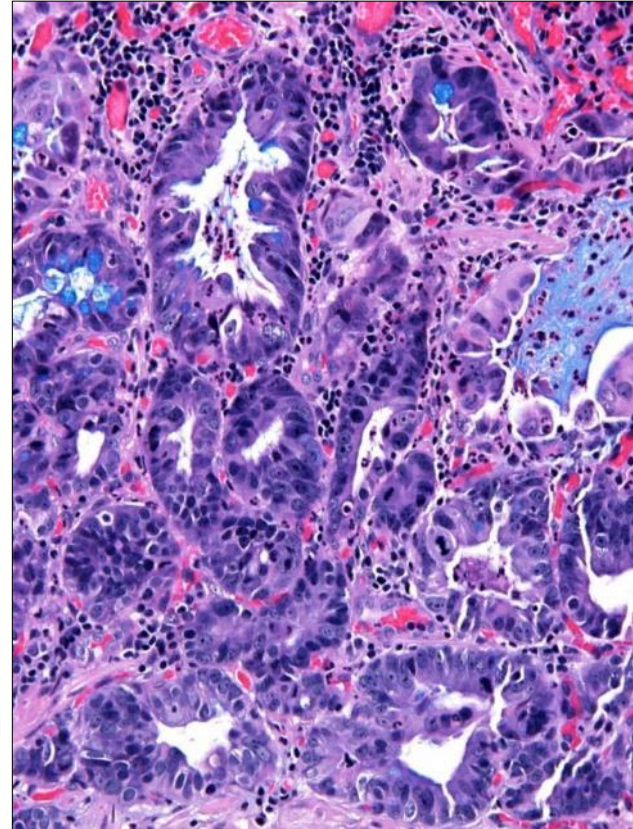
Tumorji žlez slinavk

Adenokarcinom: znaki žlezne diferenciacije

Tvorba mucina (intra ali ekstracelularno)



Tvorba žleznih struktur (tubuli, acinusi, resice)



Tumorji žlez slinavk

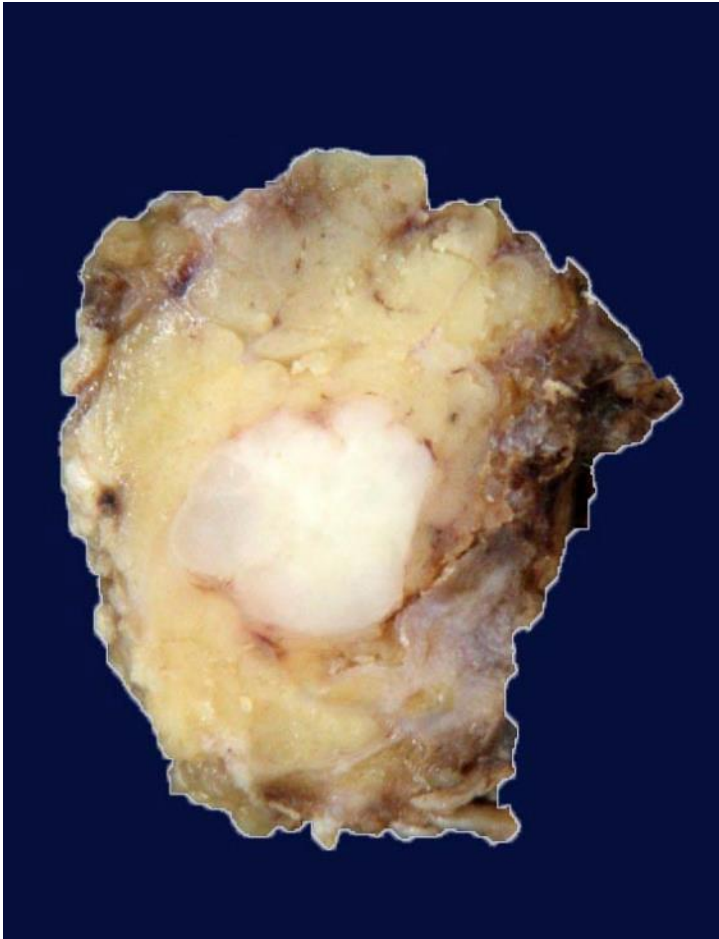
- benigni

- Pleomorfni adenom
- Whartinov tumor

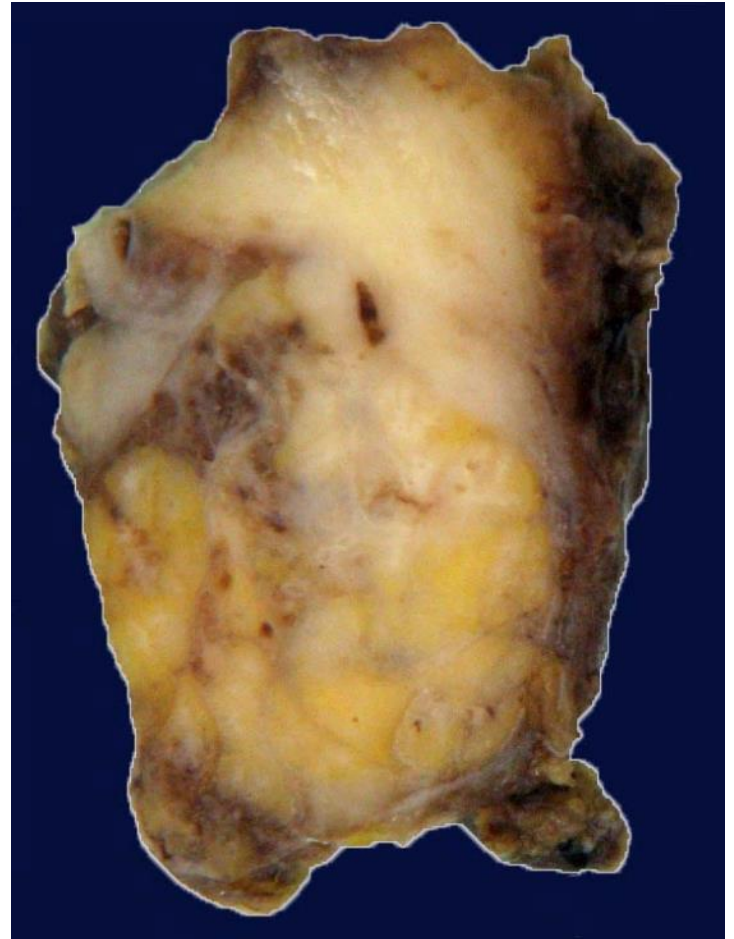
- maligni

- Adenoidno cistični karcinom
- Mukoepidermoidni ca
- Epitelijsko-mioepitelijski ca
- Mioepitelijski karcinom
- Karcinom salivarnega voda
- Polimorfni adenokarcinom
- Bazalnocelični adenokarcinom
- Sekretorni karcinom
- Limfom

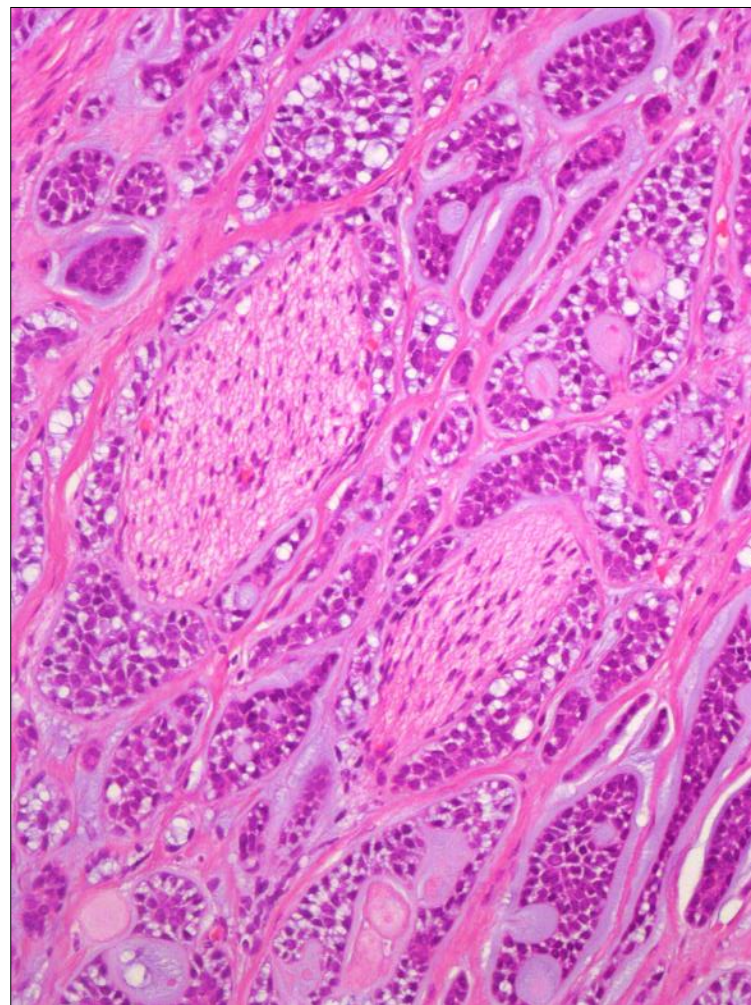
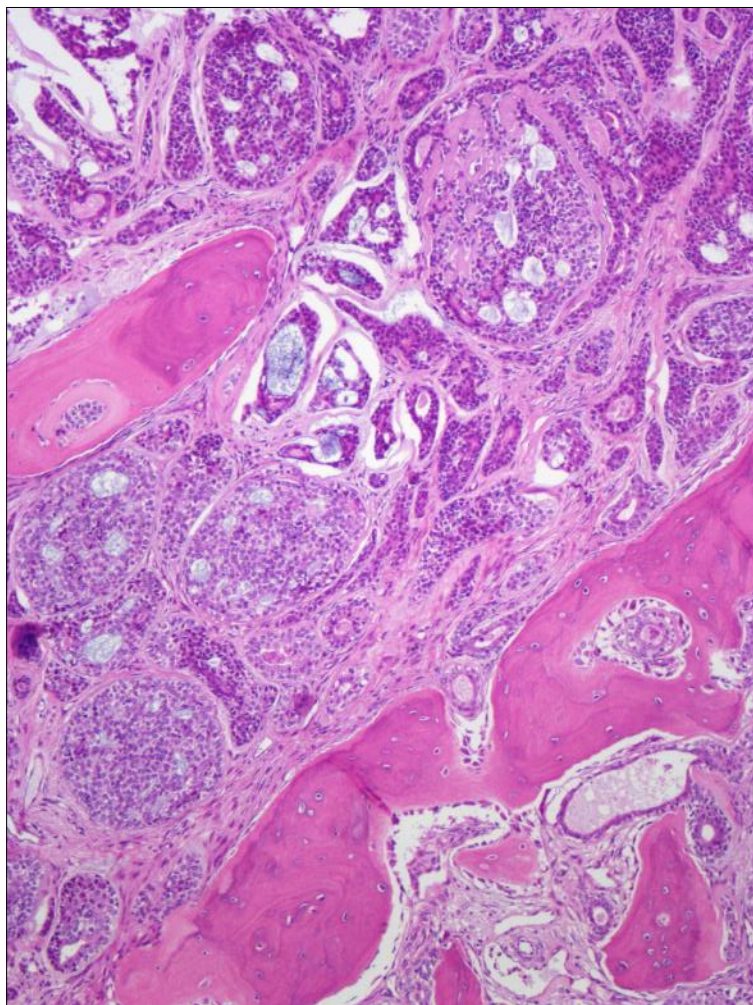
Pleomorfni adenoma



Karcinom salivarnega voda



Adenoidno-cistični karcinom: perinevralna invazija

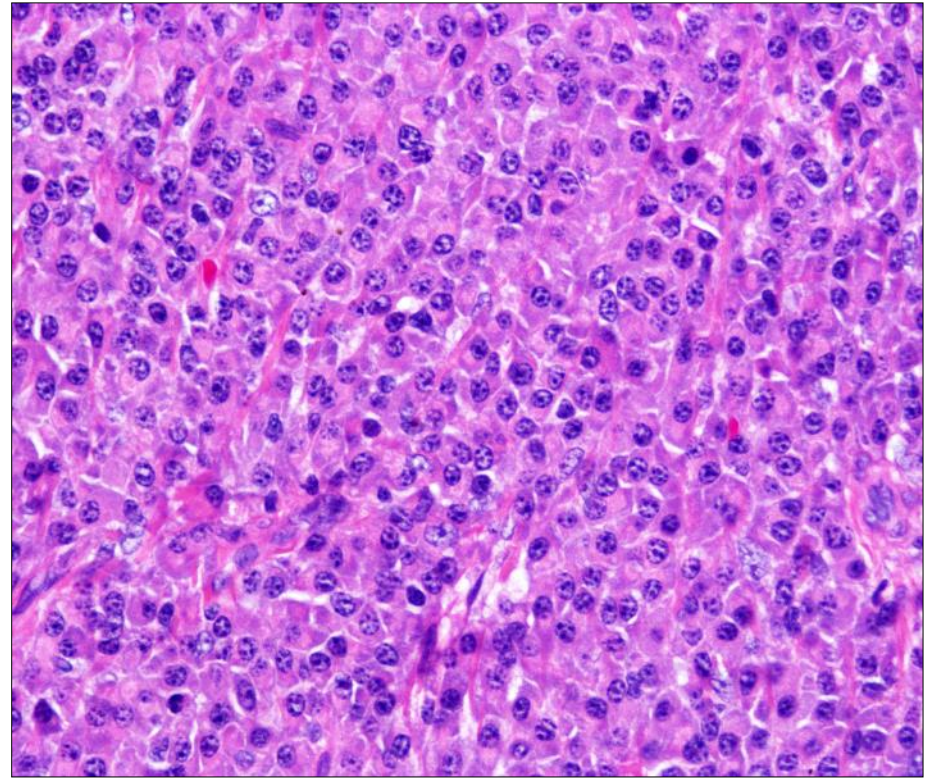
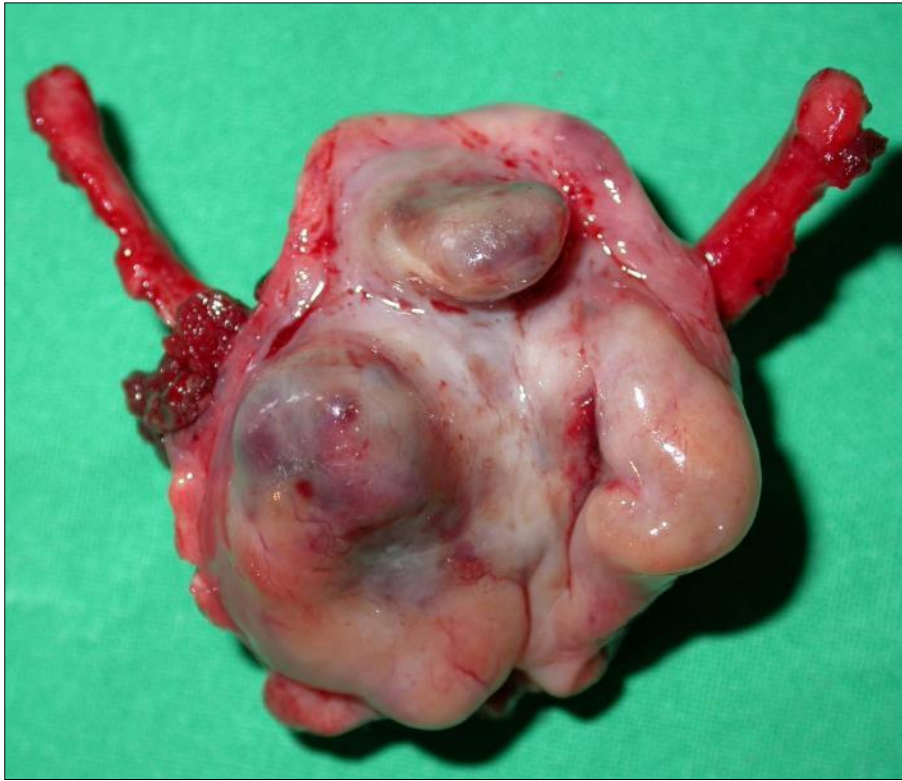


Limfom

Limfomi

- Hodgkinov, neHodgkinov limfom, limfatične levkemije, plazmacitom
- Bezgavke (nodalni limfomi)
- “Mucosa-associated lymphoid tissues” (MALT): pridobljeni MALT (slinavke), prirojeni (Waldeyerjev obroč)

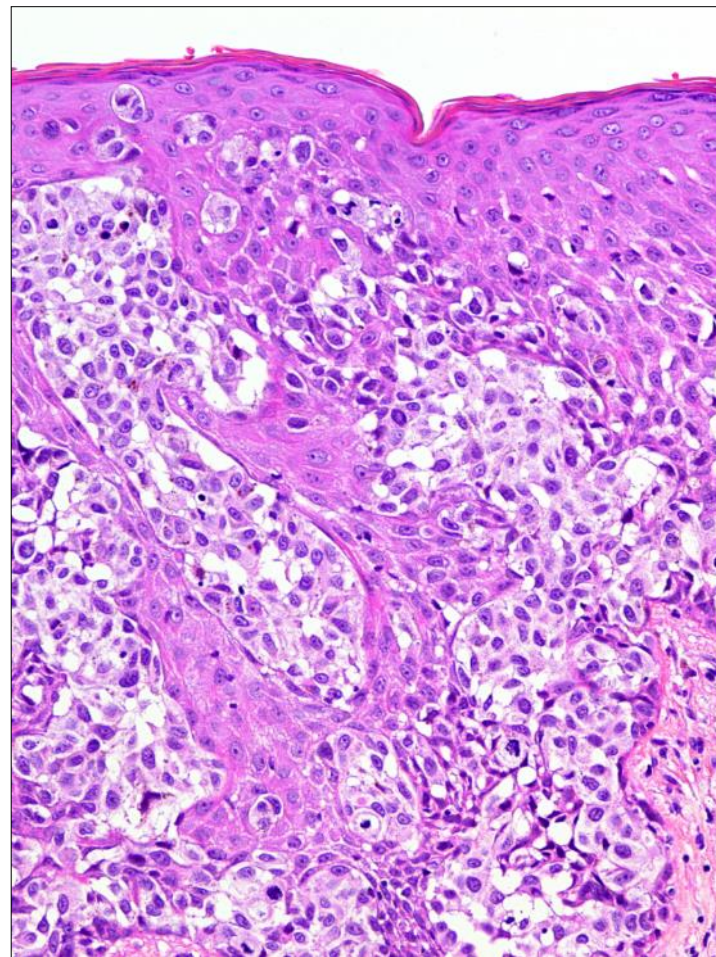
Supraglotisna laringektomija: ekstramedularni plazmacitom



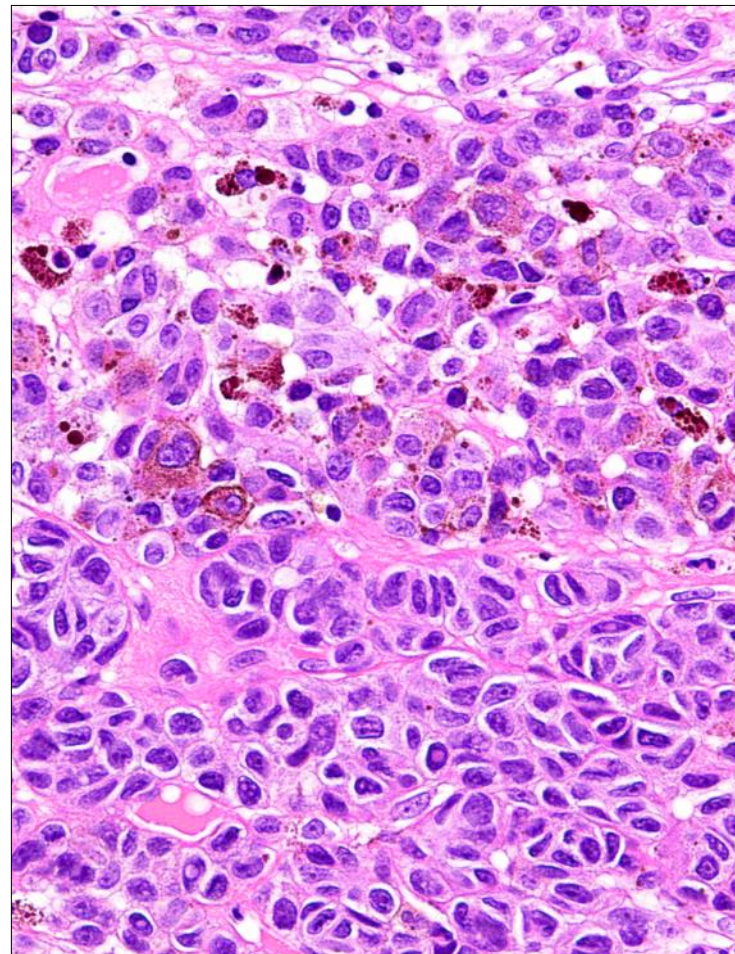
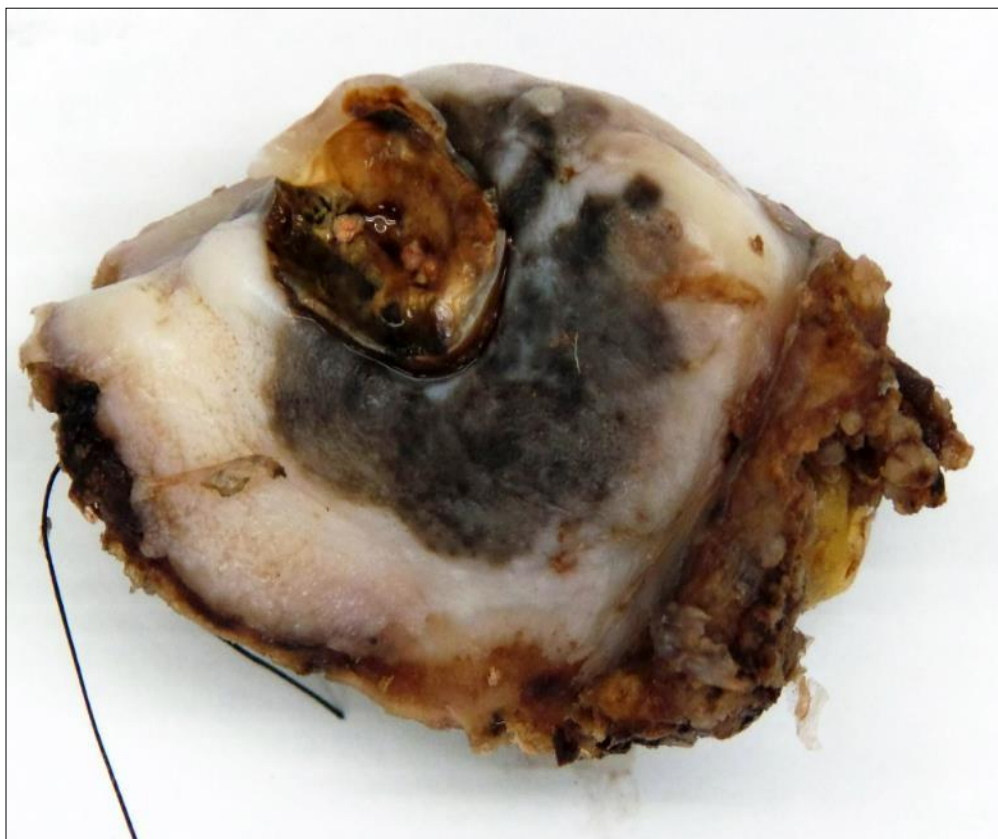
Melanom glave in vratu

Melanom

- Koža
- Sluznice (nosna, ustna)
- Agresiven, slaba prognoza
- Mukozni melanomi običajno pozno odkriti



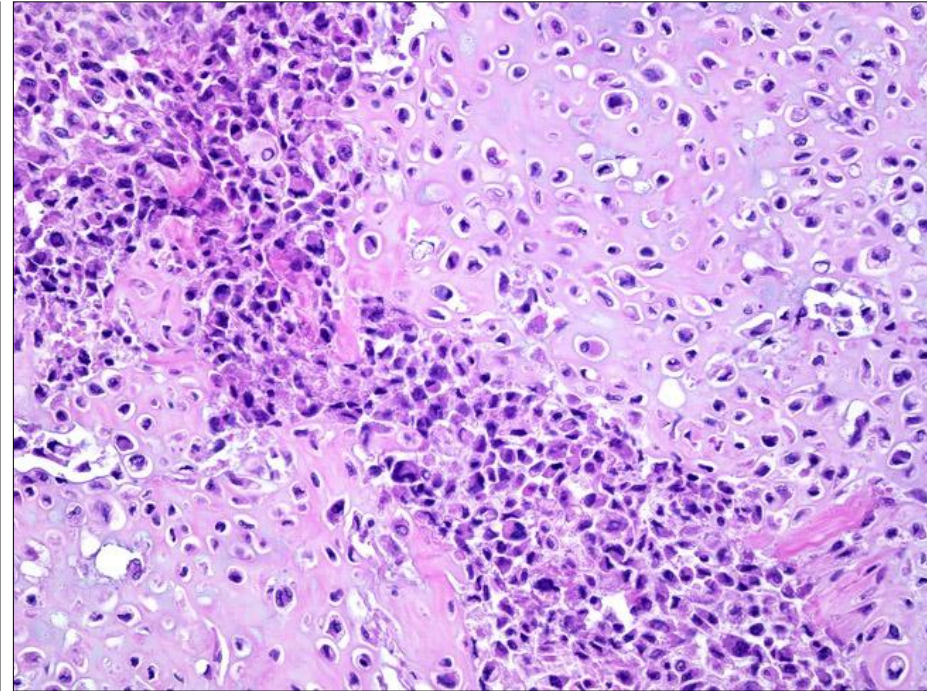
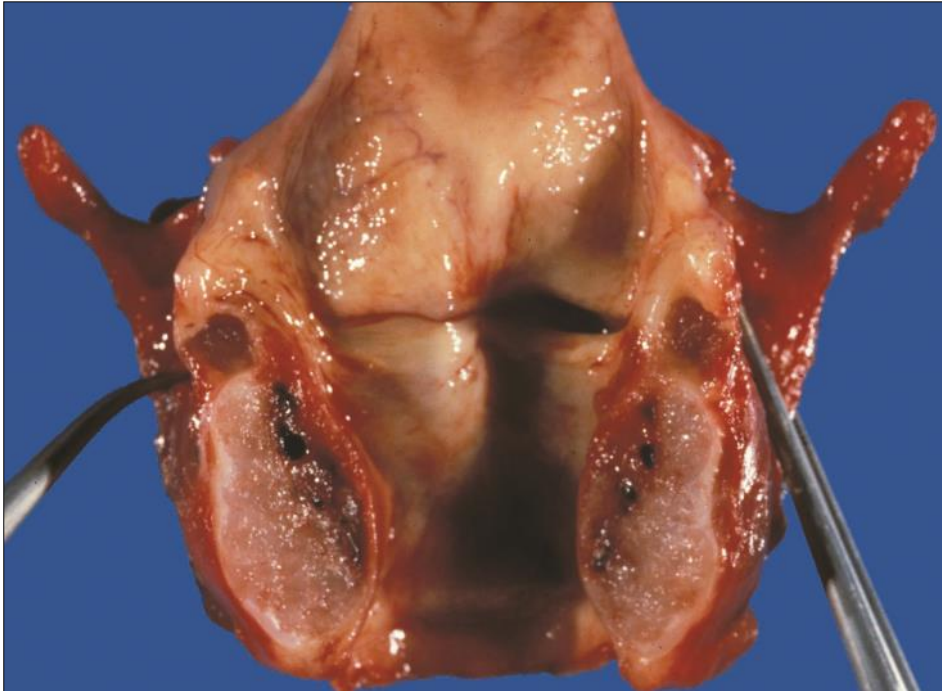
Melanom trdega neba in maksile



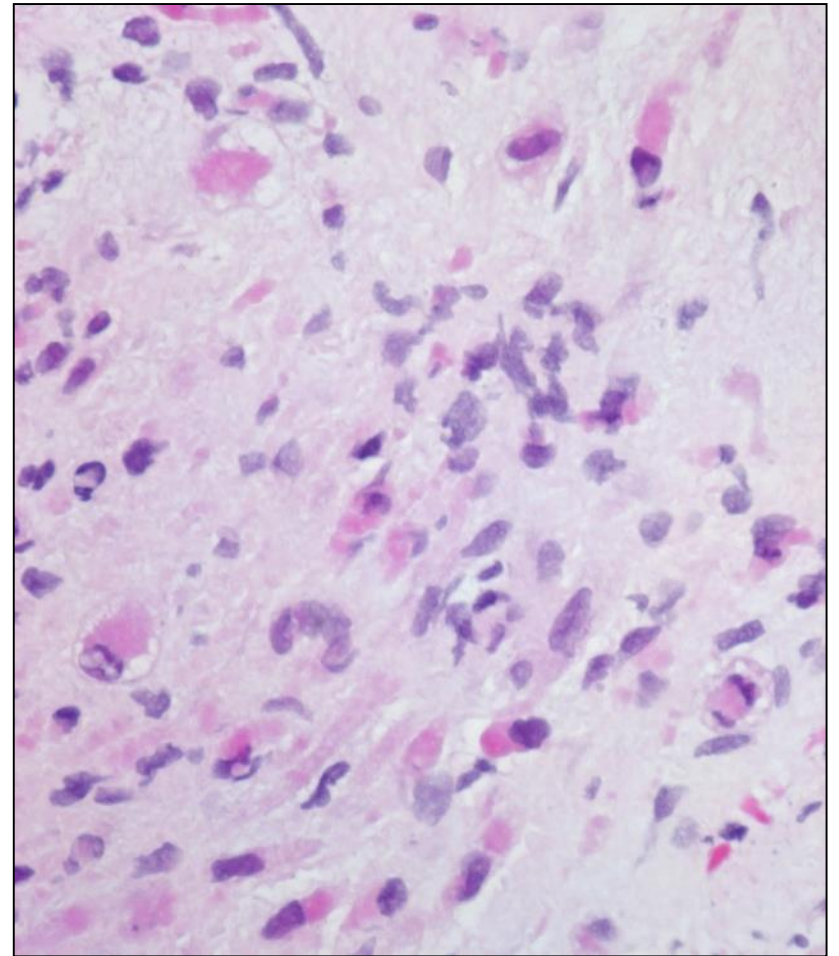
Tumorji mehkih tkiv in kosti

- **Benigni:** lipom, hemangiom, schwannom, fibrom, leiomiom, hondrom
- **Maligni (sarkomi):** liposarkom, hondrosarkom, leiomiosarkom, miksoidni fibrosarkom, MPNST
- **Benigni:** osteom, osteoblastom, osteoid-osteom, gigantocelični tumor
- **Maligni:** osteosarkom, Ewingov sarkom, PNET, limfom, plazmacitom

Hondrosarkom grla



Rabdomiosarkom mandibule



Zaključki

Tumorjev ne moremo in ne smemo opredeljevati na osnovi makroskopske / klinične slike.

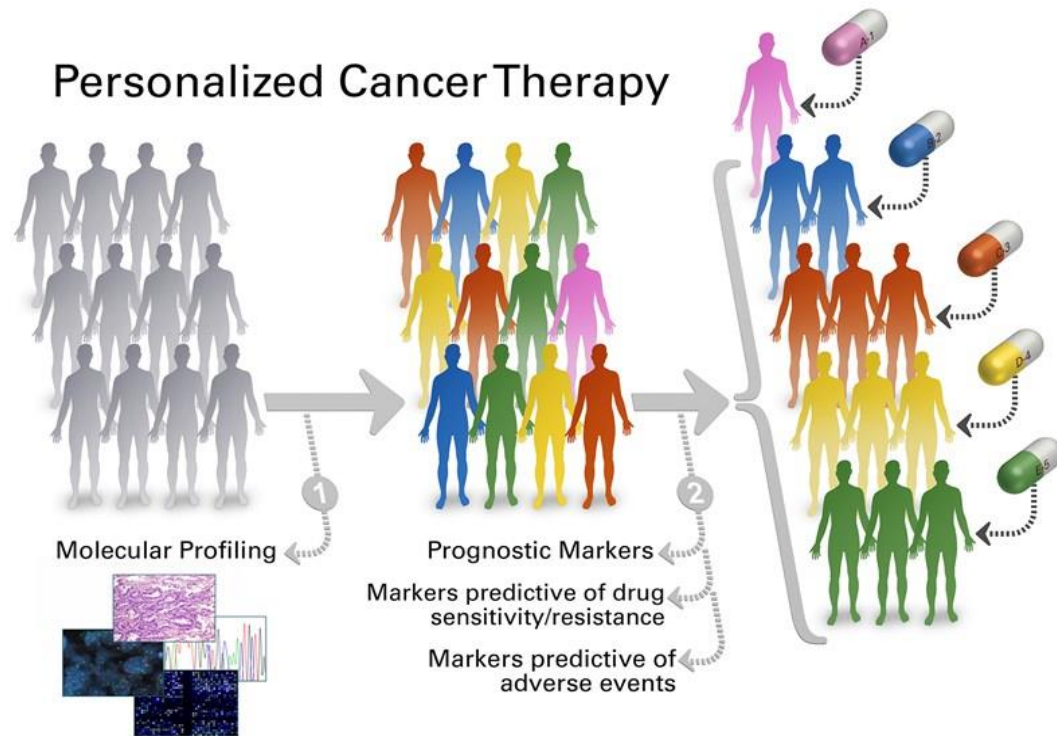
BIOPSIJA je nujna za opredelitev tumorjev (citopatologija, histopatologija).

Biopsije ne morejo in ne smejo nadomestiti molekularno genetske preiskave.

Novi načini zdravljenja

- tarčna zdravila
- zaviralci imunskih kontrolnih točk

“Therapy with the right drug at the right dose in the right patient”



Vir: <https://pct.mdanderson.org/>

PD-1 = programmed death 1 receptor

- **akt. limfociti T**
- NK celice
- makrofagi
- dendritične celice

PD-L1 = programmed death 1 ligand

- **normalne celice**
- Ag predst. celice
- akt. limfociti B in T
- **tumorske celice**

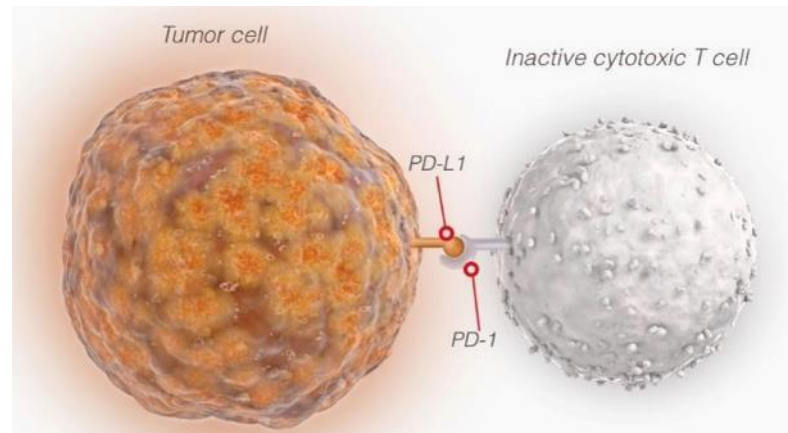
Funkcija

- Regulacija vnetnega odgovora na infekt
- Preprečevanje avtoimunskega odgovora

Interakcija PD-L1 na tumorskih celicah in PD-1 na T limfocitih

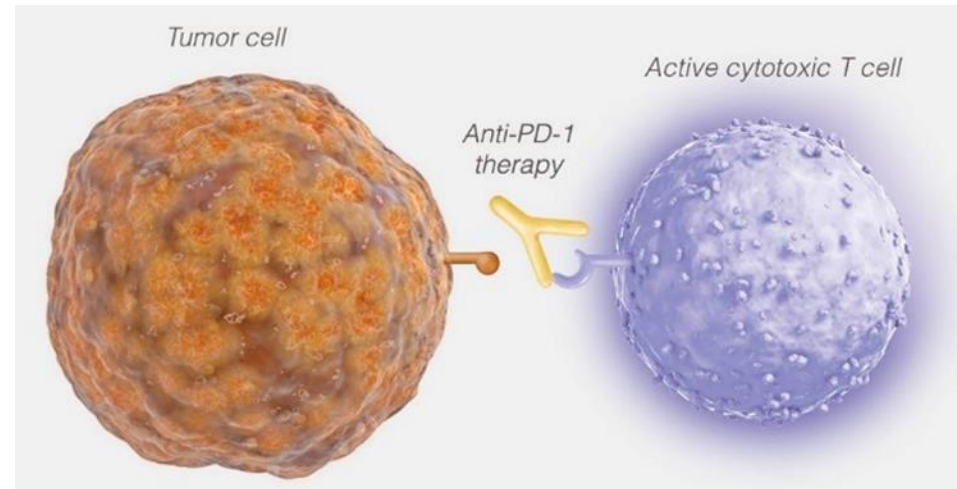


Tumorske celice preko PD-L1 inaktivirajo T limfocite, zavrejo imunski odziv, kar omogoča nadaljno rast tumorja.

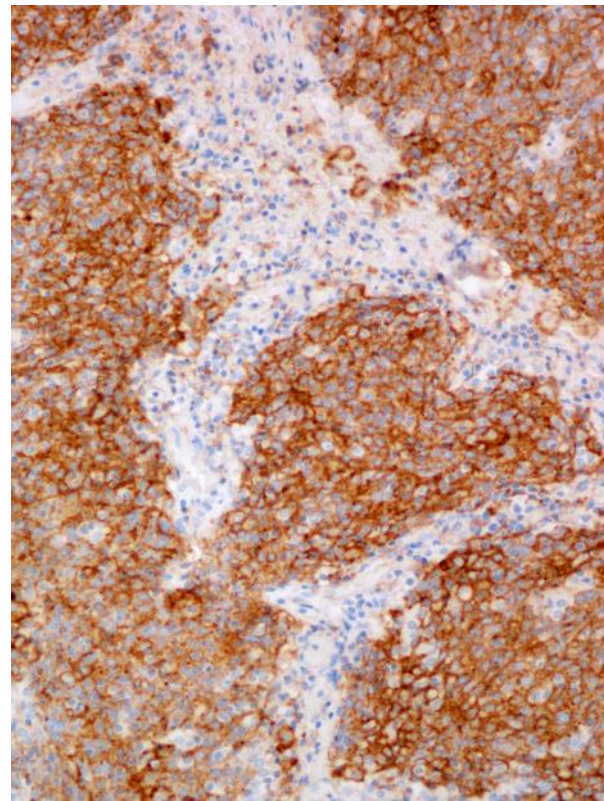
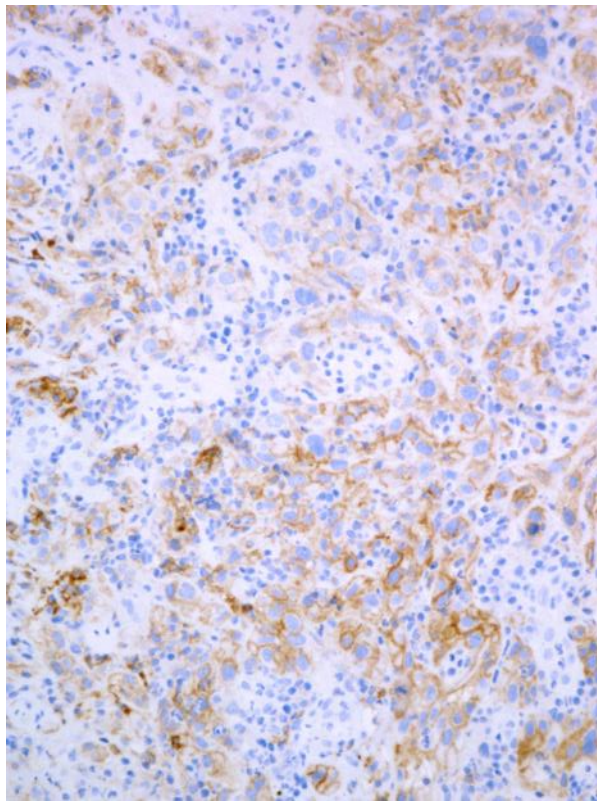
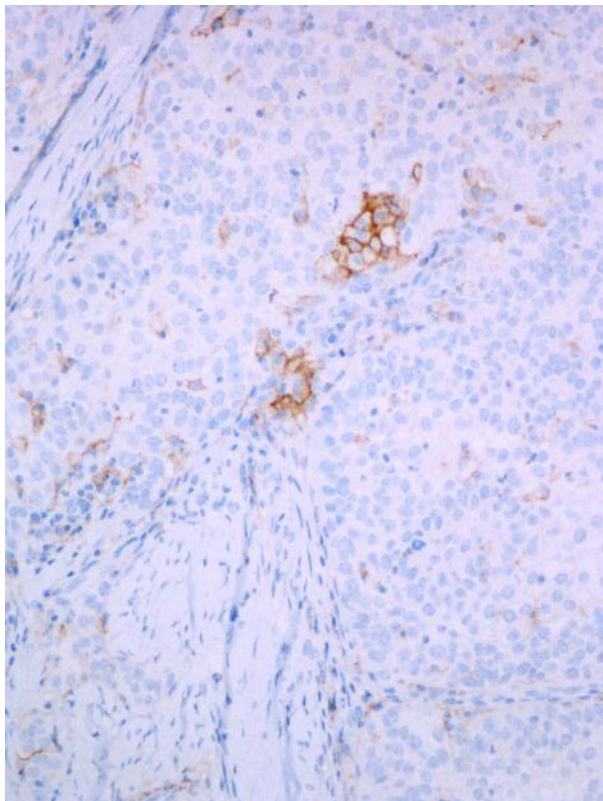


PD-1 inhibitorji (immune checkpoint inhibitors)

- pembrolizumab, nivolumab, cemiplimab
- inhibirajo interakcijo PD-L1 na tumorskih celicah z PD-1 receptorjem na T limfocitih
- prepreči tumorskim celicam, da ubeži imunskemu sistemu
- 2017: PD-1/PD-L1 inhibitorji odobreni za zdravljenje 9 vrst raka



Izražanje PD-L1 v karcinomu sp. žrela



Pomen okužbe s HPV v razvoju karcinoma glave in vratu



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The Search for Infectious Causes of Human Cancers: Where and Why (Nobel Lecture)**

*Harald zur Hausen**

Angew. Chem. Int. Ed. 2009, 48, 5798–5808



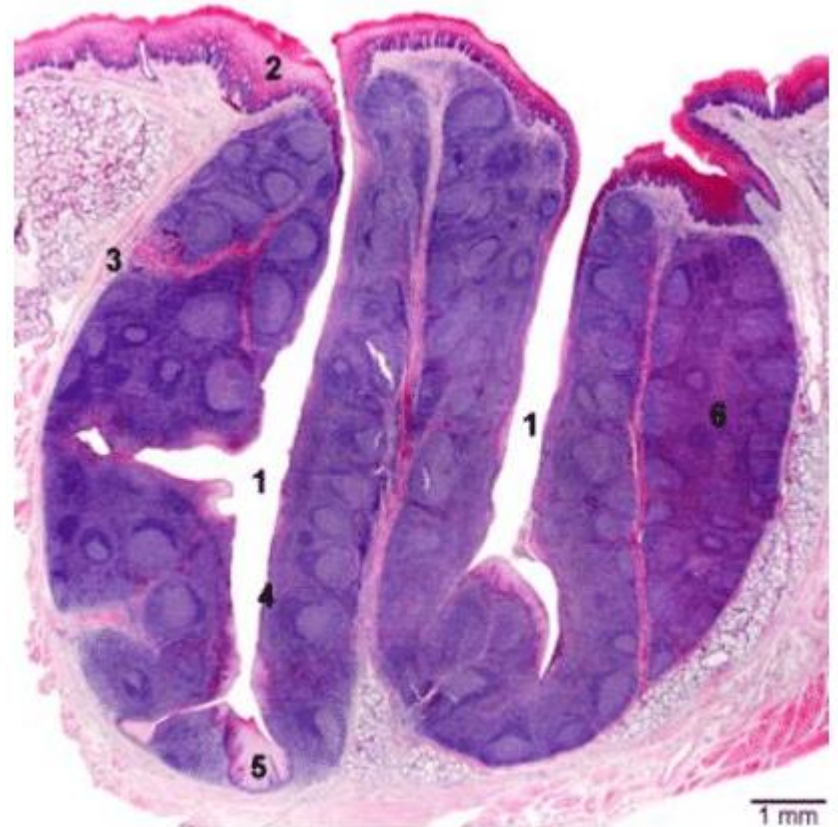
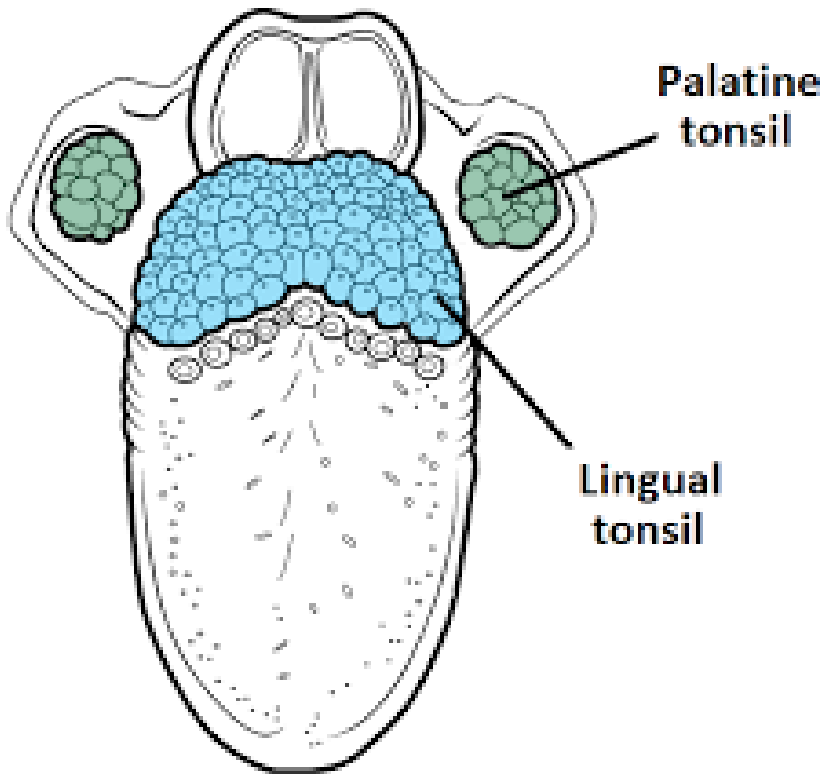
Harald zur Hausen – Nobelova nagrada 2009

Vsebina

- HPV in karcinom ustnega žrela
- HPV in sinonazalni karcinom
- Diagnostika HPV okužbe
- HPV in karcinom grla in ustne votline

HPV-poz. ploščatocelični karcinom
ustnega žrela

HPV-poz. karcinom ustnega žrela: tonsilla palatina, koren jezika



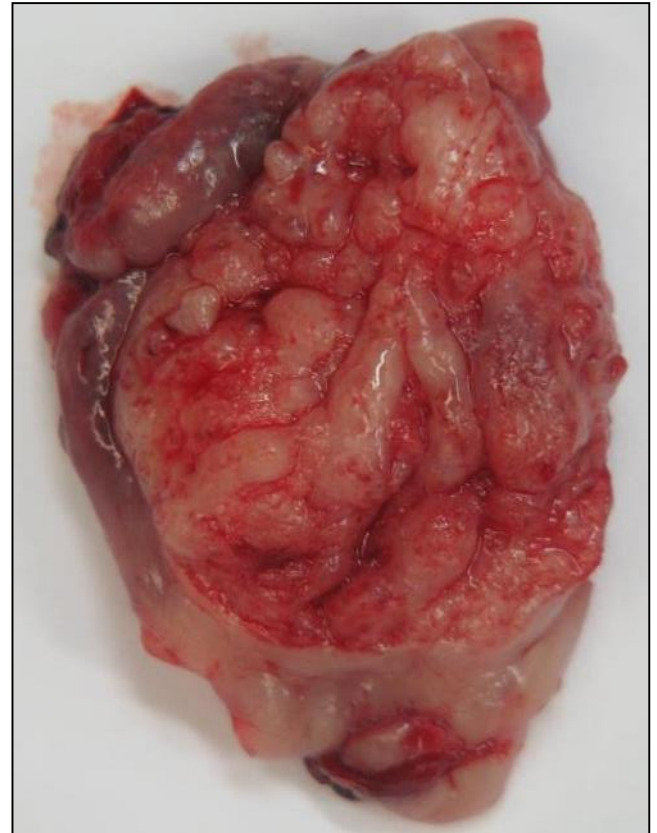
Characteristics	HPV-positive SCC	HPV-negative SCC
Median age	50-56 years	60-70 years
Risk factors	Sexual behaviour	Smoking and alcohol abuse
Lymph node metastases	Frequently cystic	Uncommonly cystic
Postulated origin	Reticulated epithelium of invaginated crypts	Surface epithelium
Dysplasia	Rare	Often present
Morphology	Commonly non-keratinizing	Conventional SCC
Grading	Not applicable	Applicable
p16 immunohistochemistry	Positive	Negative
Overall survival (3 years)	82%	57%

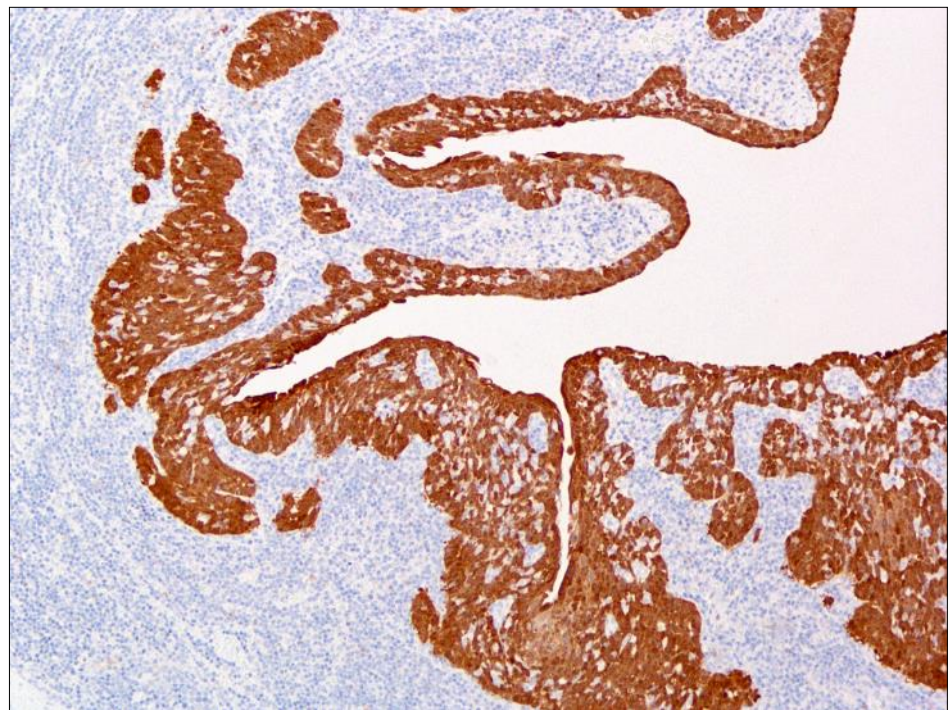
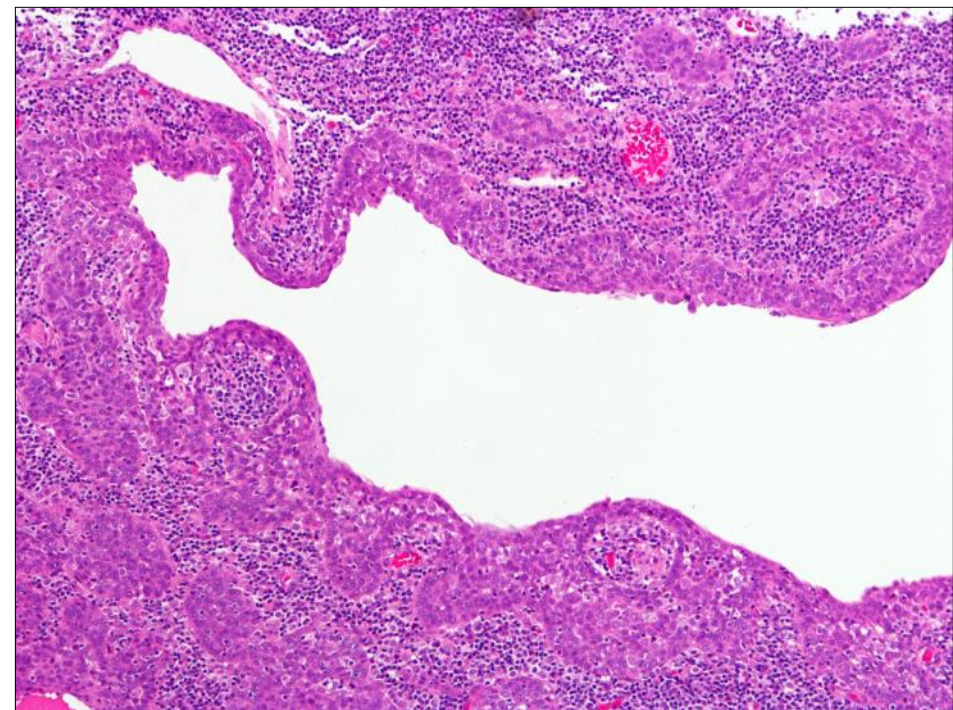
El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, eds. WHO Classification of Head and Neck Tumours. 4th ed. IARC: Lyon; 2017

HPV-poz. karcinom ustnega žrela

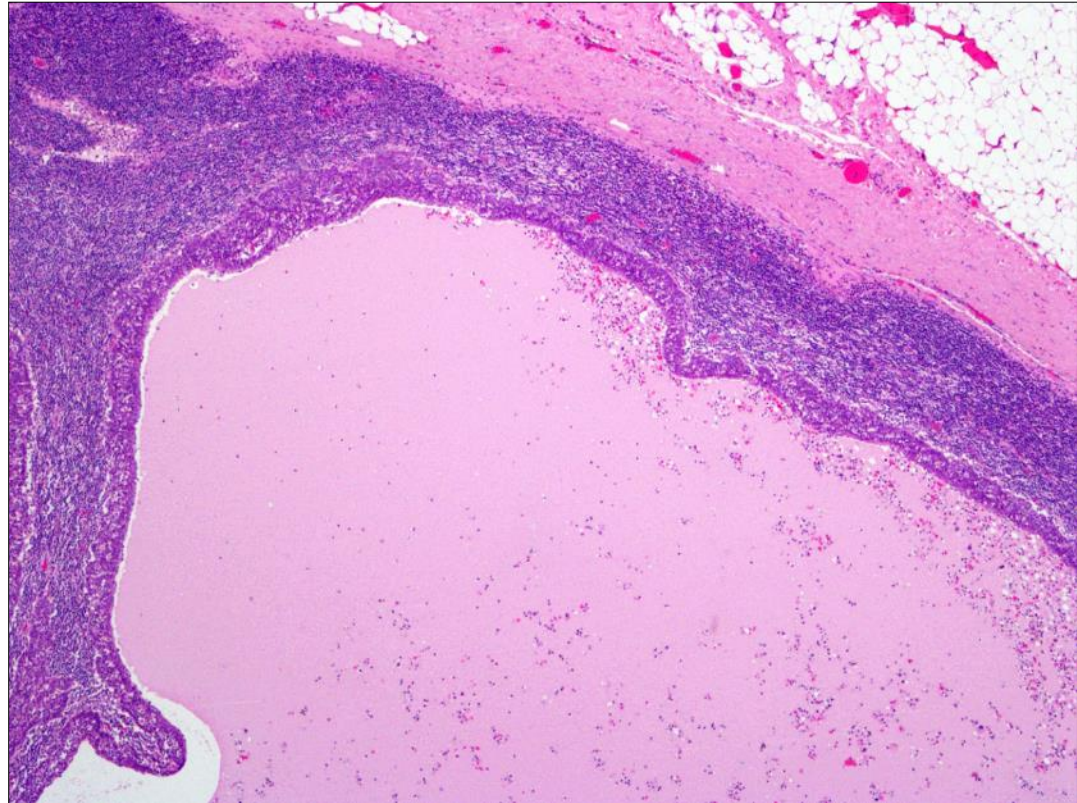
- HPV16 (85%), 18, 31, 33, 35, 39, 45, 51, 52, 56, 59, 68, 69, 73,
- 35-80 % v ZDA, 13-20 % v nekaterih evropskih državah
- pri mlajših bolnikih
- ni povezave s kajenjem in uživanjem alkohola
- povezava s spolnimi navadami
- palatinalna in lingualna tonzila, neporoženevajoča morfologija
- zgodaj zaseva v področne bezgavke
- odličen odgovor na obsevanje
- boljša prognoza: preživetje: 85% za HPV+ PK, 50% za HPV neg PK

Ang KK, Harris J, Wheeler R et al. HPV and survival of patients with oropharyngeal cancer. N Engl J Med 2010; 363: 24-35





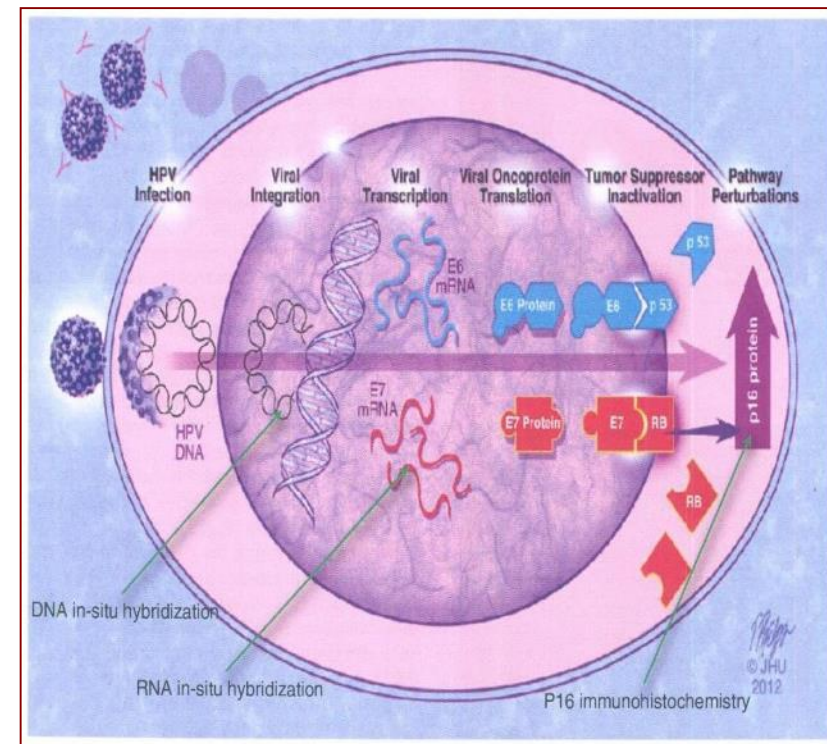
Cistični zasevki v bezgavkah



Diagnostika HPV-poz. karcinomov

Patogeneza HPV-poz. karcinoma

- HPV integracija v genom gostitelja
- ekspresija virusne mRNA
- translacija virusnih onkoproteinov
- porušena tumor supresorska pot
- virusna E6 in E7: inhibicija p53 in Rb
- prekomerno izražanje p16



Diagnostika HPV-poz. karcinoma

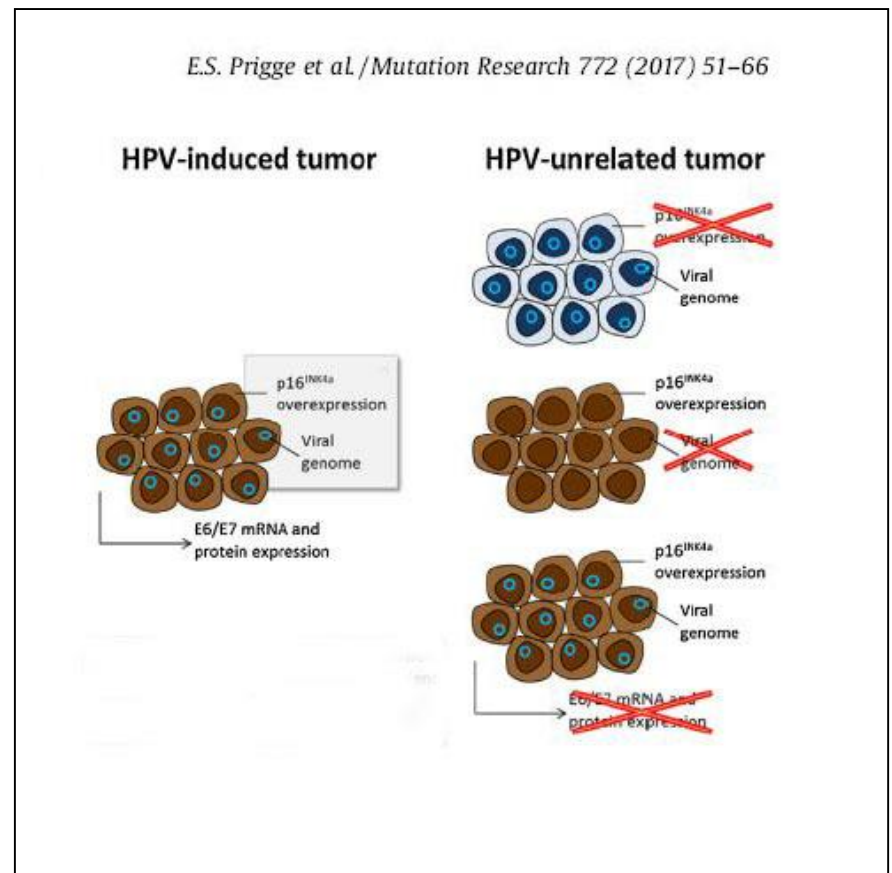
prekomerno izražanje

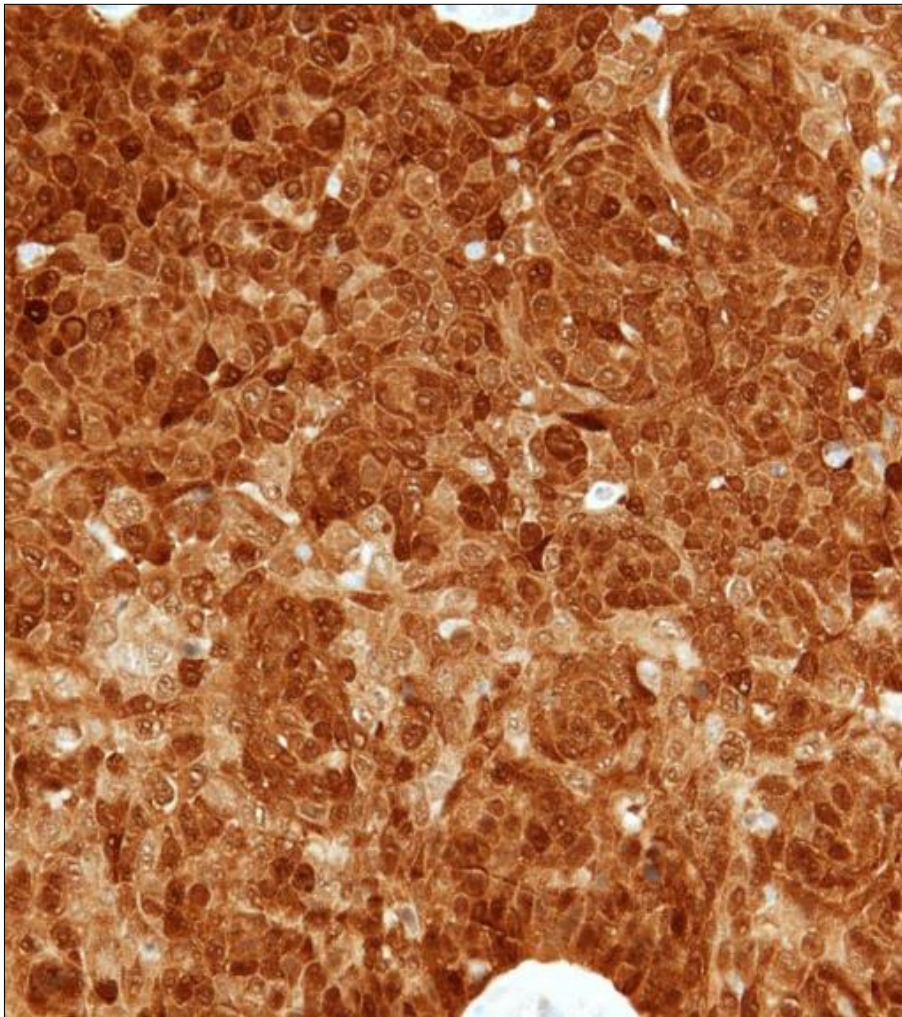
p16^{INK4}

+

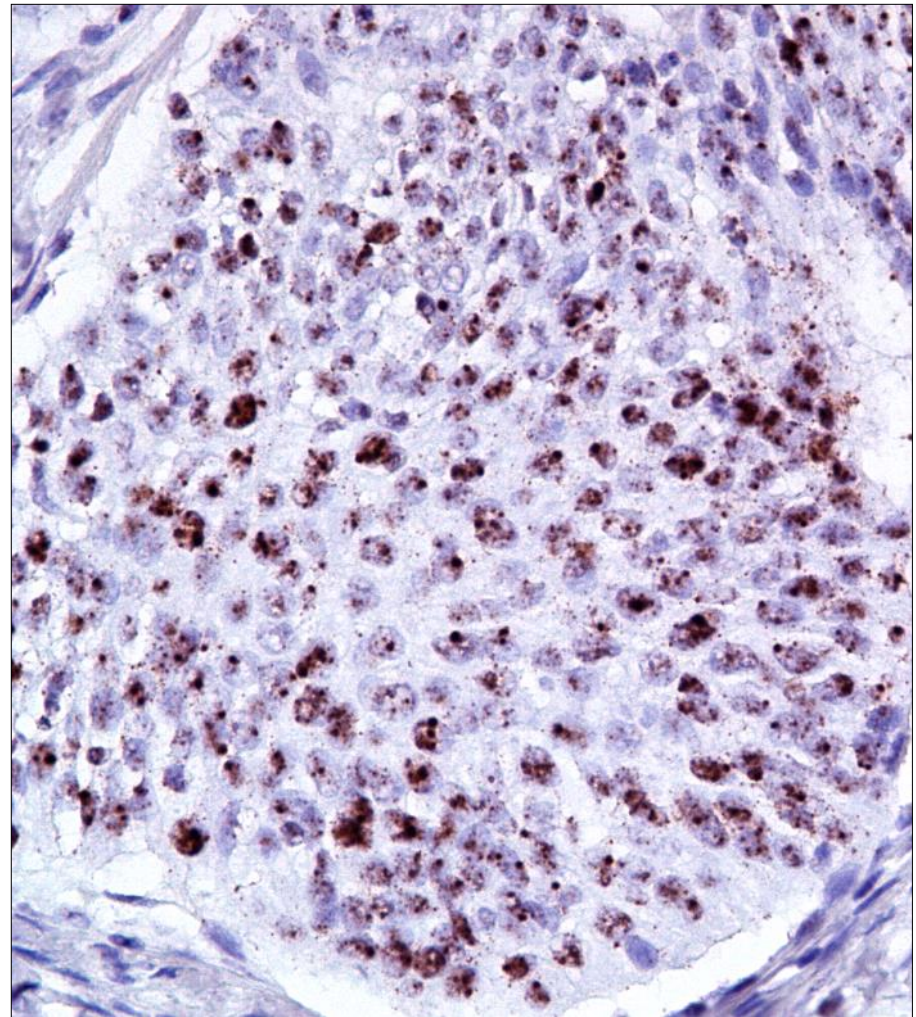
izražanje E6/E7 mRNA

visokorizičnih HPV





p16



E6/E7 mRNA in situ hibr.

HPV-poz. karcinom nosne votline in obnosnih sinusov

HPV in sinonazalni karcinom

- 2. najpogostejša lokacija v področju glave in vratu
- HPV v 20-30 % sinonazalnih tumorjev
- HPV 16, 18, 31, 33
- neporoženevajoč sinonazalni PK (41%)
- poroženevajoč sinonazalni PK (5%)
- Nova entiteta: **HPV-poz. multifenotipični sinonazalni karcinom**
- ostali tumorji (papilarni, bazaloidni, adenoskvamozni, nevroendokrini karcinom)

HPV in karcinom grla in ustne votline

Prevalenca HPV v karcinomu grla in ustne votline: <4%

J Cancer Res Clin Oncol

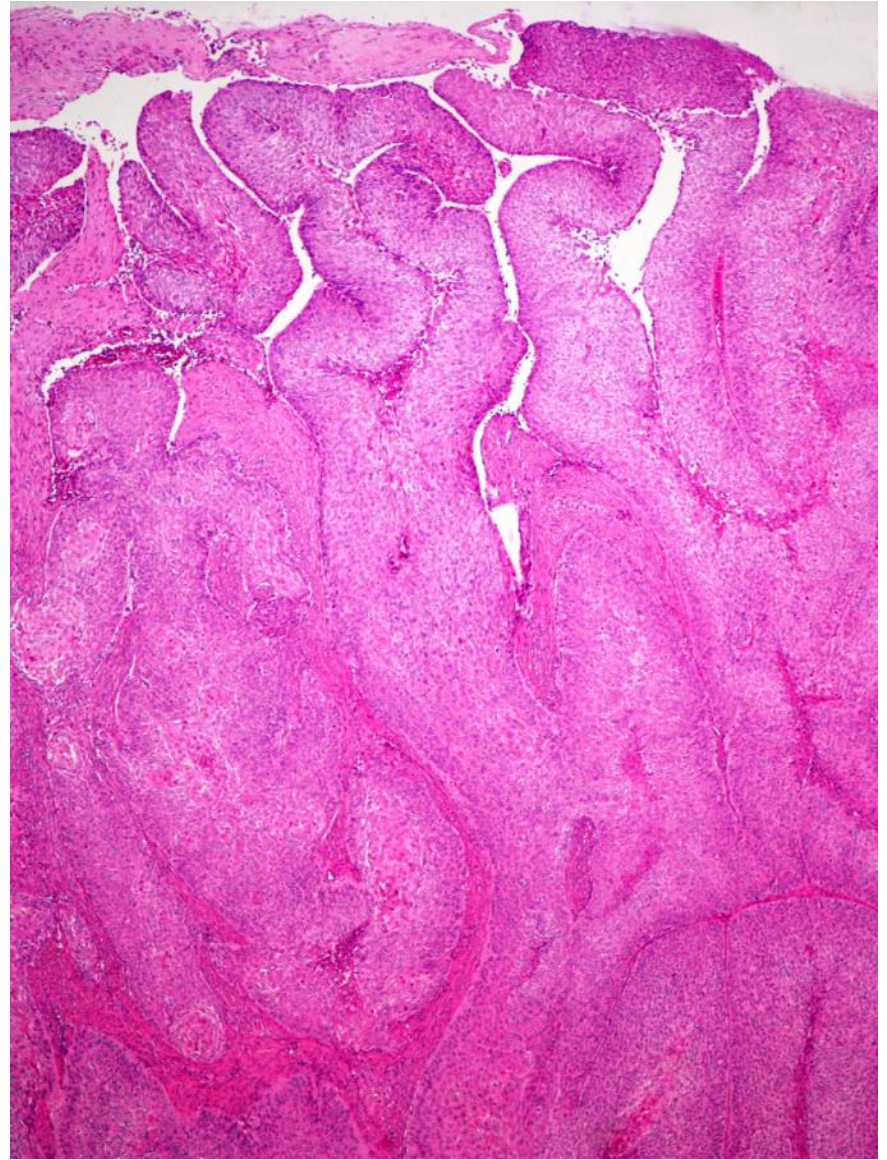
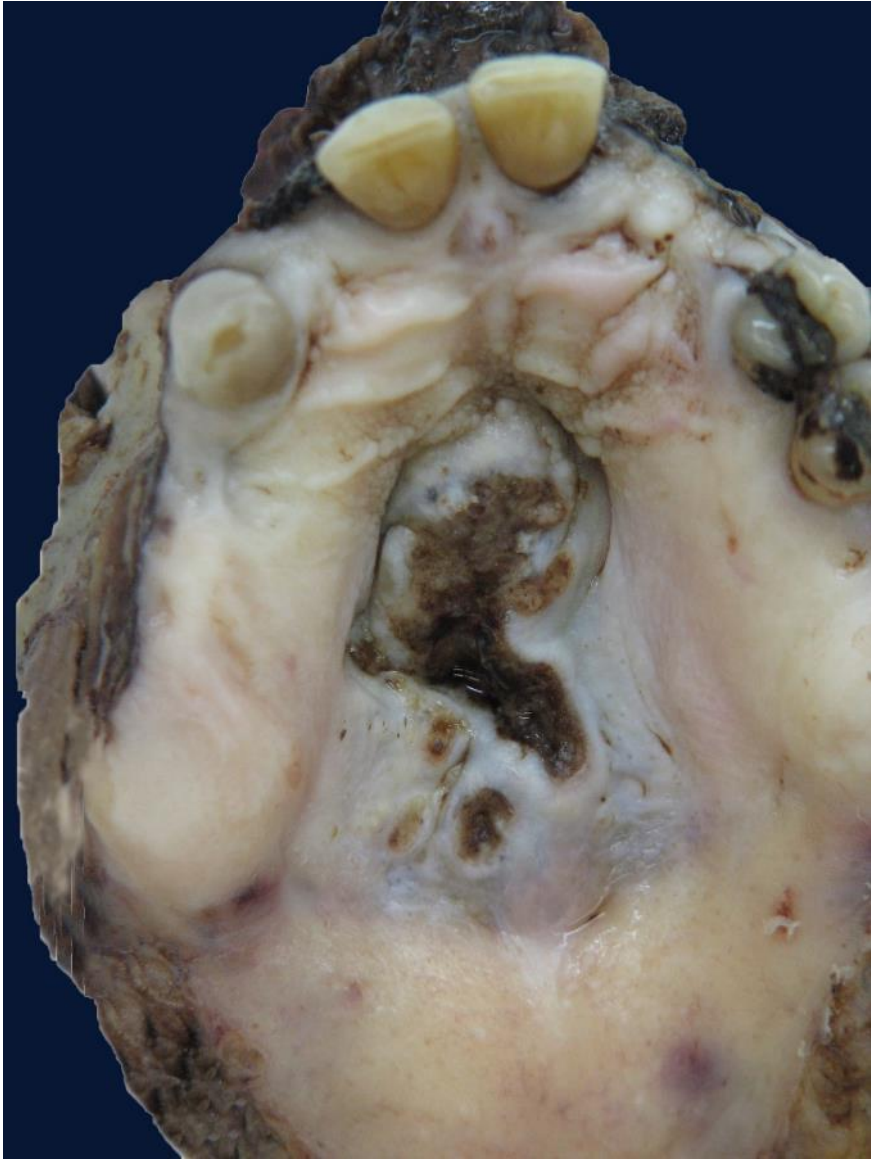
DOI 10.1007/s00432-017-2481-8

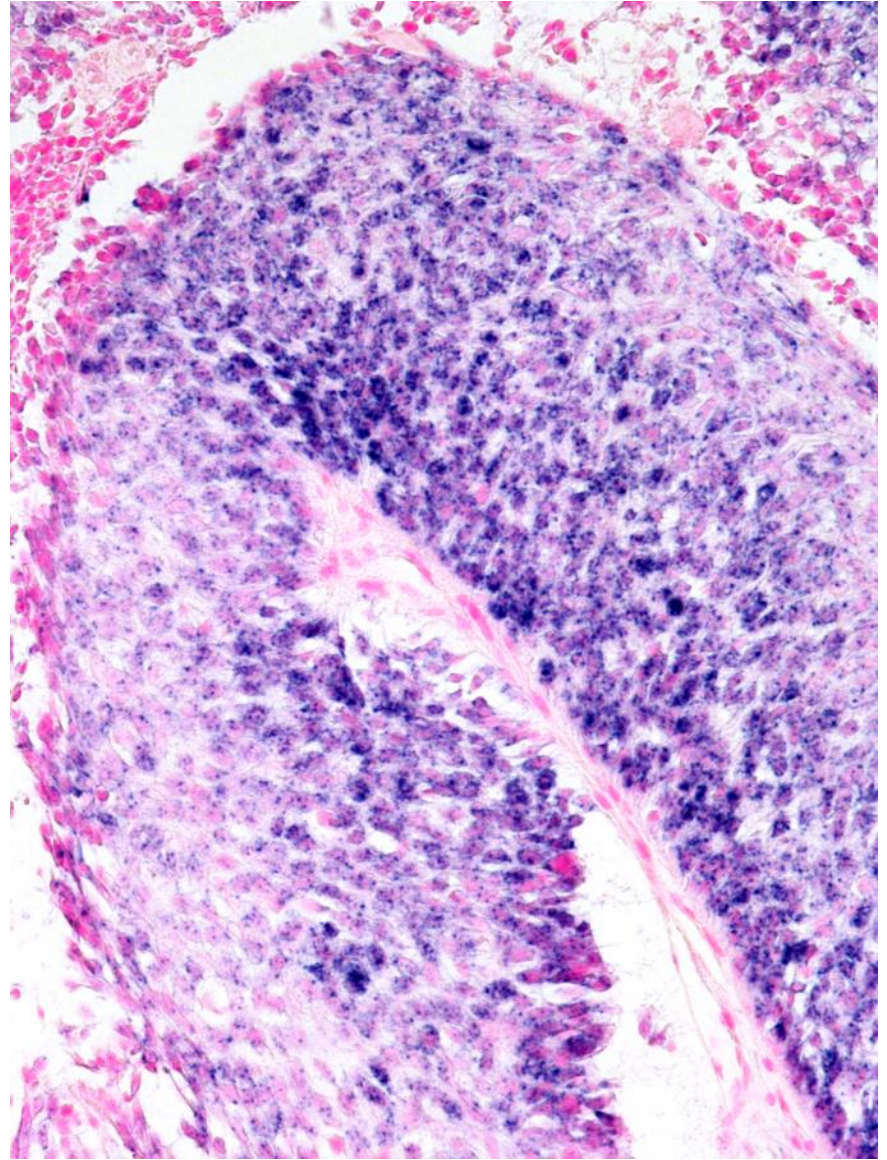
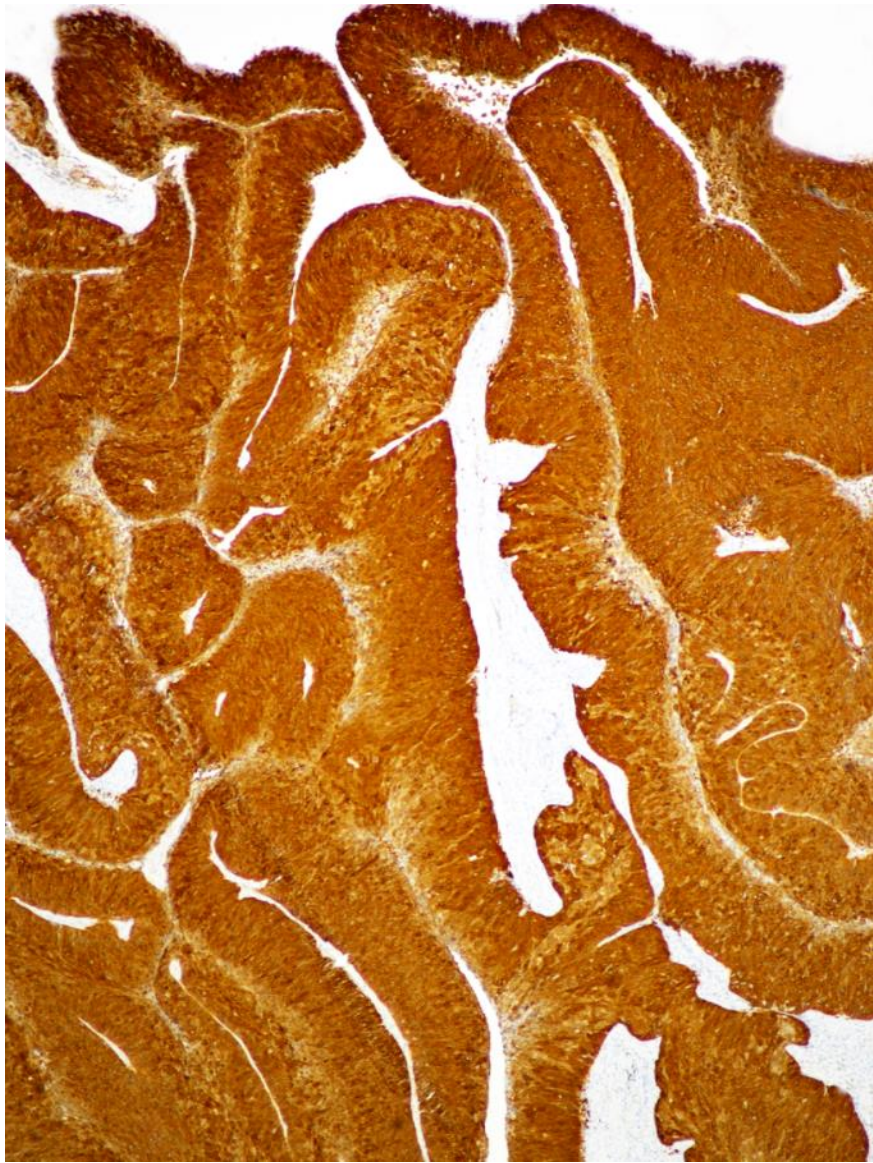
ORIGINAL ARTICLE – CLINICAL ONCOLOGY

**Prognostic implications of human papillomavirus status
for patients with non-oro-pharyngeal head and neck squamous cell
carcinomas**

Huaising C. Ko¹ · Paul M. Harari¹ · Ryan M. Sacotte² · Shuai Chen³ ·
Aaron M. Wieland⁴ · Menggang Yu³ · Andrew M. Baschnagel¹ · Justine Y. Bruce⁵ ·
Randall J. Kimple¹ · Matthew E. Witek¹

Overall survival was significantly higher for patients with HPV-
pos. versus HPV-neg. non-oro-pharyngeal SCC.





Tehnika zaledenelega reza



INSTITUTE OF PATHOLOGY

UNIVERSITY OF LJUBLJANA ♦ FACULTY OF MEDICINE

Tehnika zaledenelega reza

- intraoperativna/urgentna diagnostika
- izvid v 10 min
- omejitve
- kvaliteta preparatov slabša
- pomembna pravilna indikacija
- pomembne izkušnje sodelujočih

“I wish you pathologists could tell us if a tissue is cancer or not while the patient is on the table.”
(dr. William Mayo, 1905)



Patolog dr. Louis B. Wilson, Mayo klinika, Rochester, ZDA, I. 1905

Journal of American
Medical Association (JAMA)
dec. 1905

1737

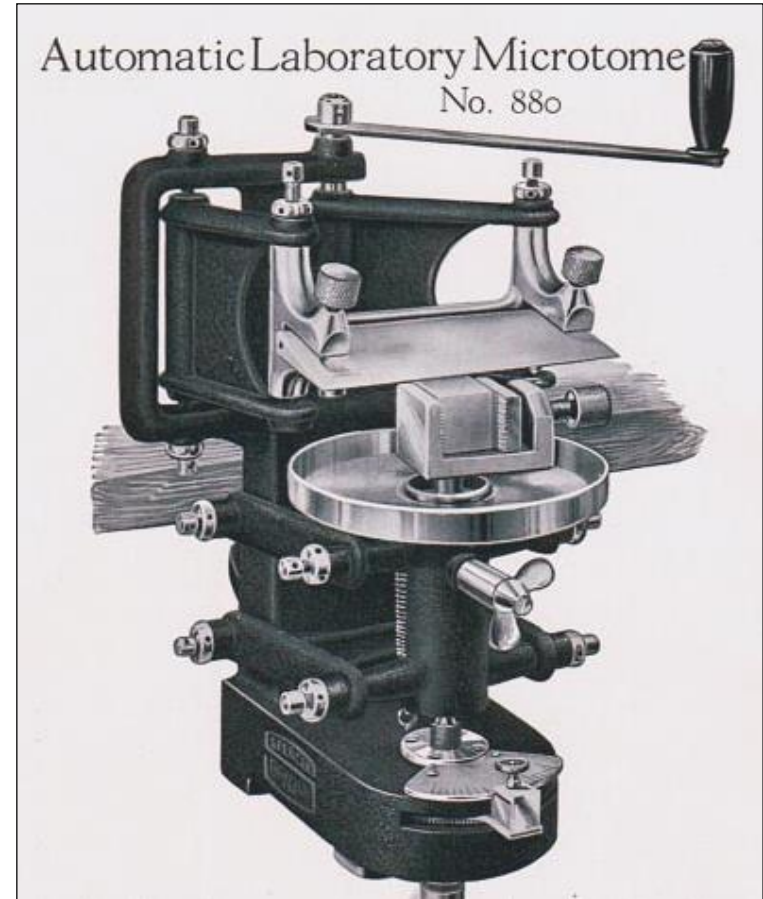
A METHOD FOR THE RAPID PREPARATION OF FRESH TISSUES FOR THE MICROSCOPE.

LOUIS B. WILSON, M.D.
Pathologist St. Mary's Hospital.
ROCHESTER, MINN.

While engaged in general pathologic work I shared the common distrust of frozen sections of fresh tissues for microscopic diagnosis. On taking charge recently of the laboratories of the Drs. Mayo, surgeons, I carefully tested the various methods hitherto published and found them either too slow for results while the patient waits under the anesthetic or else giving poorly differentiated cell detail. After considerable experimentation the following technic was discovered, and for the last six months it has given uniformly excellent preparations:

1. Bits of fresh tissue not more than 2x10x10 mm. are frozen in dextrin solution and cut in sections of from 10 to 15 microns thick.
2. The sections are removed from the knife with the tip of the finger and allowed to thaw thereon.
3. The sections are unrolled with camel's-hair brushes in 1 per cent. NaCl solution.
4. The sections are stained from 10 to 20 seconds in neutral Unna's polychrome methylene blue.
5. They are washed out in 1 per cent. NaCl solution.
6. They are mounted in Brun's glucose medium.

Patolog dr. Louis B. Wilson, Mayo klinika, Rochester, ZDA, I. 1905



Tehnika zaledenelega reza:

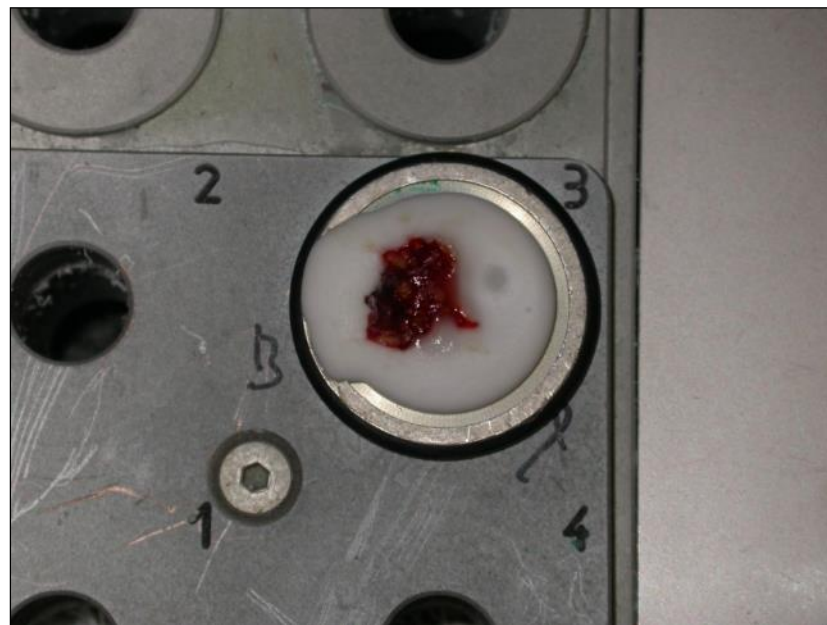
kriostat z mikrotomom, medij, izkušena ekipa, indikacije



Tehnika zaledenelega reza



Tehnika zaledenelega reza



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Tehnika zaledenelega reza



Indikacije za intraoperativno/urgentno diagnostiko (z zaledenelim rezom)

"There is a very simple question that the surgeon should ask himself in deciding whether a frozen section should be done or not: will the result of the frozen section examination influence in any way the surgical procedure?"

(Juan Rosai)

Indikacije za intraoperativno/urgentno diagnostiko (z zaledenelim rezom)

1. Postavitev diagnoze
2. Ugotoviti, ali je odvzeto tkivo ustrezno za postavitev diagnoze
3. Ugotoviti razširjenost tumorja (“staging”)
4. Ugotoviti, če je tumor odstranjen v celoti (če kirurški robovi potekajo v zdravem)
5. Biopsija varovalne bezgavke