Fabiola Medeiros, MD

Director, Gynecology, Placental and Perinatal Pathology
at Cedars Sinai Medical Center, Los Angeles

#GYNPath

Uterine Biphasic Tumors: A Practical Guide with Emphasis on Differential Diagnosis

JULY 7, 2020/ 12:00PM ET (UTC-5H)

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What are uterine biphasic tumors?

- Also known as mixed epithelial mesenchymal tumors
- Composed of both epithelial and mesenchymal components
- Either or both components may be benign or malignant

Uterine biphasic tumors

Adenosarcoma

Carcinosarcoma

Atypical polypoid adenomyoma

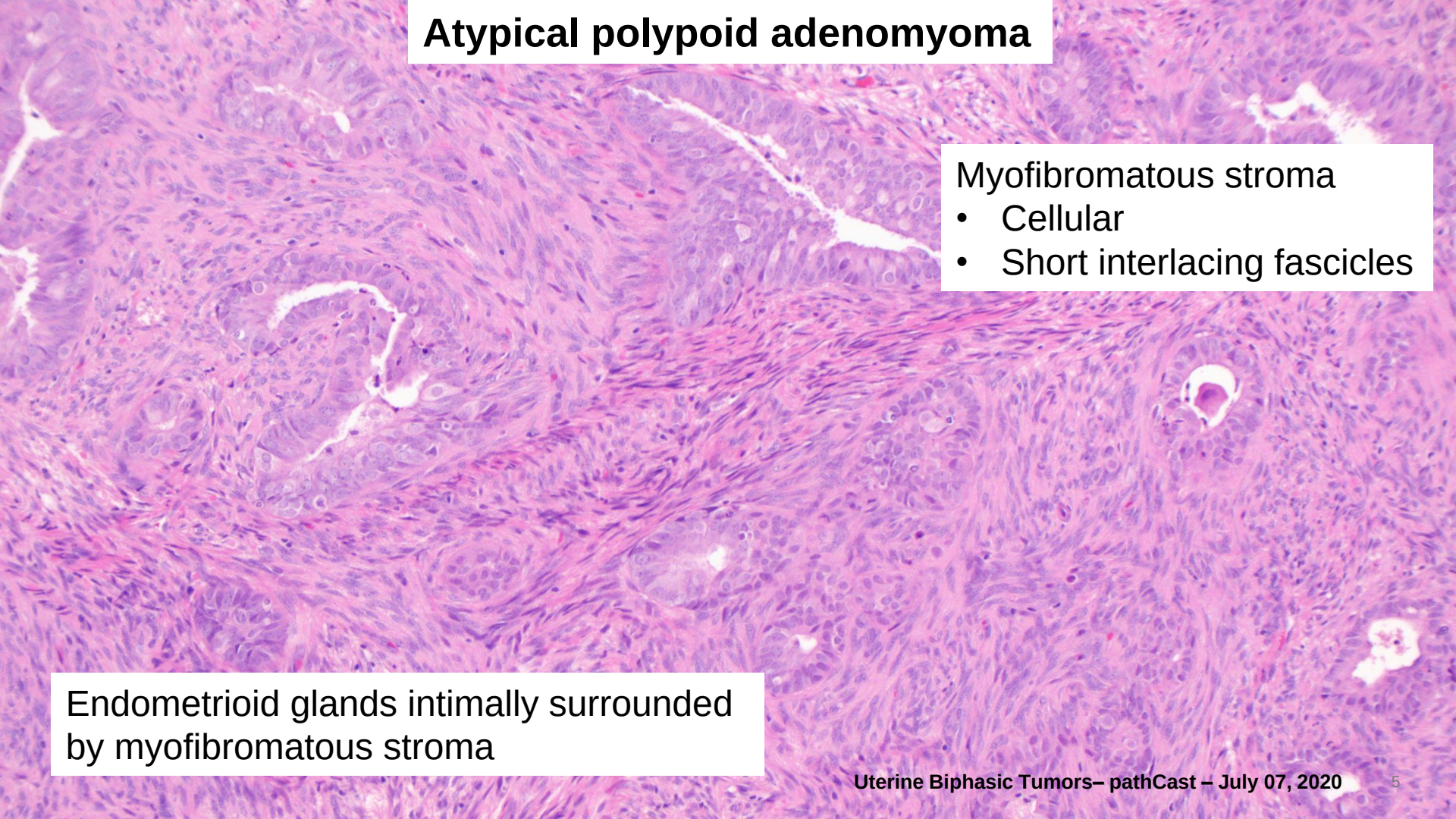
Adenomyomatous polyp

Adenomyoma

Atypical polypoid adenomyoma (APA)

- **Premenopausal women**
- **Polypoid with a broad base**
- **LUS, uterine corpus and cervix**

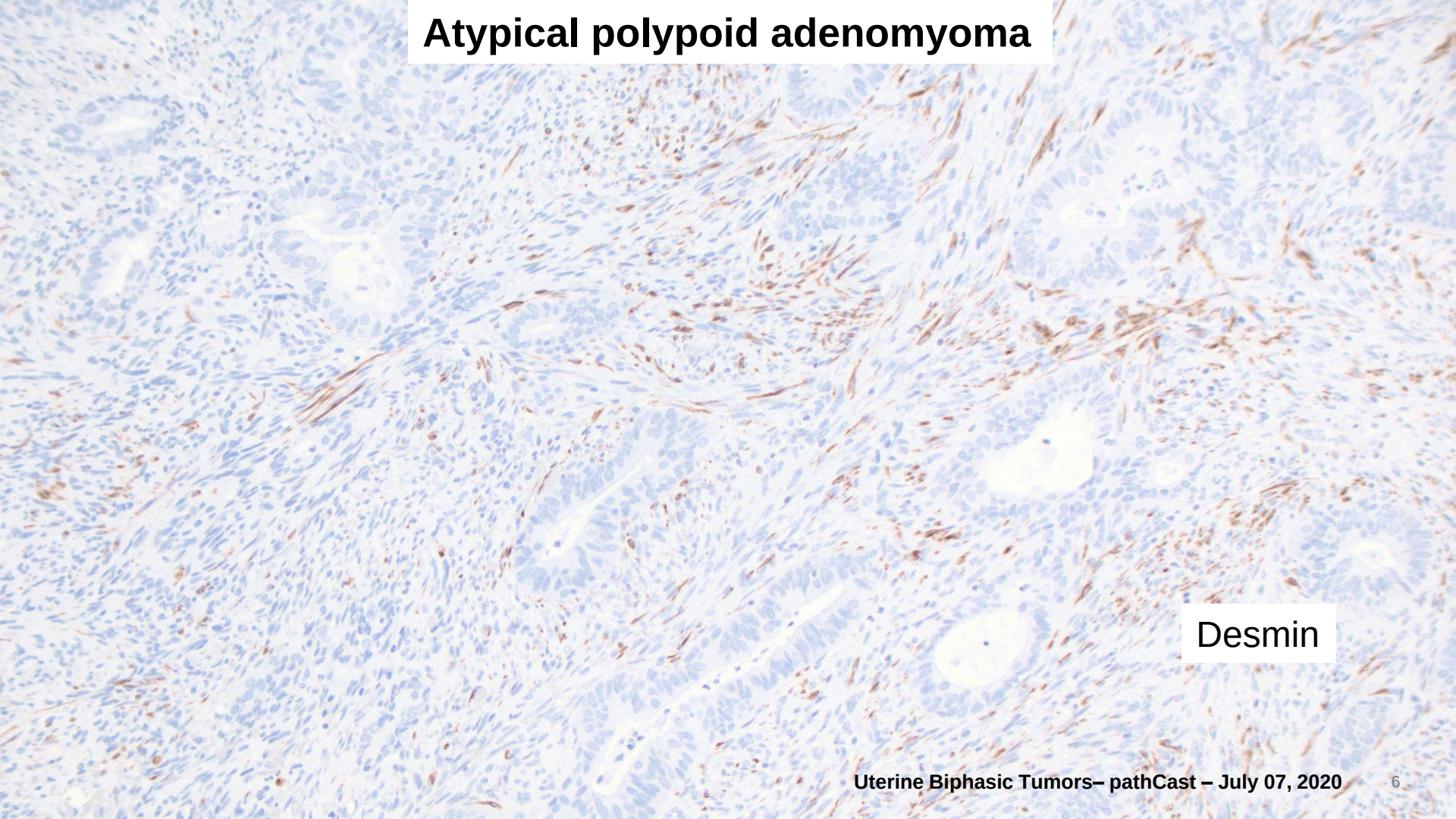
Atypical polypoid adenomyoma



Myofibromatous stroma
- Cellular
- Short interlacing fascicles

Endometrioid glands intimally surrounded by myofibromatous stroma

Atypical polypoid adenomyoma



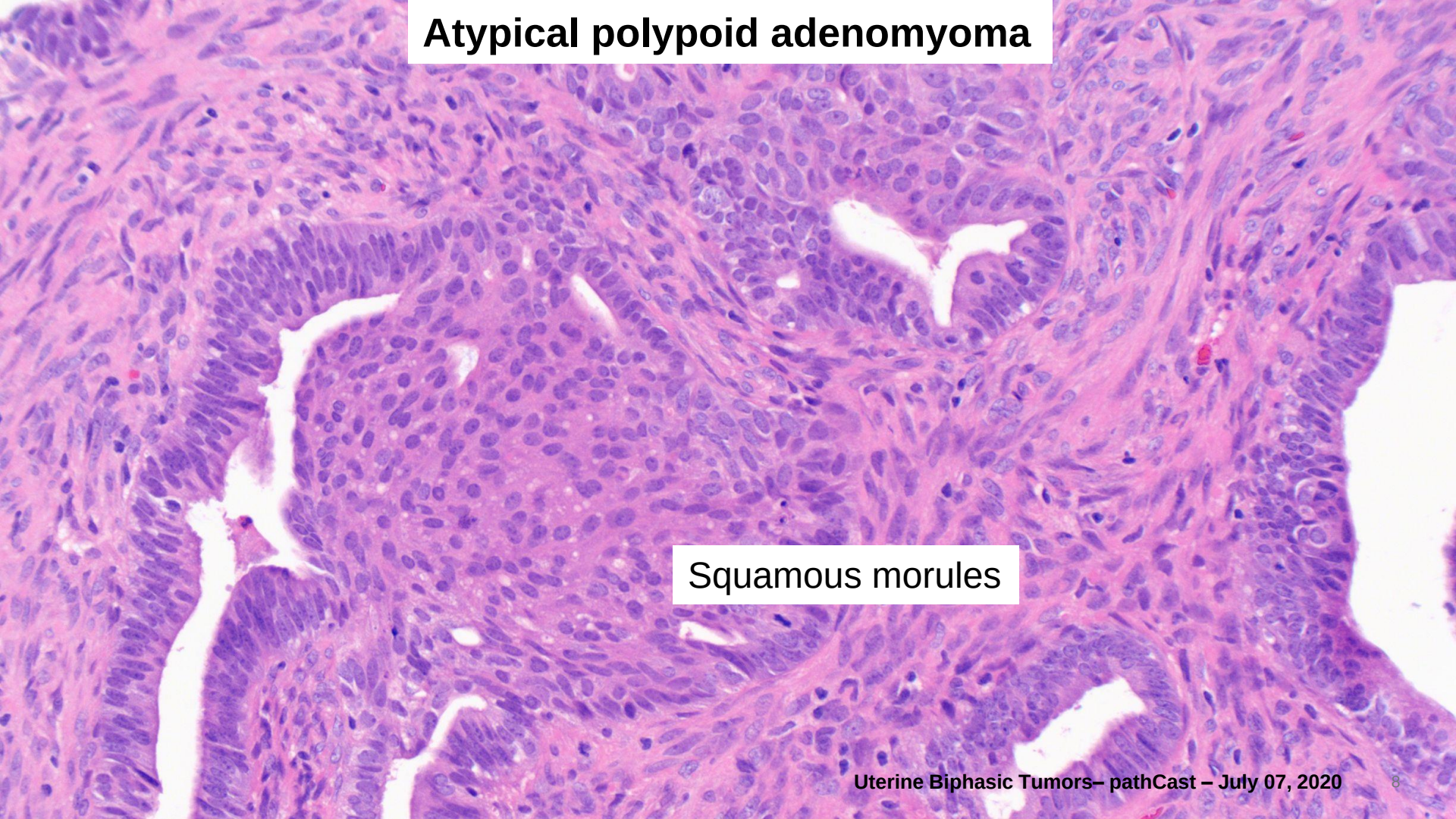
Atypical polypoid adenomyoma

Slide presentation

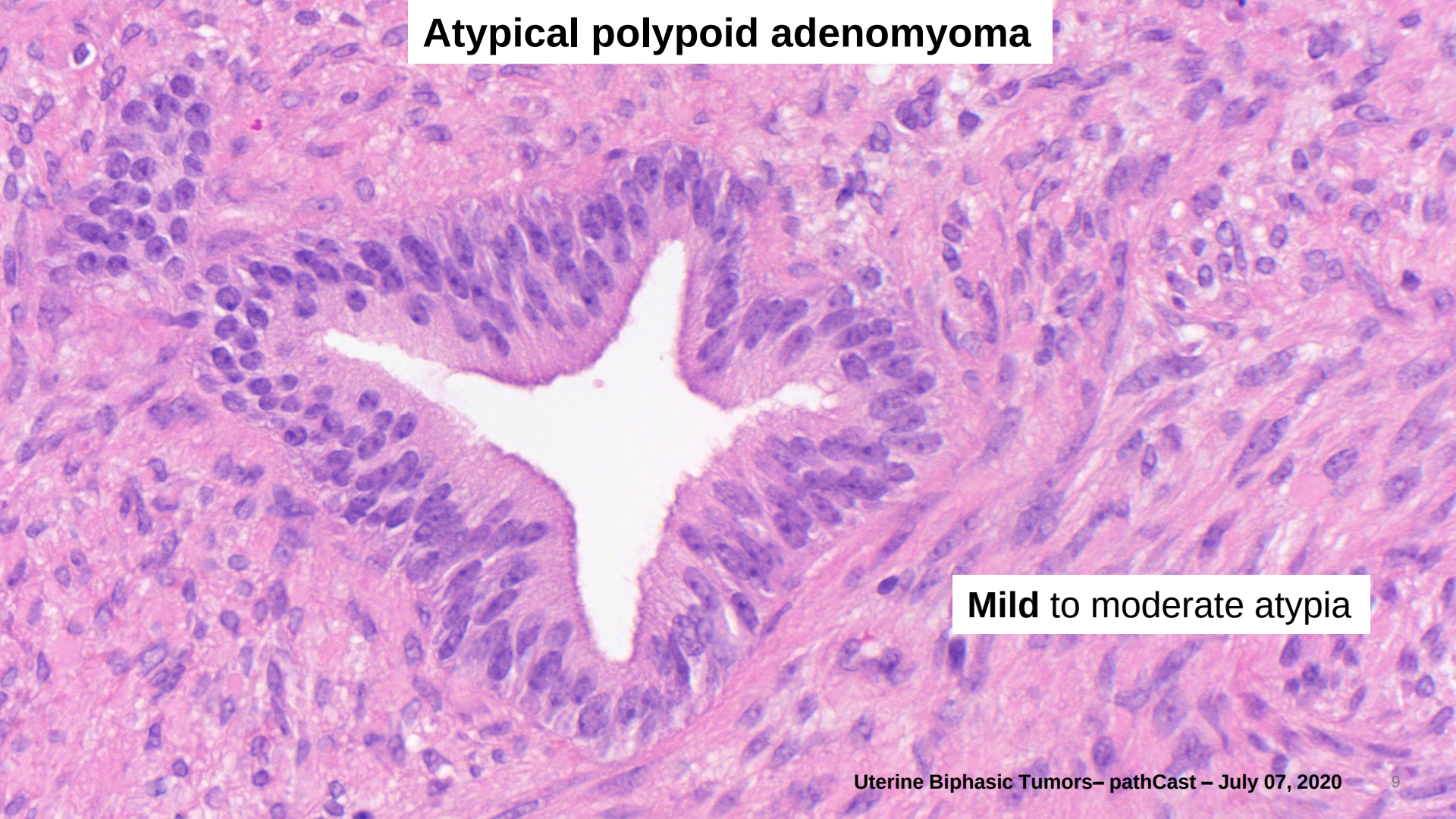
Low power appearance

Broad base

Atypical polypoid adenomyoma

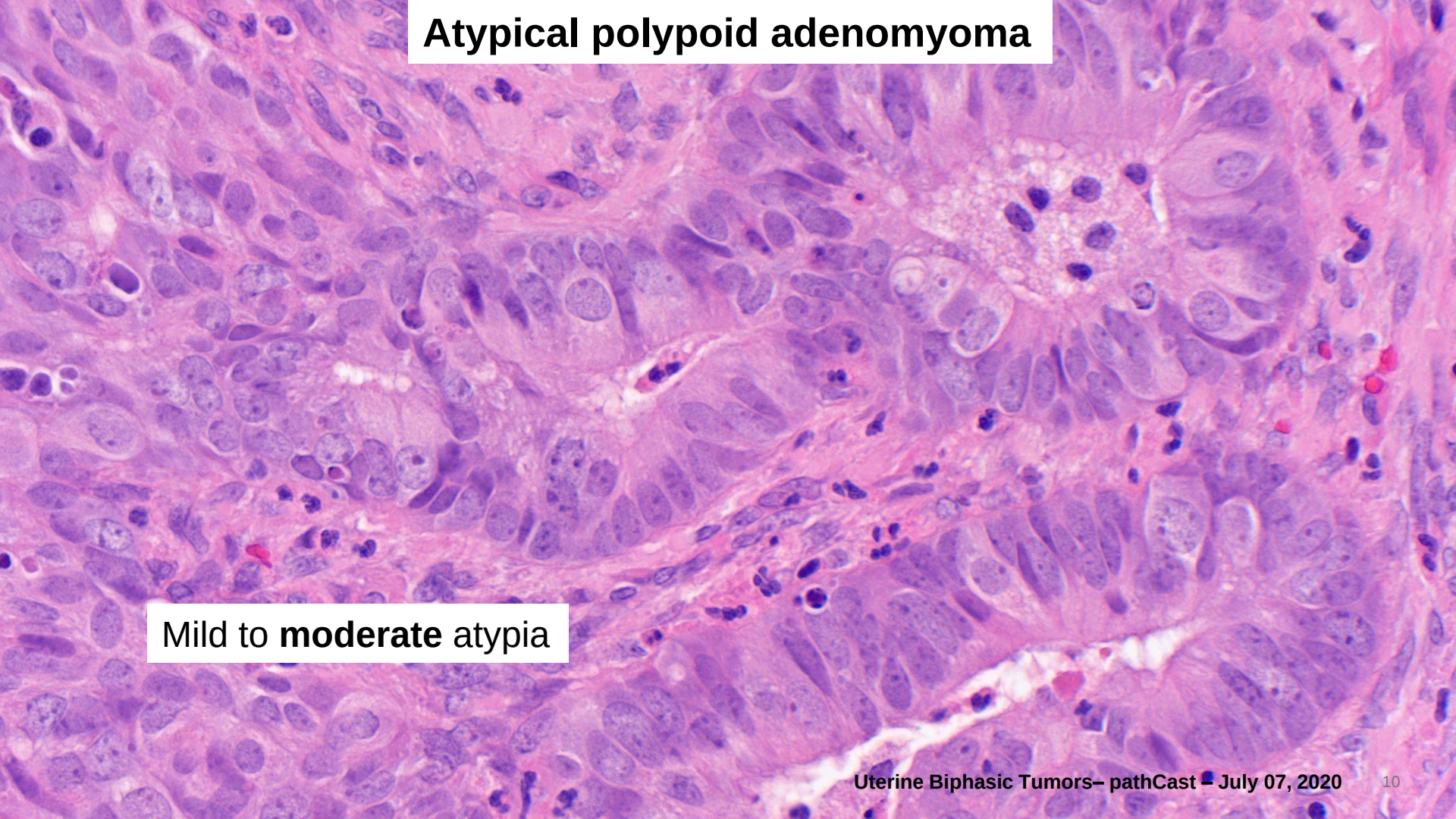


Atypical polypoid adenomyoma

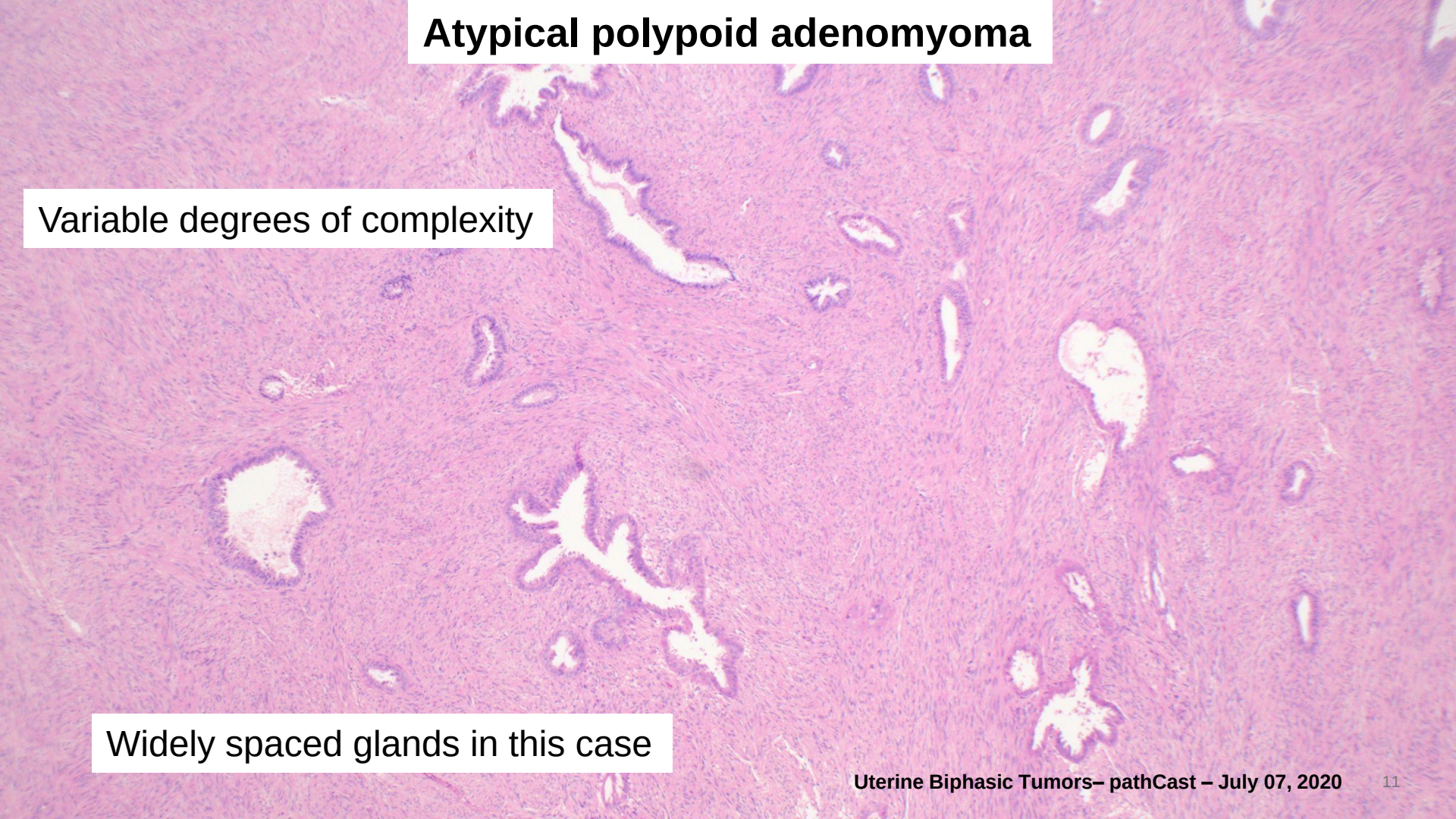


Mild to moderate atypia

Atypical polypoid adenomyoma



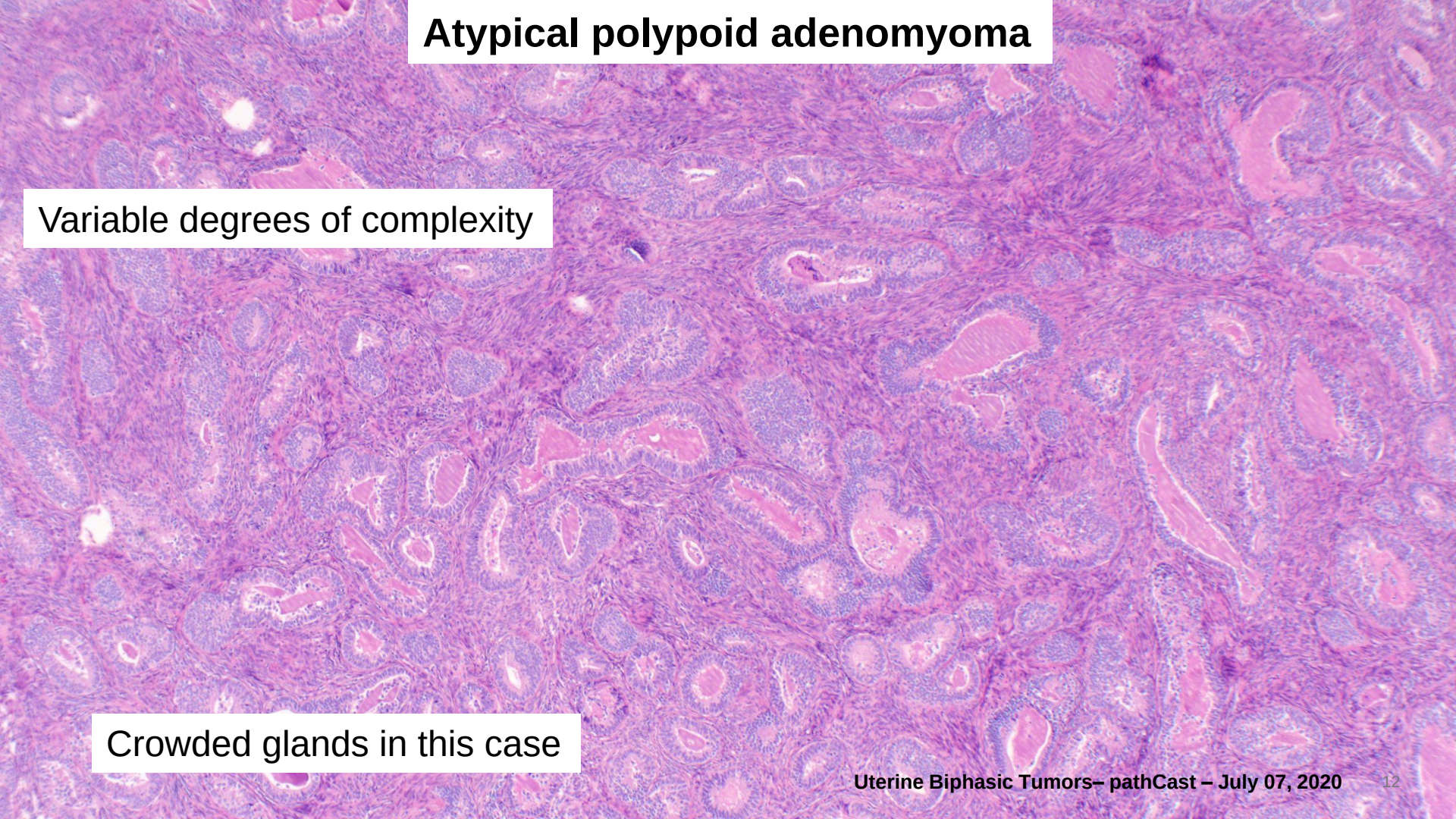
Atypical polypoid adenomyoma



Variable degrees of complexity

Widely spaced glands in this case

Atypical polypoid adenomyoma



Variable degrees of complexity

Crowded glands in this case

Atypical polypoid adenomyoma

How much crowding is acceptable in APA?!

Atypical Polypoid Adenomyoma of the Uterus

A Report of 27 Cases

ROBERT H. YOUNG, M.D., TAMARA TREGER, M.D., AND ROBERT E. SCULLY, M.D.

cm). Microscopic examination almost always confirms the sharp delineation of the lesion, although occasionally the margin is slightly irregular. The presence of atypical endometrial glands, usually showing squamous differentiation, scattered within intersecting fascicles of smooth muscle is distinctive. The glands resemble those of a hyperplastic endometrium with varying degrees of atypicality up to and including carcinoma *in situ*. The stromal component may also exhibit mild to moderate atypicality with occasional mitotic activity, but the features do not approach those of a sarcoma.

tures are helpful in avoiding this error. First, although the cytologic and architectural atypicality of the glands warranted a possible diagnosis of carcinoma *in situ*[22] in 3 of our 27 cases, in none of the cases were the abnormalities sufficiently marked to justify a diagnosis of invasive carcinoma. Second, if the highly atypical glands within the

(Young, Treger and Scullly, 1986)

Atypical Polypoid Adenomyofibromas (Atypical Polypoid Adenomyomas) of the Uterus: A Clinicopathologic Study of 55 Cases

Longacre, Teri A. M.D.; Chung, H. M.D.; Rouse, Robert V. M.D.; Hendrickson, Michael R. M.D.

Abstract

We present the clinicopathological and immunohistochemical features of 55 atypical polypoid adenomyofibromas, a definitional expansion of an entity previously reported as "atypical polypoid adenomyoma" (APA) of the uterus. Patients ranged in age from 25 to 73 (mean, 39.9) years. All but two of the patients were premenopausal, and 14 were undergoing evaluation for infertility. Histologically, the lesions featured a biphasic proliferation of architecturally complex and cytologically atypical endometrial glands within a myofibromatous stroma. The histologic pattern ranged from widely separated and loosely clustered irregular but branched glands embedded in broad zones of cellular myofibromatous stroma to those possessing crowded, markedly complex, branching glands separated by sparse intersecting fascicles of fibromuscular tissue. The stroma in all cases was actin or desmin positive or both. Morular/squamous metaplasia was present in all but two cases and florid in most. All cases exhibited architecturally complex glands, and in 25 cases the architectural complexity was indistinguishable from that of well-differentiated endometrial adenocarcinoma, as we have defined it; that is, they had a high architectural index. Twenty-nine patients were initially treated with polypectomy or curettage followed by hormonal therapy; persistent or recurrent APA developed in 45% of the patients in this group (33% with low architectural index vs. 60% with high architectural index). Five patients had successful pregnancies despite persistent disease. Superficial myoinvasion was identified in the hysterectomy specimen in two of 12 APAs with a high architectural index but not in 21 APAs with a low architectural index. All patients are alive and well 1 to 112 months after diagnosis (mean, 25.2 months). On the basis of this study, we propose that APAs with markedly complex glands (high architectural index) be designated "atypical polypoid adenomyofibromas of low malignant potential" (APA-LMP) to emphasize the potential risk for myometrial invasion. A treatment program featuring local excision accompanied by close follow-up is warranted for APA despite the presence of recurrent or persistent disease. Patients with APA-LMP may also, in selected cases, be managed with less than hysterectomy, although (as with the usual well-differentiated carcinoma) there is a small but definite risk associated with this approach.

Atypical polypoid adenomyoma

Reporting

- **Non-atypical hyperplasia is part of APA spectrum**
- **Report the presence of EIN and adenocarcinoma**
  - In APA
  - And background endometrium
- **DO NOT diagnose myoinvasion in biopsy/curettage!**

Atypical polypoid adenomyoma

- Recurrence/Residual disease estimated at 30%
- 8% background endometrial hyperplasia
- 8% associated carcinoma
- Hysterectomy is the treatment of choice
- Preservation of fertility is possible

(Heatley, 2006)

Atypical polypoid adenomyoma

Differential Diagnoses

Myoinvasive endometrioid carcinoma

Adenomyomatous polyp

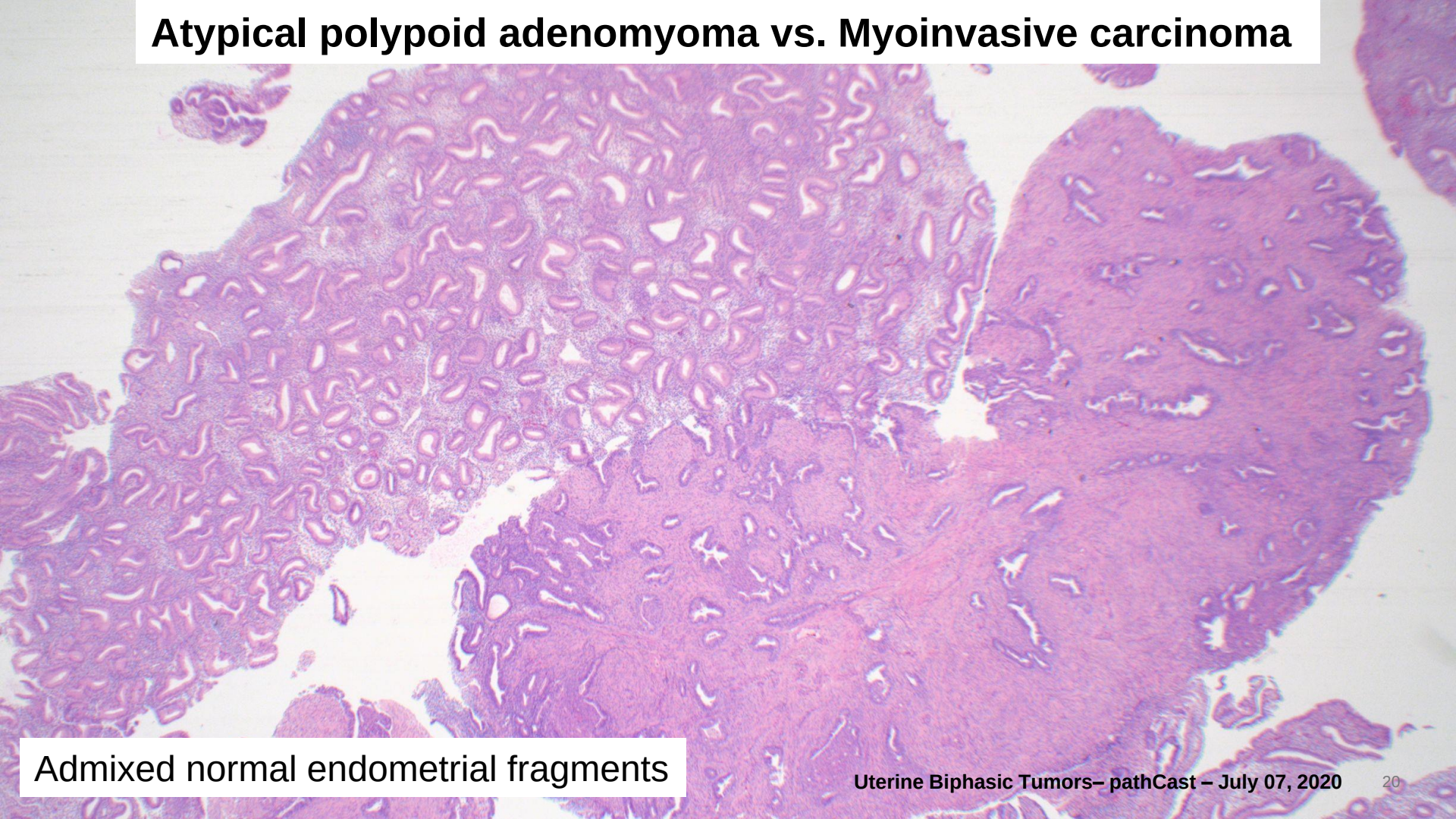
Endometrioid-type adenomyoma

Atypical polypoid adenomyoma

Differential Diagnoses

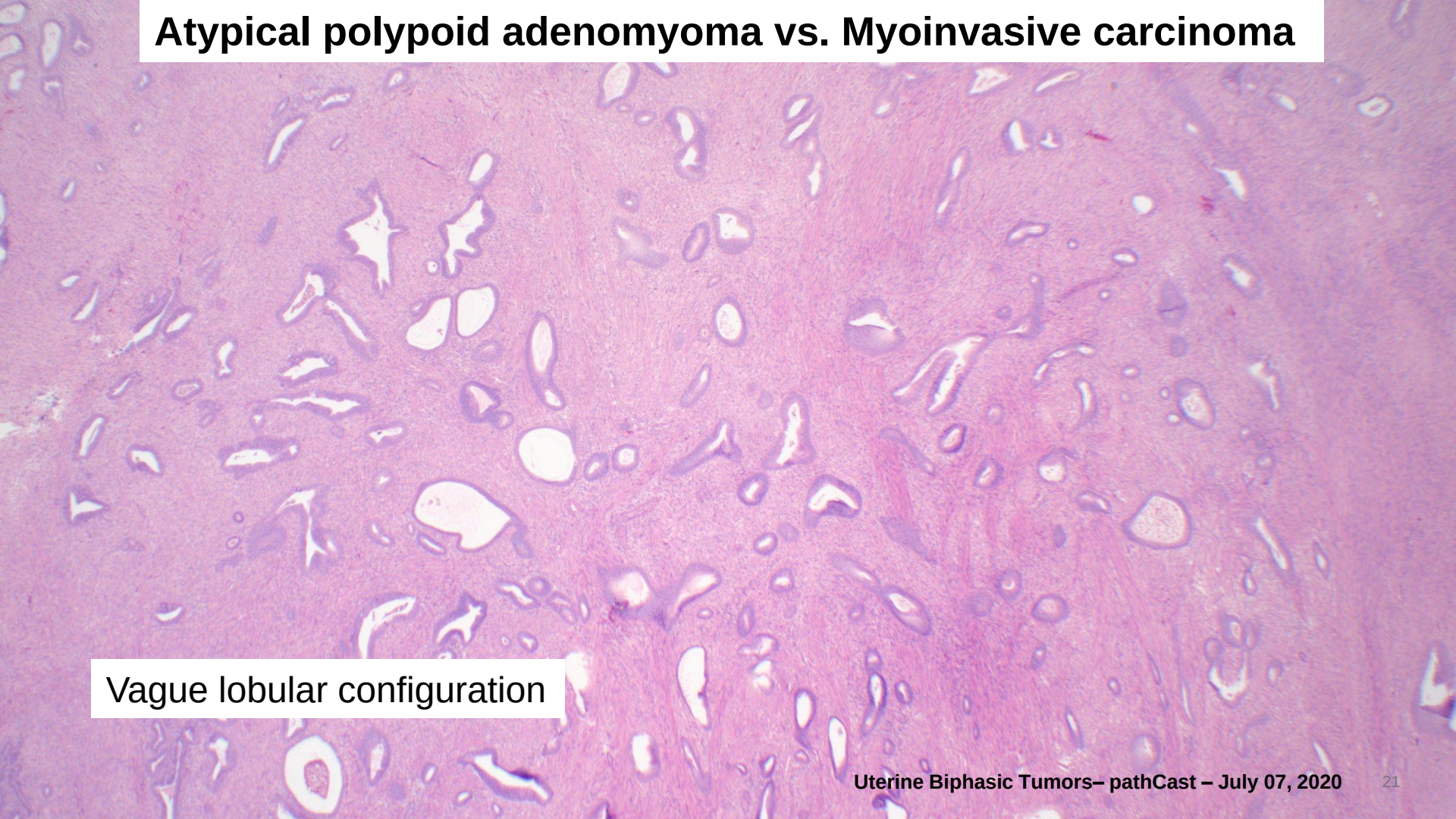
Myoinvasive endometrioid carcinoma

Atypical polypoid adenomyoma vs. Myoinvasive carcinoma



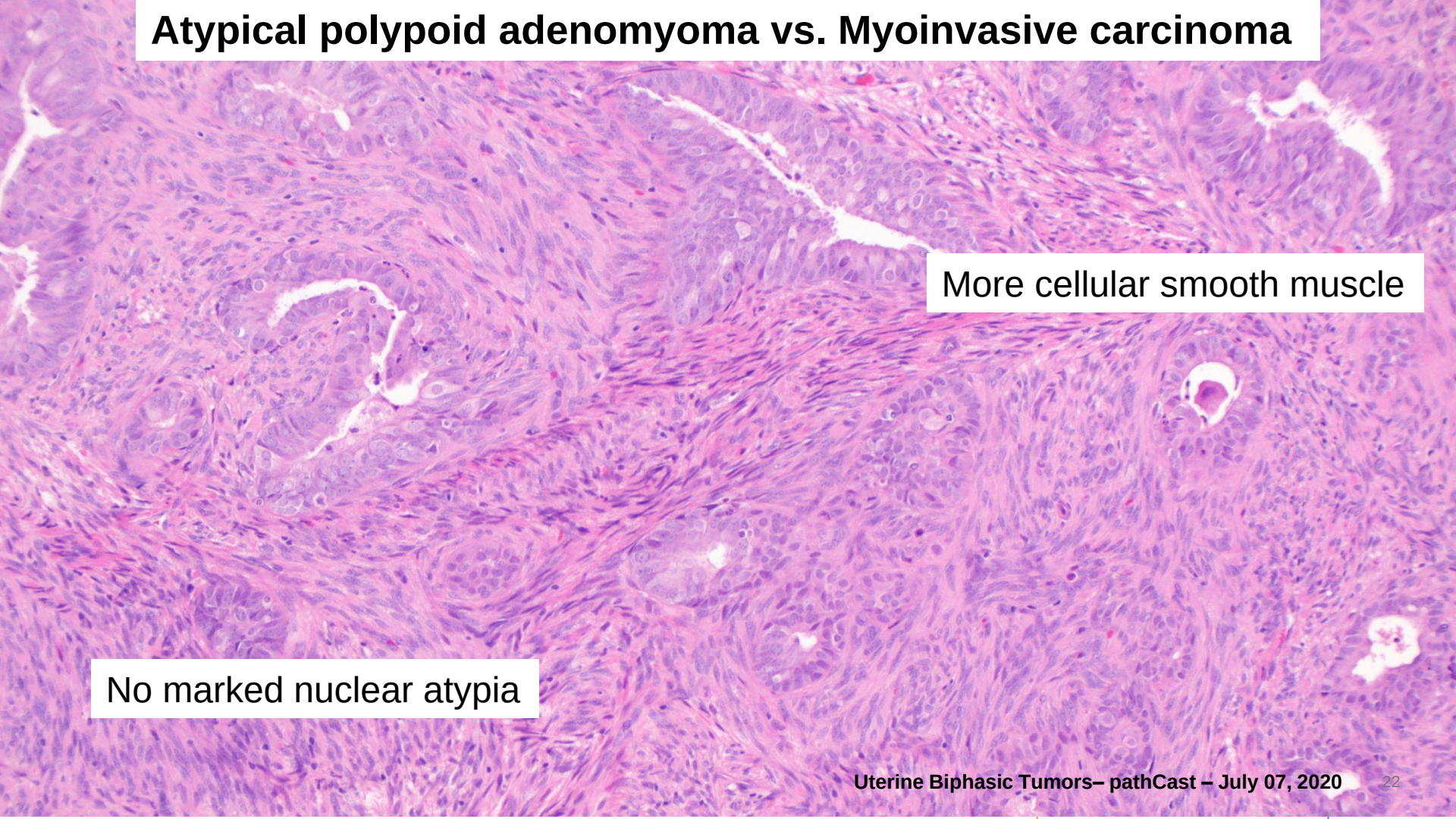
Admixed normal endometrial fragments

Atypical polypoid adenomyoma vs. Myoinvasive carcinoma



Vague lobular configuration

Atypical polypoid adenomyoma vs. Myoinvasive carcinoma



Immunohistochemistry may be helpful

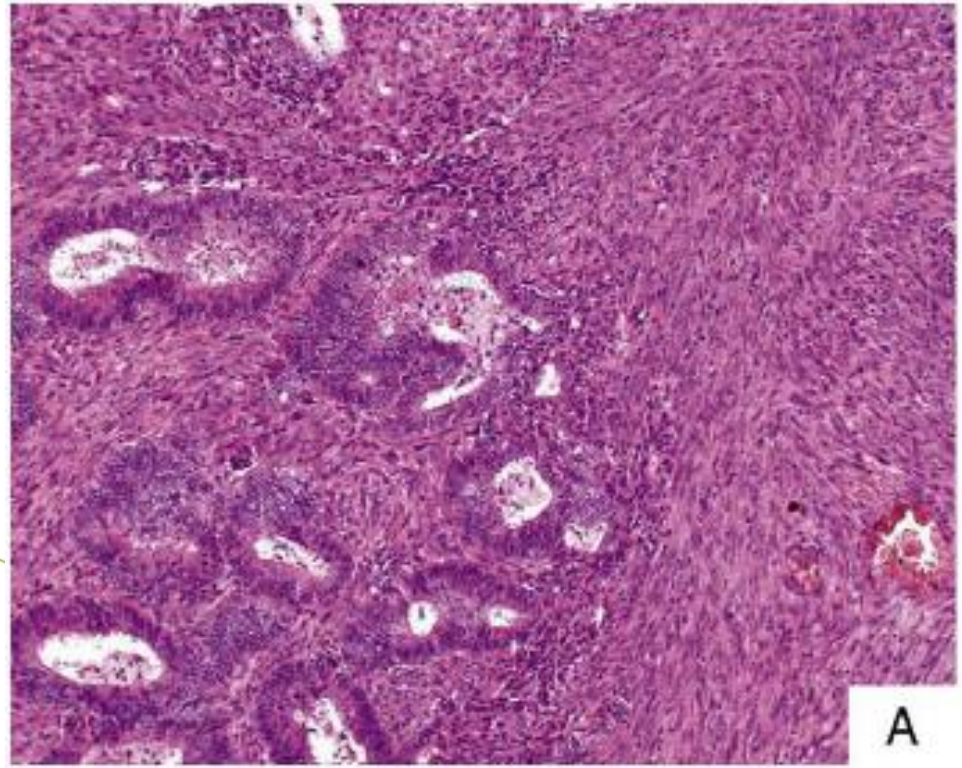
Atypical polypoid adenomyoma

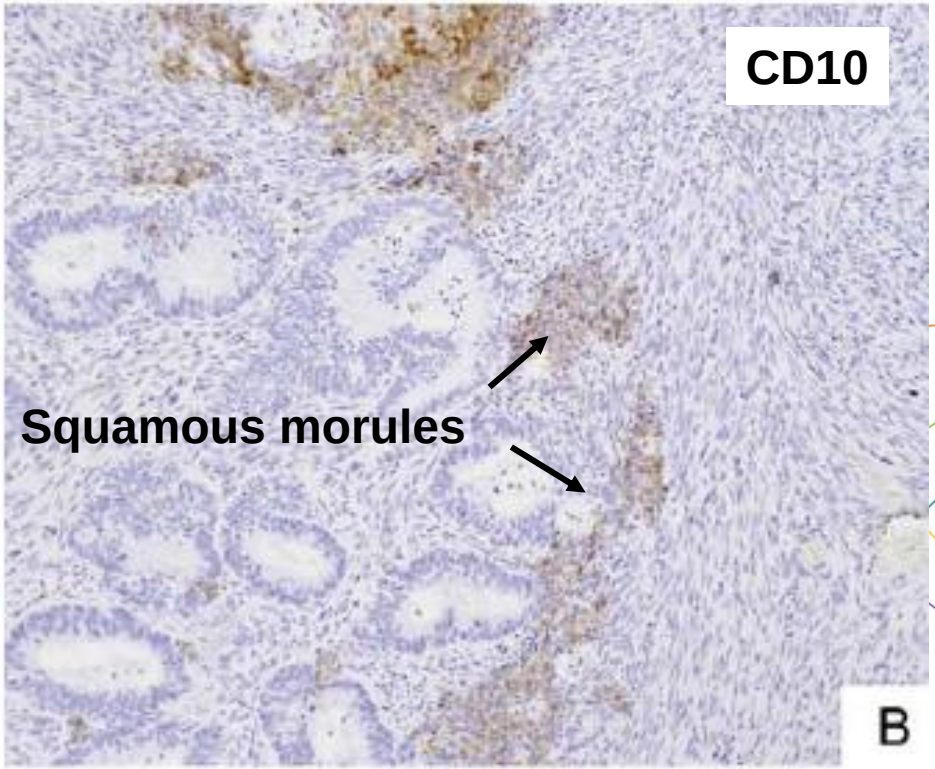
- CD10 negative or focal
- Caldesmon negative or focal
- p16 positive
- SMA and desmin not helpful

Myoinvasive carcinoma

- CD10 immediate periglandular area, can be negative
- Caldesmon diffusely positive, some focal or negative
- p16 negative
- SMA and desmin not helpful

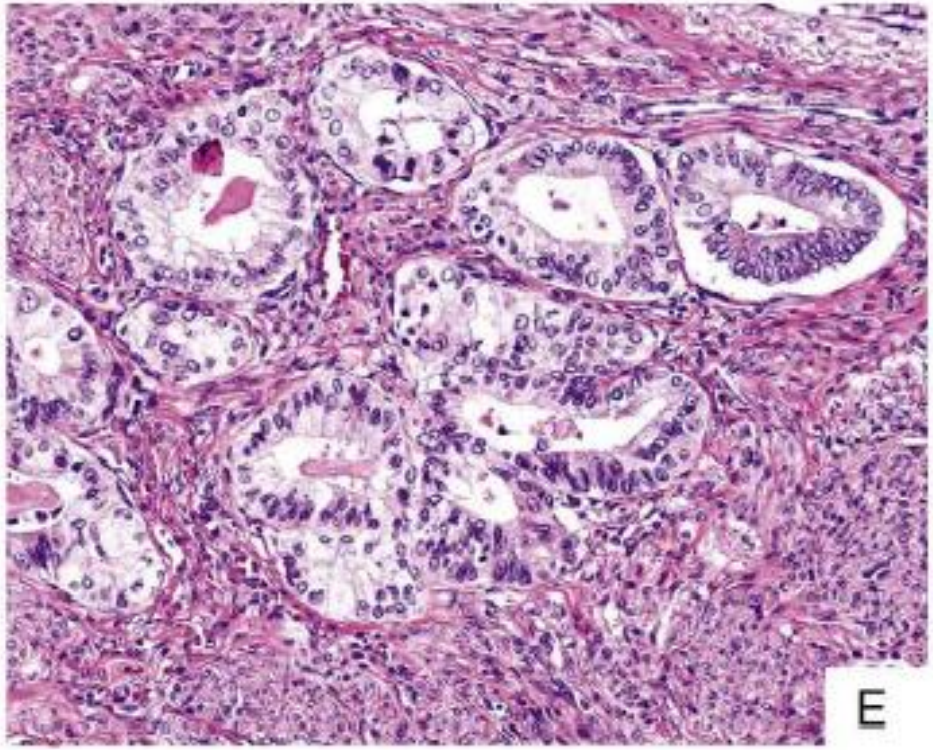
Atypical polypoid adenomyoma

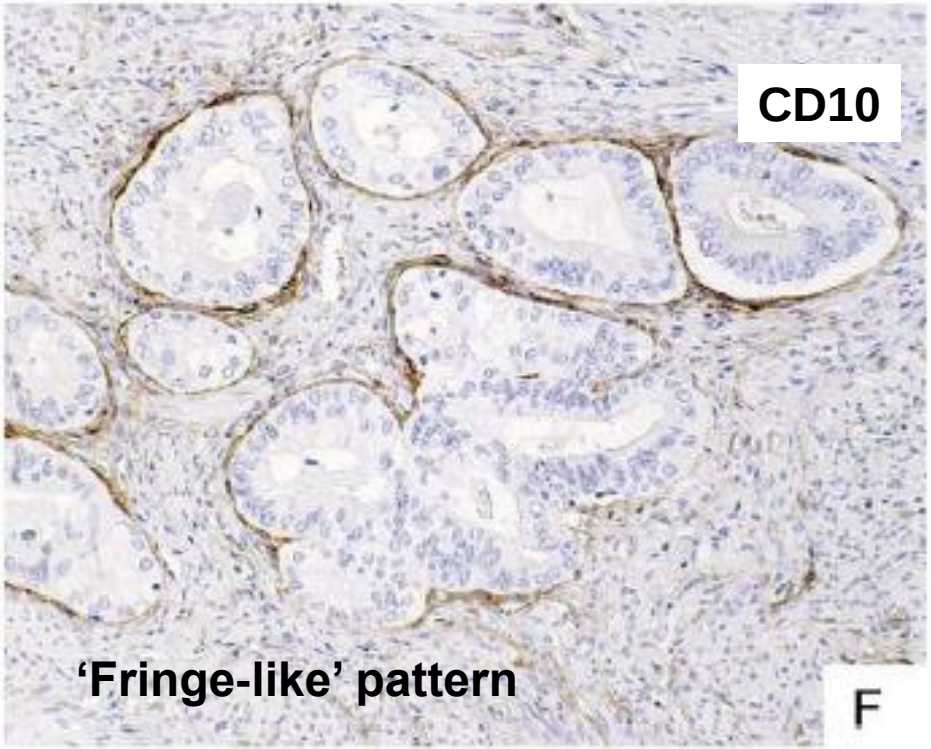




(Ohishi et al., 2008)

Myoinvasive carcinoma





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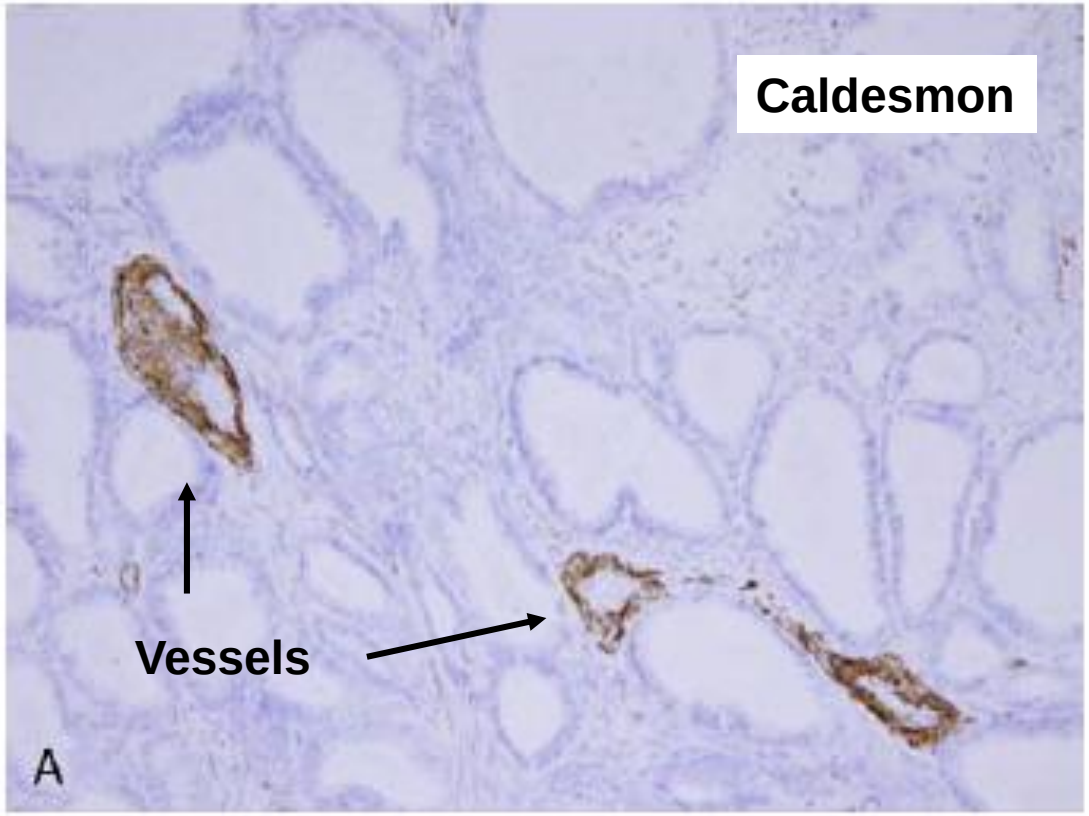

(Horita et al. 2011)

Myoinvasive carcinoma

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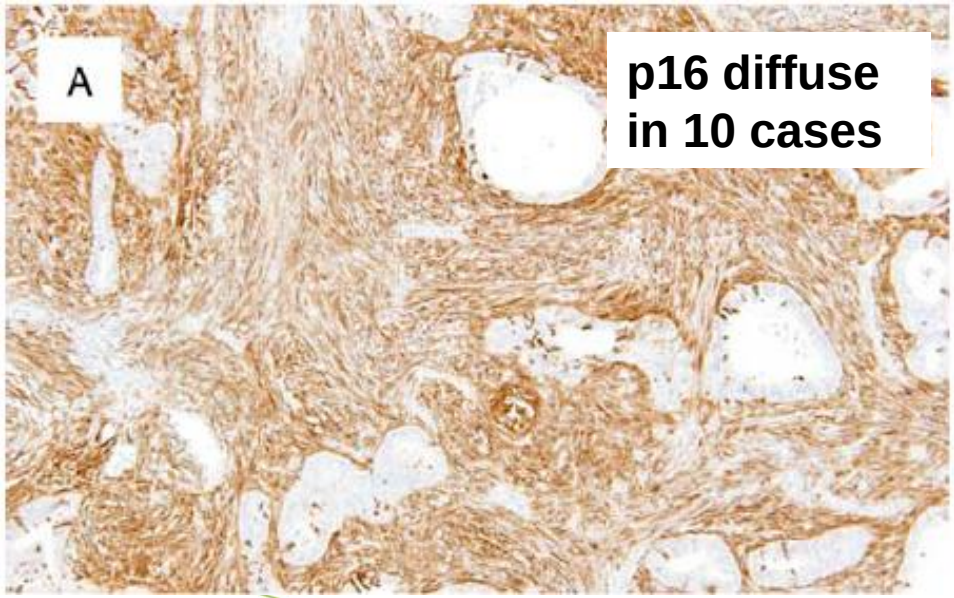
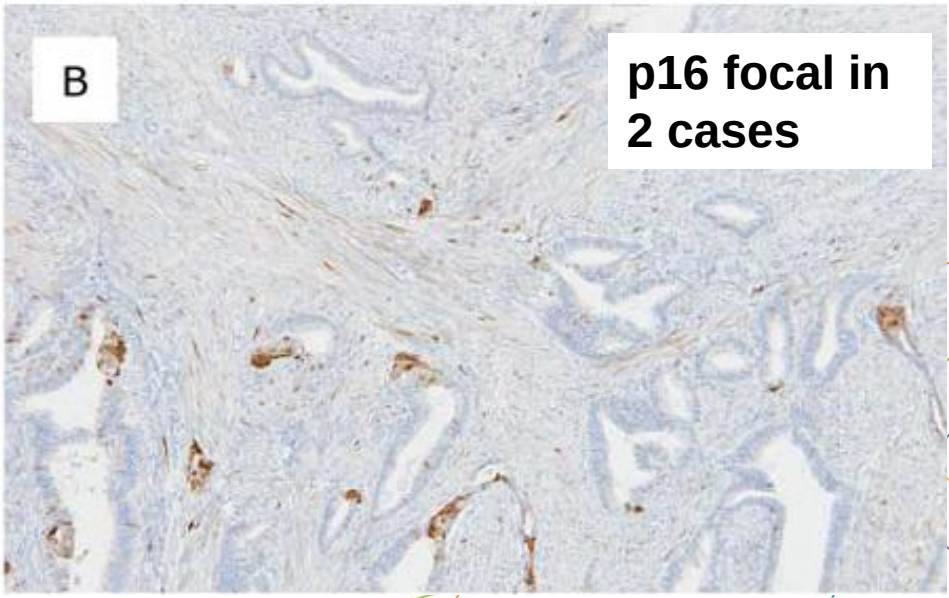
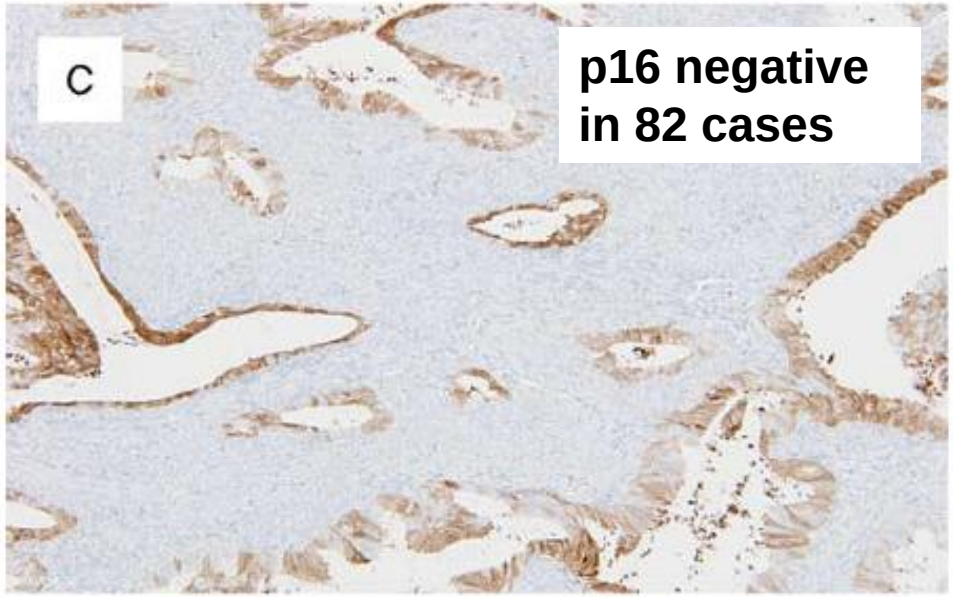
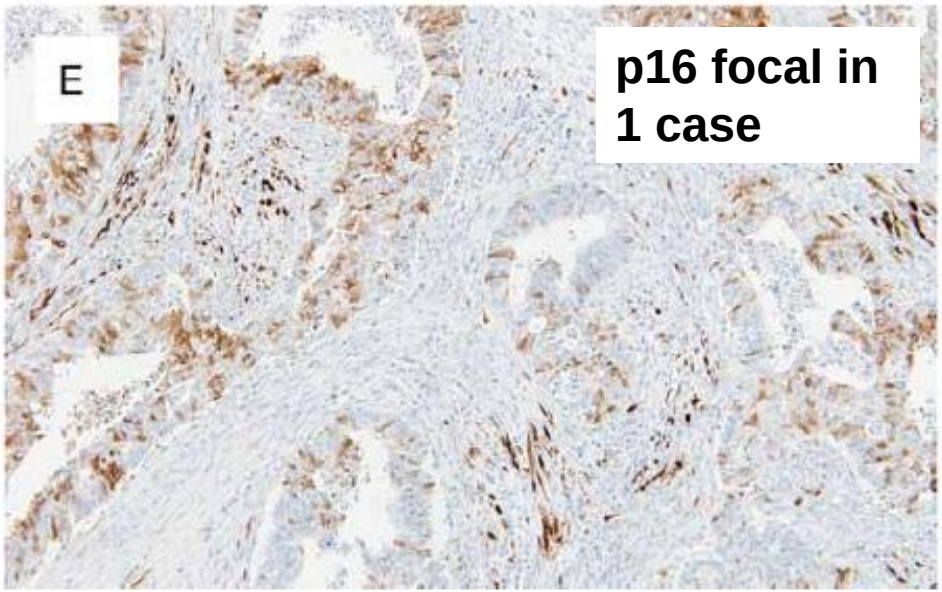




(Kihara et al., 2019)

Myoinvasive carcinoma





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Atypical polypoid adenomyoma

Differential Diagnoses

Myoinvasive endometrioid carcinoma

Adenomyomatous polyp

Endometrioid-type adenomyoma

Atypical polypoid adenomyoma

Differential Diagnoses

Adenomyomatous polyp

Adenomyomatous polyp

- **‘Benign adenomyomatous polyp’ preferred to ‘Polypoid adenomyoma’**
- **Two subtypes recently described**
  - Type 1: Vaguely fascicular myomatous stroma intimately admixed with glands
  - Type 2: Well-defined stalk of smooth muscle entrapping glands
- **Benign**

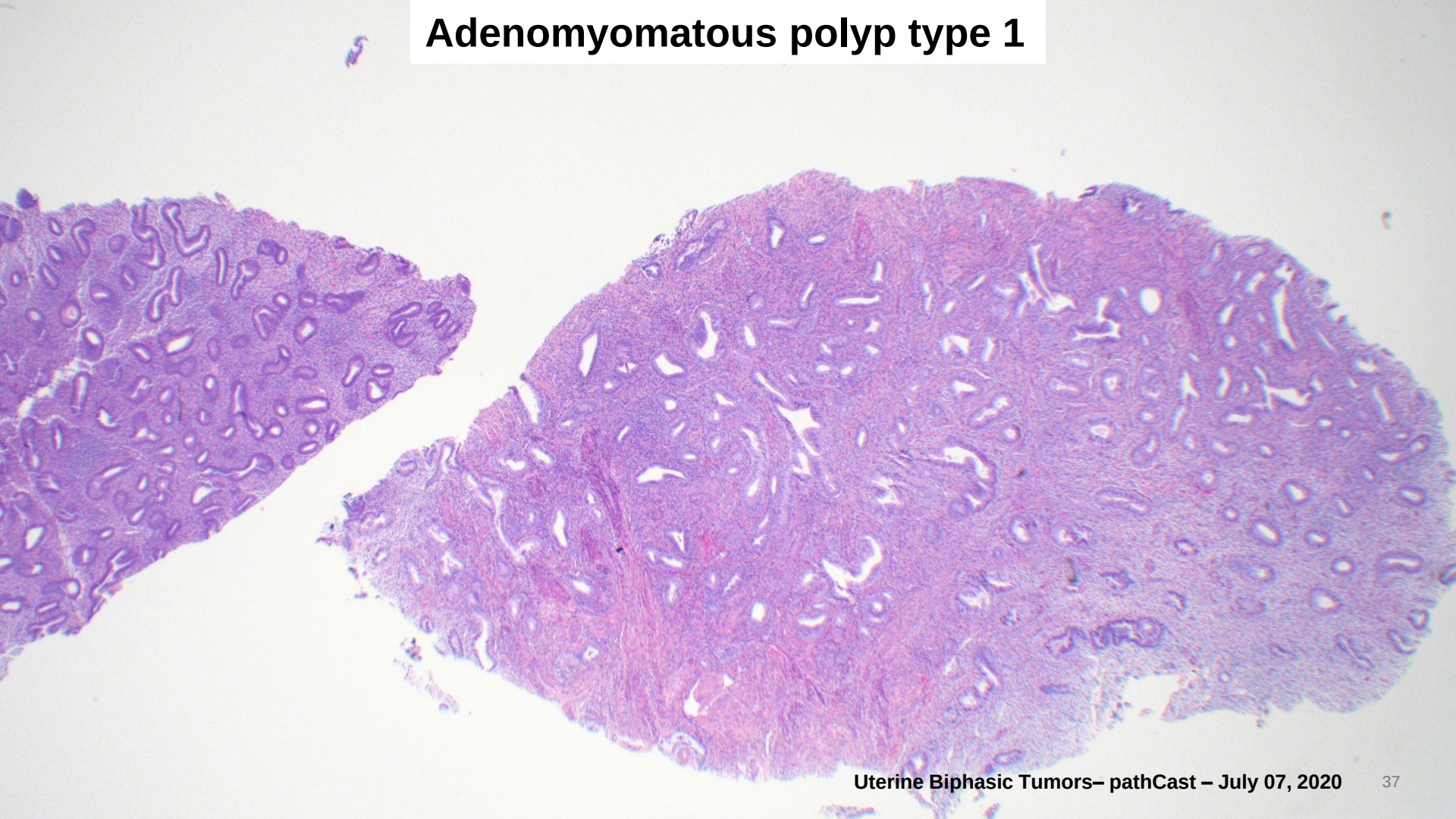
(Strickland et al., 2019)

Atypical polypoid adenomyoma

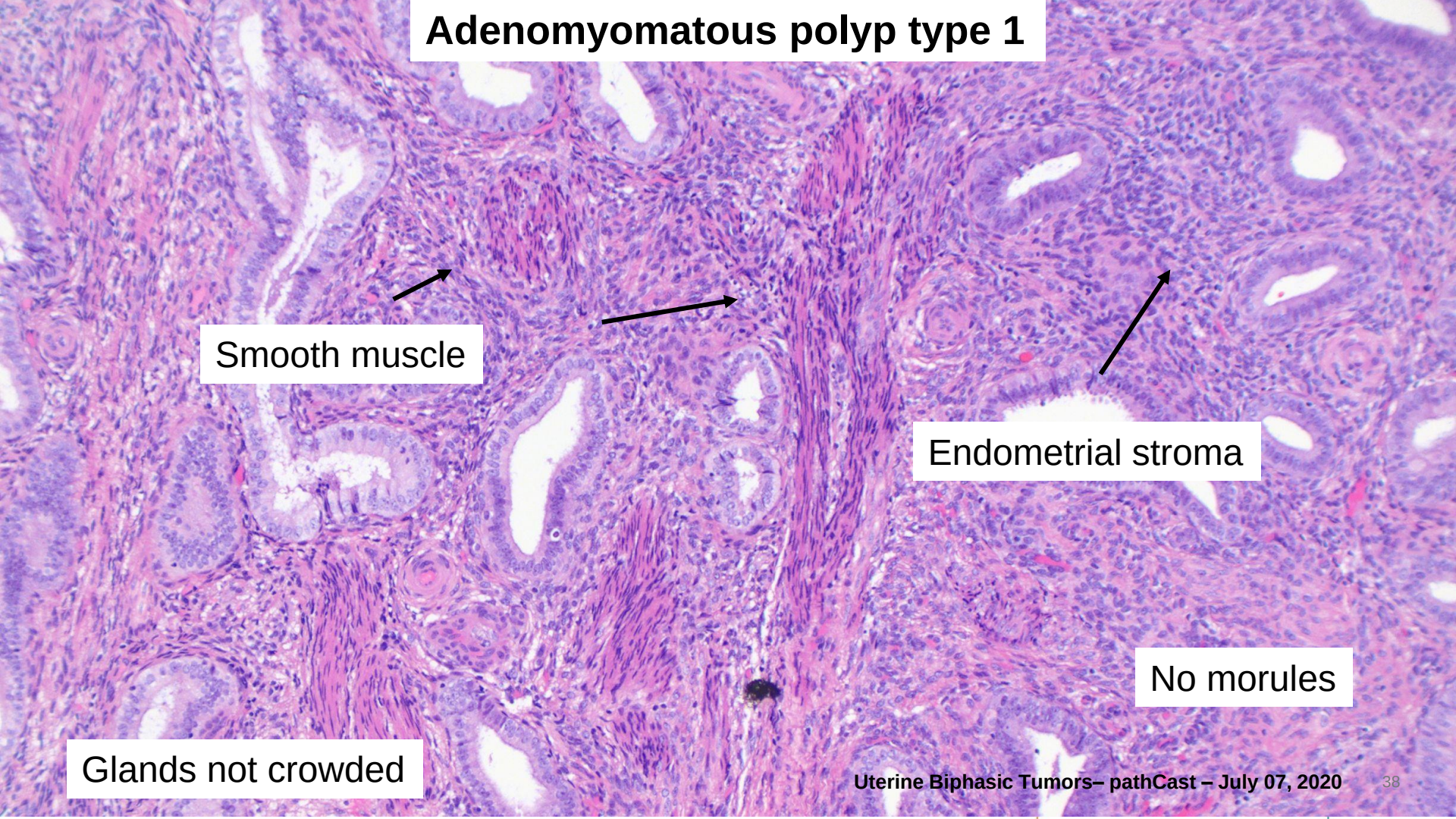
Differential Diagnoses

Adenomyomatous polyp type 1

Adenomyomatous polyp type 1



Adenomyomatous polyp type 1



Atypical polypoid adenomyoma

VERSUS

Adenomyomatous polyp type 1

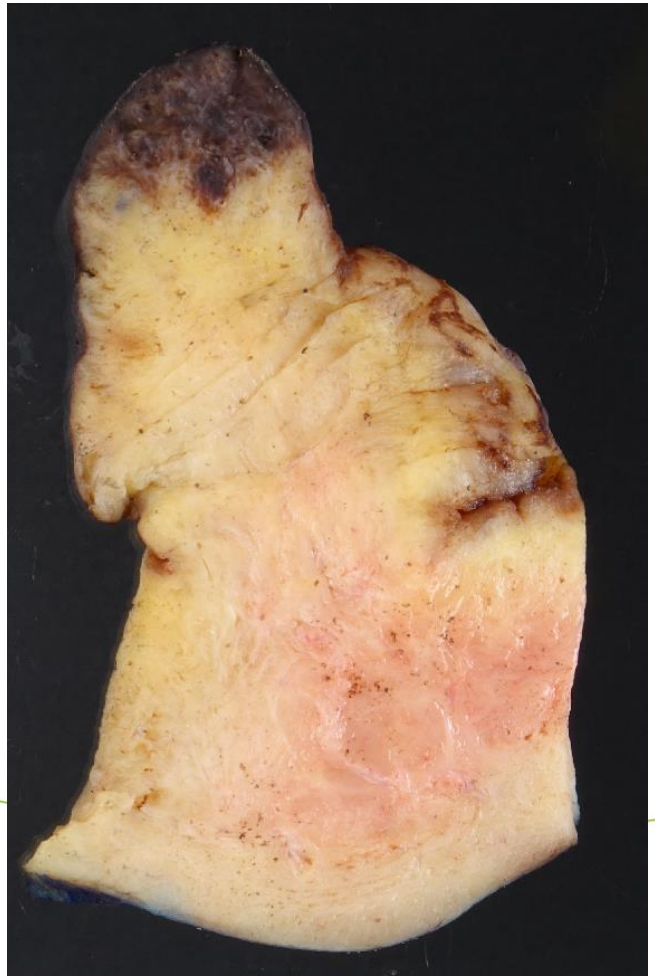
Slide presentation

Atypical polypoid adenomyoma

Differential Diagnoses

Adenomyomatous polyp type 2

Adenomyomatous polyp type 2



Adenomyomatous polyp type 2

Slide presentation

Stalk of smooth muscle as a central core

Endometrial glands + Stroma radiate towards the periphery

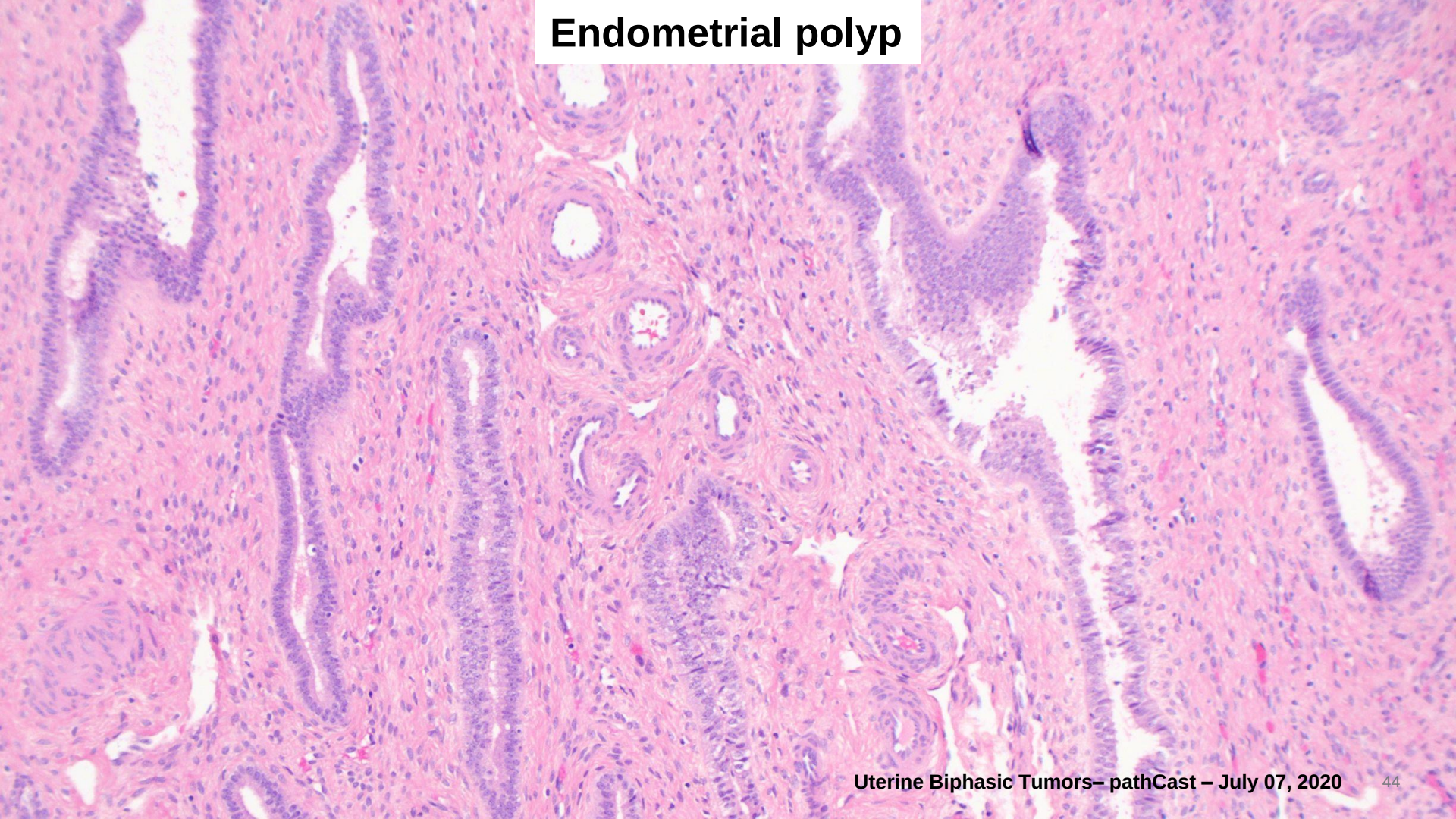
Adenomyomatous polyp type 2

Slide presentation

Smooth muscle stalk is positive for desmin and caldesmon

Endometrial stroma is positive for CD10

Endometrial polyp



Atypical polypoid adenomyoma

Differential Diagnoses

Myoinvasive endometrioid carcinoma

Adenomyomatous polyp

Endometrioid-type adenomyoma

Atypical polypoid adenomyoma

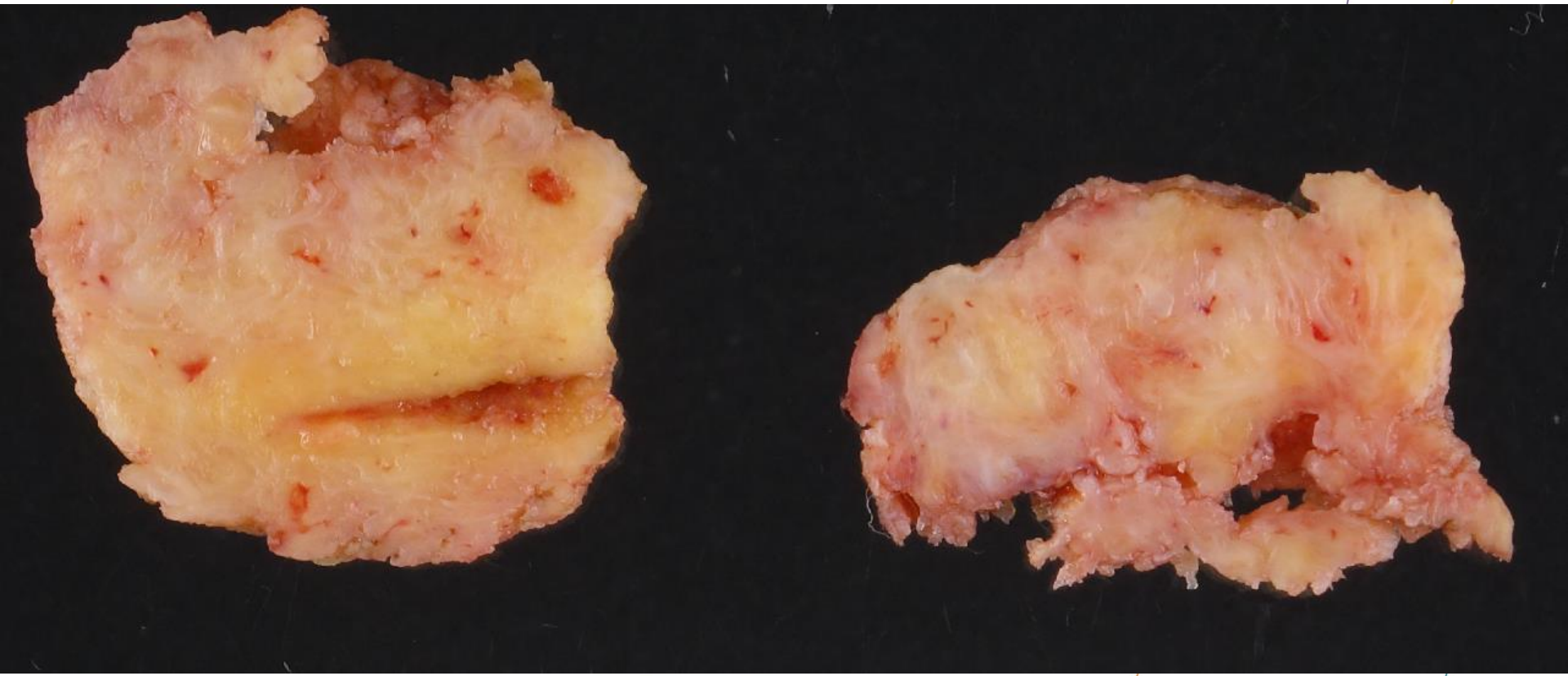
Differential Diagnoses

Endometrioid-type adenomyoma

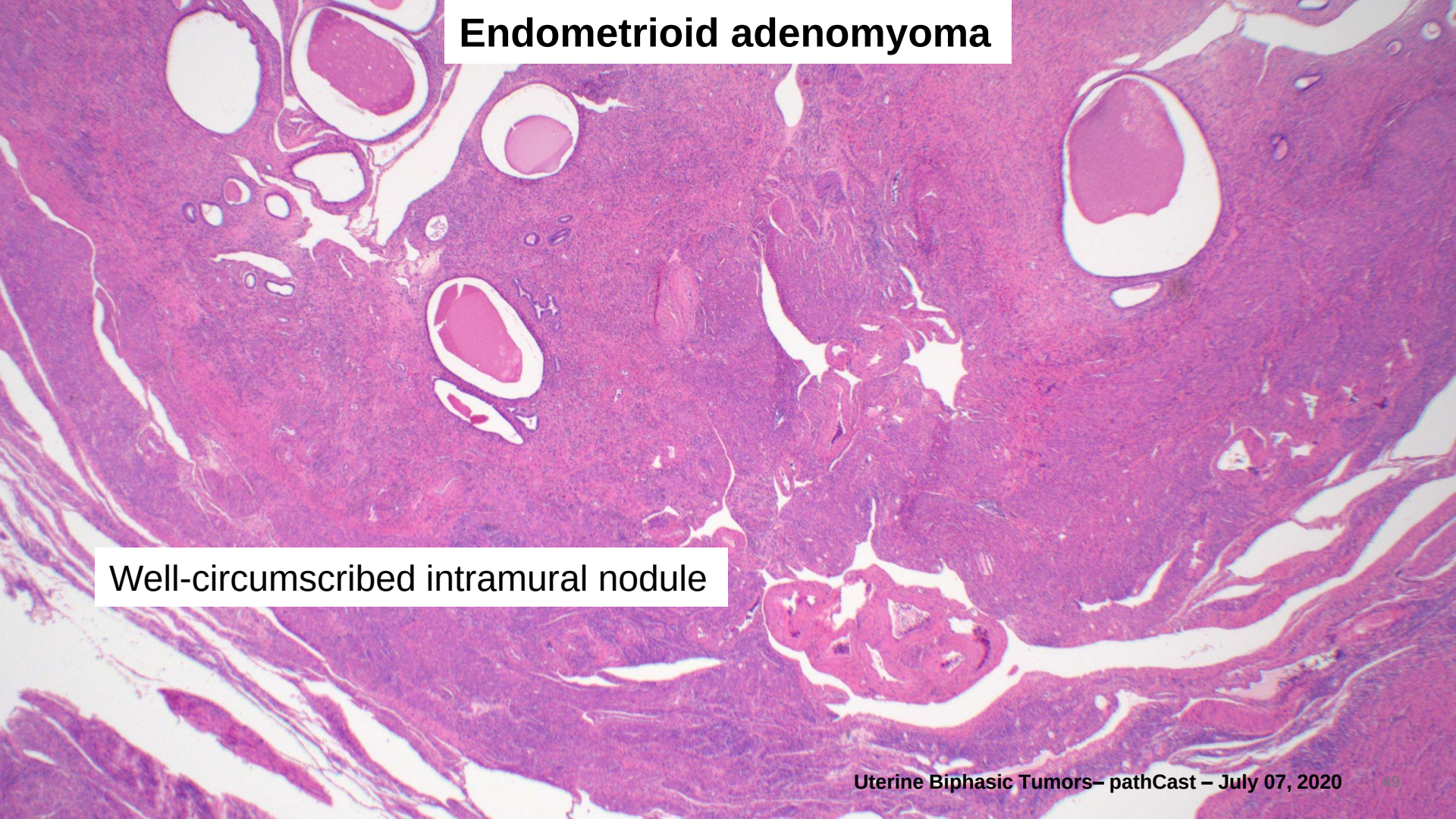
Endometroid adenomyoma

- Endometrioid glands surrounded by endometrial stroma within a ‘leiomyoma’
- Intramural lesions, may bulge into the cavity but are not predominantly polypoid
- Benign

Endometrioid adenomyoma

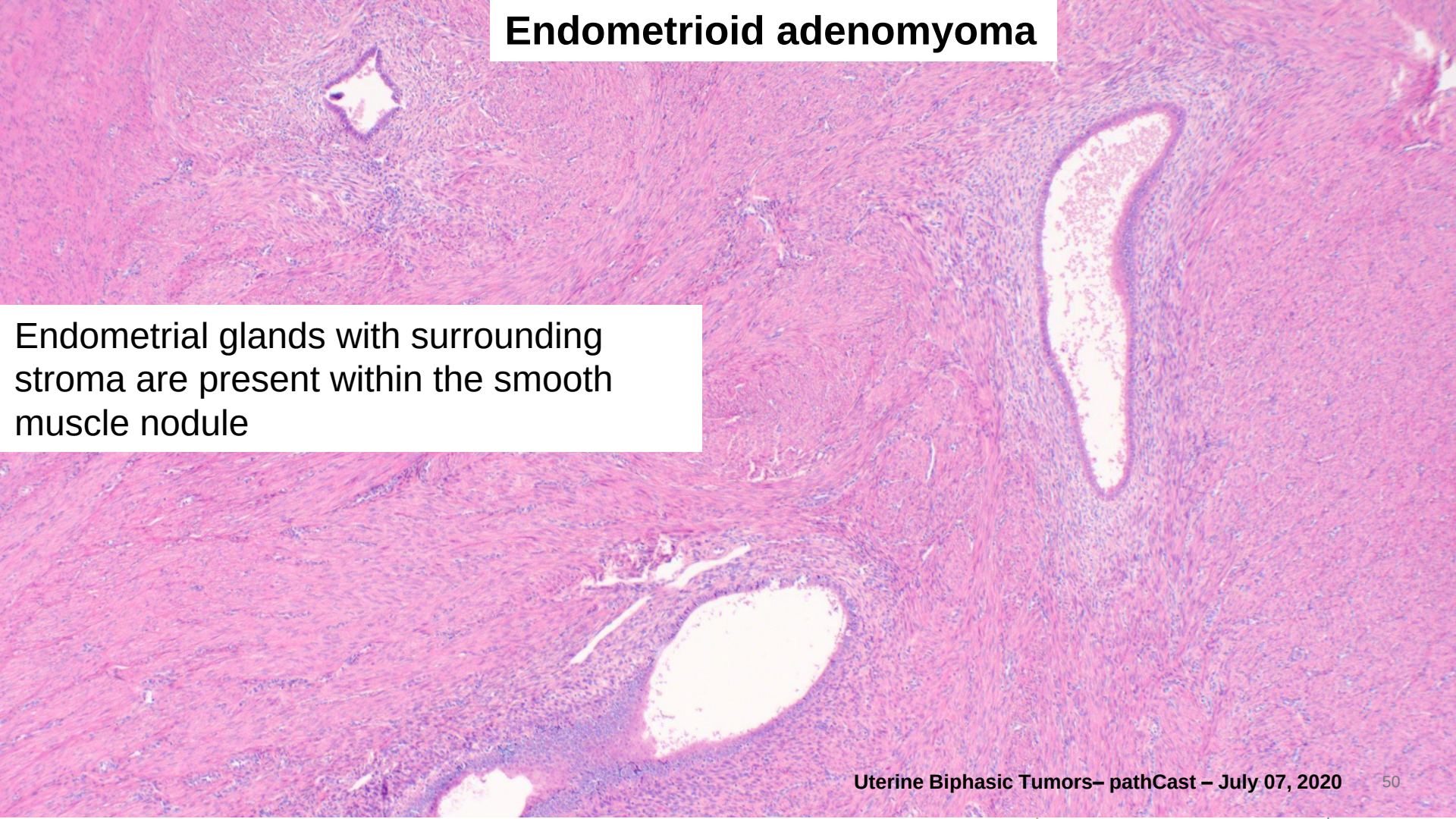


Endometrioid adenomyoma



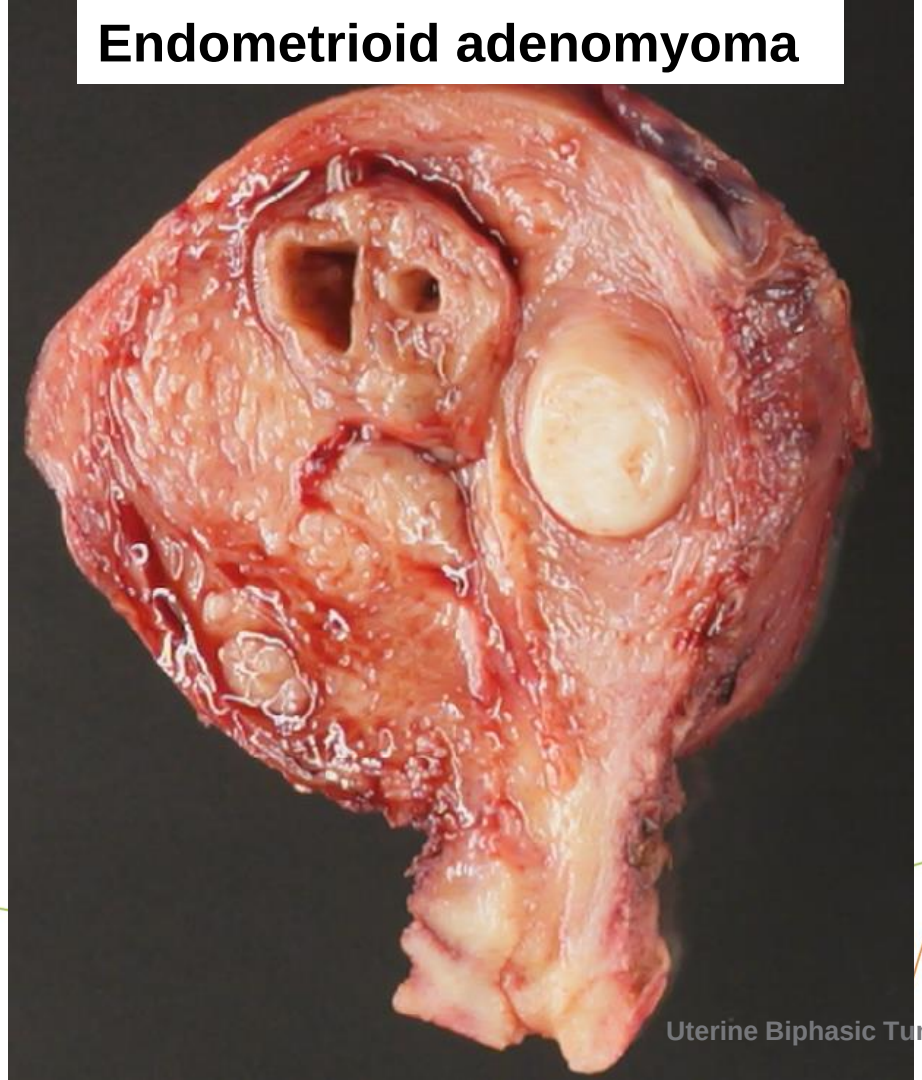
Well-circumscribed intramural nodule

Endometrioid adenomyoma



Endometrial glands with surrounding stroma are present within the smooth muscle nodule

Endometrioid adenomyoma



Submucosal endometrioid adenomyoma

VERSUS

Adenomyomatous polyp type 2

Slide presentation

Atypical polypoid adenomyoma

Differential Diagnoses

Myoinvasive endometrioid carcinoma

Adenomyomatous polyp type 1

Adenomyomatous polyp type 2

Endometrioid-type adenomyoma

Uterine biphasic tumors

Adenosarcoma

Carcinosarcoma

Atypical polypoid adenomyoma

Adenomyomatous polyp

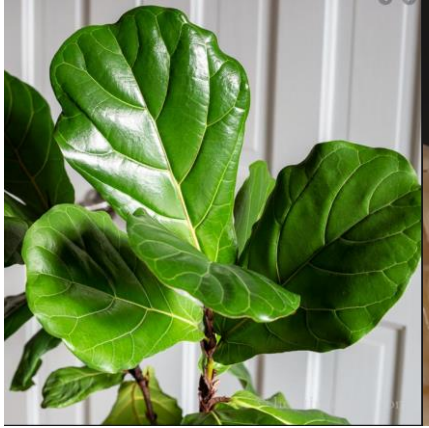
Adenomyoma

Müllerian adenosarcoma

- **More common in postmenopausal women but also reproductive-age women**
- **More often in uterine corpus, but also cervix and extra-uterine locations**

(Friedlander et al, 2014)

Müllerian adenosarcoma

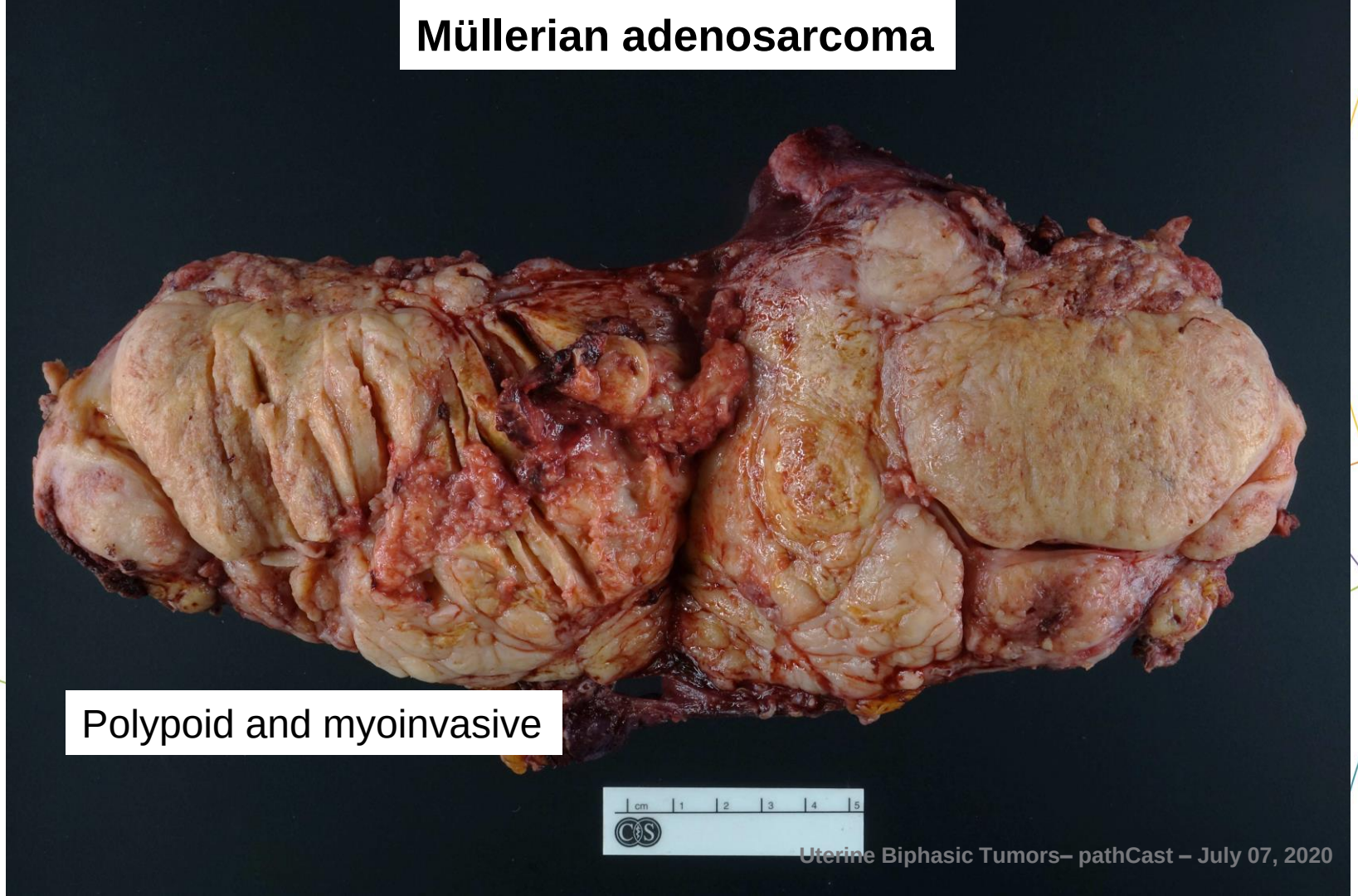


Broad leaf-like growth

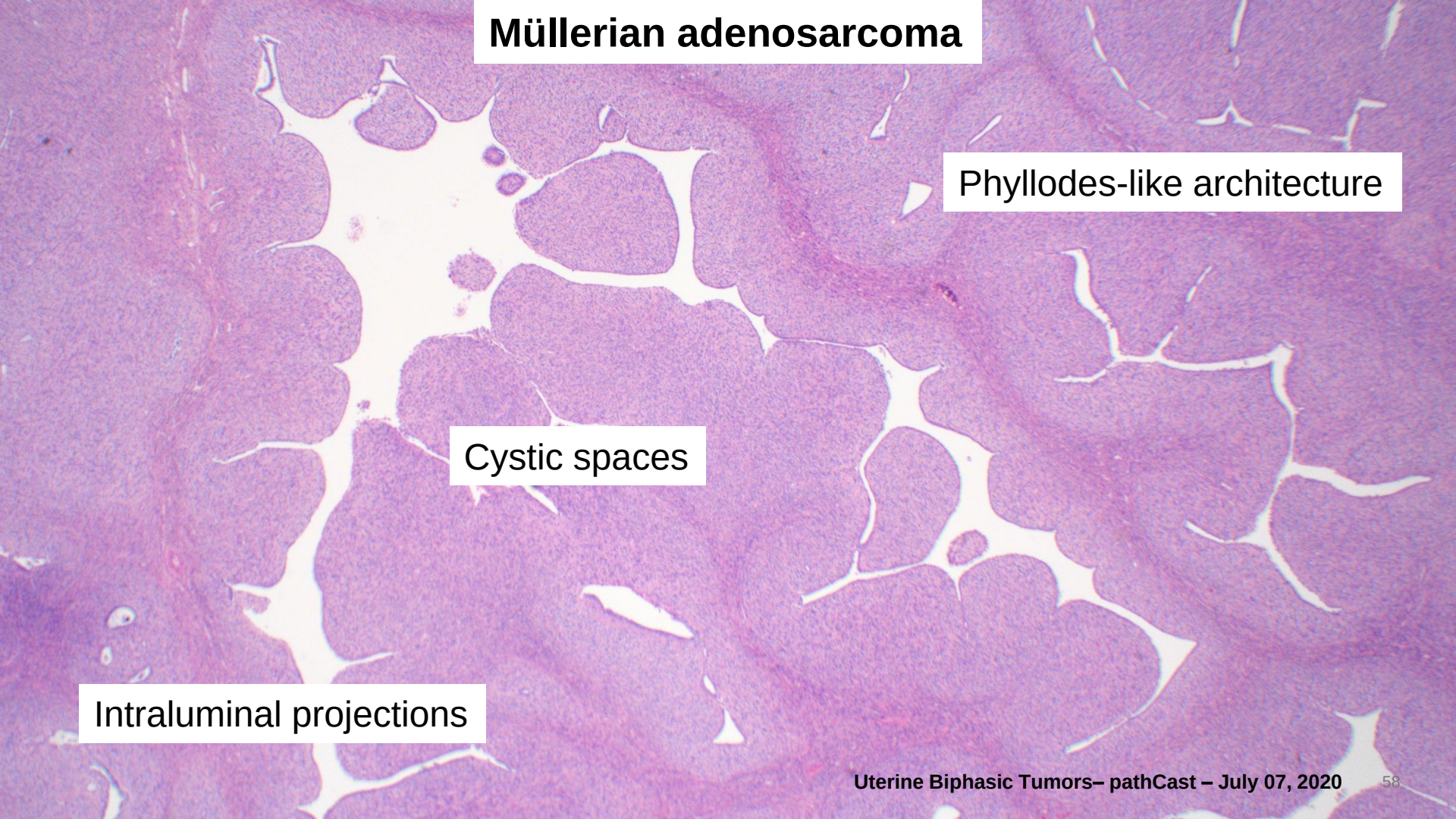
Polypoid

Cystic areas with papillary fronds

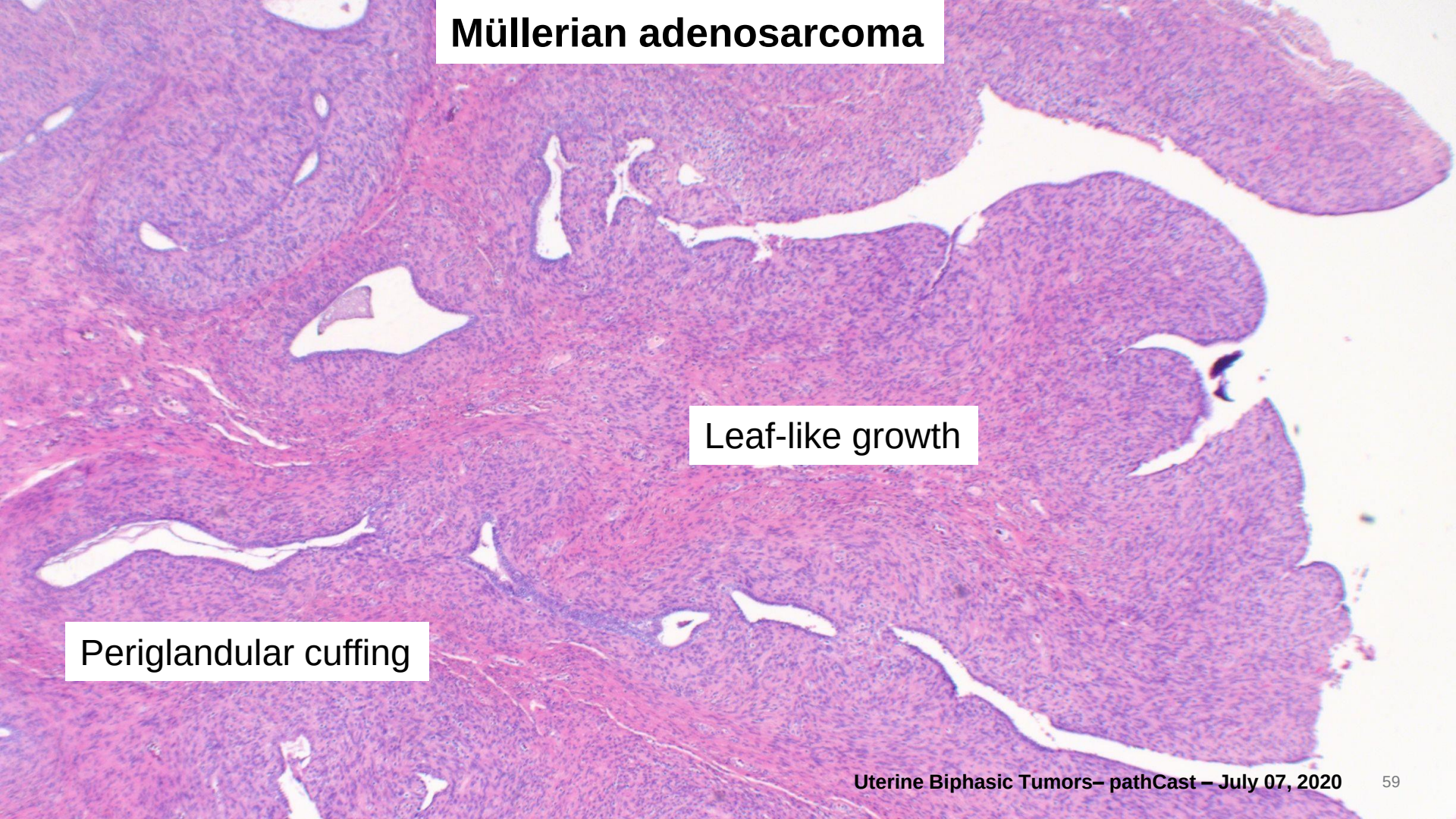
Müllerian adenosarcoma



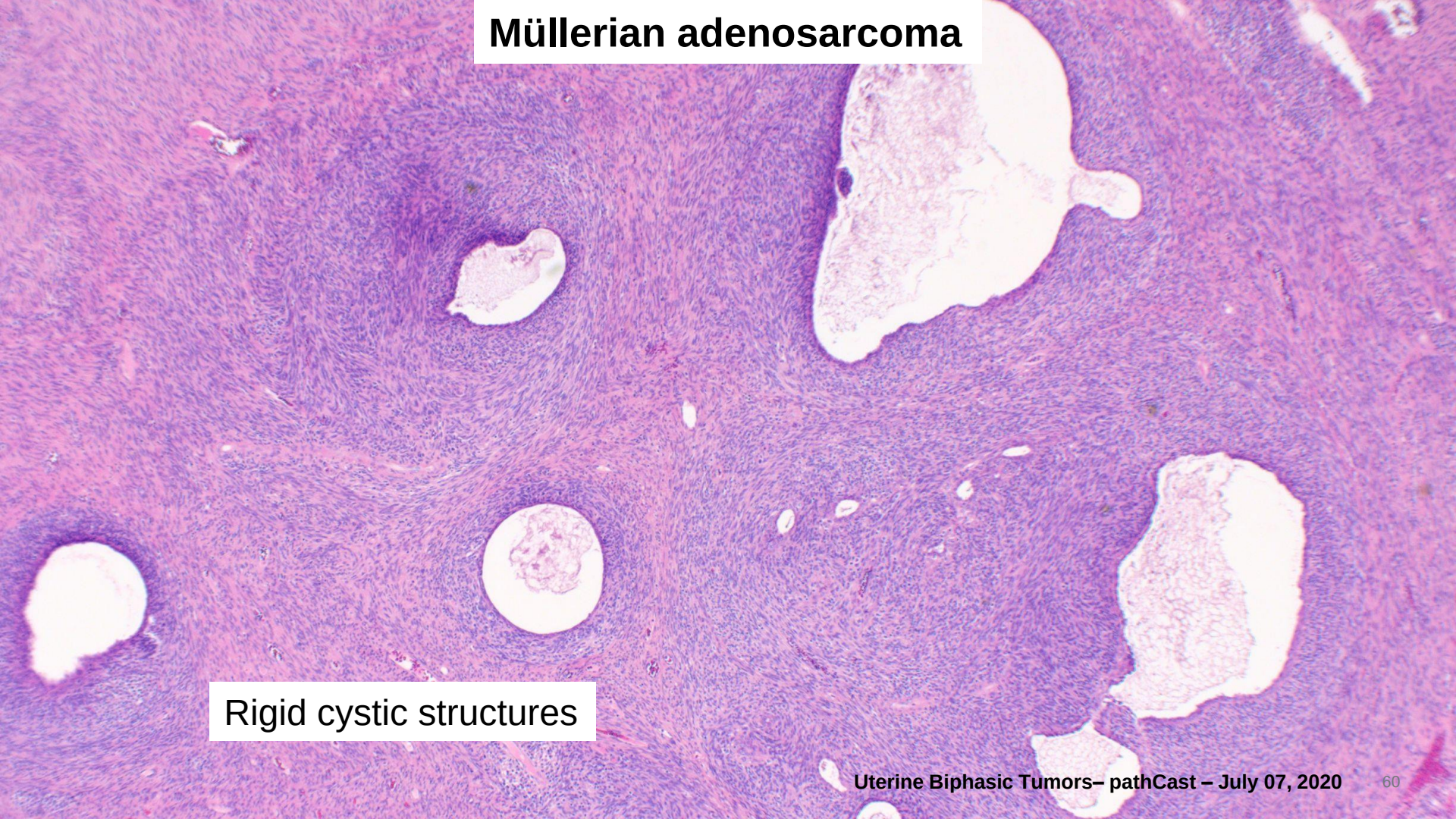
Müllerian adenosarcoma



Müllerian adenosarcoma

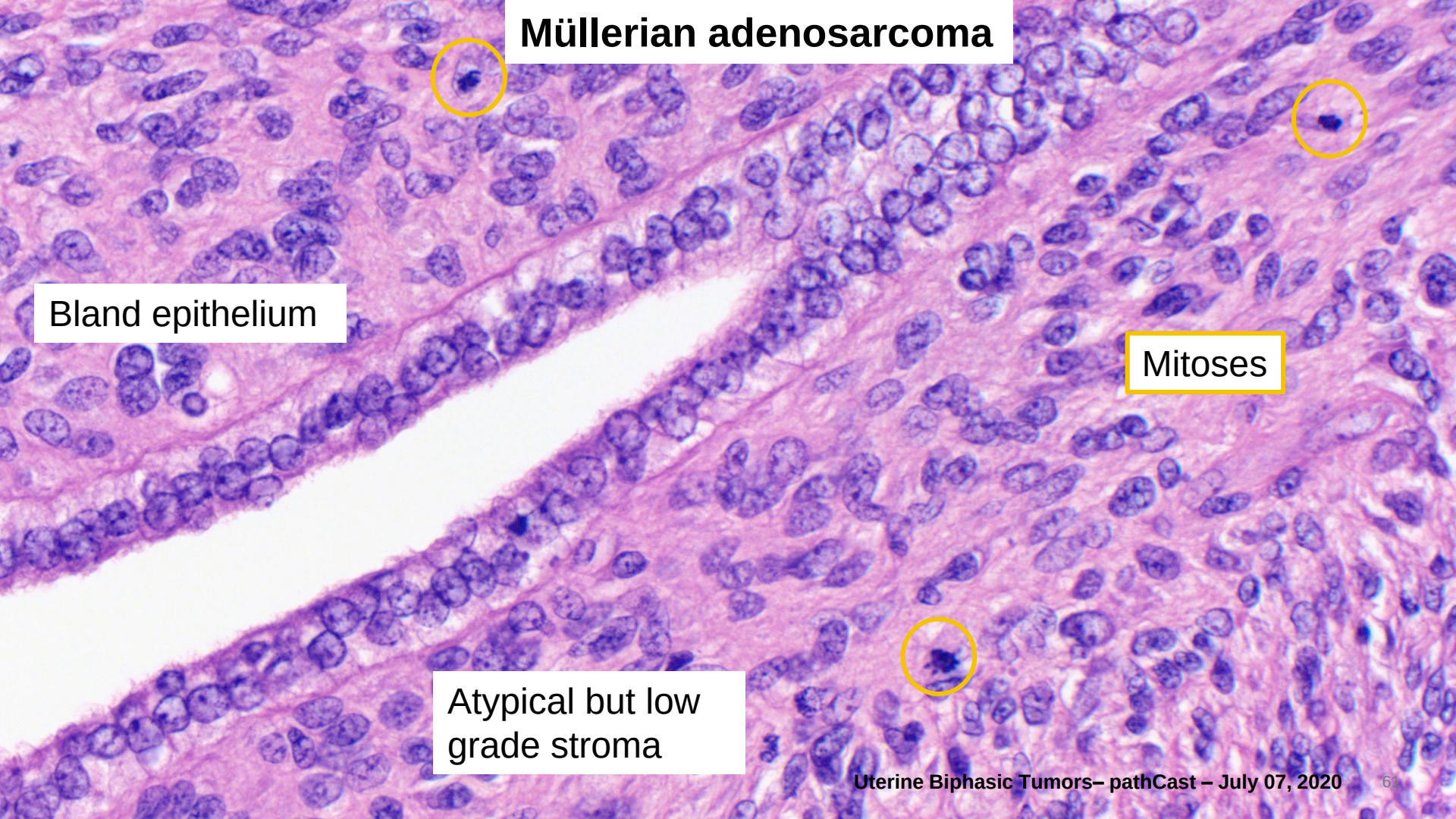


Müllerian adenosarcoma



Rigid cystic structures

Müllerian adenosarcoma

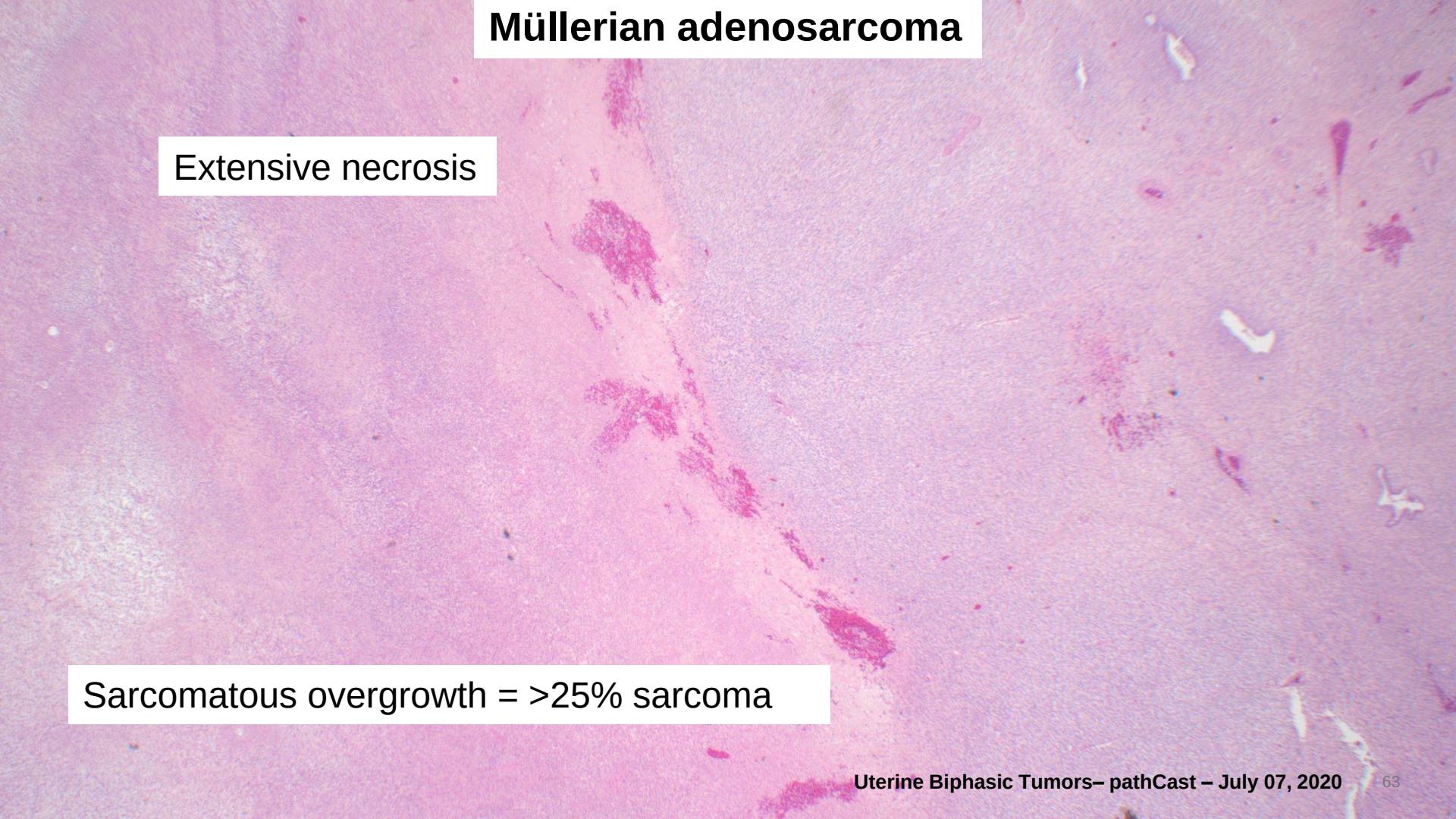


Müllerian adenosarcoma

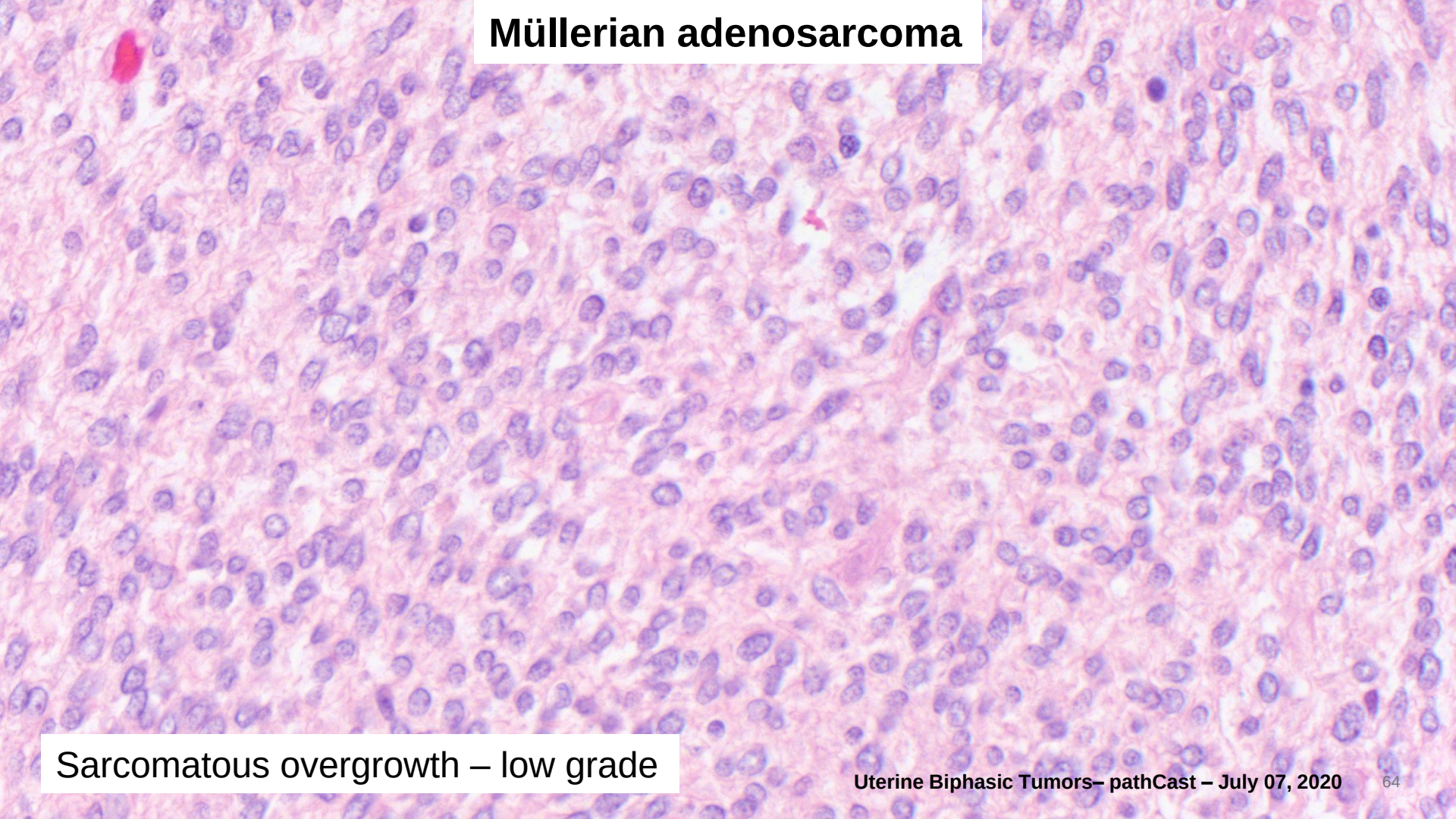
- **Mesenchyme most commonly low grade and resembling low grade endometrial stromal sarcoma**
- **WHO cut off is 2 mitosis per 10 HPF**
- **Stromal cytologic atypia and mitoses are usually seen, can be variably present and, according to some, are not necessarily required for diagnosis**

(McCluggage 2010) (McCluggage 2016)

Müllerian adenosarcoma

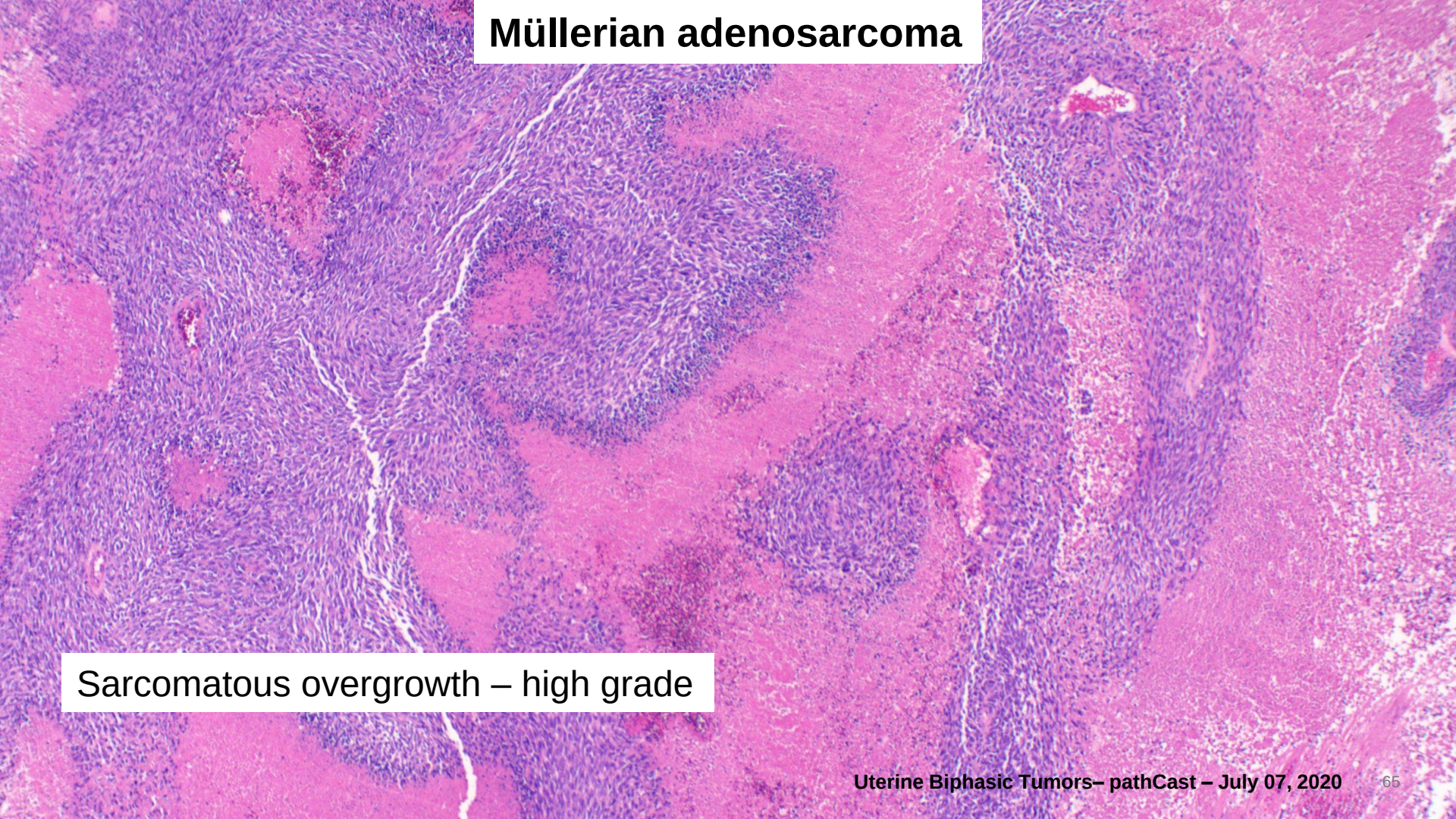


Müllerian adenosarcoma



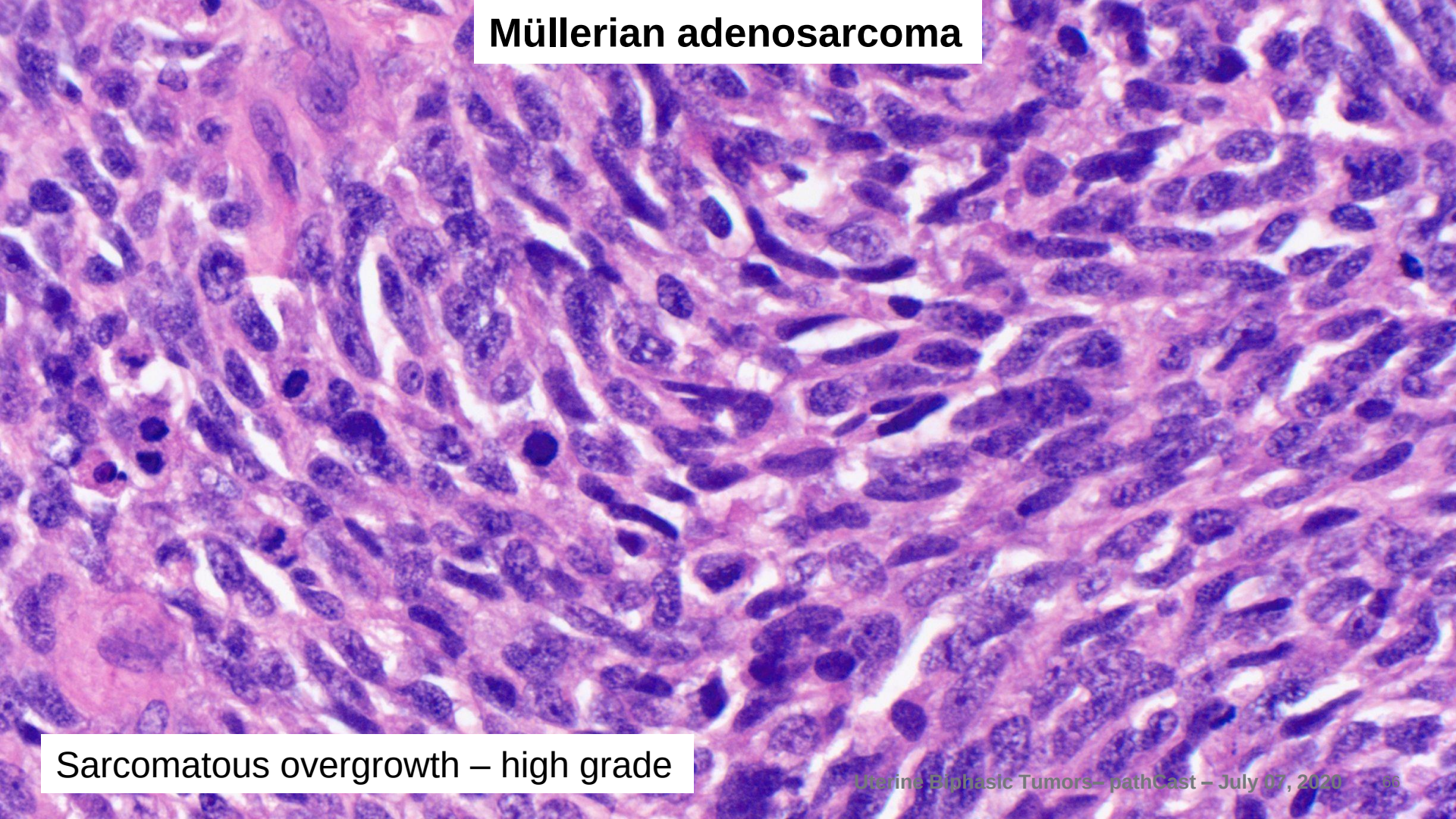
Sarcomatous overgrowth – low grade

Müllerian adenosarcoma



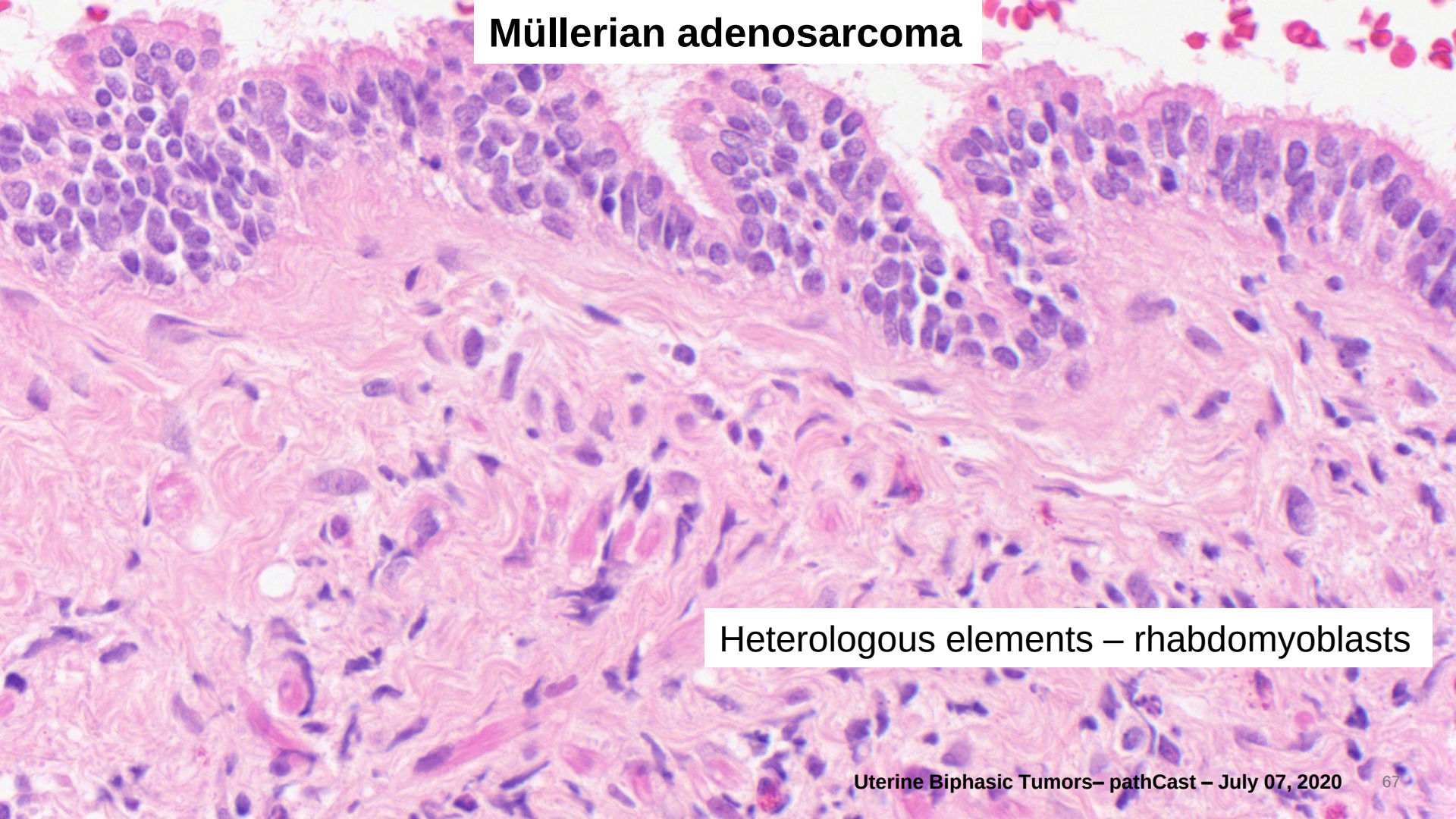
Sarcomatous overgrowth – high grade

Müllerian adenosarcoma



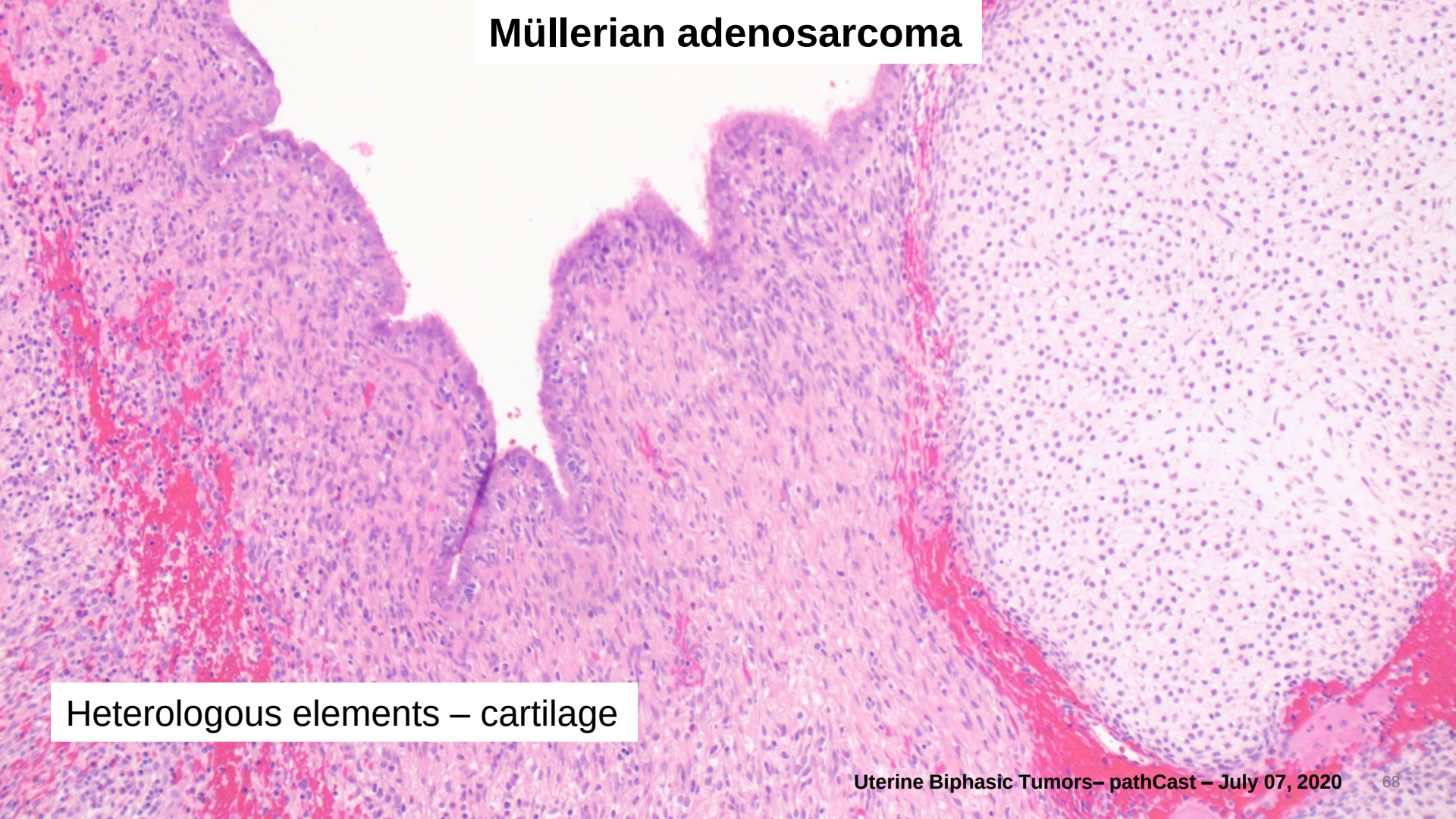
Sarcomatous overgrowth – high grade

Müllerian adenosarcoma



Heterologous elements – rhabdomyoblasts

Müllerian adenosarcoma



Heterologous elements – cartilage

Müllerian adenosarcoma

Differential Diagnoses

- Adenofibroma
- Endometrial stromal sarcoma
- Endometrial polyps with adenosarcoma-like features
- Undifferentiated uterine sarcoma
- Carcinosarcoma
- Rhabdomyosarcoma

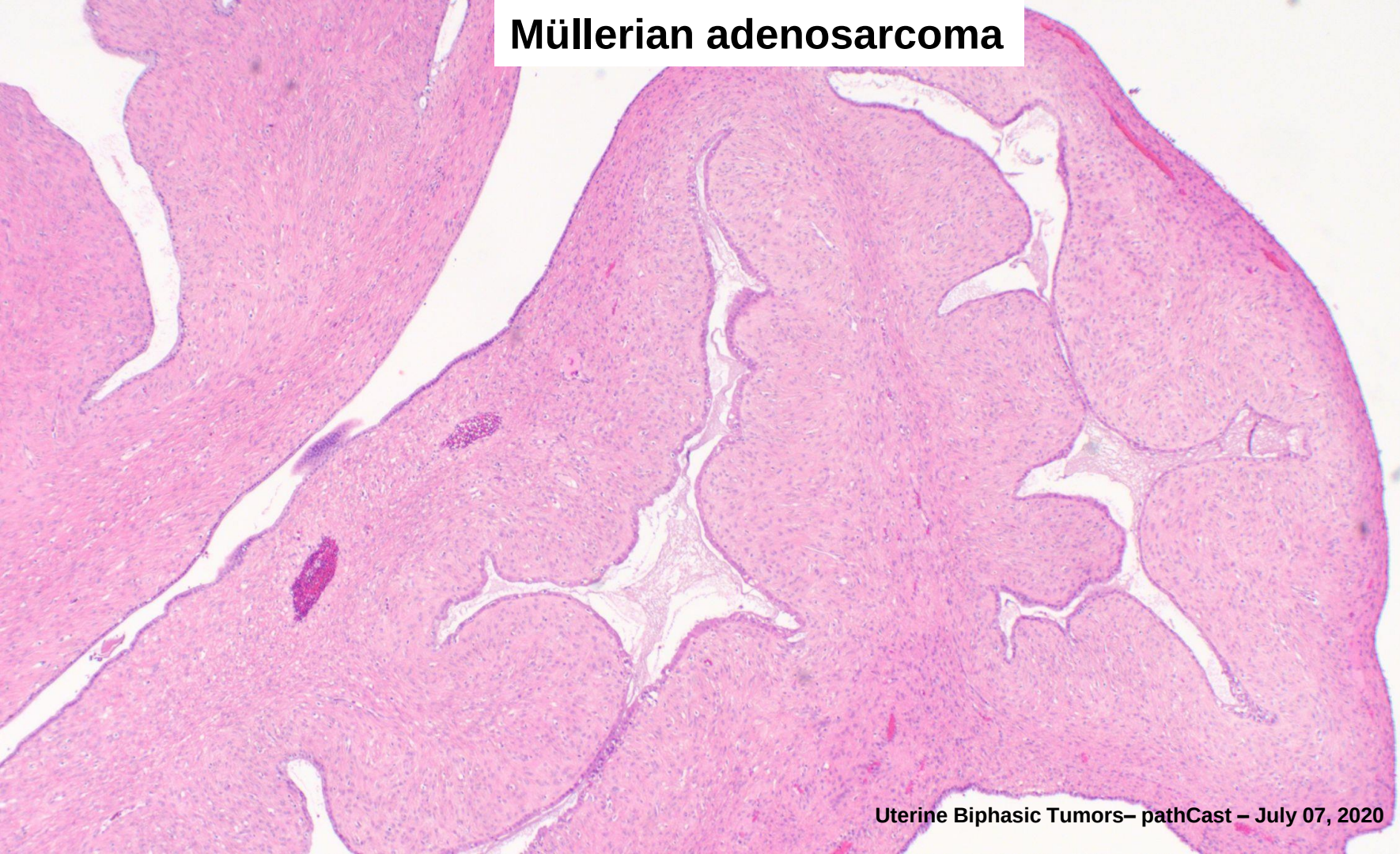
Müllerian adenosarcoma

Differential Diagnoses

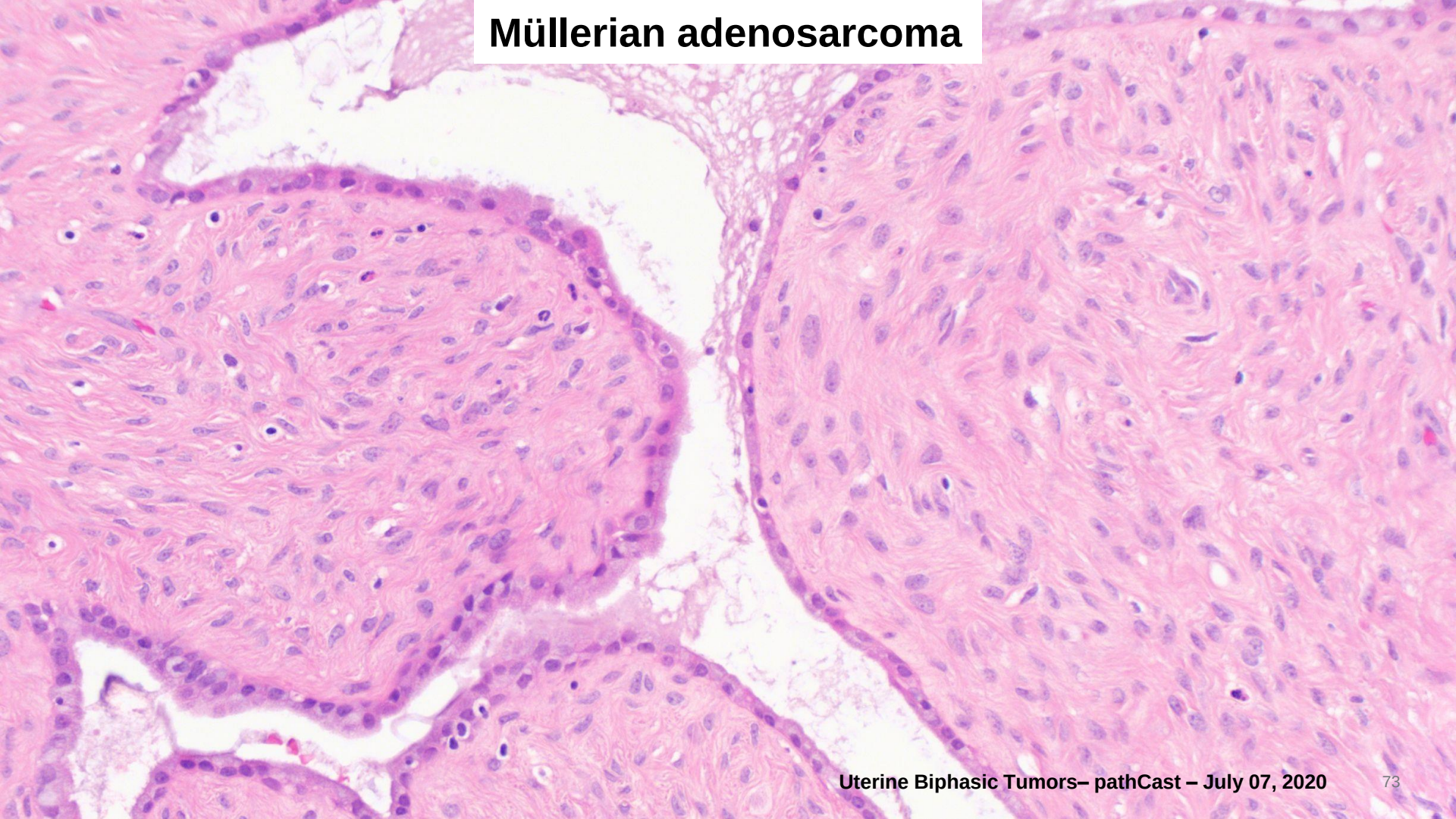
Adenofibroma

Müllerian adenosarcoma

Müllerian adenosarcoma



Müllerian adenosarcoma



Müllerian adenosarcoma

Differential Diagnoses

- Adenofibroma
- Endometrial stromal sarcoma
- Endometrial polyps with adenosarcoma-like features
- Undifferentiated uterine sarcoma
- Carcinosarcoma
- Rhabdomyosarcoma

Müllerian adenosarcoma

Differential Diagnoses

Endometrial polyps with adenosarcoma-like features

Endometrial polyps with adenosarcoma-like features

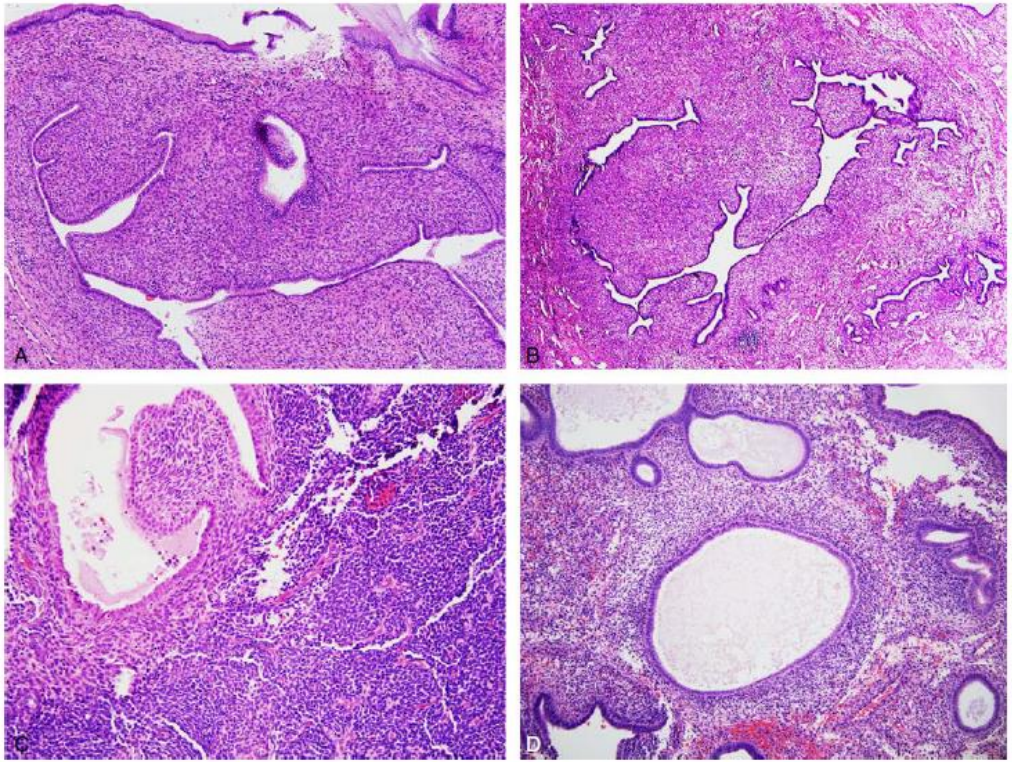


FIGURE 2. Architectural changes in uterine polyps with unusual features. A and B, Subtle phyllodes-like growth pattern. C, Intraglandular polypoid projection. D, Rigid cyst formation.

(Howitt, Quade and Nucci 2015)

Endometrial polyps with adenosarcoma-like features

TABLE 1. Morphologic Features of Uterine Polyps With Atypical Features

Feature	No. Cases With Feature (%)
Intraglandular polypoid projections	27/29 (93)
Phyllodes-like architecture	22/29 (76)
Periglandular stromal alteration	23/29 (79)
Rigid cyst formation	14/29 (48)
Mitoses $\geq$ 2/10 HPF	10/29 (34)
Stromal atypia*	2/29 (7)

*Stromal atypia when present was focal and mild.

(Howitt, Quade and Nucci 2015)

Müllerian adenosarcoma

VERSUS

Endometrial polyp with adenosarcoma-like features

Slide presentation

Endometrial polyps with adenosarcoma-like features

TABLE 3. Histologic Features of MA in Comparison With Benign Uterine Polyps

	Benign Uterine Polyps	MA
Size	Typically <3 cm (EMP avg 2.3 cm; ECP majority <1 cm)	Usually >3 cm; may produce large masses filling endometrial cavity
Phyllodes-like architecture	Poorly developed or focal	Well-developed, diffuse
Stromal atypia	Absent or only mild nuclear enlargement; rarely symplastic change/bizarre nuclei	Often present and diffuse, with coarse chromatin, nuclear enlargement, and irregular nuclear membranes
Mitoses	Variable	Variable; generally >2/10 HPF

ECP indicates endocervical polyp; EMP, endometrial polyp.

(Howitt, Quade and Nucci 2015)

Müllerian adenosarcoma

Reporting

- **How to report cases that fall short of diagnostic criteria for adenosarcoma in biopsy/curettage?**

‘Endometrial polyp with atypical features. See Comment.’

Müllerian adenosarcoma

Differential Diagnoses

- Adenofibroma
- Endometrial stromal sarcoma
- Endometrial polyps with adenosarcoma-like features
- Undifferentiated uterine sarcoma
- Carcinosarcoma
- Rhabdomyosarcoma

Müllerian adenosarcoma

Differential Diagnoses

Carcinosarcoma

Müllerian adenosarcoma

Differential Diagnoses

Slide presentation

Carcinosarcoma

Carcinoma Arising in Adenosarcoma

As stated earlier, the epithelial component of adenosarcoma may contain areas which amount to atypical hyperplasia.[2] Rarely, a carcinoma, usually low-grade endometrioid in type, arises within a preexisting adenosarcoma. Although theoretically this equates to a carcinosarcoma with a malignant epithelial and a malignant mesenchymal component, this term should not be used given the adverse prognostic implications of a diagnosis of carcinosarcoma (in carcinosarcoma, both the epithelial and stromal components are typically morphologically high-grade). Rather, this should be termed a carcinoma arising in an adenosarcoma.[16] Occasionally, atypical hyperplasia or carcinoma involves the endometrium away from the adenosarcoma.

(McCluggage, 2010)

Müllerian adenosarcoma

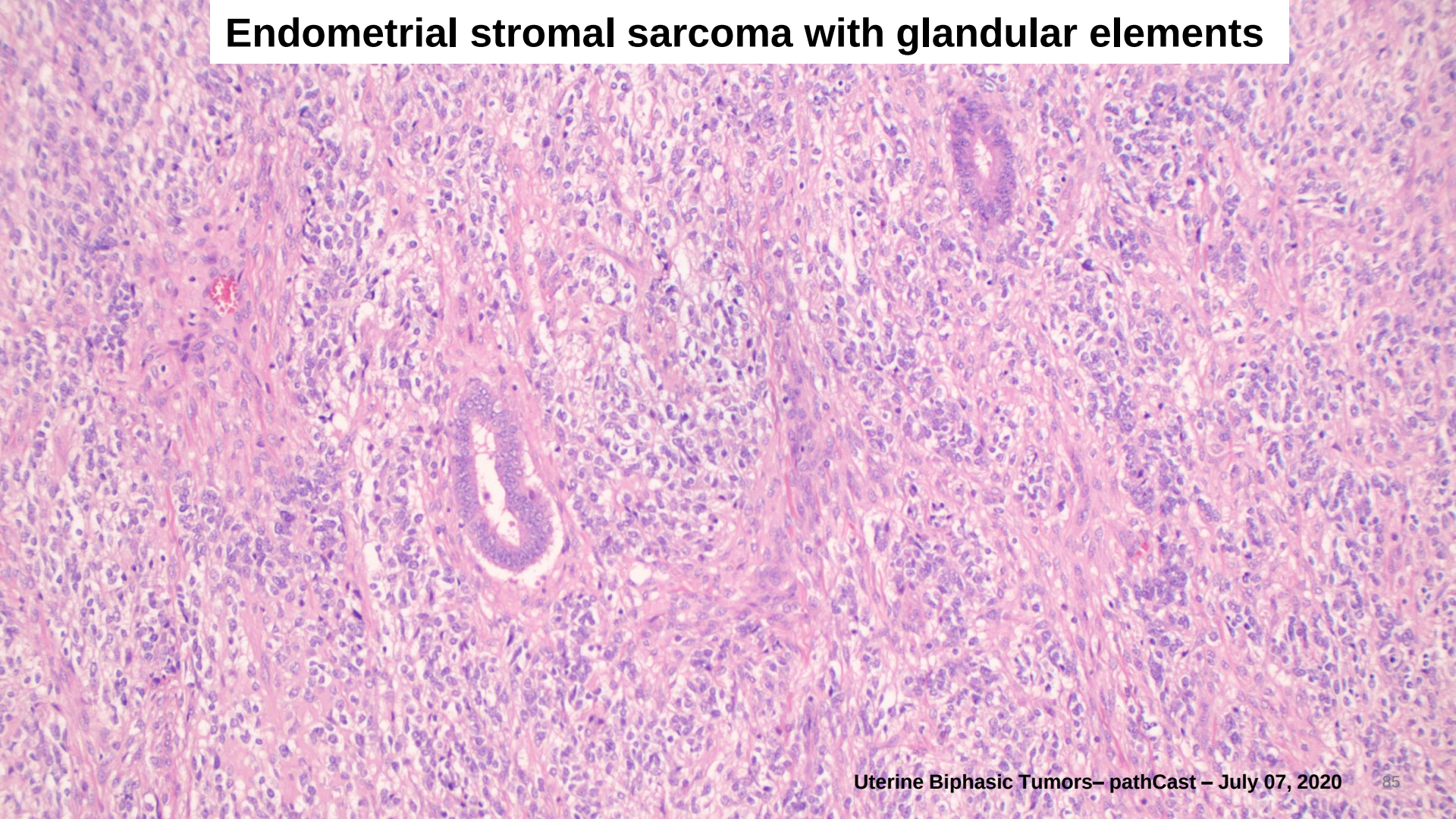
Differential Diagnoses

Endometrial stromal sarcoma

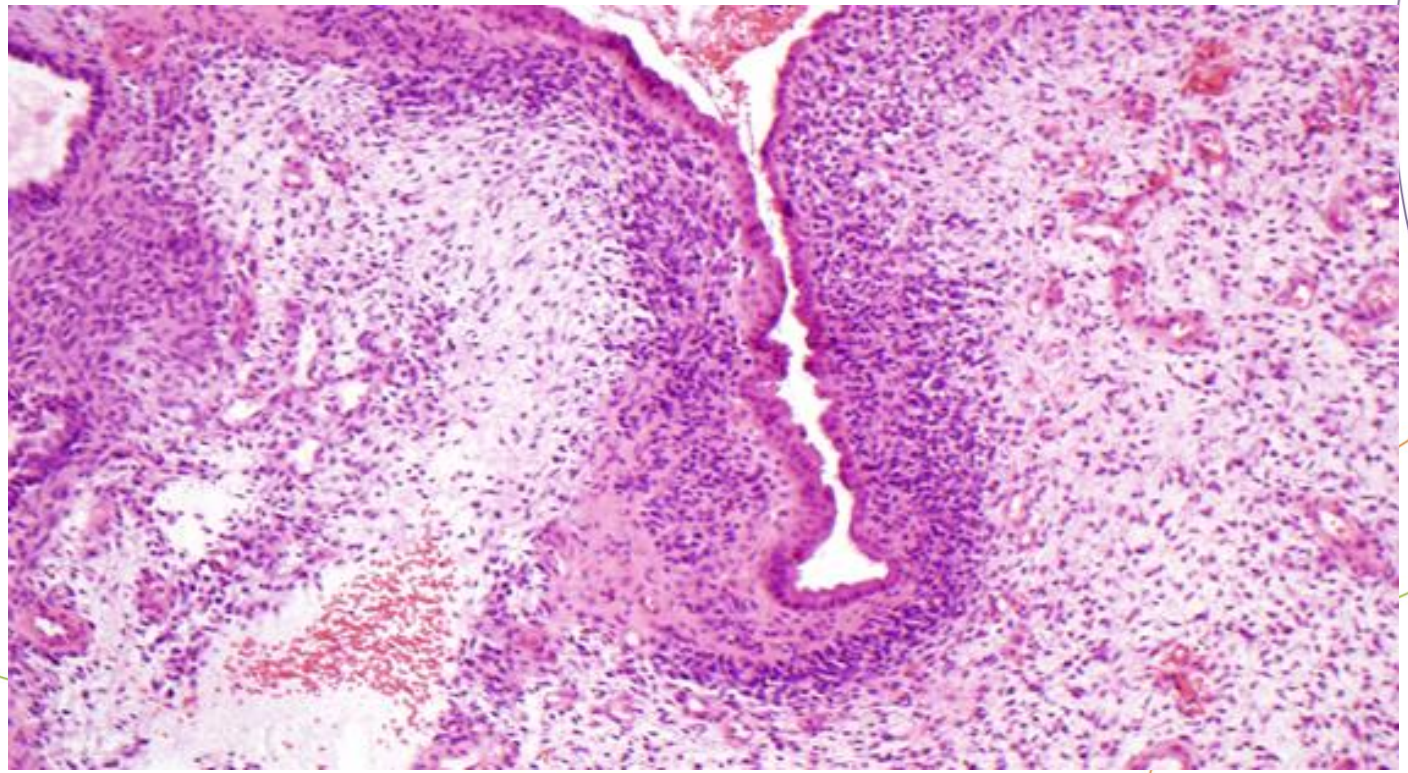
Undifferentiated uterine sarcoma

Rhabdomyosarcoma

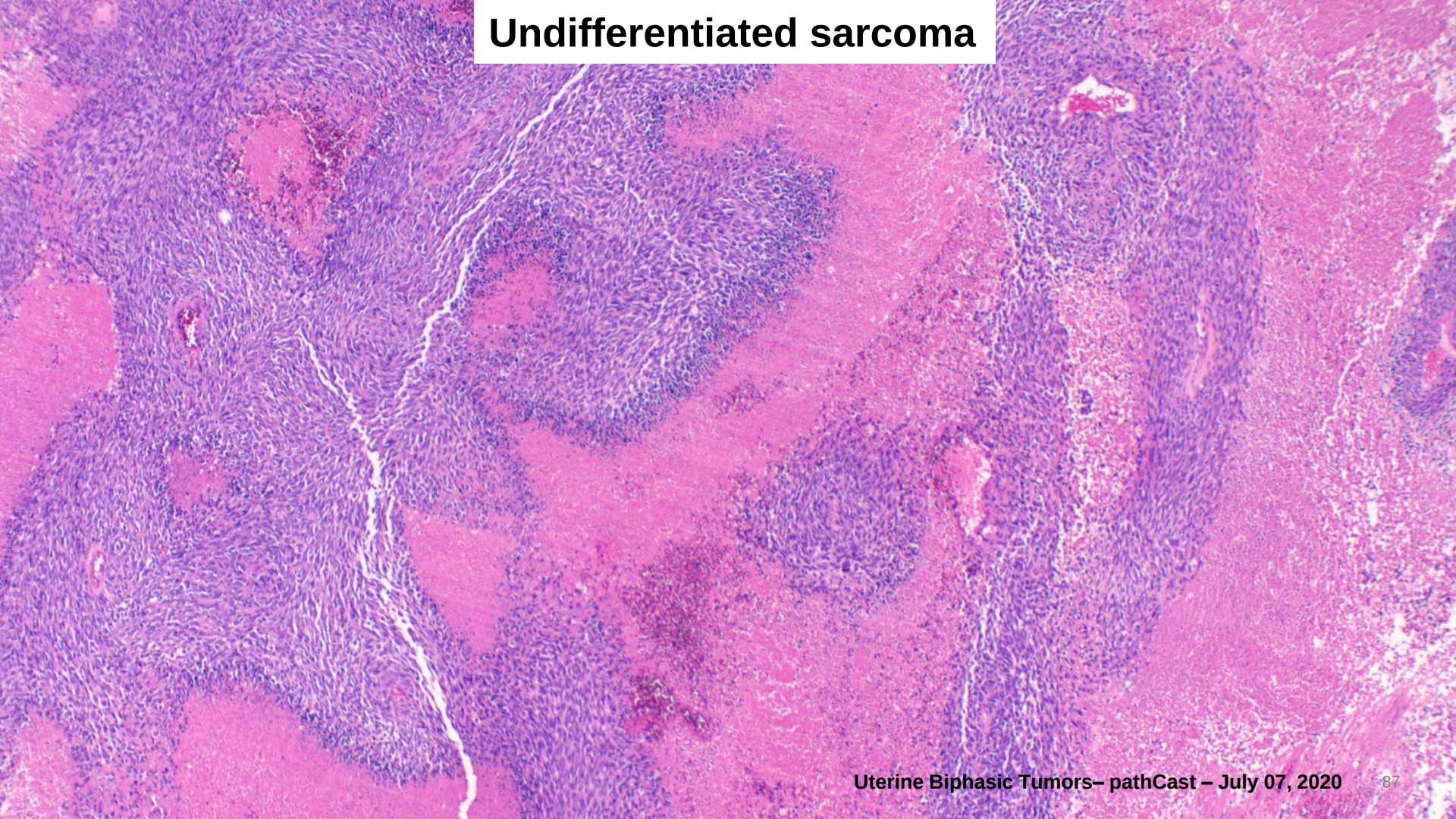
Endometrial stromal sarcoma with glandular elements



Embryonal rhabdomyosarcoma (Sarcoma botryoids)



Undifferentiated sarcoma



Müllerian adenosarcoma

- IHC usually not required for diagnosis
- Stroma is typically CD10+, ER+, PR+ with none or focal smooth muscle markers
- IHC useful to characterize high grade sarcomatous overgrowth
- No recurring diagnostic molecular alterations

BCOR Expression in Mullerian Adenosarcoma

A Potential Diagnostic Pitfall

Nuclear BCOR expression is frequently observed in the mesenchymal component of Mullerian adenosarcomas, including both low-grade and high-grade lesions with and without stromal overgrowth. Moderate to strong staining in at least 70% of tumor cells in the sarcomatous component is present in 45% of tumors and does not appear associated with grade, stromal overgrowth, or clinical outcomes. This extent of BCOR expression does not correspond with the presence of *BCOR* rearrangement in adenosarcomas, suggesting that using BCOR expression alone as a surrogate marker of *BCOR* fusion-positive high-grade endometrial stromal sarcoma may represent a potential diagnostic pitfall. Rare adenosarcomas with BCOR overexpression may, however, harbor *BCORL1* gene fusion. These findings suggest that molecular assessment of *BCOR* and *BCORL1* rearrangement status may be helpful in the diagnostic evaluation of any uterine sarcoma demonstrating BCOR overexpression.

(Muthukumarana et al. 2020)

NTRK fusion cervical sarcoma: a report of three cases, emphasising morphological and immunohistochemical distinction from other uterine sarcomas, including adenosarcoma

Aims: A unique fibrosarcoma-like tumour of the uterine cervix harbouring a rearrangement of a neurotrophic tyrosine kinase receptor (NTRK) gene (*NTRK1* or *NTRK3*) has recently been described in 11 young women, some with recurrence and/or metastasis. The aims of this study were to expand the morphological spectrum of this tumour by reporting three additional cases that showed adenosarcoma-like features not previously described, one of which is the first reported to respond to targeted therapy, and to evaluate 19 conventional uterine adenosarcomas for evidence of *NTRK* rearrangement.

Conclusions: Unusual adenosarcoma-like spindle cell neoplasms of the cervix may represent an *NTRK* fusion sarcoma, which can be detected by S100 and pan-Trk staining and confirmed by *NTRK* molecular testing. Conventional uterine adenosarcomas do not harbour *NTRK* rearrangements.

(Rabban et al. 2020)

***DICER1* mutations are frequent in müllerian adenosarcomas and are independent of rhabdomyosarcomatous differentiation**

Significantly Greater Prevalence of DICER1 Alterations in Uterine Embryonal Rhabdomyosarcoma Compared to Adenosarcoma

Müllerian adenosarcoma

- **Good prognosis, except for high grade sarcomatous overgrowth**
- **Recurrences usually only contain the sarcomatous elements**
- **Other poor prognostic factors:**
  - Deep myometrial invasion
  - Lymph-vascular invasion
  - Spread outside the uterus
  - Heterologous elements in the primary tumor

Uterine biphasic tumors

Adenosarcoma

Carcinosarcoma

Atypical polypoid adenomyoma

Adenomyomatous polyp

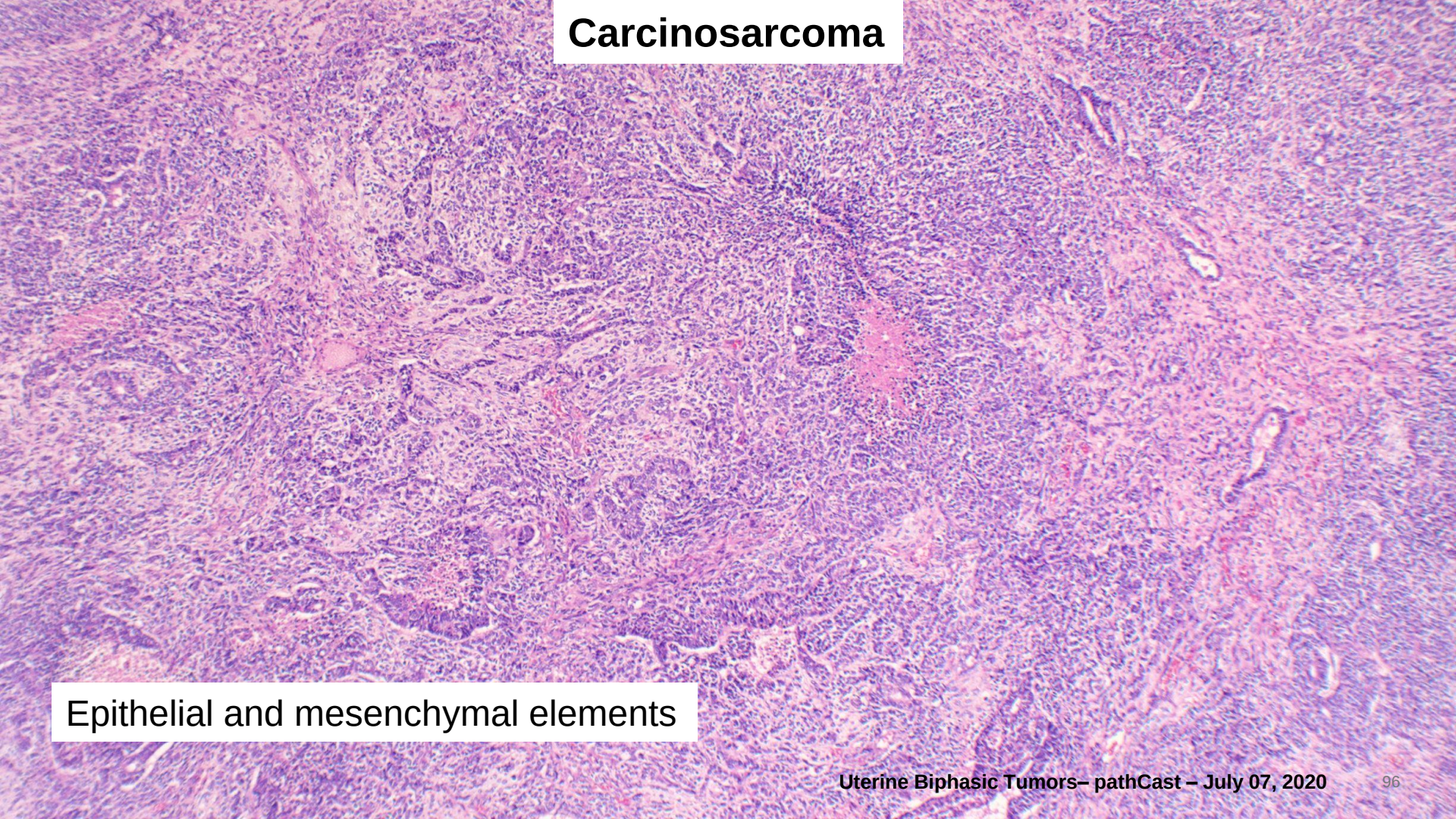
Adenomyoma

Carcinosarcoma

- A.k.a ‘malignant mixed müllerian tumor’ (MMMT)
- Elderly women

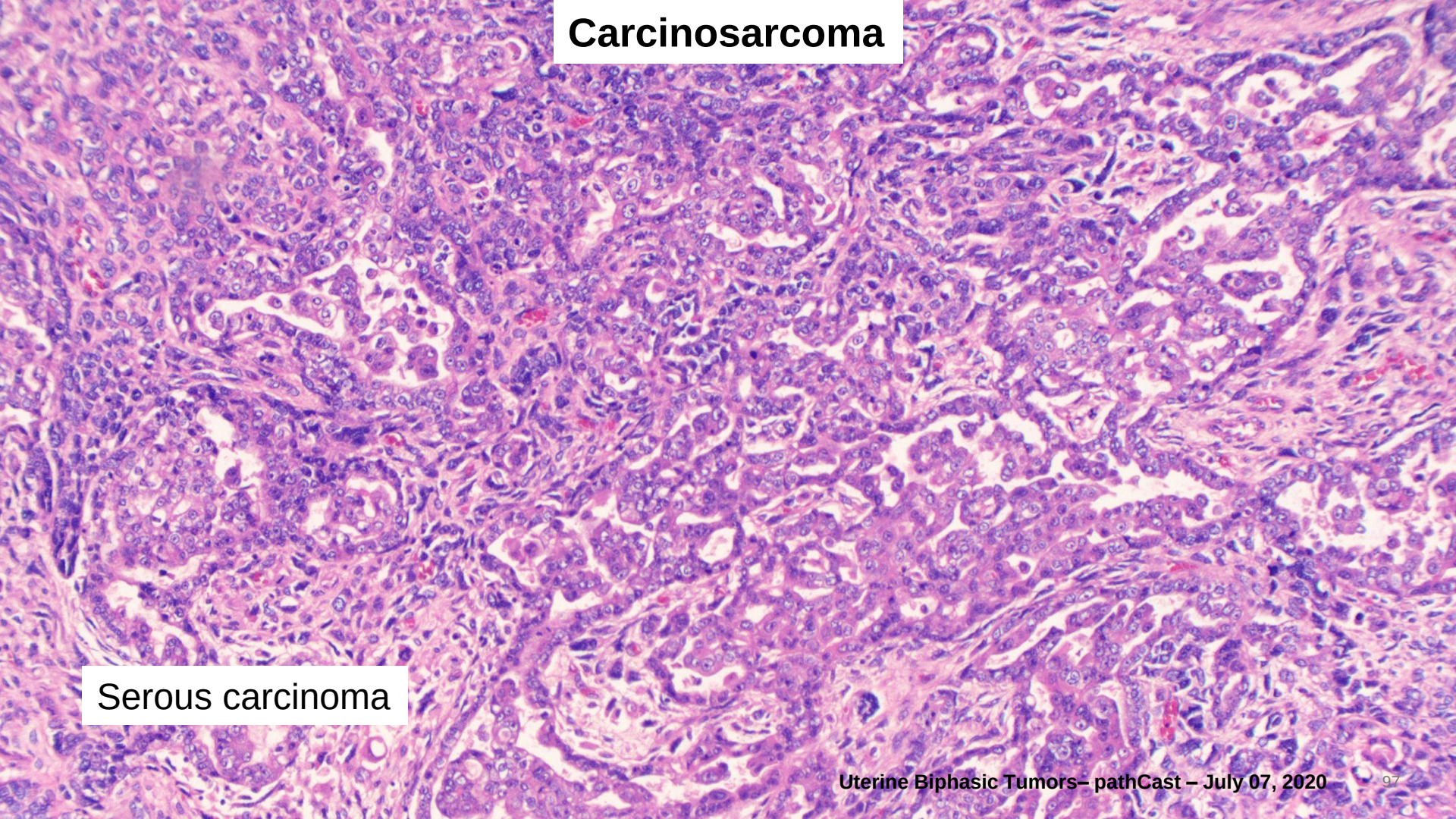
Carcinosarcoma

Carcinosarcoma

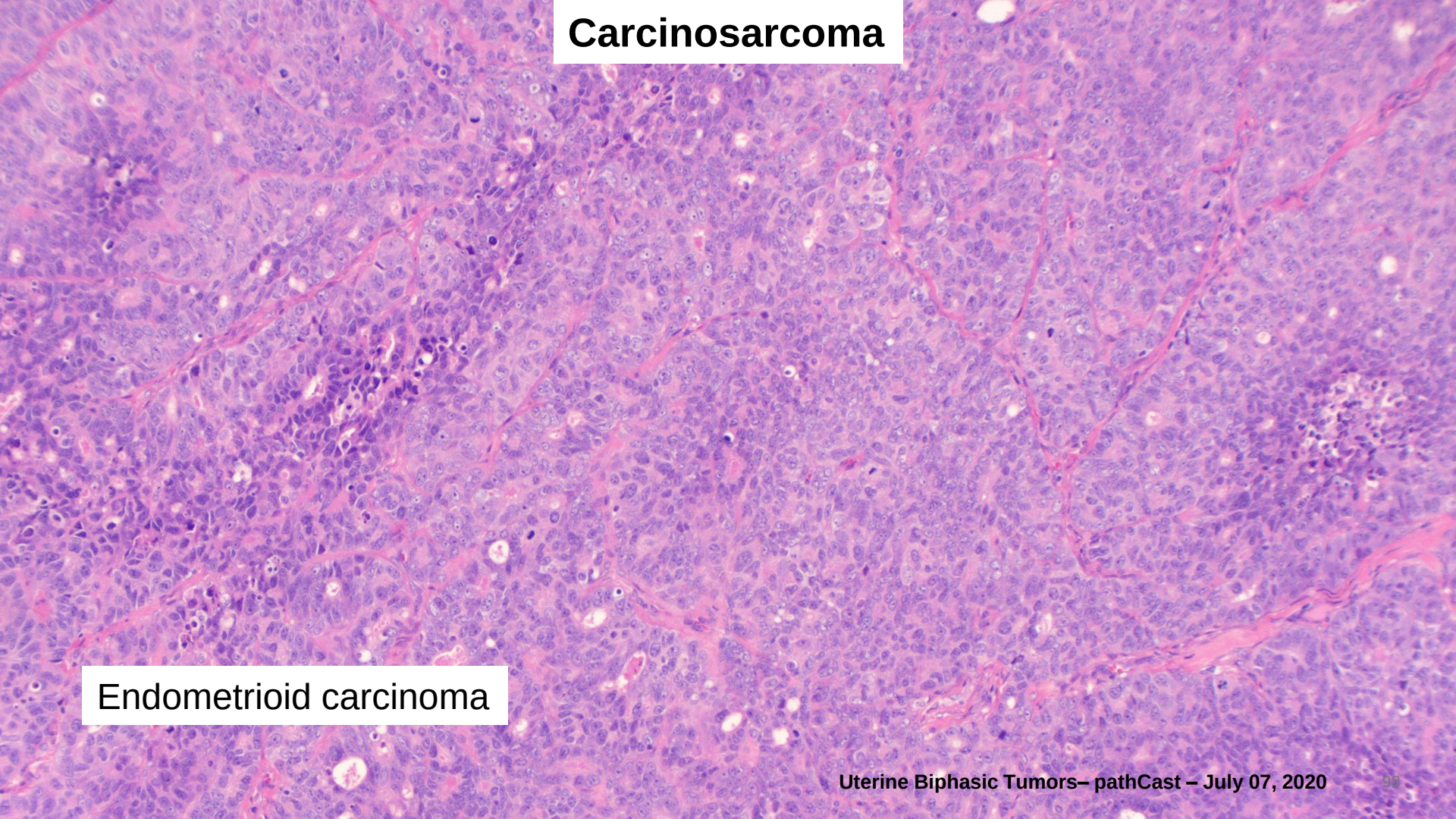


Epithelial and mesenchymal elements

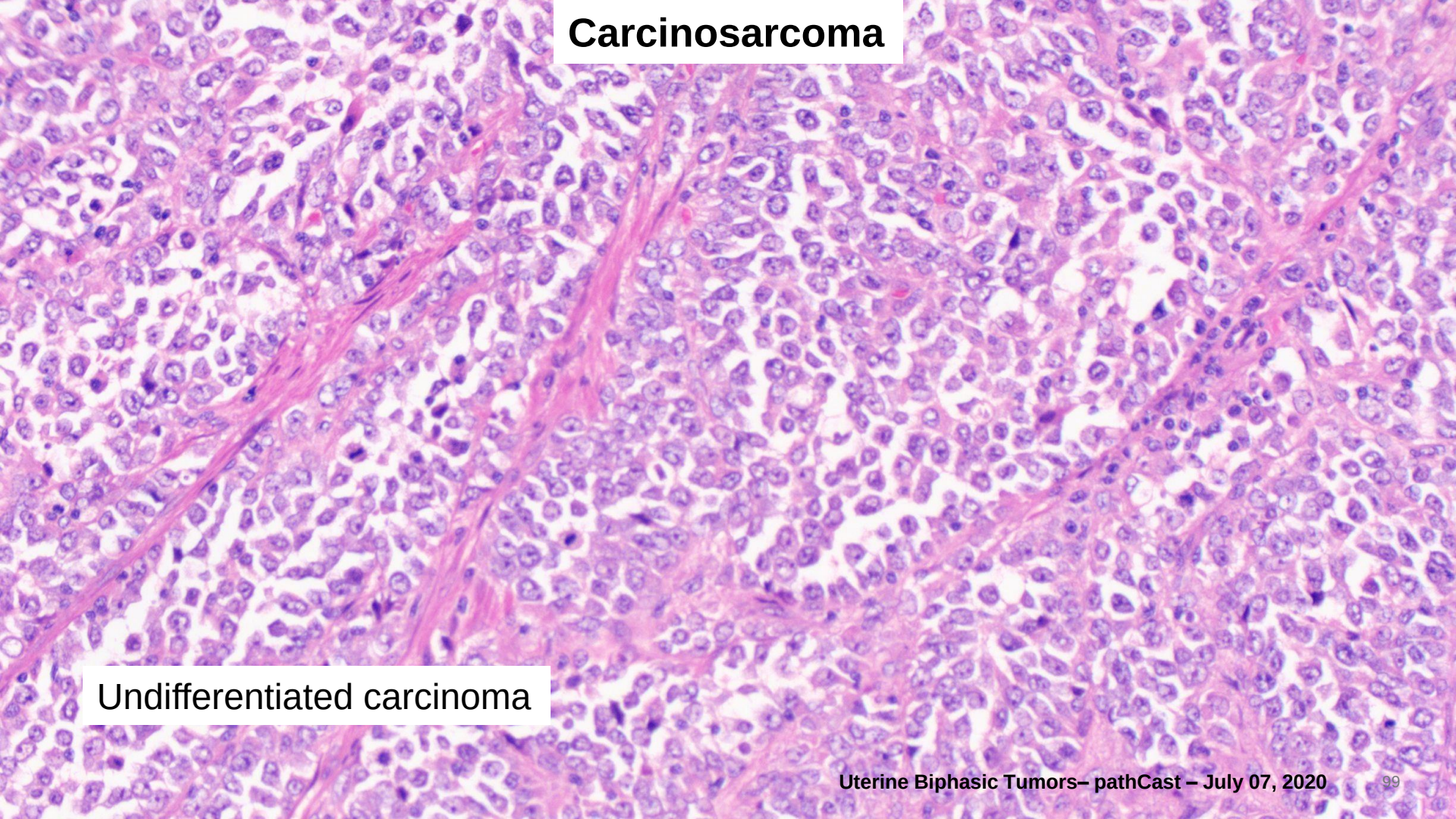
Carcinosarcoma



Serous carcinoma

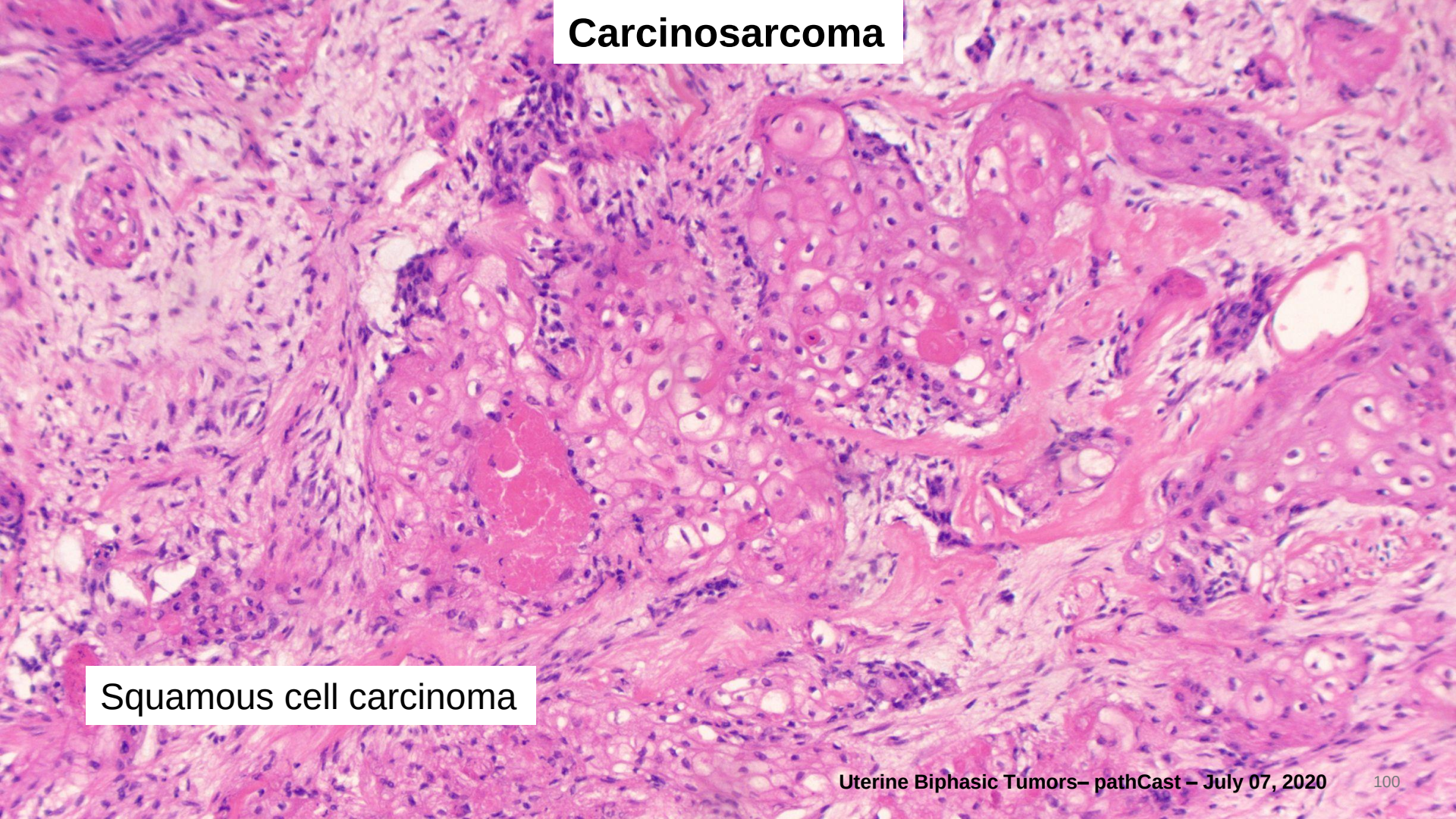

Carcinosarcoma
Endometrioid carcinoma

Carcinosarcoma



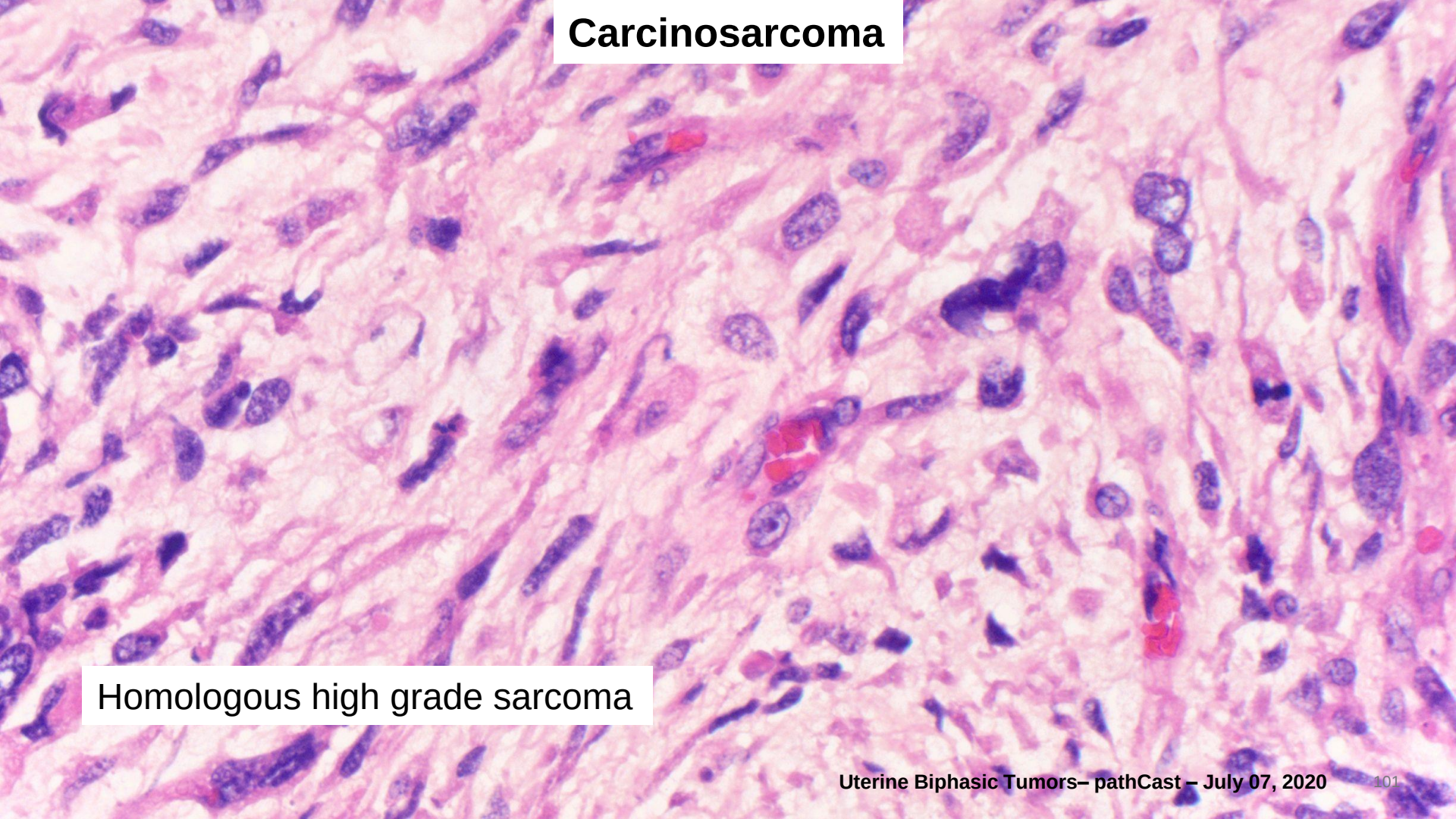
Undifferentiated carcinoma

Carcinosarcoma



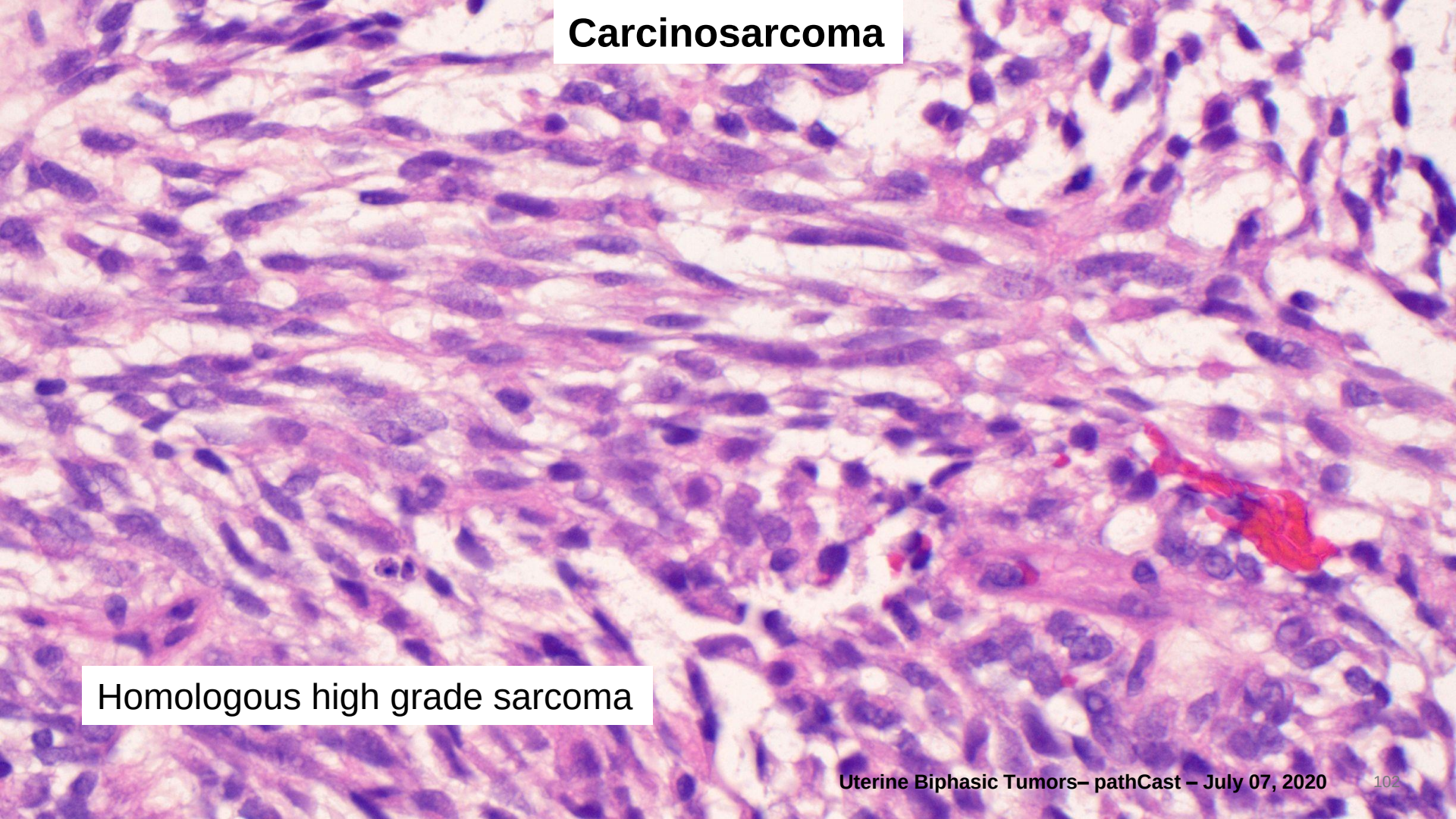
Squamous cell carcinoma

Carcinosarcoma



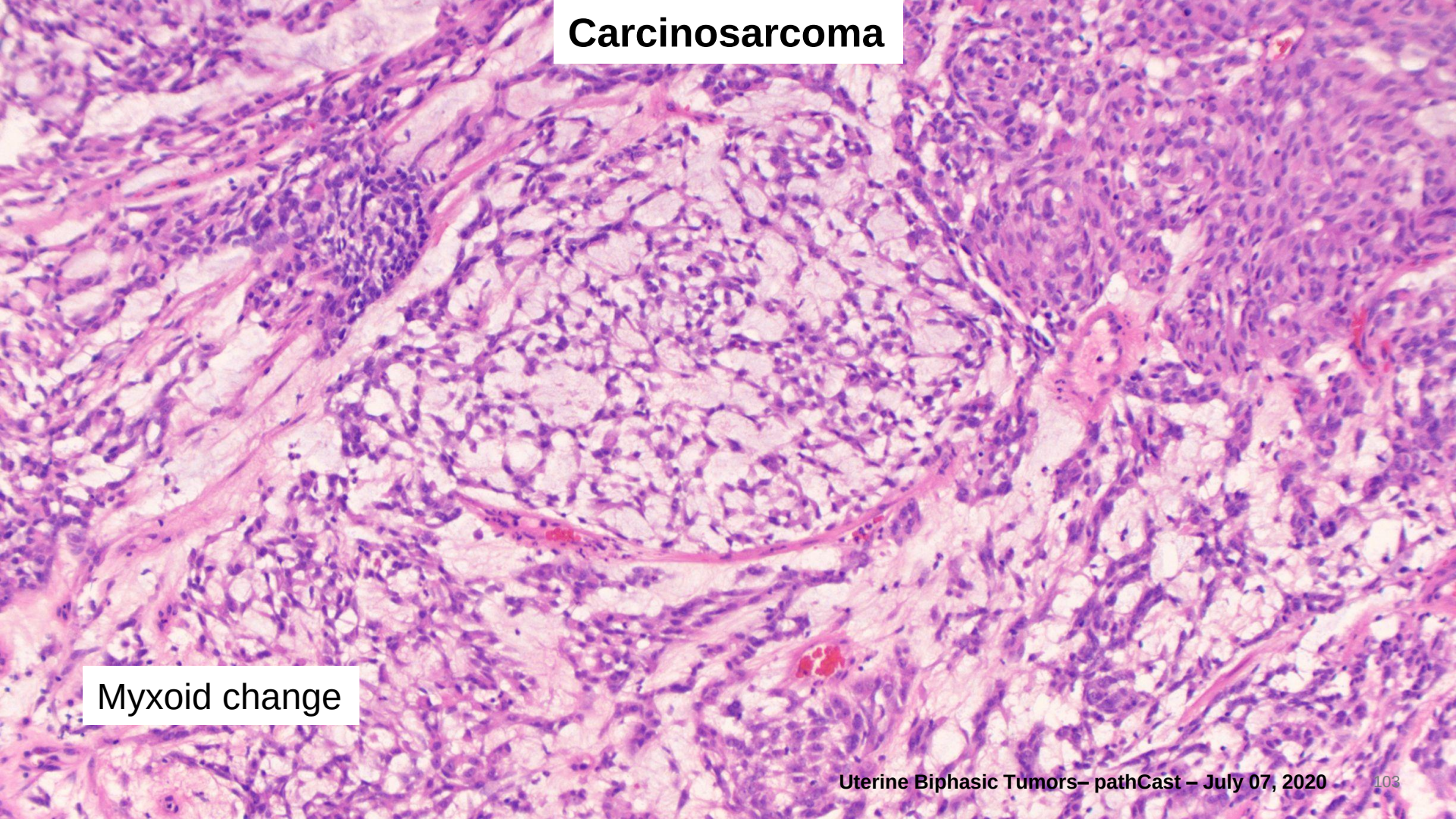
Homologous high grade sarcoma

Carcinosarcoma

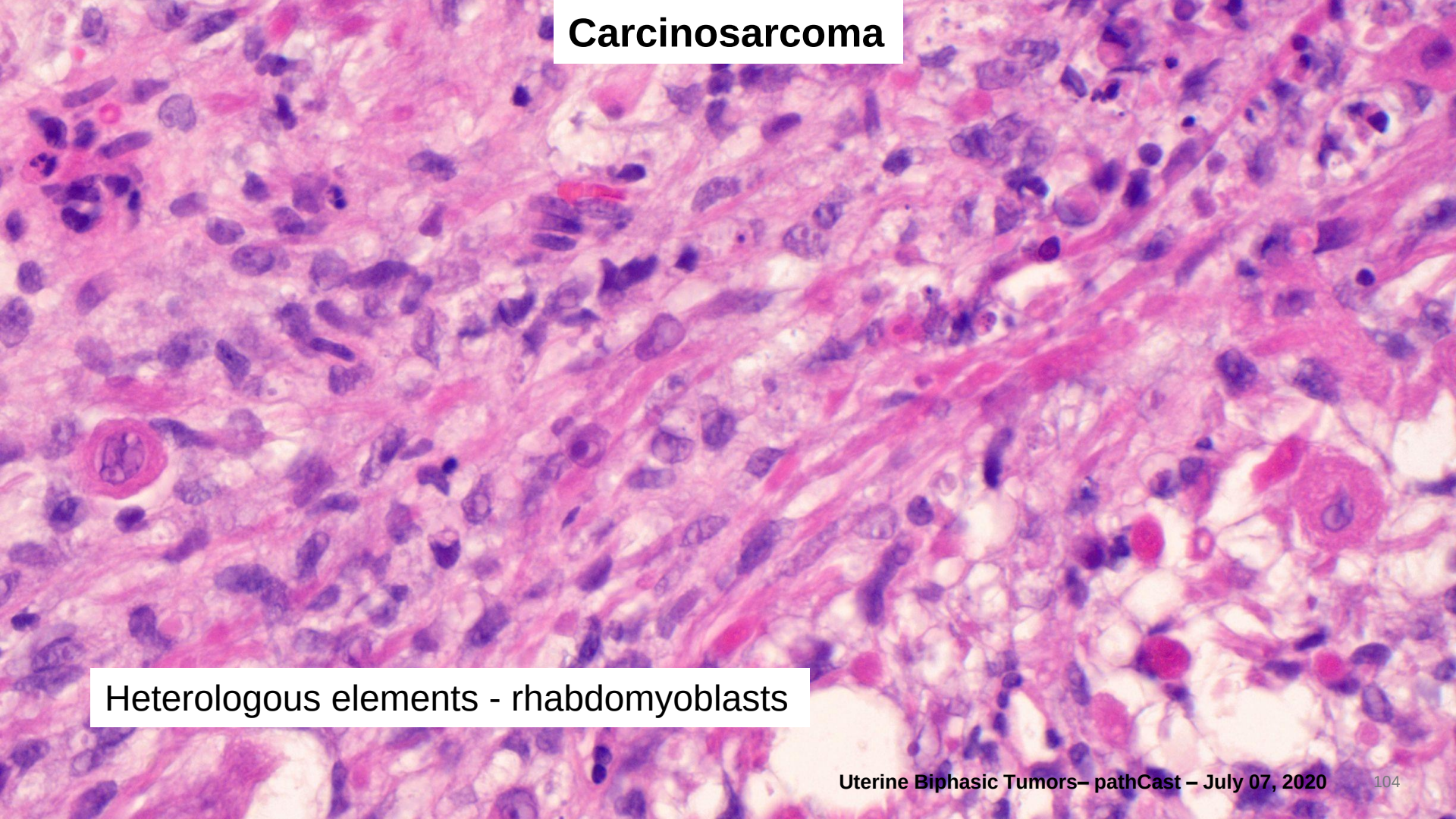


Homologous high grade sarcoma

Carcinosarcoma

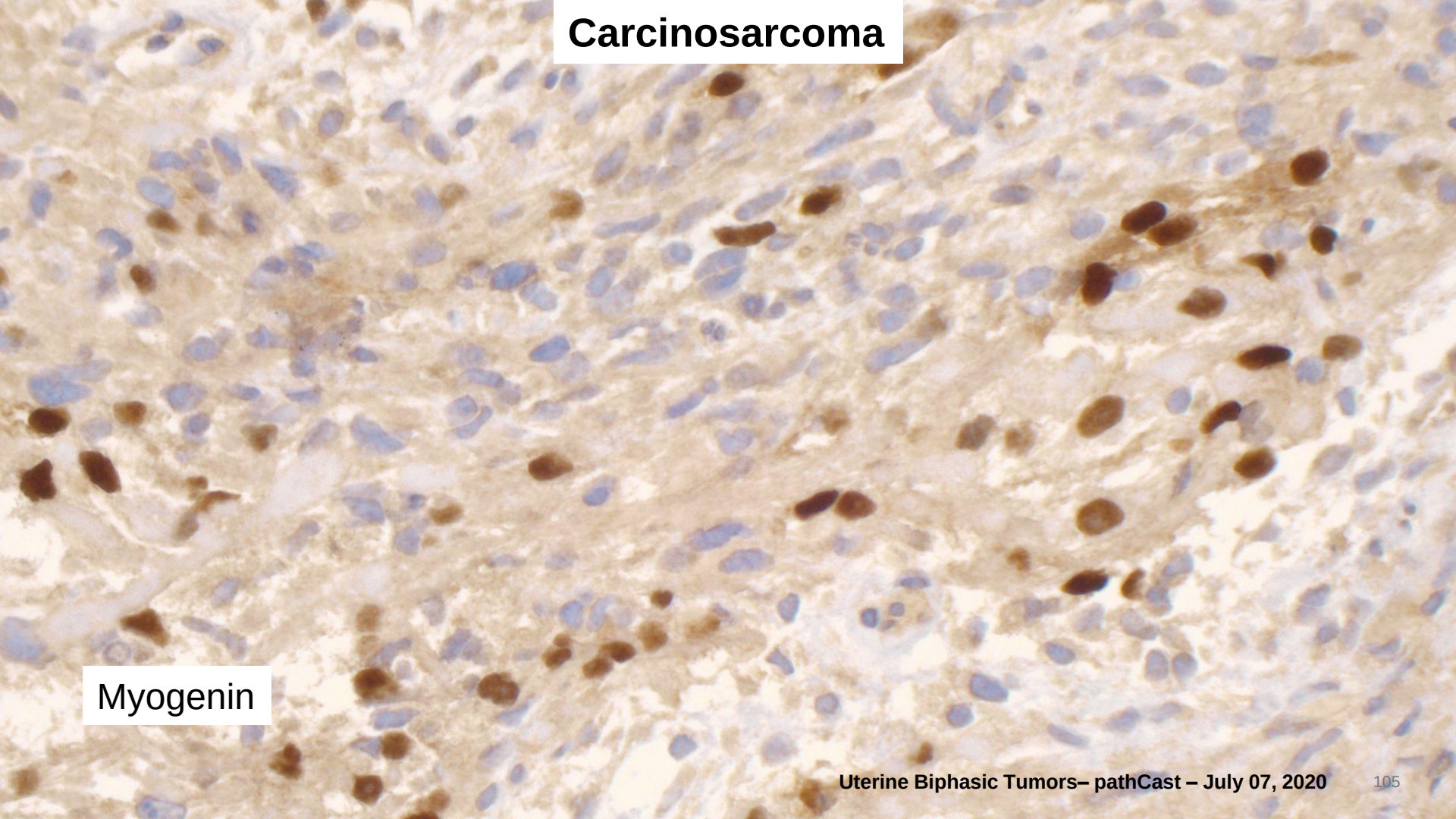


Carcinosarcoma

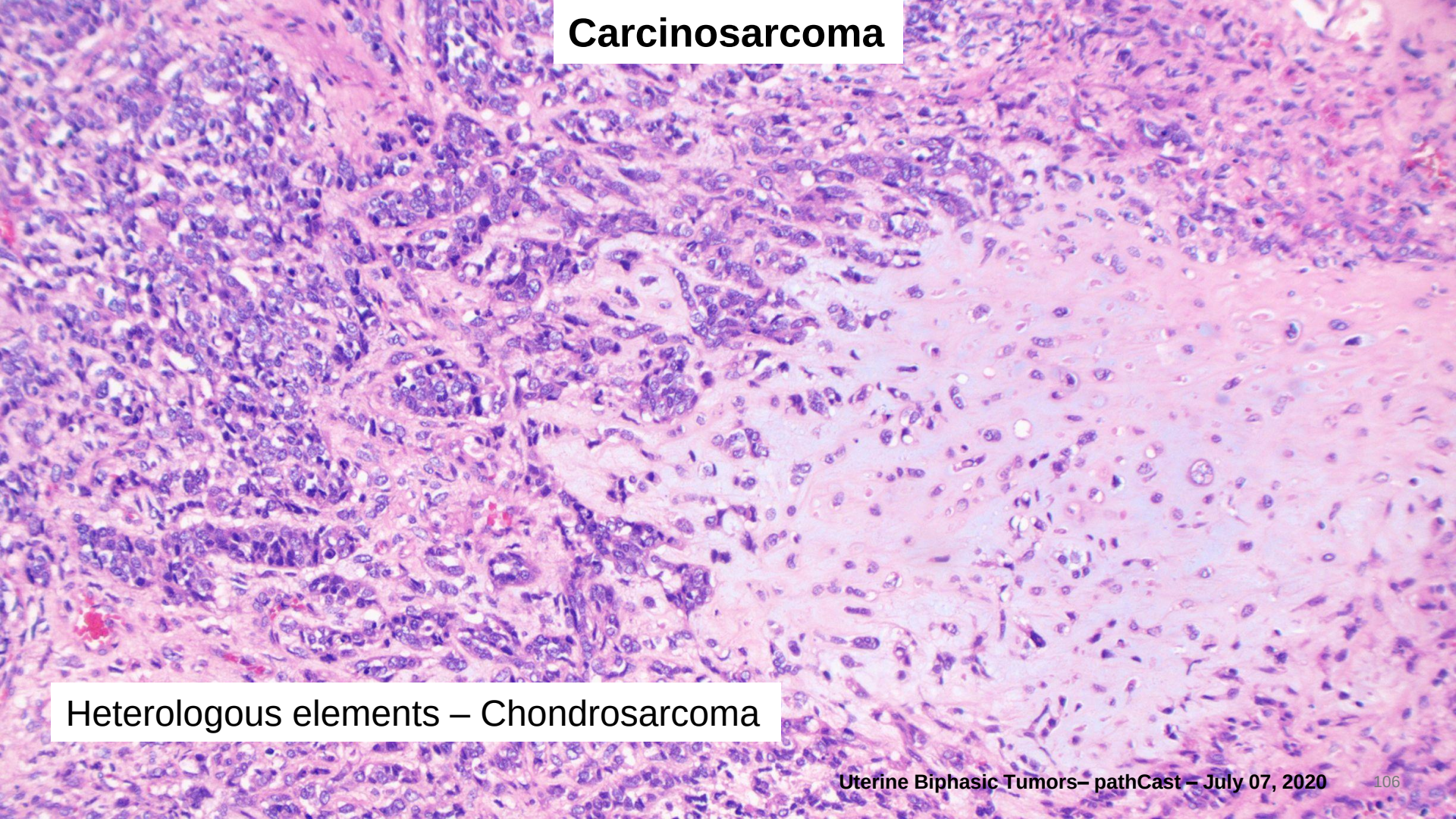


Heterologous elements - rhabdomyoblasts

Carcinosarcoma

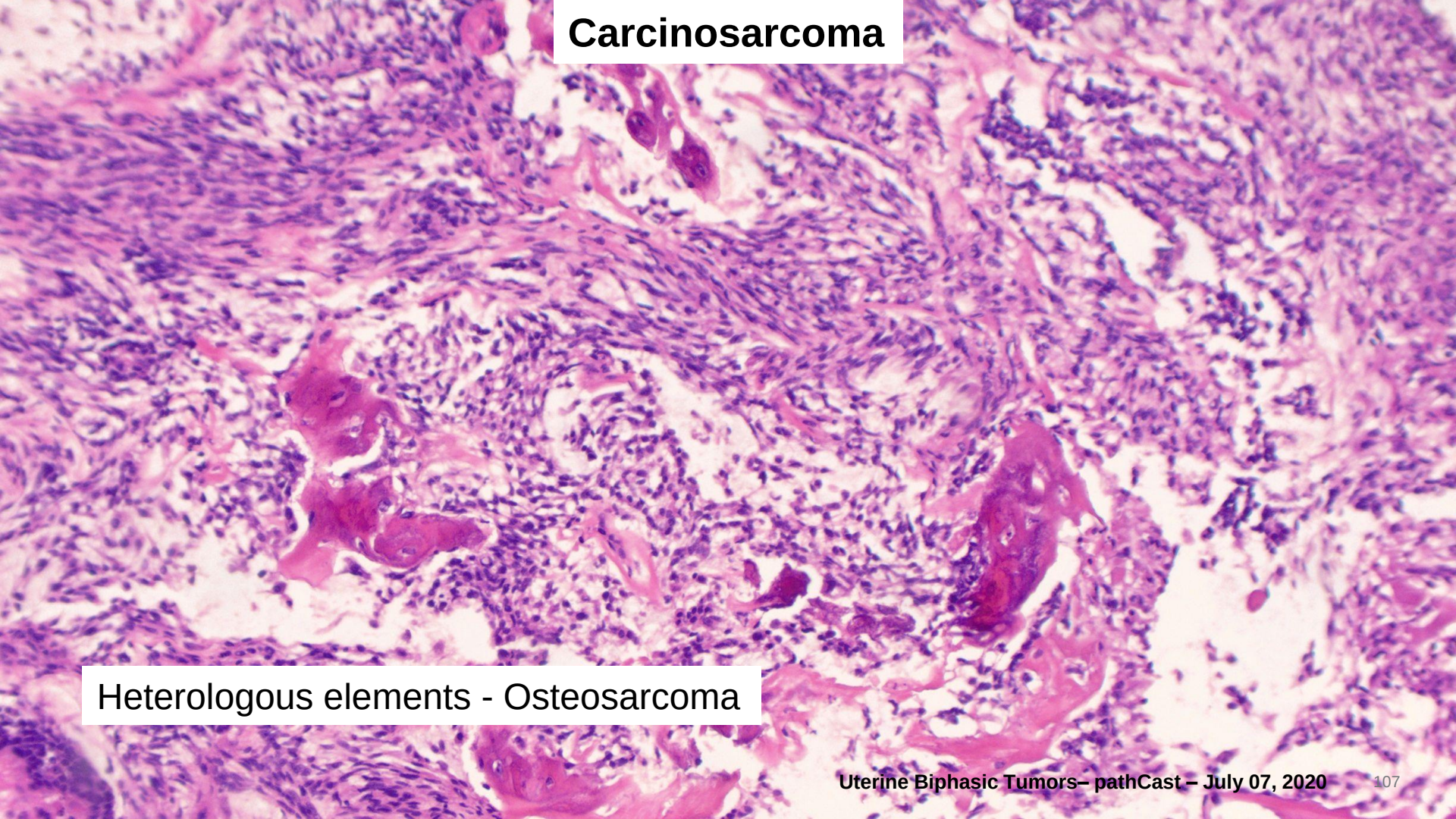


Carcinosarcoma



Heterologous elements – Chondrosarcoma

Carcinosarcoma



Heterologous elements - Osteosarcoma

Carcinosarcoma

Differential Diagnoses

Endometrioid carcinoma - variants

Dedifferentiated endometrial carcinoma

Uterine sarcomas

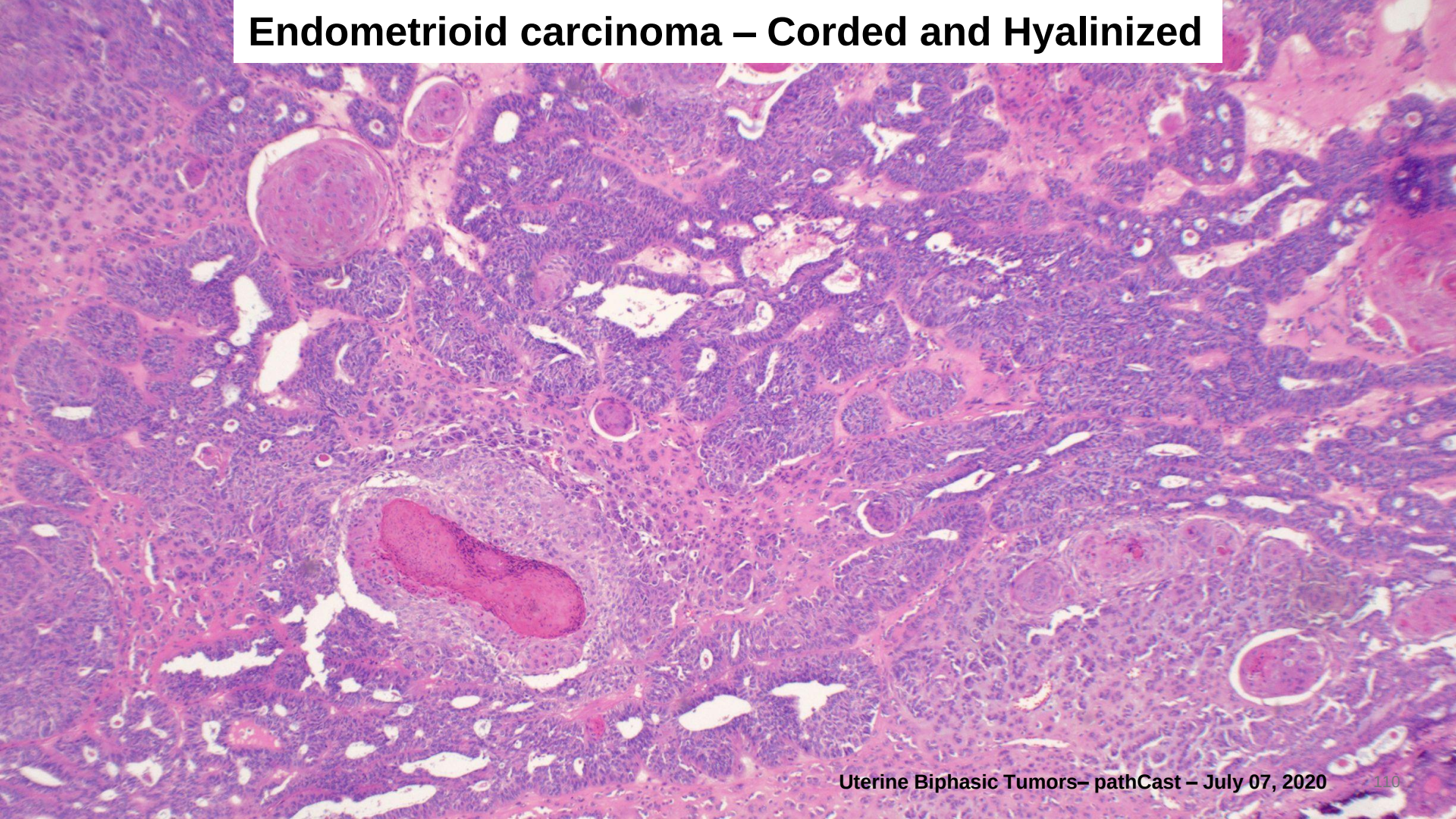
Adenosarcoma

Carcinosarcoma

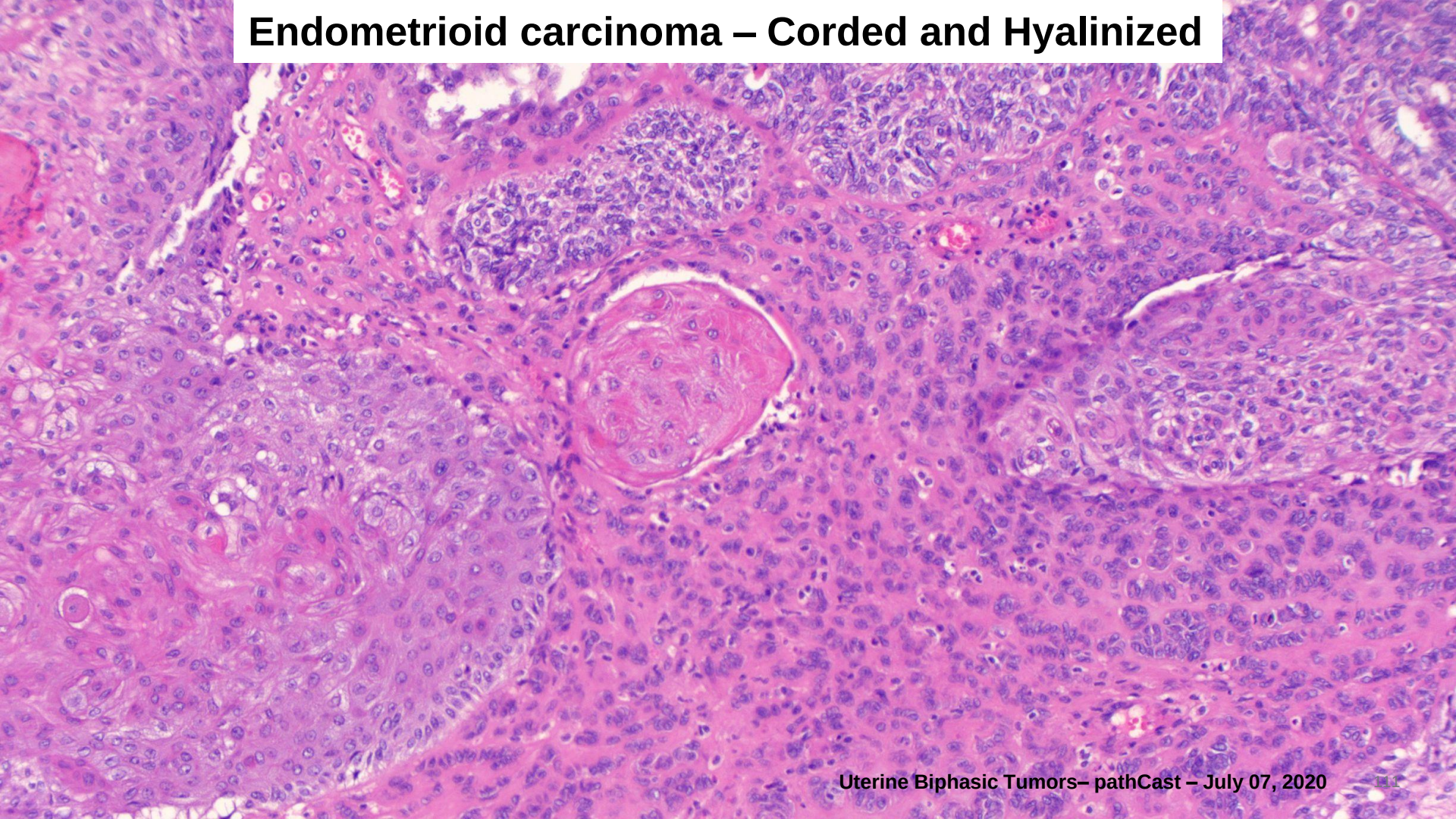
Differential Diagnoses

Endometrioid carcinoma - variants

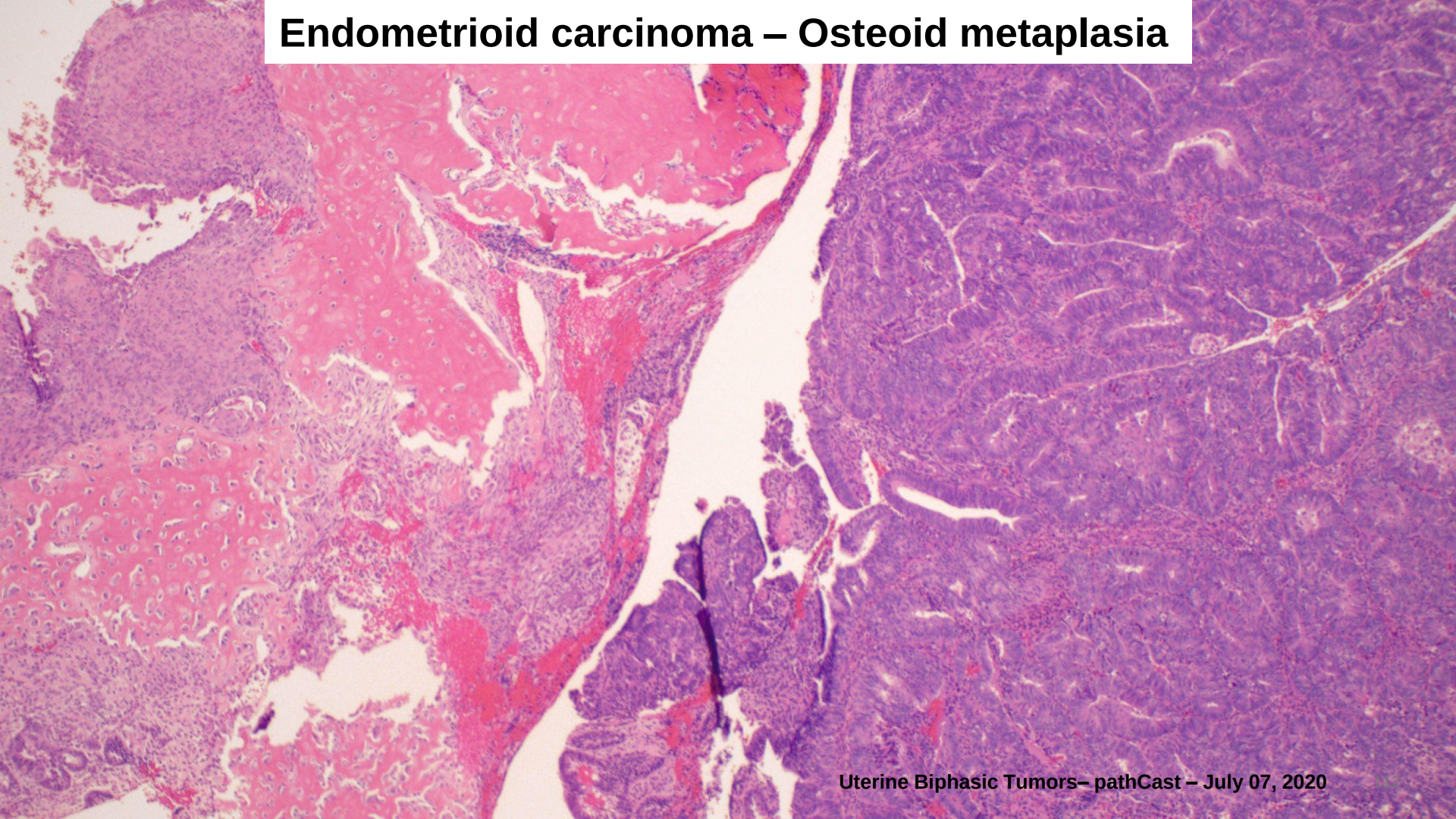
Endometrioid carcinoma – Corded and Hyalinized



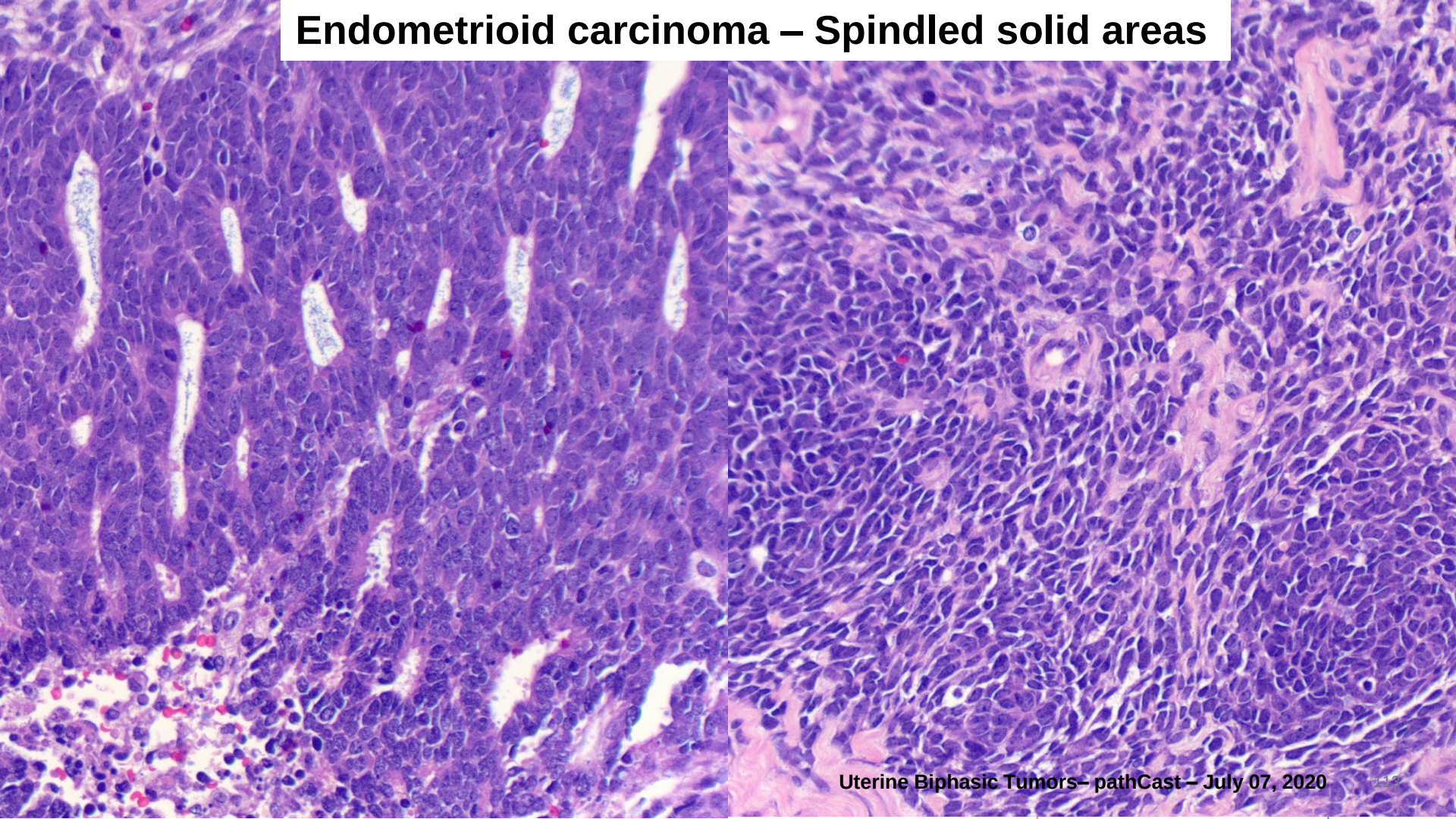
Endometrioid carcinoma – Corded and Hyalinized



Endometrioid carcinoma – Osteoid metaplasia



Endometrioid carcinoma – Spindled solid areas



Carcinosarcoma

- **Spreads as a high grade carcinoma**
- **Heterologous mesenchymal elements is an adverse prognostic indicator in stage I tumors, particularly rhabdomyosarcomatous**
  - xxx

(Fergunson et al 2007; Kurnit et al 2019)

Carcinosarcoma

- It is recommended by the International Collaboration on Cancer Reporting (ICCR) that percentages of the epithelial and mesenchymal components as well the morphological subtypes within the epithelial and mesenchymal components be included on the pathology report
- In practice the most important is to include if heterologous mesenchymal elements are present or absent and subtype

Uterine biphasic tumors
Common differential diagnoses

Atypical polypoid adenomyoma

- Adenomyomatous polyp type1
- Myoinvasive endometrioid carcinoma

Adenosarcoma

- Endometrial polyp with adenosarcoma-like features

Carcinosarcoma

- Endometrioid carcinoma variants
- Dedifferentiated carcinoma

Adenomyomatous polyp type 2

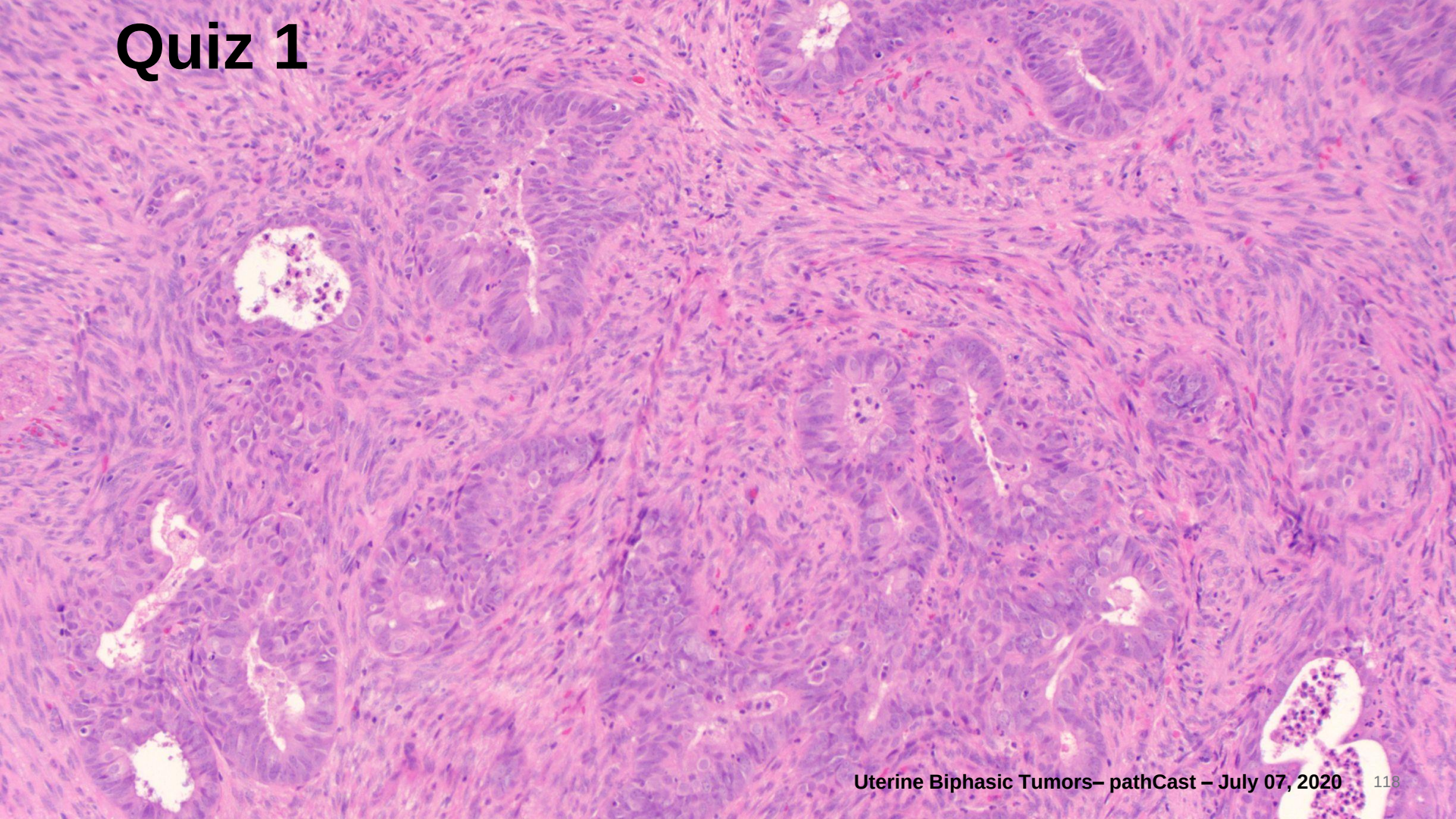
Endometrioid Adenomyoma

Uterine Biphasic Tumors
Quiz 1

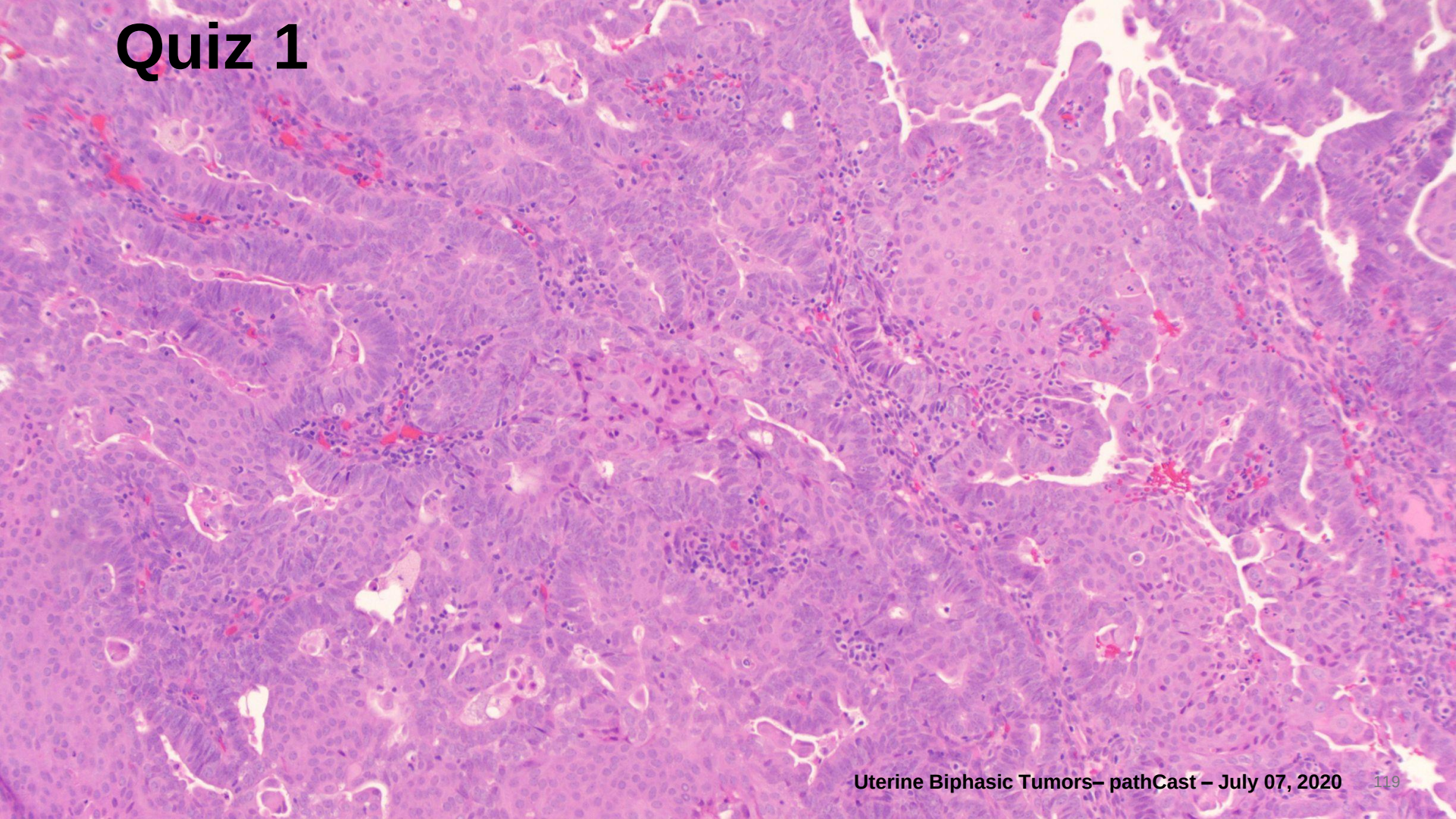
38 year-old woman. Hysteroscopic resection of endometrial polyps.

Slide presentation

Quiz 1



Quiz 1



Uterine Biphasic Tumors
Quiz 1

38 year-old woman. Hysteroscopic resection of endometrial polyps. Select the correct diagnosis.

a. **Myoinvasive FIGO 1 endometrioid carcinoma**
b. **Atypical polypoid adenomyoma, EIN and FIGO 1 endometrioid adenocarcinoma**
c. **Benign adenomyomatous polyp**
d. **Adenosarcoma**
e. **Carcinosarcoma**

Uterine Biphasic Tumors
Quiz 1

38 year-old woman. Hysteroscopic resection of endometrial polyps. Select the correct diagnosis.

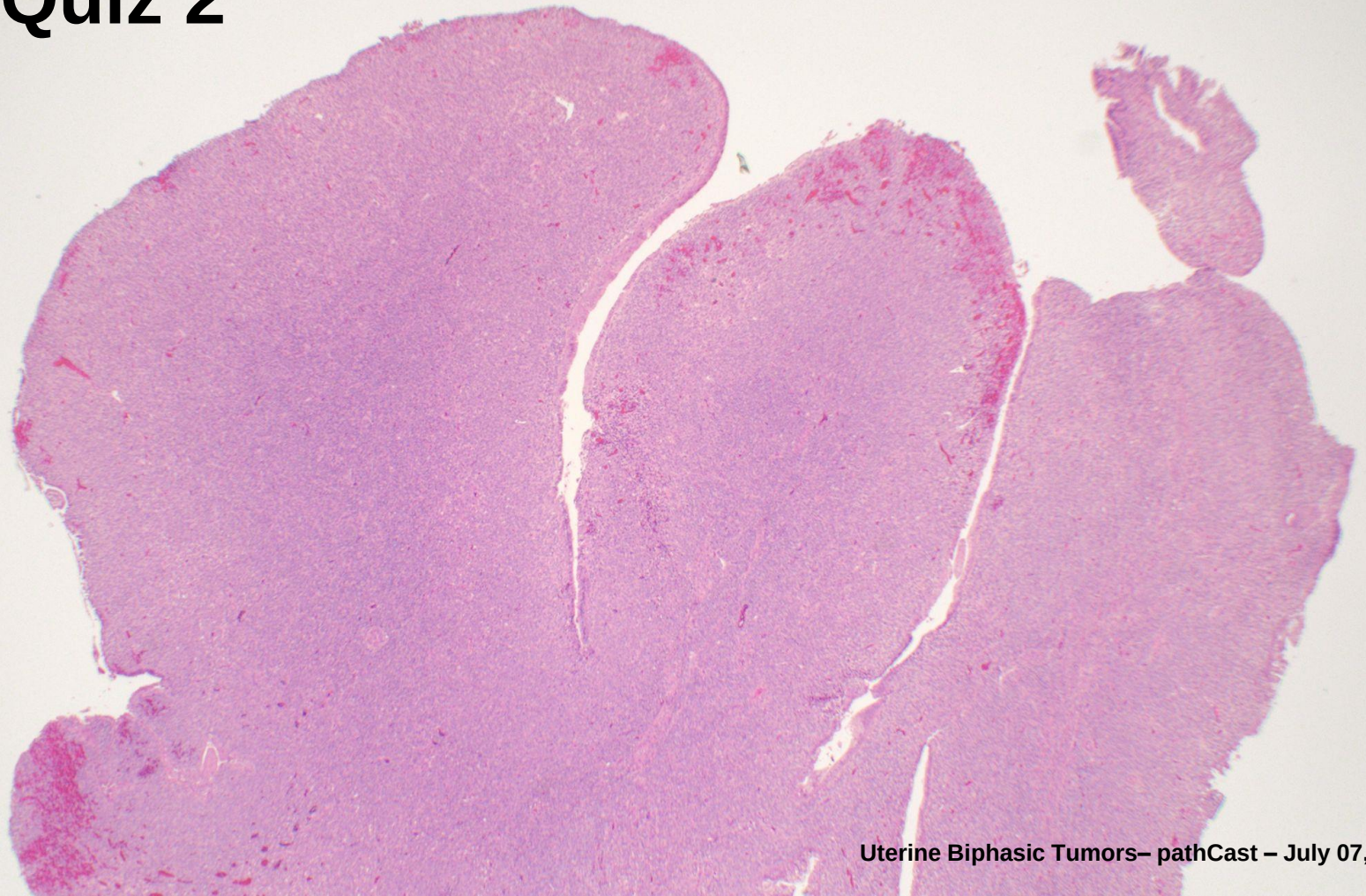
a. **Myoinvasive FIGO 1 endometrioid carcinoma**
b. **Atypical polypoid adenomyoma, EIN and FIGO 1 endometrioid adenocarcinoma**
c. **Benign adenomyomatous polyp**
d. **Adenosarcoma**
e. **Carcinosarcoma**

Uterine Biphasic Tumors
Quiz 2

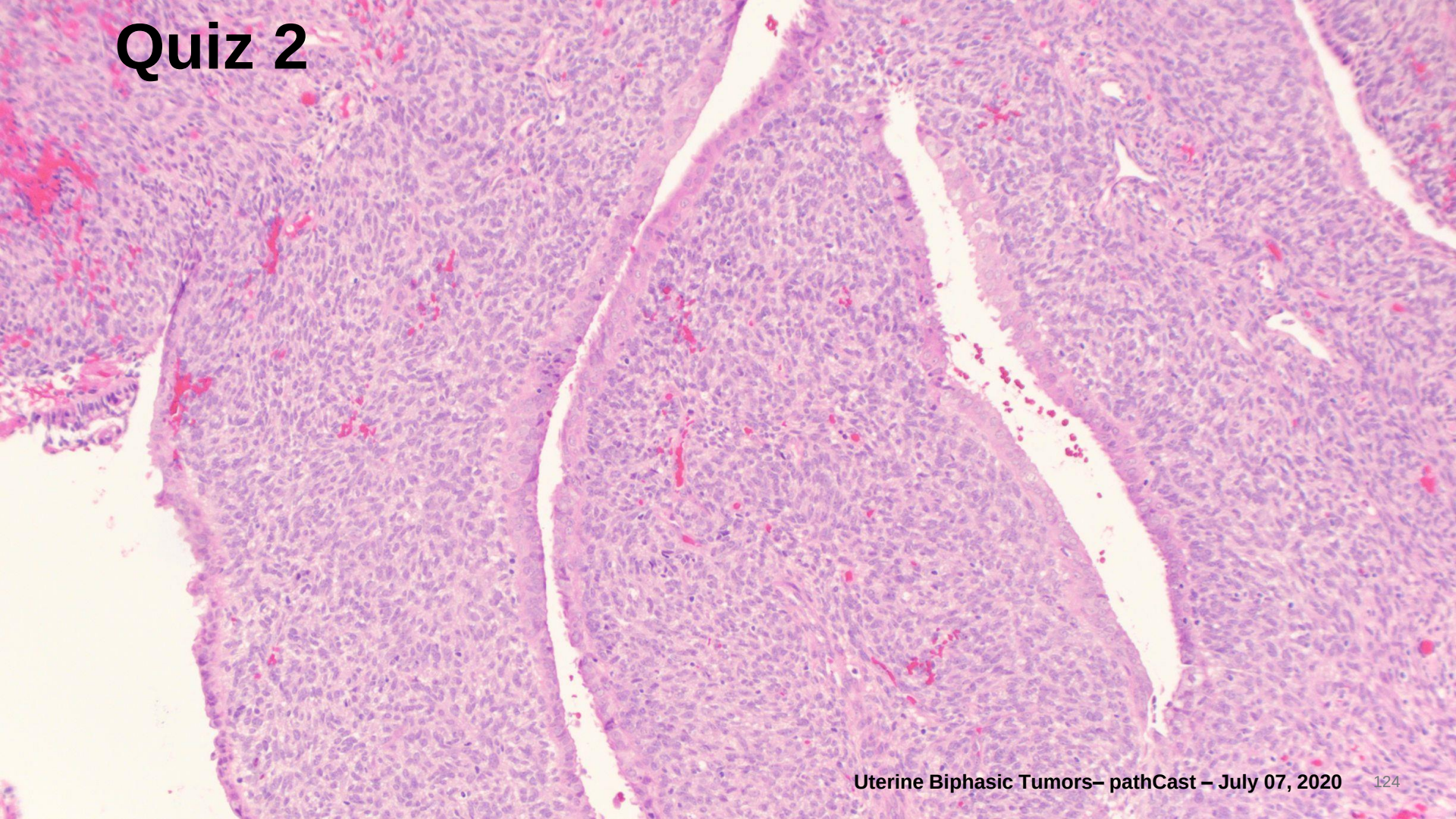
41 year-old woman. Hysteroscopic resection of endometrial polyps.

Slide presentation

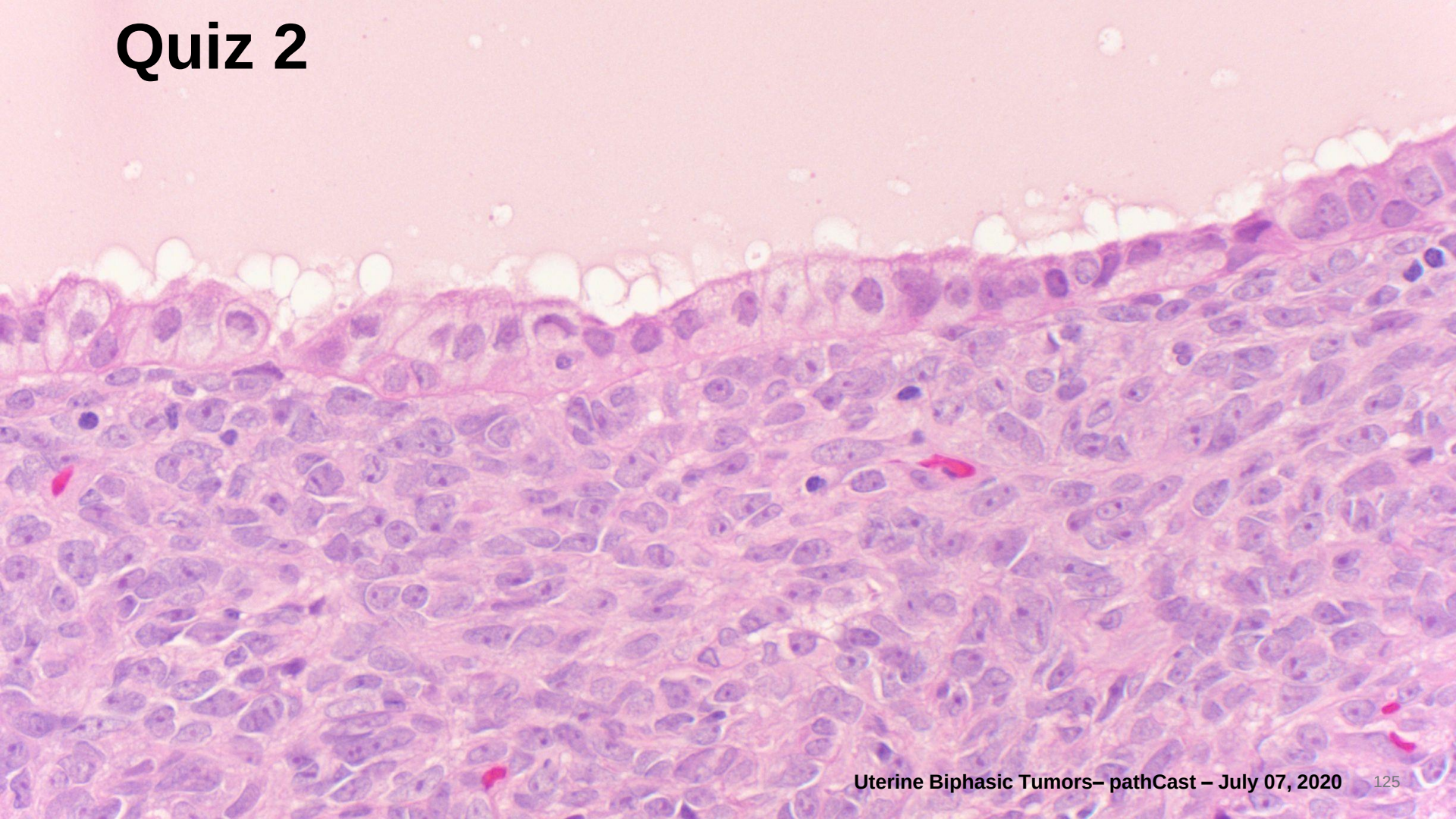
Quiz 2



Quiz 2



Quiz 2



Uterine Biphasic Tumors
Quiz 2

41 year-old woman. Hysteroscopic resection of endometrial polyps. Select the correct diagnosis.

a. **Endometrial polyp with adenosarcoma-like features**
b. **Endometrial stromal sarcoma with glandular elements**
c. **Sarcoma botryoids**
d. **Mullerian adenosarcoma**
e. **Carcinosarcoma**

Uterine Biphasic Tumors
Quiz 2

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