

Testicular Lymphoma

Clinicopathologic diagnosis, molecular biology, and relapse patterns

Pathology lecture

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Learning objectives

- Distinguish primary testicular lymphoma from germ-cell and stromal tumors.
- Recognize diffuse large B-cell lymphoma and the relevant diagnostic immunophenotype.
- Explain the basis and clinical significance of immune-privileged-site biology.
- Connect pathology to staging, central nervous system risk, and management.

An older man with an enlarging testis

An older man presents with a newly enlarged, firm testis. A solid mass is demonstrated clinically.

Hypothetical teaching case — Question

Which diagnosis becomes especially important because of his age?

Teaching answer: Primary testicular lymphoma must be considered; Germ-cell tumors remain an important differential.

Primary testicular lymphoma: The definition

A hematolymphoid malignancy presenting in the testis as the primary disease site.

- The designation “primary” requires clinical staging and exclusion of dominant systemic lymphoma.
- Histology establishes the lymphoma subtype; Location alone does not.

An uncommon testicular malignancy

2%–5%

Of testicular neoplasms in the Robbins
account

- Despite its rarity overall, testicular lymphoma is a major diagnosis in older patients.
- This estimate pertains to primary testicular lymphomas, not all lymphomas with testicular involvement.

Age changes the leading differential

Most younger adult masses

- Germ-cell tumors dominate overall.
- Seminoma and nonseminomatous GCTs are major categories.

Men older than 60 years

- Lymphoma becomes the most common testicular neoplasm in this age group.
- A “classic GCT” presumption may be misleading.

The main neoplastic lineages

Tumor family	Typical identity	Key diagnostic question
Germ-cell tumors	Seminoma and nonseminomatous GCTs	Germ-cell differentiation?
Sex cord–stromal tumors	Leydig and Sertoli lineages	Stromal / sex-cord differentiation?
Lymphomas	Mature B-cell or rarer other lineage	Hematolymphoid phenotype?

Primary versus secondary testicular involvement

Primary testicular lymphoma

- Testis is the presenting dominant disease site.
- Extragonadal disease may still be discovered on staging.

Secondary testicular lymphoma

- A pre-existing or predominant systemic lymphoma involves the testis.
- The distinction requires chronology and distribution.

Why “primary” cannot be assigned by microscopy alone

- The same DLBCL morphology can occur in both primary and secondary testicular disease.
- The clinical history and disease distribution define the primary site.
- Diagnostic reporting should describe the observed histologic type without inferring unsupported chronology.

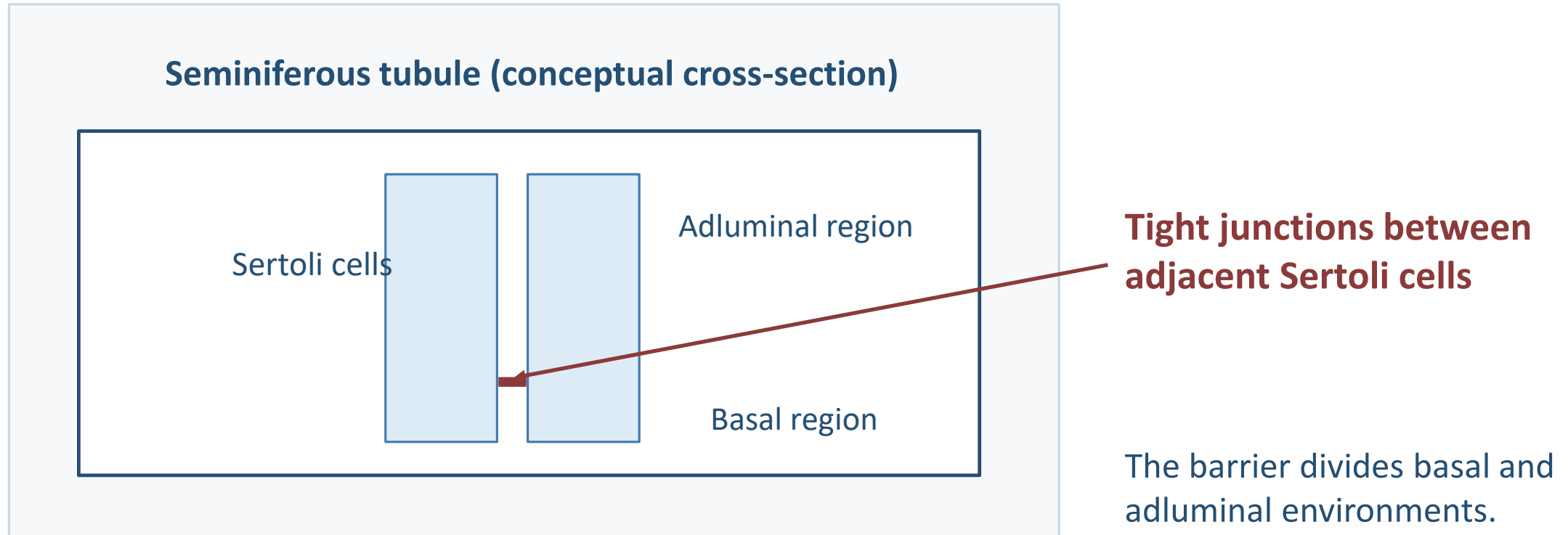
The testis is an immune-privileged site

The testicular microenvironment restricts immune exposure to developing germ cells.

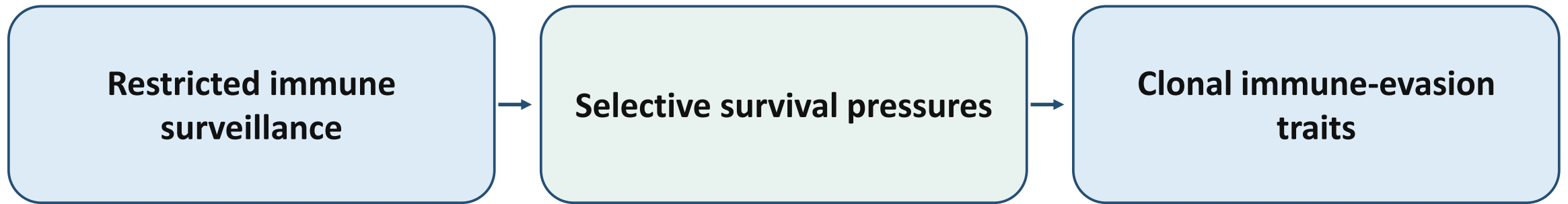
- The blood–testis barrier is created largely by junctions between Sertoli cells.
- Immune privilege modifies local immunity; It does not mean absolute immune isolation.

Blood–testis barrier: Anatomic principle

Original conceptual schematic — not a histological specimen



Immune privilege and lymphoma biology



Conceptual sequence: Mechanisms vary by tumor; Not every case carries the same alterations.

Anatomical immune barriers: The clinical connection

- The testis and CNS occupy specialized immune environments.
- Testicular DLBCL shares biological features with primary CNS / vitreoretinal large B-cell lymphomas.
- These relationships help explain their distinctive relapse patterns, but do not establish a single metastatic route.

WHO-HAEM5: Immune-privileged-site large B-cell lymphomas

Primary large B-cell lymphomas of immune-privileged sites form a shared classification group.

- The WHO-HAEM5 group covers primary CNS, vitreoretinal, and testicular large B-cell lymphomas in immunocompetent hosts.
- This grouping does not reclassify every testicular lymphoma as a large B-cell lymphoma.

Three lymphoma types named by Robbins

Relative order in text	Histologic type	Major defining axis
Most common	Diffuse large B-cell lymphoma	Aggressive mature B-cell lymphoma
Next	Burkitt lymphoma	MYC-driven mature B-cell lymphoma
Next	EBV-positive extranodal NK/T-cell lymphoma	EBV-associated NK/T-cell lineage

DLBCL is the principal testicular lymphoma subtype

Diffuse large B-cell lymphoma (DLBCL) is the diagnostic anchor.

- DLBCL consists of sheets of transformed large B cells.
- Primary testicular DLBCL commonly shows an activated B-cell / non-germinal-center phenotype.

Do not equate subtype and site

DLBCL

- Defined by large neoplastic B cells and diffuse growth.
- Can arise at many nodal and extranodal sites.

Testicular DLBCL

- DLBCL in a specific immune-privileged organ.
- Distinct clinical behavior and recurrent molecular patterns.

Burkitt lymphoma: An important alternative

- Mature B-cell neoplasm with very high proliferative activity.
- Characterized by rearrangement of MYC with immunoglobulin loci.
- Typically shows a monomorphic intermediate-sized cytology and a prominent “starry-sky” pattern.
- Testicular involvement is less frequent than DLBCL.

EBV-positive extranodal NK/T-cell lymphoma

- Listed among less frequent testicular lymphoma types.
- It belongs to a different lineage from B-cell DLBCL and Burkitt lymphoma.
- EBV demonstration and lineage-directed immunophenotyping become important in suspected cases.
- Do not label a CD20-positive large B-cell tumor as NK/T lymphoma.

Typical presentation: Testicular enlargement

A progressively enlarging, often painless testicular mass is a central presentation.

- Clinically, the mass may resemble a germ-cell tumor or inflammatory enlargement.
- Age and an infiltrative disease pattern should change the differential.

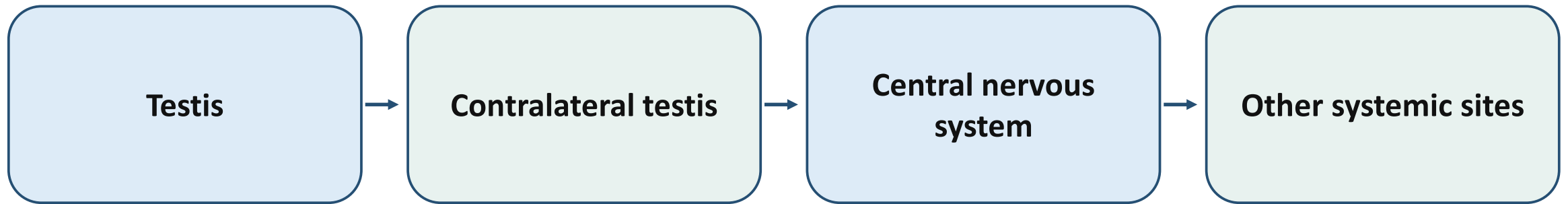
Laterality is diagnostically useful

- Testicular lymphoma may involve both testes.
- That bilaterality is more frequent than in typical germ-cell tumors.
- Contralateral involvement may be synchronous or appear later as relapse.
- A clinically normal opposite testis does not eliminate future relapse risk.

Spermatic-cord involvement

- Frequent extension to the spermatic cord.
- Pathologic assessment should document involvement when present.
- Extension is a distribution finding, not an independent proof of lymphoma subtype.

Potential sites of involvement and recurrence



Boxes represent documented disease sites; Arrows denote clinical evaluation, not a proven obligatory sequence.

The CNS is a critical relapse compartment

A high propensity for CNS involvement distinguishes testicular lymphoma.

- CNS involvement as a frequent site of recurrence.
- CNS risk informs staging, prevention strategies, and surveillance discussions.

Relapse is not restricted to the first months

- Testicular DLBCL may recur at extranodal sites after systemic therapy.
- The contralateral testis and CNS merit specific attention.
- Late relapse has been reported; A single fixed follow-up interval cannot summarize all risk.

Testicular lymphoma versus germ-cell tumor

Germ-cell tumor pattern

- Dominant testicular neoplasm group overall.
- Serum AFP/hCG may aid GCT classification and management.

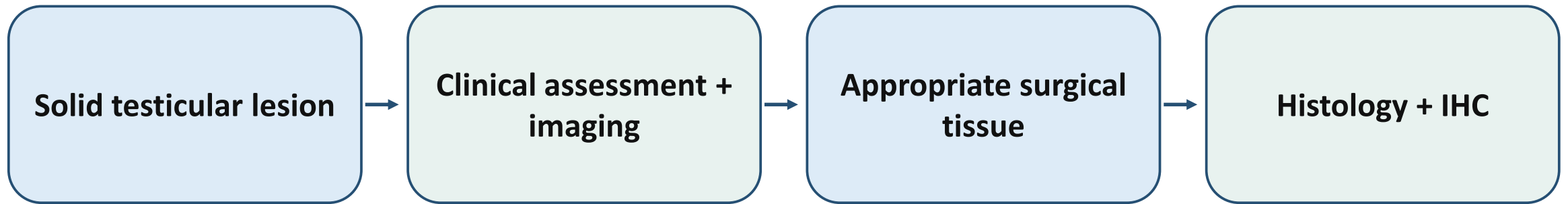
Lymphoma pattern

- Especially important after age 60.
- Bilateral and spermatic-cord involvement are characteristic clues.

Solid testicular mass: Avoid casual sampling

- Radical orchiectomy as the standard management of a suspected solid testicular neoplasm.
- Transscrotal biopsy can cause tumor spillage in the germ-cell-tumor pathway.
- An individualized tissue-acquisition strategy should be determined by the treating team when lymphoma is suspected.

Clinical entry to a tissue diagnosis



A simplified educational pathway; Not a substitute for urologic/hematologic protocols.

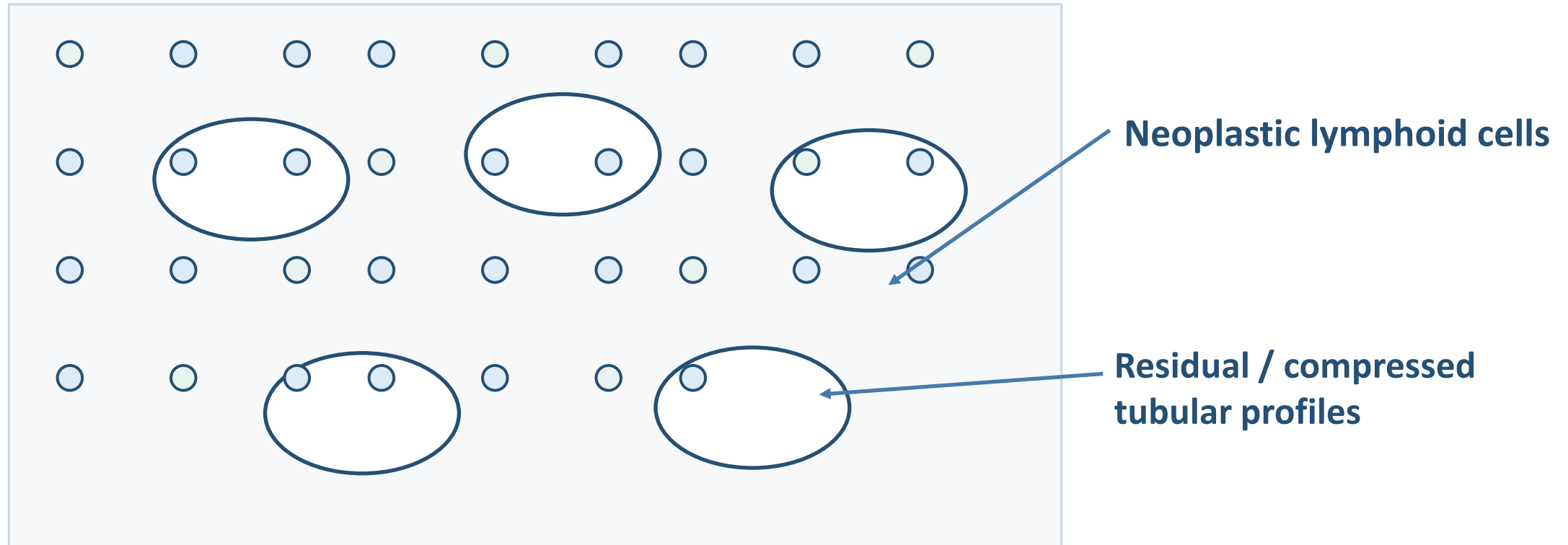
Macroscopic examination: Map the disease

A testicular specimen should be assessed for the mass and its extent.

- Describe distribution in parenchyma, relation to the capsule and rete region, and spermatic-cord involvement.
- Gross appearance alone is insufficient to subtype a lymphoma.

Histologic pattern: Lymphoma within testicular tissue

Original schematic — not a clinical histology image



DLBCL: Recognize the diffuse infiltrate

- An involved tissue may be effaced by a diffuse infiltrate of large lymphoid cells.
- Neoplastic nuclei may show open chromatin and prominent nucleoli.
- Cell size, heterogeneity, apoptosis, and mitotic activity should all be assessed.

Normal tubules versus lymphomatous infiltration

Expected architecture

- Seminiferous tubules separated by interstitium.
- Tubular profiles are recognizable at low power.

Infiltrated testis

- Neoplastic lymphoid infiltrate expands the interstitium.
- Tubules may become separated, compressed, or destroyed.

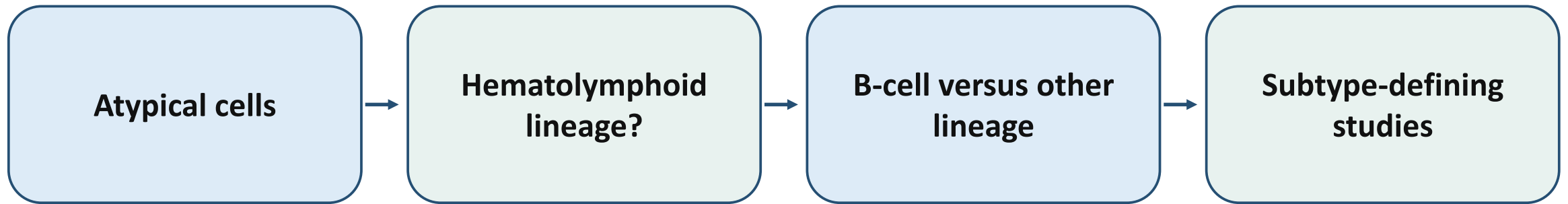
Large B-cell cytology: What to describe

- Cell size relative to adjacent small lymphocytes.
- Nuclear shape and chromatin texture; Nucleolar prominence.
- Degree of cytologic variation and mitotic activity.
- Necrosis and residual testicular structures, if present.

Atypical lymphoid infiltrate: First decisions

- Determine whether the infiltrate is neoplastic or reactive.
- Assess whether tumor cells show large B-cell, smaller monomorphic, or other morphology.
- Use an immunophenotypic panel to confirm lineage rather than relying on nuclear size alone.

A lineage-first immunohistochemistry strategy



Conceptual strategy. Test selection depends on morphology and clinical context.

Core immunophenotypic landmarks

Marker / method	Interpretive role	Limitation
CD20, PAX5, CD79a	Support B-cell differentiation	Expression must be interpreted in the tumor cells
CD10, BCL6, MUM1/IRF4	Characterize B-cell phenotype	No single marker proves testicular origin
Ki-67	Estimate proliferative fraction	High labeling is not a standalone diagnosis
EBER in situ hybridization	Detect EBV within cells	EBV status alone does not determine lineage

Confirm B-cell lineage first

The immunophenotype establishes identity before detailed molecular classification.

- Testicular DLBCL generally expresses mature B-cell antigens such as CD20 and PAX5.
- A broad panel is safer than interpreting a single strongly positive stain.

CD10, BCL6, and MUM1: Interpret together

- These markers are used in immunohistochemical cell-of-origin algorithms.
- Primary testicular DLBCL is commonly non-GCB / activated B-cell–like.
- Protein-expression algorithms are surrogates, not identical to gene-expression profiling.
- Variable staining does not by itself negate a testicular DLBCL diagnosis.

Phenotype is not synonymous with genotype

IHC cell-of-origin surrogate

- CD10 / BCL6 / MUM1 may be used in a practical algorithm.
- Results depend on assay and interpretive rules.

Molecular classification

- Recurrent mutation patterns inform tumor biology.
- Genetic classes are not reducible to one IHC stain.

Proliferation and Ki-67: Use with care

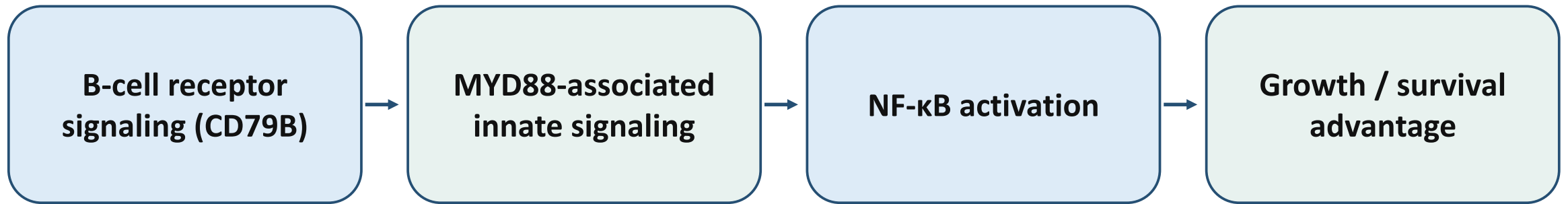
- A high Ki-67 index is consistent with aggressive lymphoma.
- Burkitt lymphoma commonly has a very high proliferation fraction.
- Ki-67 alone cannot distinguish Burkitt lymphoma from other high-grade B-cell neoplasms.
- Quantitative percentages should reflect an actual measured specimen, not a textbook stereotype.

Recurrent MYD88 and CD79B alterations

Testicular large B-cell lymphomas frequently show B-cell signaling pathway alterations.

- MYD88 and CD79B are recurrently altered in immune-privileged-site large B-cell lymphomas.
- They support a shared biological profile; Neither alteration is mandatory in every case.

A simplified B-cell survival pathway



Schematic integration of recurrent biology, not an assay-based diagnosis.

Immune escape is part of the biological picture

- Genetic changes affecting antigen presentation and immune recognition occur in this lymphoma group.
- Alterations involving the PD-L1 / PD-L2 axis have been described.
- These are biological findings; They do not automatically establish responsiveness to a checkpoint inhibitor.

Diagnostic versus prognostic versus predictive

Diagnostic / characterizing evidence

- Morphology plus B-cell markers establishes a mature B-cell lymphoma.
- Genetic findings may refine biological classification.

Outcome / therapeutic implications

- Clinical stage and CNS risk affect management.
- A therapeutic prediction requires validated evidence for that treatment context.

Burkitt: Why MYC matters

- Burkitt lymphoma is driven by MYC rearrangement, commonly with IGH or an immunoglobulin light-chain locus.
- MYC stimulates metabolic and transcriptional programs needed for rapid growth.
- It is important to distinguish this entity from DLBCL with high MYC expression or rearrangement.

Burkitt morphology: “starry sky”

A uniform field of rapidly proliferating tumor cells is punctuated by pale macrophages.

- Numerous apoptotic bodies are phagocytosed by benign tingible-body macrophages.
- The pattern is suggestive but not pathognomonic for Burkitt lymphoma.

Burkitt immunophenotype and genetics

Dimension	Typical finding	Diagnostic interpretation
Lineage	Mature B-cell markers, CD20	B-cell origin
Germinal-center program	CD10 and BCL6	Supports GC phenotype
Apoptosis / growth	Often BCL2-negative, very high proliferation	Biologically coherent, not unique
Defining genetics	MYC rearrangement	Needs context; Avoid MYC-only classification

When the tumor is not B-cell DLBCL

- Rarer lineages require a fresh diagnostic approach.
- An EBV-positive extranodal NK/T-cell process is explicitly included in the Robbins testicular lymphoma spectrum.
- EBER in situ hybridization and appropriate T/NK-associated markers are useful in lineage workup.
- The exact panel follows morphology and local hematopathology practice.

Subtype comparison: High-yield distinctions

Type	Morphologic tendency	Strongest contextual clues
DLBCL	Pleomorphic large lymphoid cells	Mature B-cell phenotype; Commonest type
Burkitt	Monomorphic, intermediate-sized cells; Starry sky	MYC-driven biology, GC B-cell phenotype
Extranodal NK/T	Not a mature B-cell tumor	EBV association and NK/T lineage studies

Seminoma versus lymphoma

Feature	Seminoma	Testicular DLBCL
Usual clinical context	Younger adult testicular tumor	Particularly important in older men
Tumor lineage	Germ-cell differentiation	Mature lymphoid B-cell differentiation
Architecture	Germ-cell tumor pattern	Diffuse lymphoid infiltration
Useful phenotype	Germ-cell marker panel	CD20 / PAX5 and lymphoma panel

Other germ-cell and non-GCT differentials

- Embryonal carcinoma and mixed germ-cell tumors require germ-cell lineage assessment.
- Leydig and Sertoli cell neoplasms can mimic a solid testicular malignancy grossly.
- Immunophenotype and architecture are more reliable than gross appearance alone.
- AFP and hCG belong to the germ-cell tumor workup; They do not establish lymphoma subtype.

Inflammation versus neoplastic infiltration

Inflammatory orchitis

- Mixed inflammatory cells and accompanying tissue response may occur.
- Clinical infection context can support a reactive process.

Lymphoma

- A destructive or monomorphic atypical lymphoid infiltrate increases concern.
- Clonality and immunophenotype may be needed in difficult cases.

A diagnostic pitfall: Reactive background cells

- Large neoplastic B cells may be intermixed with reactive T lymphocytes and histiocytes.
- Identify which cells carry the lineage-marker signal.
- A sparse tumor population can be missed if the entire infiltrate is interpreted as benign.

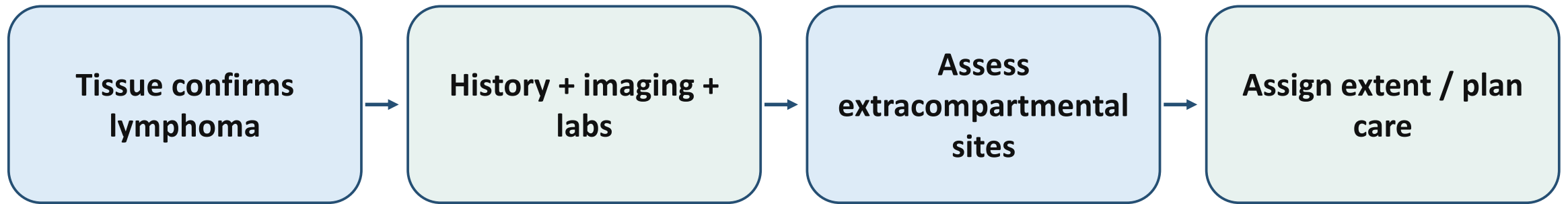
A diagnostic pitfall: “CD20-positive” is not enough

- B-cell lineage does not distinguish DLBCL from all other mature B-cell lymphomas.
- Morphology, proliferation, other immunostains, and molecular findings may be needed.
- Clinical disease distribution distinguishes primary from secondary testicular involvement.

The useful pathology report

Element	What to communicate
Histologic diagnosis	Lymphoma lineage and most defensible subtype
Immunophenotype	Relevant positives, negatives, and interpretive limitations
Tumor distribution	Parenchyma, tunica / adjacent tissue, spermatic cord if sampled
Uncertainty	Pending studies and limitations of tissue sampling

Staging question: Testicular-only or disseminated?



Primary versus secondary designation and treatment require clinical staging; Specifics follow the treating team.

CNS assessment: Why it enters the initial workup

- Testicular lymphoma carries a distinct propensity for CNS relapse.
- Symptoms and baseline risk guide the neurological assessment and staging discussion.
- Decisions about CSF testing or neuroimaging depend on current clinical guidance and the individual patient.

Pathology initiates a multidisciplinary pathway

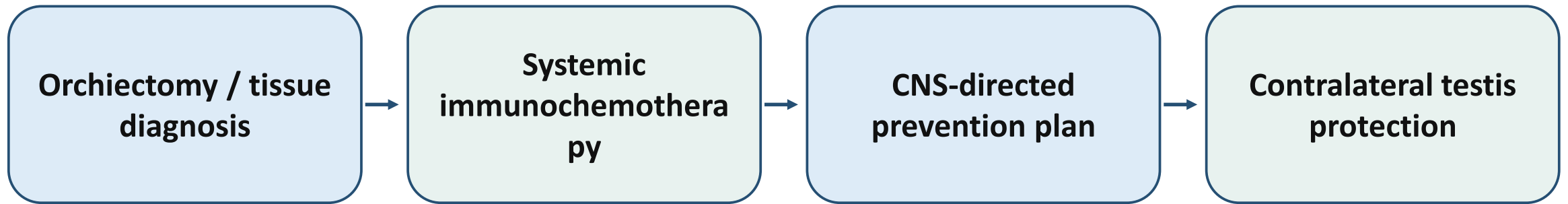
A tissue diagnosis is the beginning of integrated disease management.

- Urology, hematopathology, hematology/oncology, radiation oncology, and neurology/neuro-oncology may contribute.
- High CNS and contralateral testis risks require explicit care planning.

Orchiectomy: Diagnostic and local-control roles

- Radical inguinal orchiectomy commonly provides definitive tissue diagnosis and local control.
- Systemic lymphoma treatment is generally required beyond surgery alone.
- Gross and histologic assessment should identify disease extent in the resected specimen.

Integrated treatment framework



Treatment is individualized; This is a conceptual overview, not a prescription.

Why systemic treatment is necessary

Localized surgery cannot address occult lymphoma cells outside the testis.

- Rituximab-containing chemotherapy is generally used for CD20-positive testicular DLBCL.
- Exact regimen, intensity, and supportive care reflect stage, fitness, and current protocols.

CNS-directed prophylaxis: Rationale and limits

- Historical and contemporary regimens often incorporate CNS prophylaxis for testicular DLBCL.
- Intrathecal and/or systemic methotrexate-based approaches require specialist selection.
- The optimal prevention strategy remains an area of debate; Avoid presenting one pathway as universally proven.

Protecting the contralateral testis

- Contralateral testicular relapse is a distinctive concern.
- Prophylactic radiation to the uninvolved contralateral testis is included in many multimodality treatment protocols.
- The risk–benefit discussion includes age, hormonal function, fertility, and individual treatment context.

Longitudinal clinical surveillance

- Disease control must be evaluated systemically and at extranodal risk sites.
- New neurological symptoms warrant attention because CNS relapse is clinically consequential.
- New contralateral testicular findings require prompt assessment.
- Follow-up schedules should be derived from current clinical protocols rather than invented here.

What pathology can and cannot predict alone

Pathology can establish

- Lymphoma type and immunophenotype.
- Molecular features when tested.
- Anatomic spread within the resection specimen.

Requires clinical integration

- Full disease stage.
- Individual CNS relapse risk.
- Best treatment plan and outcome probability.

Case exercise: Older patient

A man in his seventh decade has a firm testicular mass. The tissue shows diffuse sheets of large CD20-positive lymphoid cells.

Hypothetical teaching case — Question

Which diagnosis is the leading histologic consideration?

Teaching answer: DLBCL involving the testis. Staging is necessary before assigning “primary testicular” disease.

Case exercise: Bilateral disease

An older man with testicular DLBCL is subsequently found to have a lesion in the opposite testis.

Hypothetical teaching case — Question

Which clinical feature of testicular lymphoma does this illustrate?

**Teaching answer: The propensity for bilateral / contralateral testicular involvement.
Reassessment for systemic and CNS disease is essential.**

Case exercise: High proliferation

A testicular lymphoma shows monomorphic intermediate-sized cells, abundant apoptotic debris, and very high proliferative activity.

Hypothetical teaching case — Question

Which additional lymphoma subtype should be actively excluded?

Teaching answer: Burkitt lymphoma; Evaluate its mature B-cell phenotype and MYC-driven genetic context.

Common errors to avoid

- Calling every solid testicular mass a germ-cell tumor.
- Calling a lymphoma primary based on pathology alone.
- Using a single marker to determine hematolymphoid subtype.
- Ignoring contralateral testicular and CNS relapse patterns.

Diagnostic synthesis: The clinical-pathology loop

Older patient with solid testicular mass

Clinical and imaging assessment



Histology shows atypical lymphoid cells

Confirm B-cell vs other lineage



Subtype and characterize

DLBCL; Exclude Burkitt and rarer variants



Integrate staging

Primary vs secondary; CNS and contralateral risks

Final synthesis

- Rare overall, but the leading testicular neoplasm in men older than 60 years.
- DLBCL predominates; Burkitt and EBV-positive extranodal NK/T-cell lymphoma are rarer.
- Diffuse lymphoid infiltration plus an appropriate immunophenotype establish tissue identity.
- CNS and contralateral testicular involvement make this an organ-specific lymphoma problem.

Selected references and source boundaries

Primary textbook: Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 21, p. 886; germ-cell tumor context pp. 881–886.

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