

Tumors of extravascular trophoblasts

Placental site trophoblastic tumor (PSTT) • Epithelioid trophoblastic tumor (ETT)

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What this lecture will enable

- Identify the two malignant extravillous trophoblastic tumors
- Recognize their contrasting growth patterns and immunophenotypes
- Distinguish them from choriocarcinoma and epithelial mimics
- Apply the updated FIGO 2026 framework

Where PSTT and ETT fit in GTD



Gestational trophoblastic disease spans non-neoplastic, premalignant, and malignant proliferations • PSTT and ETT are uncommon malignant gestational trophoblastic neoplasms • Their cell of origin differs from the dual trophoblastic pattern of choriocarcinoma

Extravillous trophoblast: The parent lineage



Intermediate/extravillous trophoblast normally infiltrates the maternal implantation site • It participates in remodeling and interacting with maternal vessels • Neoplastic variants retain recognizable features of this invasive phenotype

Two differentiation patterns

PSTT

Implantation-site type

Infiltrative sheets / cells

HPL, CD146: Often diffuse

ETT

Chorionic-type intermediate trophoblast

Nodules / cohesive nests

P63: Often positive

Why these are not typical choriocarcinomas

PSTT / ETT	Choriocarcinoma
Intermediate trophoblast	Two trophoblast populations
Often modest hCG	Often markedly raised hCG
Surgery central	Usually chemotherapy-responsive

Clinical recognition begins with pregnancy history

- Both entities typically arise after a gestational event
- Presentation may follow term pregnancy, loss, or molar gestation
- Absence of a recent pregnancy does not exclude these tumors

Think beyond the serum hCG result

Low hCG $\neq$ no trophoblastic malignancy

- A uterine neoplasm after pregnancy may be trophoblastic despite only moderate hCG elevation
- Tumor histology should not be overruled by an unimpressive biochemical result
- Symptoms, imaging and pathology must be interpreted together

Diagnostic problems that matter

- Recognizing infiltrating trophoblast among myometrial fibers
- Separating PSTT from ETT on morphology and targeted stains
- Excluding choriocarcinoma and cervical squamous carcinoma
- Assessing local extent and metastatic disease

PSTT: Core pathologic identity

Infiltrative implantation-type tumor

- A malignant tumor of implantation-type extravillous trophoblast
- Typically presents as a mass involving the uterus
- Locally infiltrative, particularly at the myometrial interface

PSTT: Antecedent gestation

- That about half follow a normal pregnancy
- Spontaneous abortion and hydatidiform mole are other antecedents
- The type and timing of pregnancy inform the clinical history

PSTT: Presenting symptoms

- Abnormal uterine bleeding is a major presentation
- Amenorrhea can replace or accompany bleeding
- A uterine mass may be discovered during evaluation

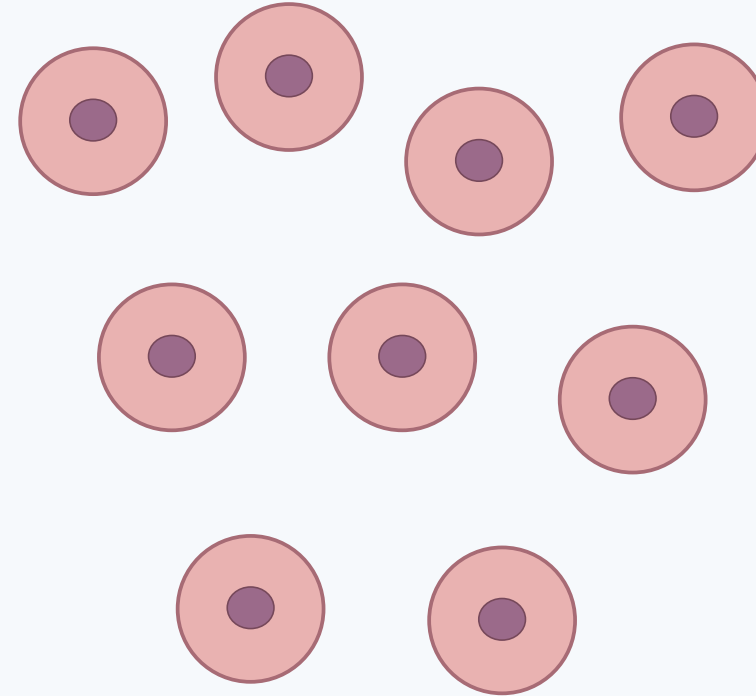
PSTT: Serum hCG profile

Moderate hCG • significant tumor

- Moderately elevated hCG
- The hCG level may under-represent the size or seriousness of tumor
- Do not use the high hCG profile of choriocarcinoma as the diagnostic template

PSTT: Microscopic cellular composition

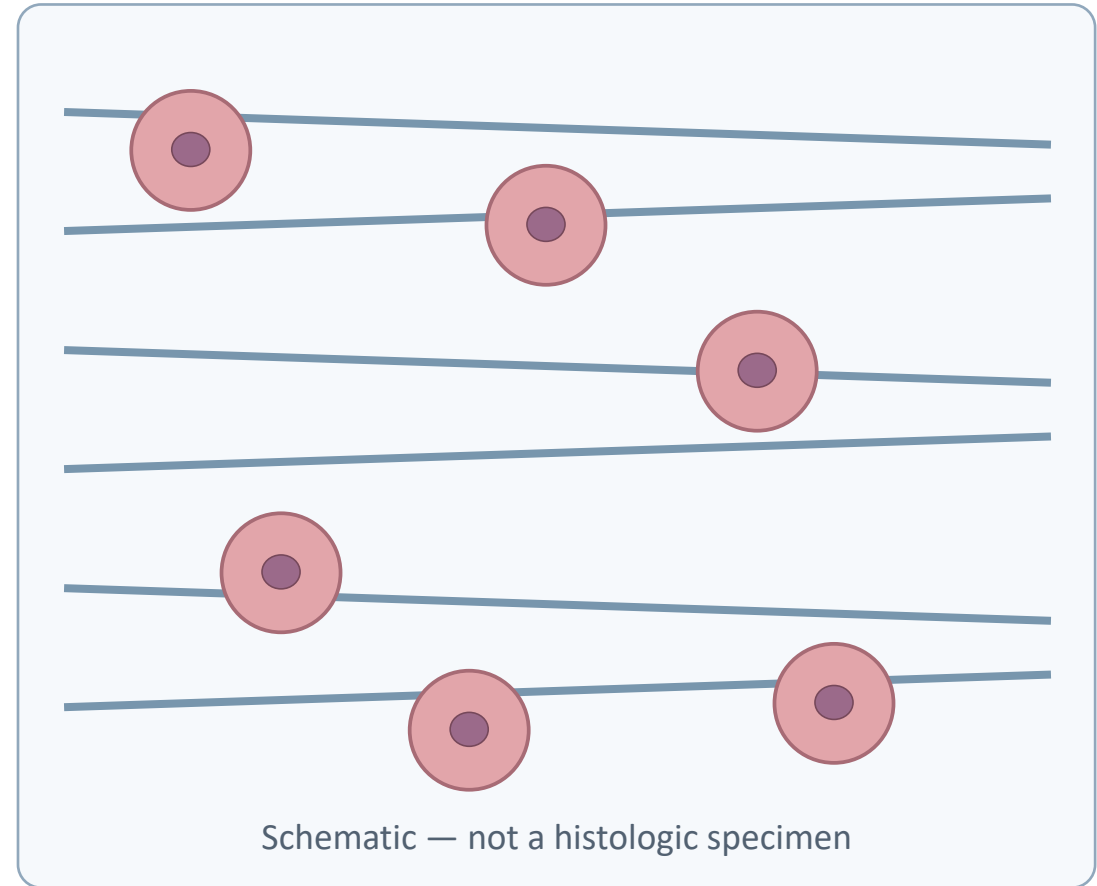
- Polygonal mononuclear trophoblasts predominate
- Binucleated cells may be admixed
- Neoplastic cells characteristically have abundant cytoplasm



Schematic — not a histologic specimen

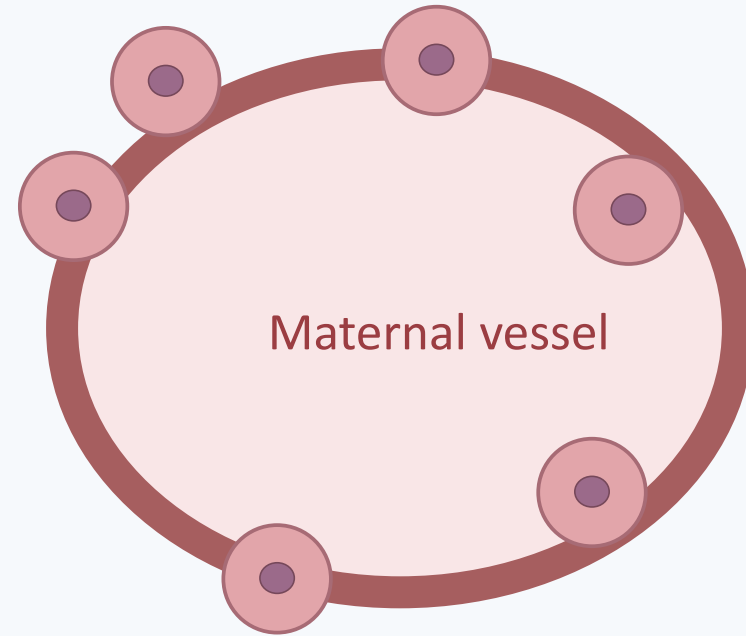
PSTT: Growth through myometrium

- Tumor cells insinuate between individual smooth-muscle fibers
- This splaying pattern reflects infiltrative growth
- The pattern is particularly helpful at the tumor–myometrium boundary



PSTT: Tropism for maternal vessels

- Malignant extravillous trophoblast often engages maternal vessel walls
- The vascular relationship recalls physiologic extravillous trophoblast
- Vascular involvement helps prioritize PSTT in the differential



Schematic — not a histologic specimen

PSTT: Invasion need not be hemorrhagic

PSTT

Infiltrative interstitial growth

Maternal vessel-wall affinity

Hemorrhage not required

Choriocarcinoma

Destructive hemorrhagic growth

Marked vascular destruction

Hemorrhage often extensive

PSTT: Cytologic clues

- Intermediate trophoblast may show cytologic atypia
- Abundant eosinophilic or clear cytoplasm supports trophoblastic differentiation
- Variable pleomorphism requires architectural and immunophenotypic correlation

PSTT: Architectural clues

- Diffuse or sheet-like growth is more typical than compact nodules
- Individual infiltrating cells can be prominent
- Vessel-wall involvement and myometrial infiltration are highly informative

PSTT: HPL staining

HPL: Typically diffuse

- Human placental lactogen is commonly strong and widespread
- A diffuse hPL pattern supports implantation-type differentiation
- Interpret staining with morphology and controls, not as an isolated diagnosis

PSTT: CD146 staining

CD146: Often widespread

- CD146 (Mel-CAM) is commonly expressed by implantation-site trophoblast
- Diffuse expression supports PSTT in an appropriate context
- No single marker is infallible across all tumors

PSTT: P63 is a discriminator

PSTT

P63 usually negative

HPL commonly diffuse

Vessel affinity

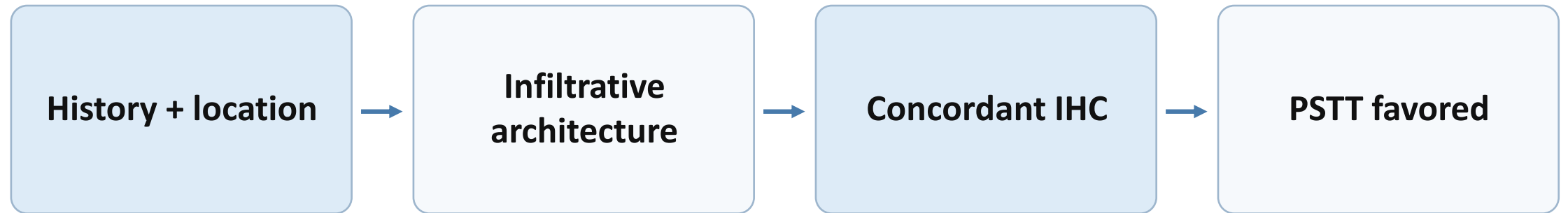
ETT

P63 usually positive

HPL commonly focal

Hyaline matrix / nodules

PSTT: Coherent diagnostic pattern



Postgestational uterine tumor • Mononuclear/polygonal trophoblast with abundant cytoplasm
• Myometrial splaying and maternal-vessel affinity • Diffuse hPL / CD146 with absent or limited p63

PSTT: Major pathological mimics

- Exaggerated placental site can show implantation-site trophoblast
- Choriocarcinoma differs in cellular composition and hemorrhage
- ETT is more nodular and often p63 positive
- Poorly differentiated uterine malignancy requires a considered panel

PSTT: Localized disease

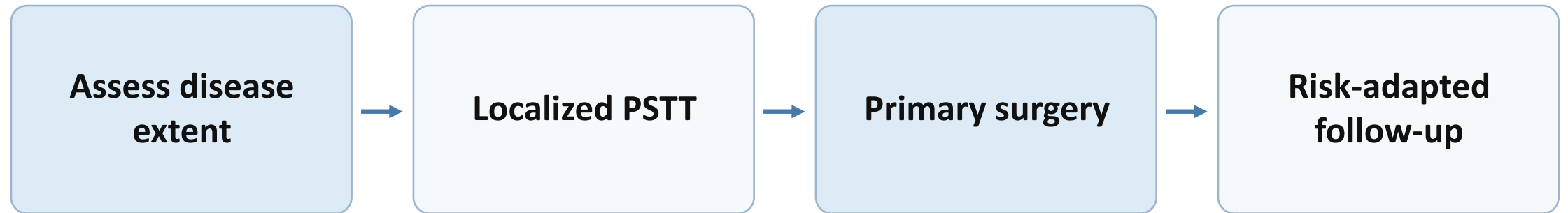
- The extent of uterine invasion determines local surgical assessment
- Favorable outcomes with surgery for localized tumors
- Complete anatomic assessment remains essential because metastasis is possible

PSTT: Metastatic potential

Potentially lethal after dissemination

- Malignancy is real despite relatively indolent-appearing invasion
- Death from disseminated disease in about 10%–15%
- A localized pathologic appearance cannot substitute for staging

PSTT: Why surgery dominates treatment



PSTT is less sensitive to chemotherapy than typical choriocarcinoma • Hysterectomy is the central treatment for most localized disease • Metastatic or high-risk cases need specialized multidisciplinary assessment

PSTT: Pathologist's report priorities

- Establish trophoblastic tumor type using morphology and an IHC panel
- Document depth/extent of myometrial and vascular involvement
- Describe necrosis and mitotic activity without unsupported cutoffs
- Communicate uncertainty or mixed morphology explicitly

ETT: Core pathologic identity

Nodular chorionic-type tumor

- Malignant tumor of chorionic-type intermediate trophoblast
- Usually composed of cohesive mononuclear epithelioid cells
- Often forms a relatively circumscribed/nodular mass

ETT: Relationship to preceding pregnancy

- Usually detected after a prior pregnancy
- An interval of years may occur before clinical presentation
- Record the index pregnancy and its timing for prognostic assessment

ETT: Principal anatomic sites

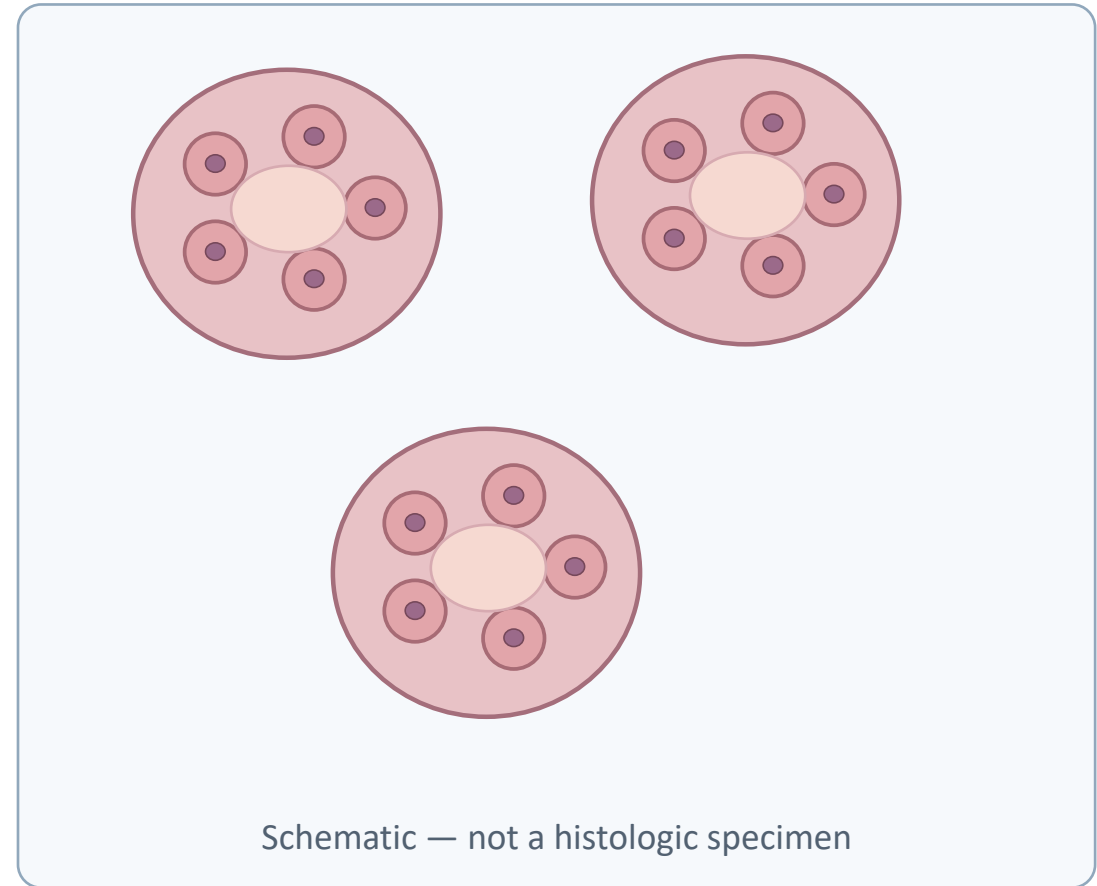
- Most occur within the uterus or cervix
- The lower uterine segment/cervix is an important diagnostic setting
- Extrauterine presentations also occur

ETT: Presenting symptoms

- Amenorrhea is commonly
- Some patients have a clinically palpable mass
- Symptoms do not reliably indicate tumor location or stage

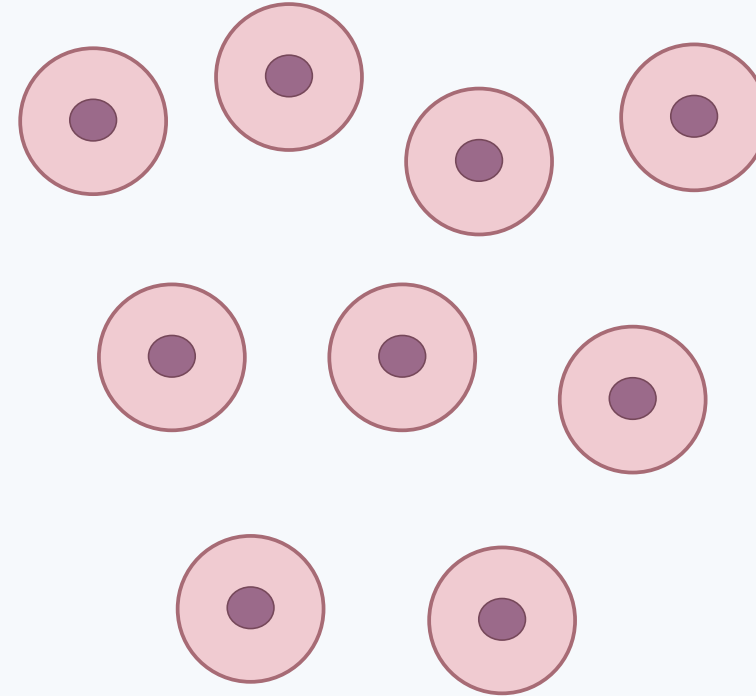
ETT: Cohesive tumor architecture

- Cohesive nests, sheets and nodules predominate
- Growth is often more expansile than the dispersed PSTT pattern
- This distinction is relative—not proof of benign behavior



ETT: Cells and cytoplasm

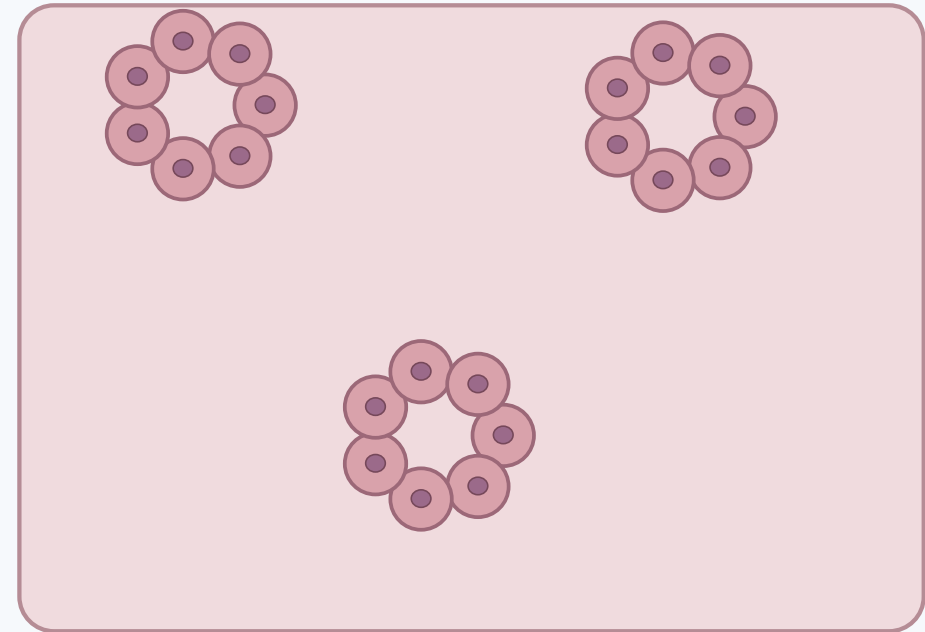
- Predominantly mononuclear epithelioid trophoblast
- Cytoplasm may be clear or eosinophilic
- Relatively uniform cells can mimic an epithelial carcinoma



Schematic — not a histologic specimen

ETT: Extracellular hyaline material

- Characteristic eosinophilic/pink hyaline material can surround tumor nests
- Hyalinization is a valuable histologic architectural clue
- This material may resemble keratin and complicate differential diagnosis

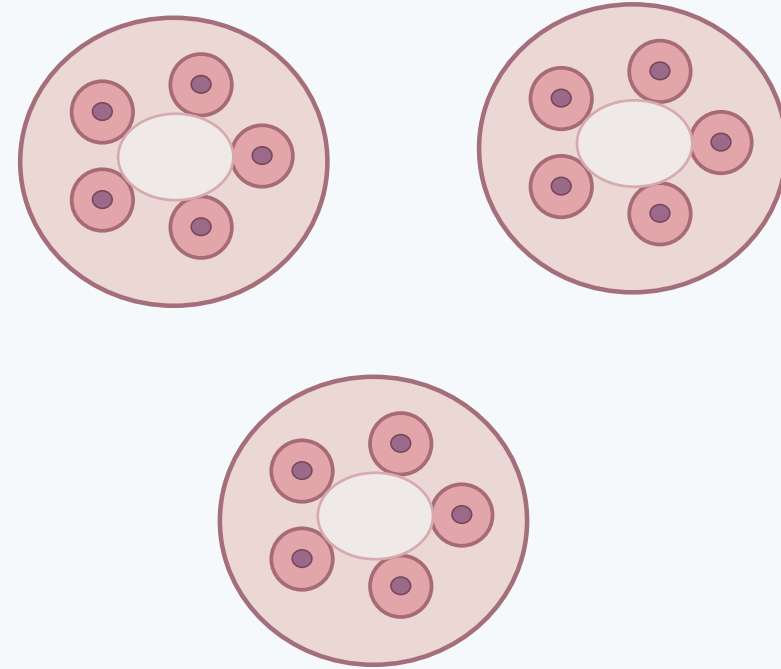


Hyalinized extracellular matrix

Schematic — not a histologic specimen

ETT: Geographic necrosis

- Geographic necrosis is frequently associated with ETT nodules
- A necrotic core bordered by viable epithelial-like cells is a useful pattern
- Necrosis must not be mistaken for keratinization alone



Schematic — not a histologic specimen

ETT: Invasion versus metastasis

Local appearance

Nodules can be relatively discrete

Limited obvious vessel infiltration

Epithelial-like architecture

Biologic behavior

May metastasize

Hematogenous spread possible

Trophoblastic malignancy

ETT: P63 supports chorionic-type lineage

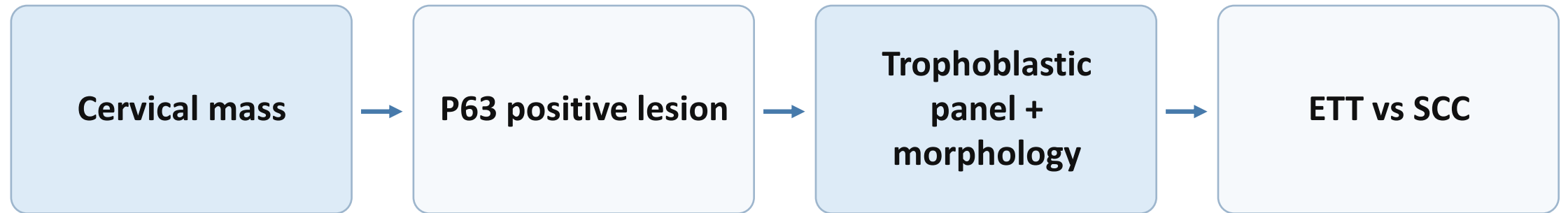
P63 positive is not specific for ETT

- Nuclear p63 expression is typically a feature of ETT
- P63 supports distinction from implantation-type PSTT
- P63 cannot by itself exclude a cervical squamous neoplasm

ETT: HPL and CD146 are less diffuse

- HPL may be absent or focal rather than broadly expressed
- CD146 expression is typically less extensive than in PSTT
- A combined panel is more robust than any single stain

ETT: Potential squamous carcinoma mimic



Cervical site, epithelioid morphology, hyaline material and p63 cause overlap • Use gestational history and trophoblastic markers together • Interpret the relationship to native cervical epithelium in the tissue section

ETT: Placental site nodule mimic

- Placental site nodules represent a different, generally benign lesion
- Atypical placental site nodules require careful separation from ETT
- Cellularity, destructive features and proliferation should be integrated

ETT: Metastatic pattern

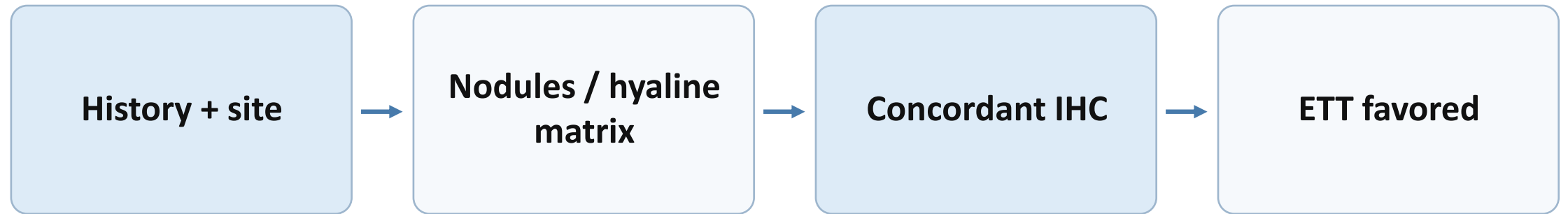
- Lung and bone as important metastatic sites
- Metastatic potential justifies full staging despite nodular architecture
- New symptoms in distant organs merit clinical evaluation

ETT: Prognosis in the source

Denominator matters in outcome claims

- Deaths among patients with metastatic ETT
- The cited 10%–15% mortality wording refers to females with metastatic disease
- Do not generalize that percentage to every ETT patient

ETT: Coherent diagnostic pattern



Postgestational tumor in uterus/cervix or other site • Cohesive epithelioid trophoblast with clear/eosinophilic cytoplasm • Hyaline matrix $\pm$ geographic necrosis • Often p63 positive with hPL/CD146 less diffuse

PSTT and ETT: Dominant phenotype

PSTT

Single infiltrating cells / sheets

Maternal vessel-wall affinity

Implantation type

ETT

Nests / nodules

Hyaline material / necrosis

Chorionic type

PSTT and ETT: Clinical comparison

PSTT

Uterine mass common

Bleeding or amenorrhea

Moderate hCG often

ETT

Uterine/cervical mass common

Amenorrhea $\pm$ mass

HCG often relatively low

PSTT and ETT: IHC comparison

PSTT

HPL: Often diffuse

CD146: Often diffuse

P63: Usually absent

ETT

HPL: Focal/variable

CD146: Less extensive

P63: Commonly nuclear-positive

Choriocarcinoma: A critical contrast

PSTT / ETT

Intermediate trophoblast dominant

More limited hCG in many cases

Surgery typically central

Choriocarcinoma

Bi-/multicellular trophoblast

Often very high hCG

Chemotherapy is central

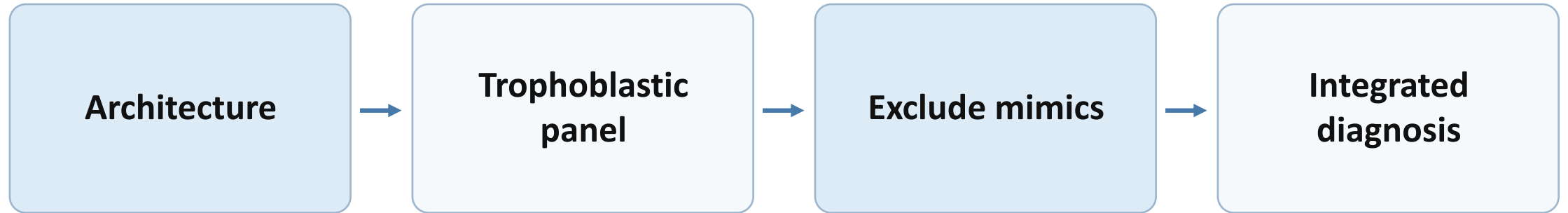
Exaggerated placental site: Clinical pitfall

- Benign implantation-site proliferation can resemble PSTT
- Clinical gestational context and the extent of atypical proliferation matter
- Use the overall tissue architecture and proliferation, not hPL alone

Squamous carcinoma: Clinical pitfall

- An ETT in the cervix can resemble squamous carcinoma
- P63 positivity alone is not a distinguishing marker
- A tailored epithelial + trophoblastic IHC panel is required

Diagnostic workflow from biopsy to diagnosis



Confirm lesion is a true neoplastic trophoblastic proliferation • Describe infiltrative vs nodular architecture • Use p63, hPL, CD146 and relevant exclusion markers • Correlate with pregnancy and imaging history

What hCG can and cannot tell you

- HCG is valuable for assessment and serial follow-up
- A modest hCG value does not exclude PSTT or ETT
- Definitive classification still rests on histopathology and context

Diagnostic uncertainty: When to refer

- Tiny curettage fragments may not capture diagnostic tumor borders
- Atypical placental site lesions may be difficult to subtype
- Expert gestational trophoblastic pathology review is appropriate in equivocal cases

Contemporary update: FIGO 2026

2026 FIGO: Stage + pregnancy interval

- A specific FIGO staging scheme now addresses PSTT and ETT
- Histologic PSTT/ETT can establish gestational trophoblastic neoplasia
- The ordinary GTN modified WHO risk score is NOT used for PSTT/ETT

FIGO 2026: Stages I and II

Stage I

Uterine corpus / cervix only

No extrauterine spread

Stage II

Extension beyond uterus/cervix

Still limited to genital structures

FIGO 2026: Stages III and IV

Stage III

Lung metastases

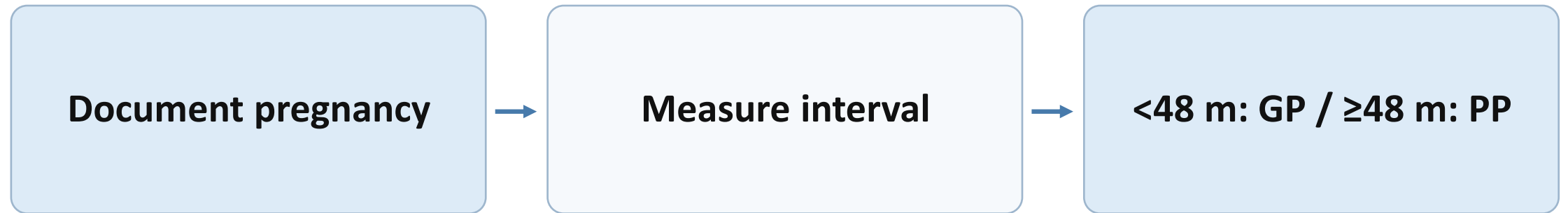
Nodes below diaphragm

Stage IV

Other distant organs

Nodes above diaphragm

FIGO 2026: 48-month prognostic divider



For stages I–III, interval <48 months is a good prognostic factor • Interval ≥48 months is a poor prognostic factor • All stage IV disease carries poor prognosis in this system

FIGO 2026: Stage annotation

Stage I–III : GP / PP

- Represent stages I–III with GP or PP for pregnancy interval
- Example: Stage I:GP versus stage I:PP
- Do not attach the modified WHO GTN numeric score to PSTT/ETT

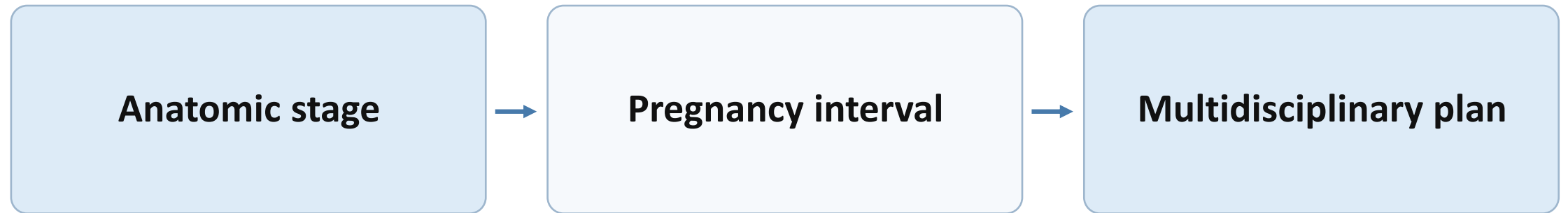
FIGO 2026: Nodal interpretation

- Nodes below diaphragm contribute to stage III; Above to stage IV
- FIGO suggests ≥ 10 mm short-axis as an imaging threshold
- Use LN r for radiologic or LN p for pathologic evidence

FIGO 2026: Imaging for local extent

- Contrast-enhanced pelvic MRI is recommended for PSTT/ETT local staging
- Assess depth of myometrial and parametrial involvement
- Ultrasound/CT alone is inadequate for detailed local staging

FIGO 2026: Why staging affects care



Local stage informs operative planning • Metastatic extent changes the need for combined modalities • Prior-pregnancy interval is part of prognostic stratification

Contemporary management: Localized disease

- Hysterectomy is primary therapy for most PSTT/ETT
- Fertility-sparing resection is considered only in carefully selected localized cases
- Management should occur with experienced trophoblastic-disease teams

Contemporary management: Advanced disease

- PSTT and ETT are relatively chemoresistant
- Selected metastatic lesions may merit surgical resection
- Combination chemotherapy can be considered by specialist teams
- Outcomes depend on disease distribution and pregnancy interval

After treatment: Surveillance logic

- Serial hCG remains useful when measurable
- Imaging and symptom assessment may be needed when hCG is not strongly informative
- The oncology team should specify individualized longitudinal follow-up

Case 1: Infiltrative uterine tumor

- A patient presents months after pregnancy with abnormal bleeding
- The uterus contains a myometrial mass; HCG is moderately elevated
- Biopsy: Polygonal trophoblasts separating muscle fibers; HPL diffuse
- Which tumor is most likely, and what feature is decisive?

Case 1: Interpretation

- PSTT is favored
- Interstitial myometrial infiltration and abundant intermediate-trophoblast cytoplasm are pivotal
- Diffuse hPL supports implantation-site differentiation
- Stage determination and specialist treatment planning are next

Case 2: Cervical epithelioid lesion

- A cervical mass appears years after a pregnancy
- Histology: Cohesive nests of mononuclear cells and hyaline matrix
- P63 is positive; HPL is only focal
- Which trophoblastic neoplasm is favored? What mimic must be excluded?

Case 2: Interpretation

- ETT is favored by the nodular/hyaline architecture and p63 profile
- Cervical squamous carcinoma remains a major mimic
- Use an integrated trophoblastic/epithelial panel and history
- Prognostic staging requires pregnancy interval and metastatic workup

Case 3: Stage and pregnancy interval

- Histologic ETT is confined to the uterus
- Treatment begins 5 years after the preceding pregnancy
- No distant lesions are detected
- What FIGO 2026 notation best describes the case?

Case 3: Interpretation

- FIGO 2026 stage I:PP
- Stage I = uterine corpus/cervix only
- Interval ≥ 48 months creates the poor-prognostic-factor suffix
- Do not calculate the standard GTN modified WHO score

Integrated diagnostic summary

- PSTT: Infiltrative implantation-site morphology, often hPL/CD146 diffuse
- ETT: Nodular epithelial-like morphology, hyaline matrix, often p63 positive
- Both are malignant despite sometimes limited hCG elevation
- Stage anatomically and apply the FIGO 2026 pregnancy-interval factor

Selected scientific sources

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed.; Ch. 22.
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- Horowitz et al. Gynecol Oncol. 2017; PSTT/ETT review.
- Ngan et al. Int J Gynaecol Obstet. 2025 and 2026 FIGO reports.