

Nasopharyngeal Carcinoma

Epidemiology · EBV association · Histopathology · Clinicopathologic correlation

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Learning objectives

- Describe the geographic and environmental associations of nasopharyngeal carcinoma.
- Recognize the WHO histologic subtypes and hallmark nonkeratinizing morphology.
- Explain tissue EBV testing and its distinction from circulating EBV assays.
- Integrate clinical presentation, diagnostic workup, and histology-related treatment response.

Disease definition and scope

- A malignant epithelial tumor arising from the nasopharyngeal mucosa.
- The major carcinomas show squamous differentiation, with variable keratinization.
- The disease is biologically distinctive because of geography, lymphoid-rich tissue, and EBV association.

Where the nasopharynx fits

NASOPHARYNX

Posterior to the nasal cavity

OROPHARYNX

Adjacent lymphoid tissue and
cervical lymphatic drainage

HYPOPHARYNX

Original teaching schematic — not a diagnostic specimen

Four recurring features of nasopharyngeal carcinoma

Geography

Marked regional variation, including endemic populations in southern China and Southeast Asia.

Lymphoid microenvironment

Carcinoma cells frequently coexist with abundant reactive lymphocytes.

Epstein–Barr virus

Strong tumor-associated EBV signal is typical of nonkeratinizing NPC.

Clinical nodal disease

Cervical nodal metastasis may be prominent even when nasal symptoms are modest.

Geographic distribution: High-incidence regions

Southern China

A major endemic region highlighted by the primary textbook.

Southeast Asia

Several populations have high NPC burden.

North Africa

The disease is geographically enriched in parts of this region.

Arctic Indigenous populations

Inuit populations in Alaska and Canada are specifically noted.

Why geographic epidemiology matters

- Geographic clustering changes the pretest probability of NPC in relevant clinical settings.
- Marked variation implies that infection alone does not fully explain risk.
- Population-level associations must not be treated as diagnostic criteria for an individual patient.

Exposure patterns linked to NPC

Diet-associated risks

- Salted fish and fermented foods are cited in high-exposure diets.
- Nitrosamines are implicated in preserved food exposures.

Environmental insults

- Tobacco smoking is listed as an associated exposure.
- Chemical fumes are another cited environmental exposure.

EBV infection is associated with—rather than synonymous with— NPC

- EBV is closely associated with nonkeratinizing NPC.
- Many individuals acquire EBV without developing nasopharyngeal carcinoma.
- Risk is multifactorial: Viral, environmental, and host-related factors may act together.

Multifactorial etiologic model

Viral association

EBV in malignant epithelial cells

Environmental exposure

Preserved foods, tobacco, and
chemical fumes

Host and population context

Regional and individual
susceptibility

Interacting associations — no fixed sequence or single sufficient cause

Conceptual schematic; Contribution of each factor varies across populations

Why tumor-associated EBV is distinctive

- EBV can be detected in malignant epithelial cells in nonkeratinizing carcinoma.
- A lymphoid-rich background does not itself establish EBV-driven carcinoma.
- Tissue localization is important: EBV must be interpreted in the tumor-cell compartment.

EBV tissue detection: The principle of EBER in situ hybridization

- EBV-encoded small RNAs (EBERs) can be demonstrated by in situ hybridization.
- A positive signal localized to malignant epithelial nuclei supports EBV-associated NPC.
- The test helps distinguish true EBV-positive tumor cells from EBV-bearing bystander lymphocytes.

EBV serology: Key Principles

- Patients with nonkeratinizing NPC often show antibodies to EBV early antigens.
- Antibodies to viral capsid antigens may also be present.
- Serologic association is not equivalent to proving EBV within the tumor tissue.

Circulating EBV DNA: Blood-based tumor marker context

- PCR detection of EBV DNA in blood serum.
- Contemporary clinical pathways commonly use pretreatment plasma EBV DNA as a biomarker.
- Blood viral DNA testing complements, but does not replace, histopathologic diagnosis.

Three EBV-related laboratory approaches

Assay	Specimen	Main interpretation
EBER in situ hybridization	Tumor biopsy	Localizes latent EBV RNA to lesional cells
EBV antibody serology	Blood	Evidence of immune response; Limited tissue specificity
EBV DNA PCR	Serum or plasma	Circulating viral DNA biomarker; Contextualize clinically

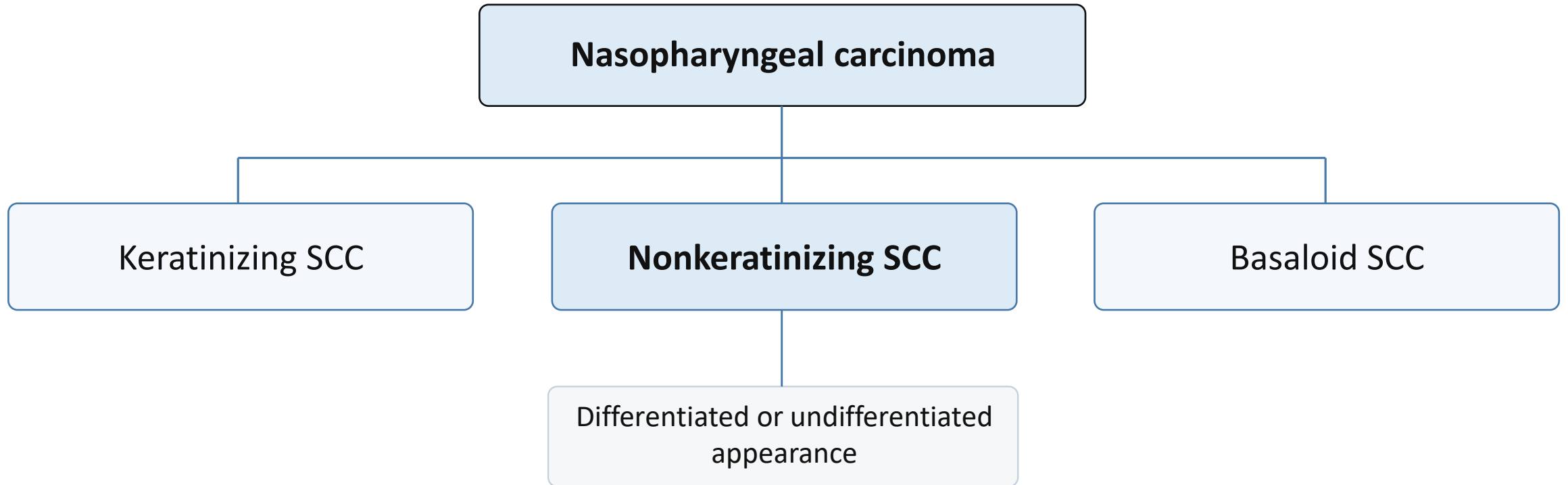
What constitutes strong diagnostic evidence?

- Morphologically malignant epithelial cells are the primary diagnostic evidence.
- Demonstrated epithelial lineage helps exclude a primary hematolymphoid neoplasm.
- EBER positivity in the tumor-cell nuclei supports EBV-associated NPC.

Current histologic classification

Subtype	Characteristic morphology
Keratinizing squamous cell carcinoma	Squamous differentiation with keratinizing phenotype
Nonkeratinizing squamous cell carcinoma	Less apparent squamous maturation; Often lymphoid-rich
Basaloid squamous cell carcinoma	Basaloid SCC phenotype; Rare in this site

Classification hierarchy



Classification branches; Not a temporal progression

Historical terminology: Why it should be avoided

- “Lymphoepithelioma” and “lymphoepithelial carcinoma” are legacy labels.
- The names reflect conspicuous lymphoid infiltration but may obscure epithelial tumor identity.
- Use contemporary WHO histologic subtype terminology in pathology reporting.

Keratinizing versus nonkeratinizing NPC

Keratinizing type

- Resembles keratinizing SCC at other mucosal sites.
- Squamous differentiation is conspicuous.
- Shows less favorable radiation response in the Robbins discussion.

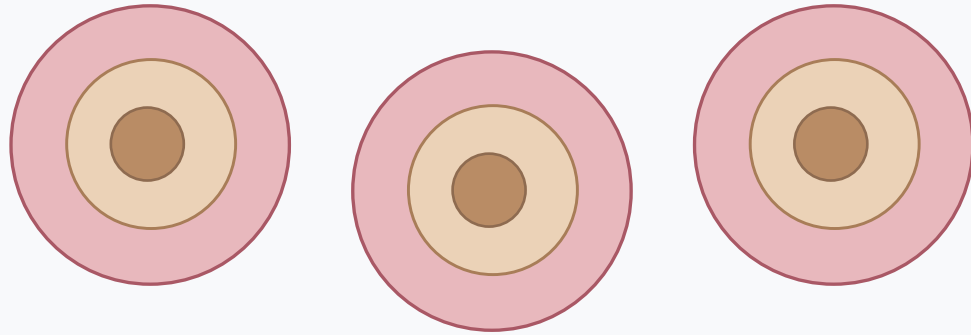
Nonkeratinizing type

- Large epithelial tumor cells may look syncytial.
- Prominent nonneoplastic T-cell-rich infiltrate is typical.
- Strong EBV association and relative radiosensitivity.

Keratinizing carcinoma: Morphologic recognition

- Histology resembles differentiated squamous cell carcinoma elsewhere in the head and neck.
- Identify overt squamous differentiation and keratin formation where present.
- Avoid labeling a carcinoma “keratinizing” solely from location or clinical context.

Keratinizing differentiation: Conceptual drawing



Squamous nests

Central keratinization

Illustrative epithelial
differentiation; Not a
photomicrograph

Original teaching schematic — not a diagnostic specimen

Nonkeratinizing carcinoma: Defining cytologic phenotype

- Large malignant epithelial cells occur in nests, sheets, or less well-demarcated aggregates.
- Nuclei are typically round or oval and vesicular, often with conspicuous nucleoli.
- Indistinct cell borders produce the appearance of multinuclear continuity (syncytium).

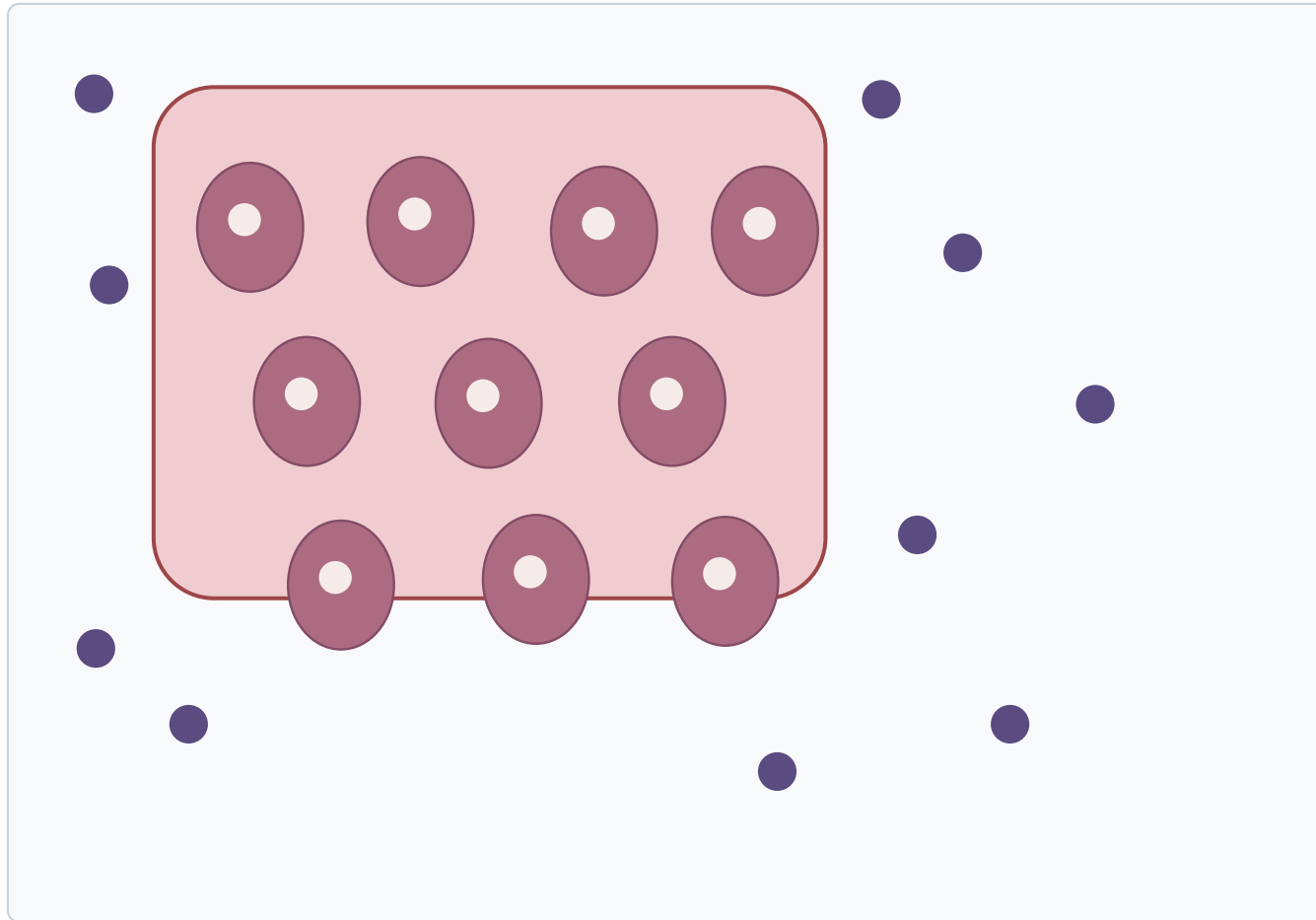
Vesicular nuclei and conspicuous nucleoli

- Open-appearing chromatin produces the vesicular nuclear appearance.
- Prominent nucleoli are a clue to the large malignant epithelial population.
- These features must be judged alongside invasion, epithelial lineage, and the inflammatory context.

Syncytial appearance: What it actually means

- Individual tumor-cell borders are difficult to resolve on H&E.
- Adjacent epithelial cells therefore appear to form a continuous sheet.
- Syncytial morphology is a visual descriptor, not proof of cell fusion or a specific molecular mechanism.

Nonkeratinizing carcinoma and lymphocytes



Tumor epithelial nuclei

Indistinct cell borders →
syncytial appearance

Small infiltrating T lymphocytes
(non-neoplastic)

Original teaching schematic — not a diagnostic specimen

Tumor-associated lymphocytes are predominantly reactive

- The lymphoid infiltrate is often abundant and normal in cytologic appearance.
- A predominant T-cell component.
- Large epithelial tumor cells—not the small lymphocytes—constitute the carcinoma.

Tumor population versus reactive lymphocytes

Carcinoma cells

- Larger cells with vesicular nuclei and prominent nucleoli.
- Epithelial lineage demonstrable by cytokeratin expression.
- Tumor-cell EBER positivity is diagnostically informative.

Lymphocytes

- Generally smaller with denser nuclear chromatin.
- Primarily T-cell-rich reactive infiltrate in classic tumors.
- Their presence does not convert the lesion into lymphoma.

Morphologic patterns within nonkeratinizing NPC

Cohesive epithelial islands

Recognizable nests may remain distinct from the lymphoid stroma.

Diffuse admixture

Malignant cells may be interspersed with dense lymphocytes.

Cytologic continuity

Vesicular nuclei and indistinct borders remain recurring clues.

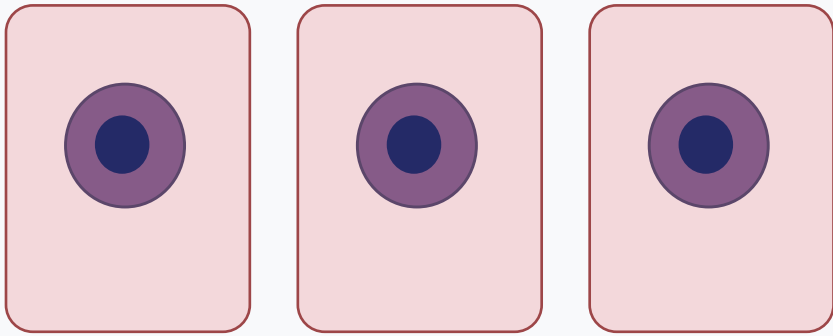
Interpretation

Patterns vary; Adequate recognition of epithelial tumor cells is essential.

Why a lymphocyte-rich carcinoma can resemble lymphoma

- Diffuse lymphocytic admixture may dominate a small or crushed biopsy.
- Poorly demarcated epithelial tumor cells may be overlooked.
- A lineage-directed panel and EBER localization help resolve the mimic.

EBER: Localization to epithelial tumor nuclei



EBER nuclear signal

In-situ hybridization localizes viral RNA inside malignant epithelial cells

Original teaching schematic — not a diagnostic specimen

EBER versus LMP1: Different analytic targets

- EBER in situ hybridization detects EBV-encoded RNA in tissue sections.
- LMP1 immunohistochemistry detects an EBV-associated protein.
- Do not assume LMP1 staining must be present in every EBV-associated carcinoma; EBER is the standard tissue assay.

Practical interpretation of EBER staining

- Confirm nuclear signal in unequivocally malignant epithelial cells.
- Account for the possibility of positive background lymphoid cells.
- A negative or technically limited result requires correlation with morphology and assay controls.

Epithelial lineage: Why cytokeratins matter

- Pan-cytokeratin positivity supports epithelial differentiation in a lymphoid-rich tumor.
- P40/p63 may support squamous differentiation in an appropriate immunophenotypic context.
- Marker expression complements morphology; No single stain should be read in isolation.

Pathology diagnosis: Integrated reasoning



- Report the contemporary NPC subtype and clinically useful ancillary findings.
- Tissue diagnosis is required before disease-directed management.

Schematic — conceptual sequence, not a quantitative or clinical measurement

Limited-biopsy pitfalls

- Crush artifact can obscure vesicular chromatin, nucleoli, and tumor boundaries.
- Reactive lymphoid tissue may dominate the sampled fragments.
- Sparse carcinoma nests may require deeper levels or targeted immunostains.

Differential: NPC versus lymphoma

Nasopharyngeal carcinoma

- Atypical epithelial cells may be dispersed among lymphocytes.
- Cytokeratin highlights the epithelial tumor population.
- Tumor-cell EBER can support nonkeratinizing NPC.

Lymphoma

- Neoplastic hematolymphoid cells comprise the primary tumor.
- Hematolymphoid lineage markers are decisive.
- EBV positivity alone never defines epithelial origin.

Differential: NPC versus other poorly differentiated tumors

Nonkeratinizing NPC

- Squamous epithelial phenotype may be subtle.
- Commonly associated with epithelial-cell EBER positivity.
- Consider anatomy and clinical findings together.

Other nasopharyngeal tumors

- Neuroendocrine, lymphoid, or undifferentiated tumors can mimic morphology.
- Use a targeted immunopanel rather than a single presumed marker.
- NUT carcinoma is an important rare head-and-neck differential.

Basaloid SCC: Classification is not a catch-all

- Basaloid SCC is a separately recognized, uncommon NPC subtype.
- A basaloid appearance does not by itself establish this specific diagnosis.
- Differential diagnosis includes other small basaloid or poorly differentiated neoplasms.

When the primary tumor is not obvious

- Cervical nodal disease can be the presenting clinical problem.
- Pathologic classification of a nodal metastasis should be integrated with nasopharyngeal examination.
- Avoid assigning the primary site from one marker or histologic feature alone.

Typical presenting symptoms

- Nasal obstruction can result from a local nasopharyngeal mass.
- Epistaxis reflects clinically evident bleeding from the upper aerodigestive site.
- Cervical lymph-node metastases are commonly present at diagnosis.

Nasal obstruction: The clinical clue

- Persistent unilateral or unexplained obstruction warrants examination when other red flags coexist.
- Symptoms can be confused with inflammatory or benign nasopharyngeal disorders.
- Structural assessment and biopsy are essential when a suspicious lesion is identified.

Epistaxis: Contextual interpretation

- Epistaxis is one of the clinical manifestations explicitly.
- It is a nonspecific symptom; Malignancy is considered in the context of a mass, nodal disease, or risk factors.
- Associated obstruction or cervical adenopathy should increase diagnostic concern.

Cervical nodal metastasis is a major presenting feature

- Ipsilateral cervical lymph-node metastases in up to 70% of patients.
- This is a quoted textbook figure, not an estimate for every population or clinical series.
- The finding underscores the need to examine both the nasopharynx and cervical lymphatic chain.

Nasopharynx to cervical nodal disease



- Retropharyngeal lymph nodes are a first-echelon drainage site in clinical staging descriptions.
- A neck mass may draw attention before the nasopharyngeal lesion is recognized.

Schematic — conceptual sequence, not a quantitative or clinical measurement

Why presentation may occur at advanced stage

- Early nasal symptoms may be subtle or attributed to common benign causes.
- The nasopharynx is not directly visible on routine external examination.
- Locoregional extension and lymph-node spread can precede definitive diagnosis.

Cranial-nerve and skull-base evaluation

- Advanced local extension can involve skull-base and adjacent neural structures.
- NCI staging guidance emphasizes careful cranial-nerve functional examination.
- New focal neurologic symptoms require integration with endoscopic and imaging findings.

Clinical diagnostic pathway



- Confirm carcinoma on tissue rather than relying on EBV serology or imaging alone.
- Plan regional and distant disease assessment after a tissue diagnosis.

Schematic — conceptual sequence, not a quantitative or clinical measurement

Imaging: The questions MRI helps answer

- MRI is especially useful for soft-tissue extent and the relationship to the skull base.
- It can help evaluate intracranial extension more fully than CT alone.
- Pathologic confirmation remains mandatory even when imaging strongly suggests NPC.

PET/CT and staging context

- PET/CT can contribute to nodal and distant metastatic evaluation.
- It may also support radiation treatment planning.
- Choice and sequencing of imaging depend on clinical stage and local guidance.

Stage assessment: What T, N, and M represent

Component	Clinical question	Typical assessment
T — primary tumor	Where has the local tumor extended?	Endoscopy and cross-sectional imaging
N — regional nodes	Which regional nodal stations are involved?	Clinical exam and imaging
M — distant metastasis	Is disease present beyond locoregional sites?	Systemic staging imaging when indicated

Staging is not the same as histologic subtype

- Histologic subtype describes the tumor's differentiation phenotype.
- TNM stage describes anatomic disease extent.
- Prognosis and treatment planning require both, together with the clinical context.

Why radiotherapy is central to NPC management

- Radiotherapy as a principal standard treatment.
- Local anatomy and tumor radiosensitivity make nonsurgical management important.
- Modern management is stage-dependent and may combine radiation with systemic therapy.

Radiation response differs by histologic subtype

Nonkeratinizing NPC

- Undifferentiated morphology is associated with greater radiosensitivity.
- A strong EBV association characterizes most of this category.

Keratinizing NPC

- Keratinizing tumors are relatively less radiosensitive.
- Substantially less favorable historical survival.

Textbook survival statistics: Interpret in context

- Approximately 60% overall 5-year survival in the passage.
- It gives stage-dependent 5-year survival of 70%–98% for nonkeratinizing tumors and about 20% for the keratinizing form.
- These are textbook-reported historical figures, not individualized predictions or a replacement for contemporary stage-specific estimates.

Advanced and recurrent disease: Treatment context

- Disease that is metastatic or no longer amenable to local therapy may require systemic treatment.
- NCI and updated clinical guidance describe multimodality management depending on stage and fitness.
- The pathology lecture emphasis is how subtype, extent, and clinical setting inform the treatment pathway.

Checkpoint inhibitors in advanced NPC

- Checkpoint-inhibitor use for selected advanced or recurrent cancers.
- Clinical decisions depend on disease setting and contemporary treatment guidelines.
- Do not infer benefit for every histologic subtype or patient from the fact that an agent is available.

Diagnostic versus prognostic biomarkers

Marker / variable	Role in NPC	Important limitation
Tumor-cell EBER	Supports EBV-associated NPC diagnosis	Interpret only in malignant epithelial cells
Circulating EBV DNA	Clinical biomarker for disease burden / prognosis	Does not replace biopsy or anatomical staging
Histologic subtype	Morphologic classification; Response association	Stage and treatment modify outcomes
Anatomic stage	Extent-based prognostic framework	Not interchangeable with differentiation

Case 1: Nasal symptoms with cervical adenopathy

A patient from a high-incidence region has persistent nasal obstruction, intermittent epistaxis, and an enlarged upper cervical lymph node. Endoscopy identifies a suspicious nasopharyngeal lesion.

- Which specimen establishes the primary diagnosis?
- Which histologic and viral features would favor nonkeratinizing NPC?

Case 1: Diagnostic reasoning



- Regional imaging helps characterize locoregional spread after pathologic confirmation.
- Risk-region background supports suspicion, but does not itself diagnose carcinoma.

Schematic — conceptual sequence, not a quantitative or clinical measurement

Case 2: A lymphocyte-rich small biopsy

An endoscopic biopsy contains numerous small lymphocytes and scattered large atypical cells with vesicular nuclei, conspicuous nucleoli, and indistinct membranes.

- What critical lineage question must be answered?
- How would cytokeratins and EBER be interpreted together?

Case 2: Resolving the lineage problem

Morphologic reasoning

- Large atypical cells stand out from small reactive lymphocytes.
- Indistinct borders suggest a syncytial epithelial tumor phenotype.

Ancillary-test reasoning

- Cytokeratin staining supports the epithelial malignant-cell population.
- EBER nuclear labeling in those cells supports EBV-associated NPC.

Diagnostic synthesis: Characteristic patterns

Feature	Nonkeratinizing NPC	Keratinizing NPC
Squamous maturation	Often subtle	Conspicuous / keratinizing
Tumor cell borders	Frequently indistinct	Often more apparent
Lymphoid background	Commonly prominent	Variable
EBV association	Strong in most cases	Less consistent
Radiosensitivity	Greater	Lower

Five high-yield recognition points

- Think of NPC when nasal symptoms coexist with unexplained cervical lymphadenopathy.
- Classify the tumor as keratinizing, nonkeratinizing, or basaloid SCC.
- Nonkeratinizing NPC often has syncytial tumor cells in a dense T-cell-rich background.
- EBER must be localized to malignant epithelial cells, not simply present in the biopsy.
- Interpret treatment response and survival using both histology and stage.

Selected references and source scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026; Ch. 16, pp. 674–675.
- WHO Classification of Tumours Editorial Board. Head and Neck Tumours. 5th ed. IARC; 2024 (NPC, pp. 117–126).
- Badoual C, et al. Update from the WHO 5th edition: Oropharynx and Nasopharynx. Head Neck Pathol. 2022.
- National Cancer Institute. Nasopharyngeal Carcinoma Treatment (PDQ), Health Professional Version.
- SEOM–TTCC clinical guideline for nasopharyngeal carcinoma (2025 update).

Primary textbook claims and newer clinical/classification material are distinguished in slide speaker notes.