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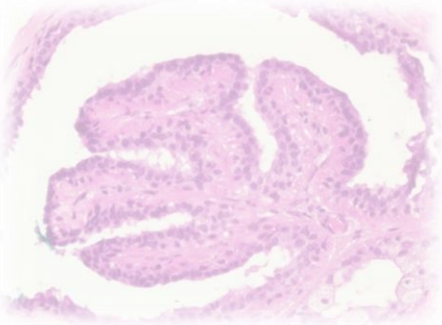
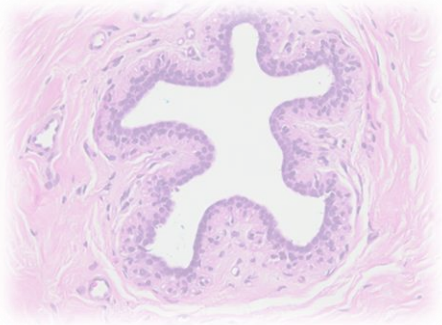
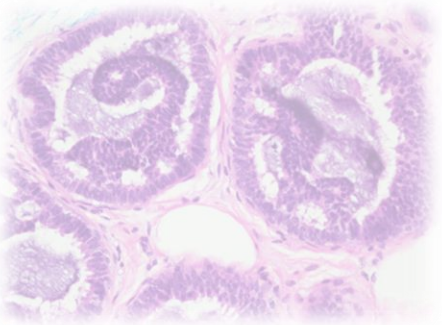
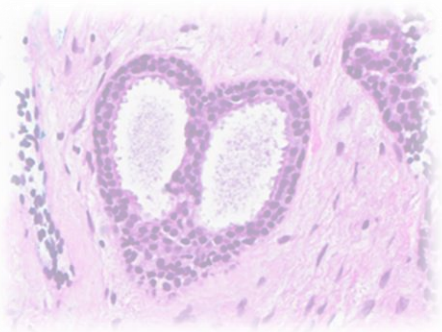
Case 29

70 year old Indian female.
Wide excision and axillary dissection for right breast invasive ductal carcinoma 10 years ago.
Clinically right breast recurrence.
Section of the current right breast mass.

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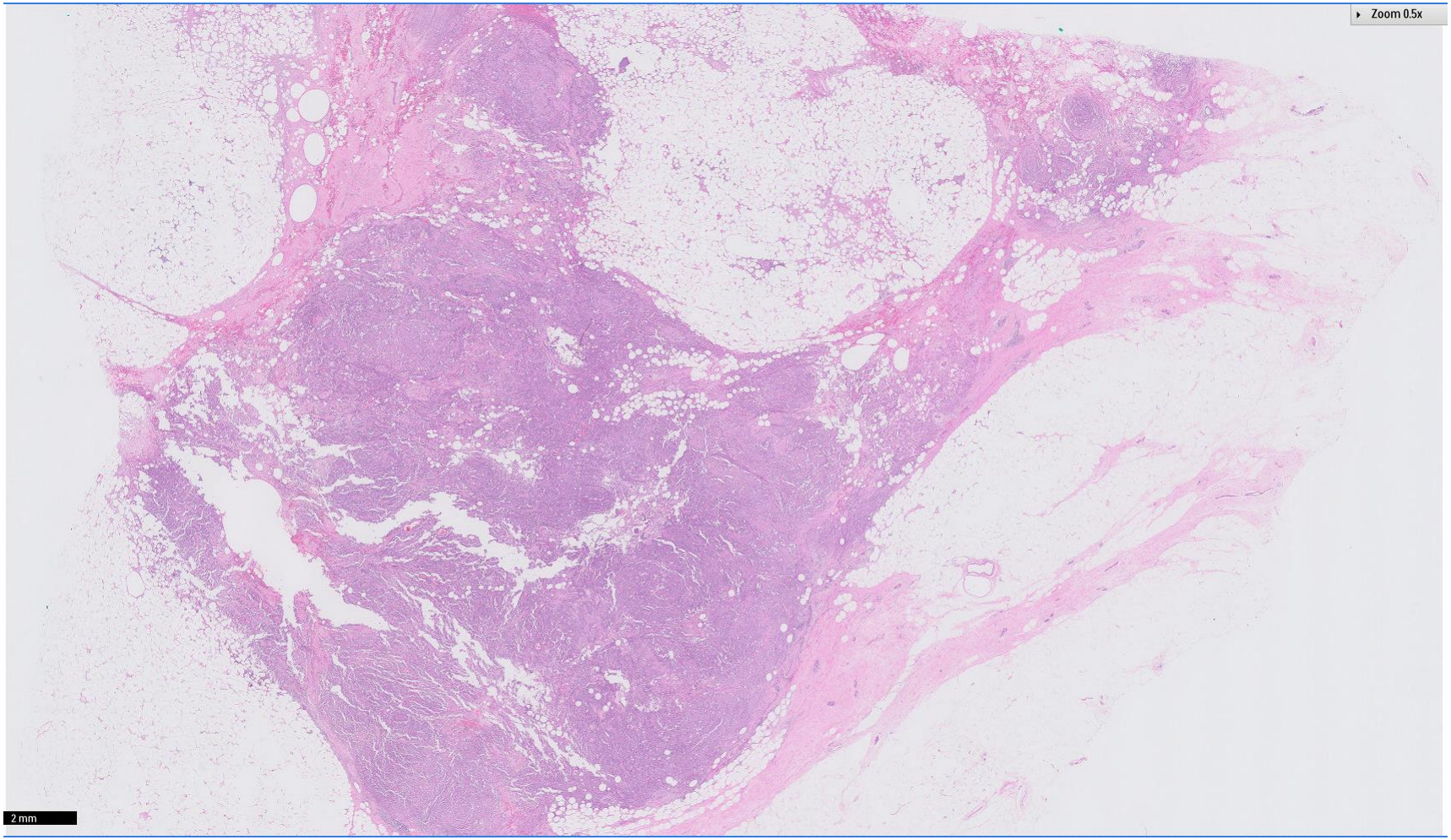

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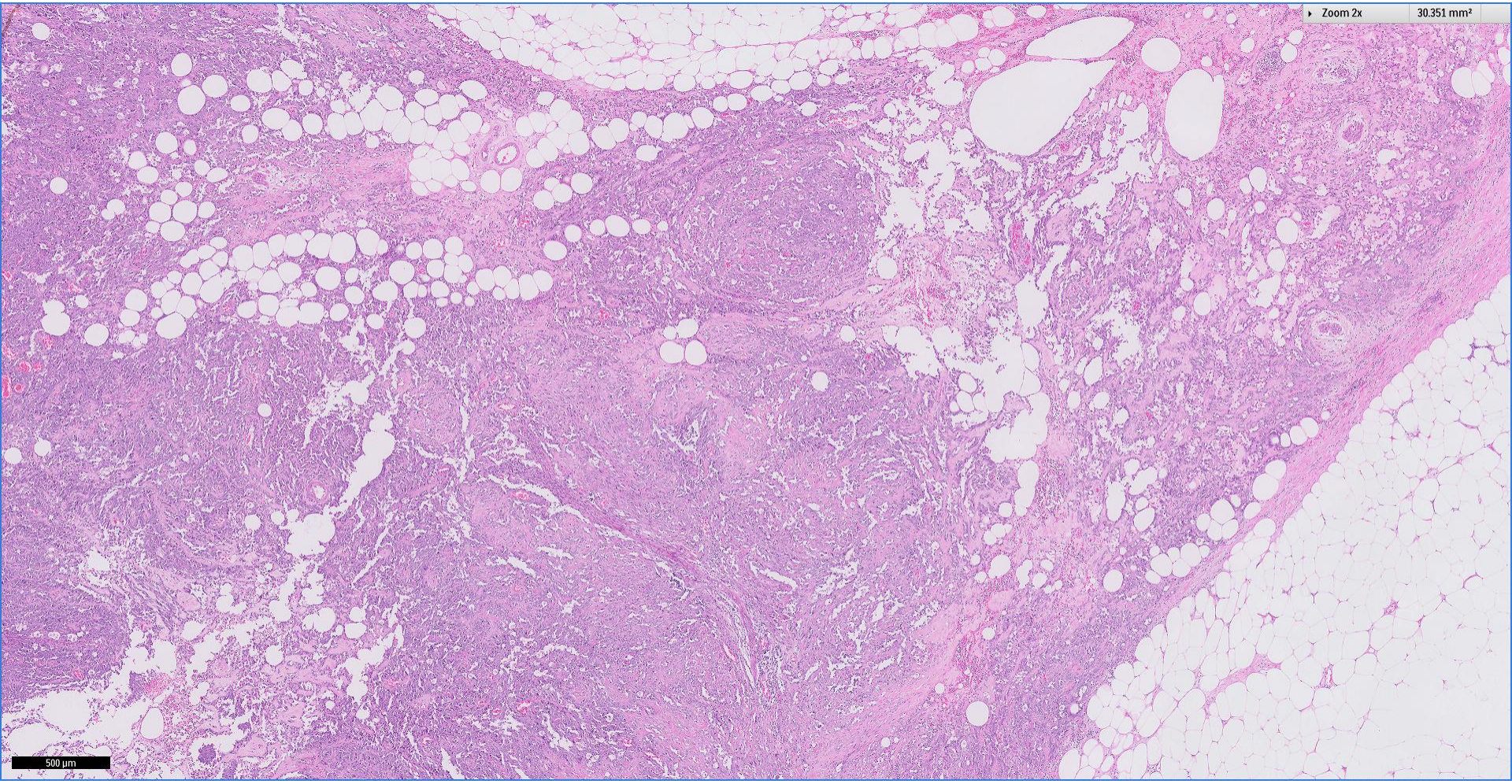

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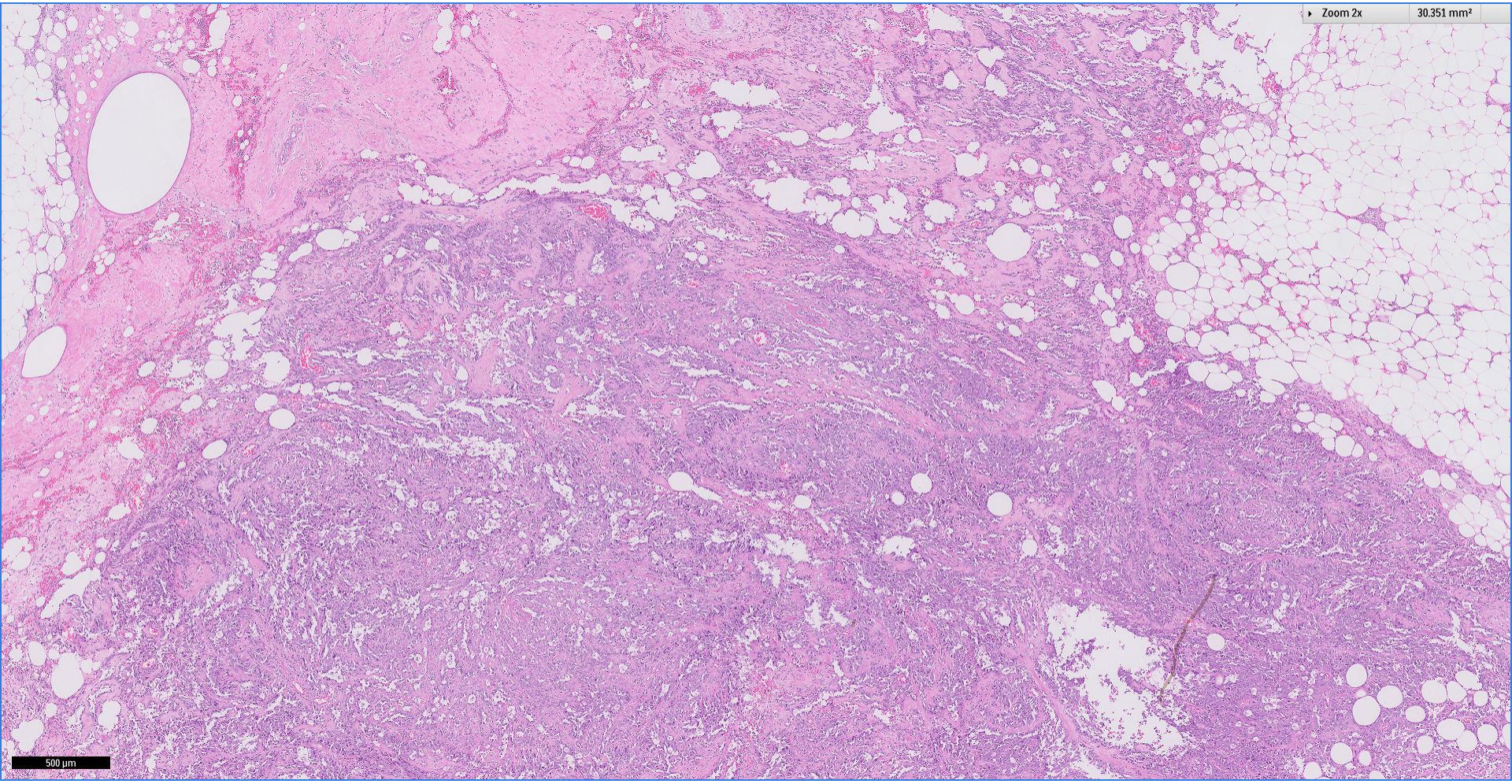

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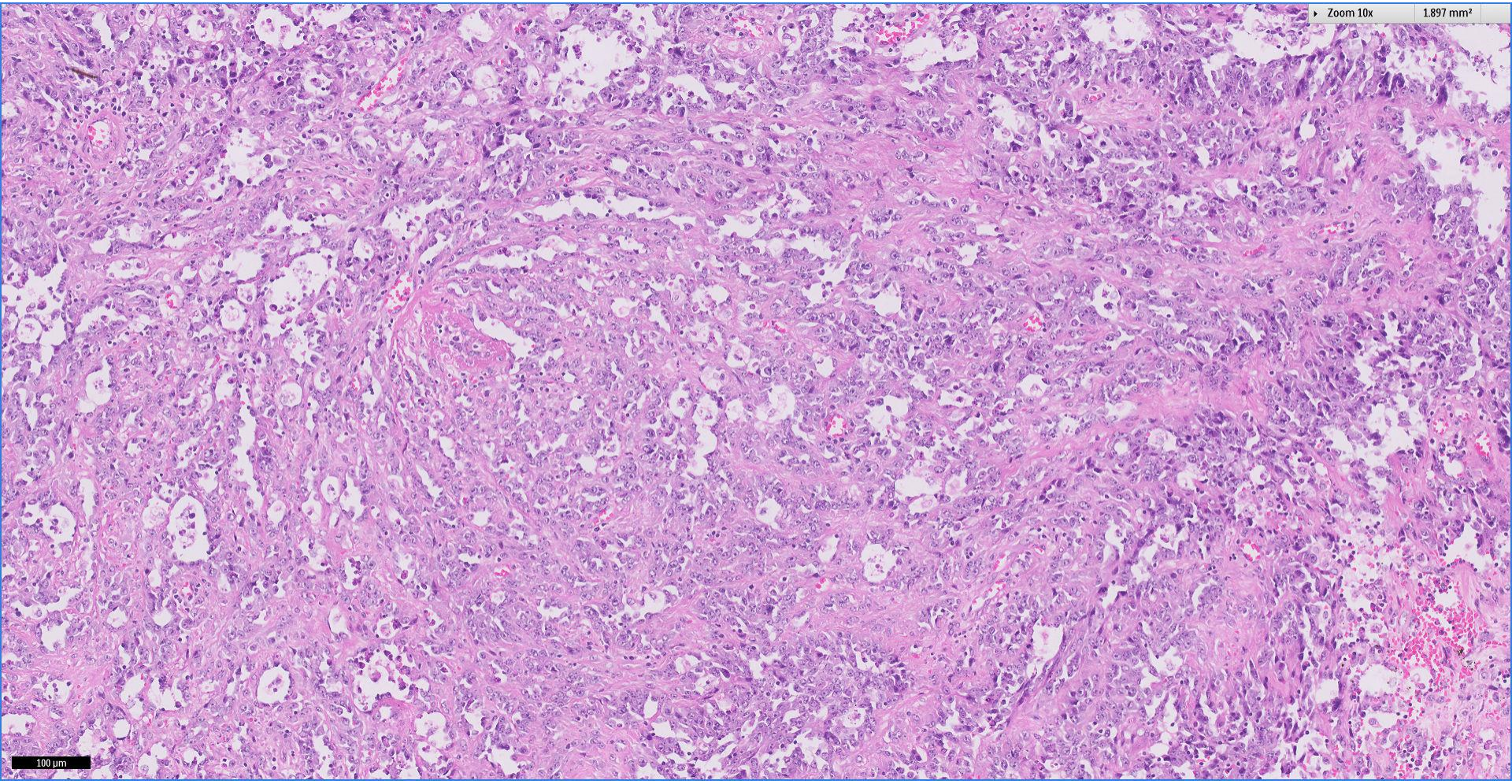

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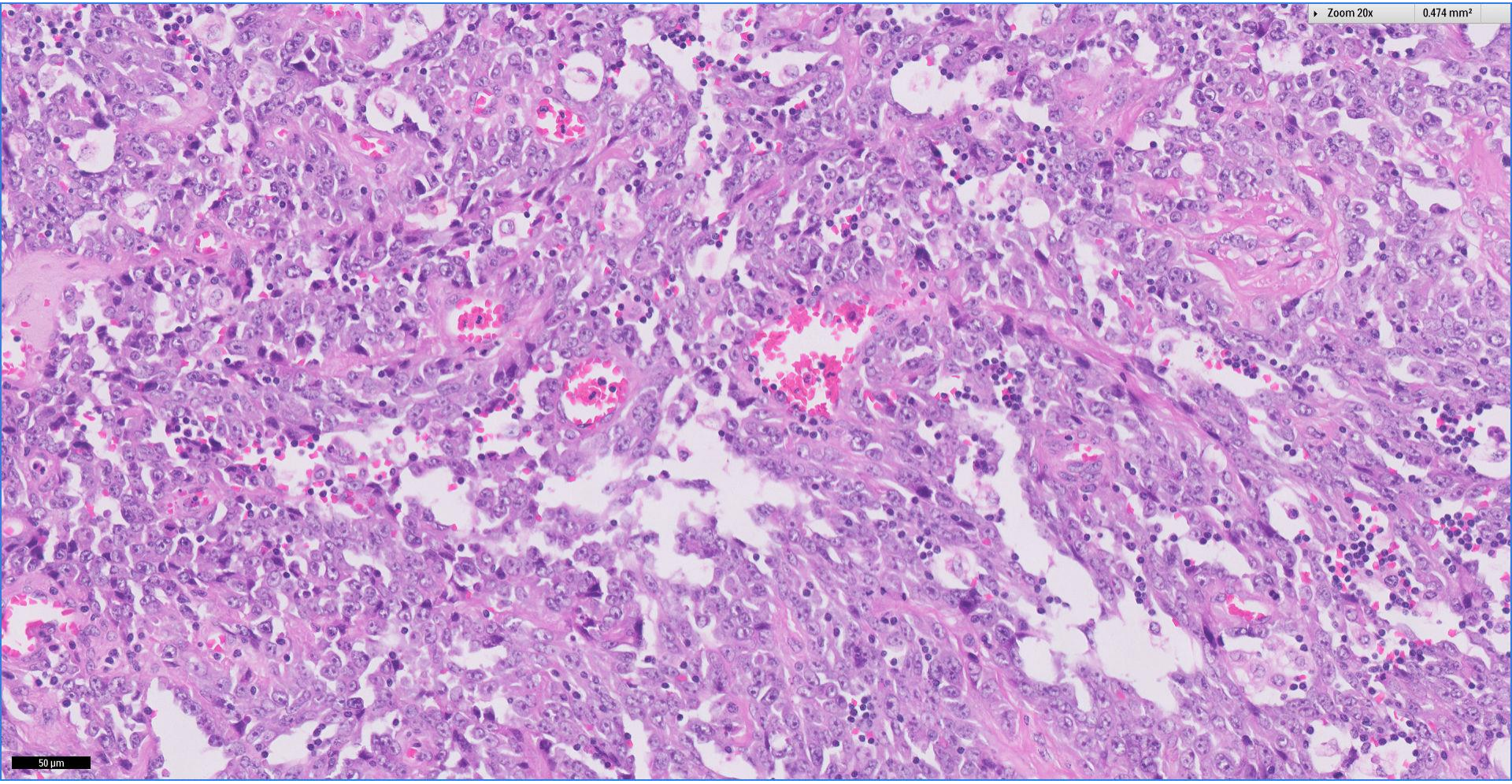

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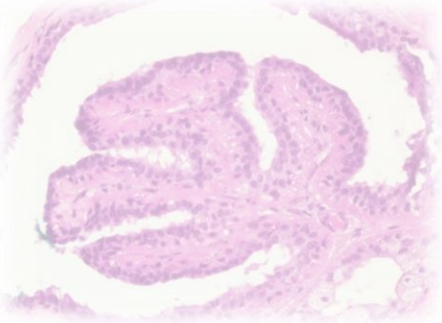
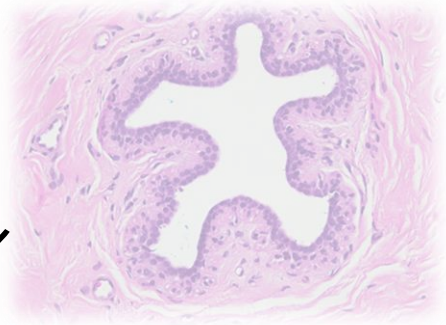
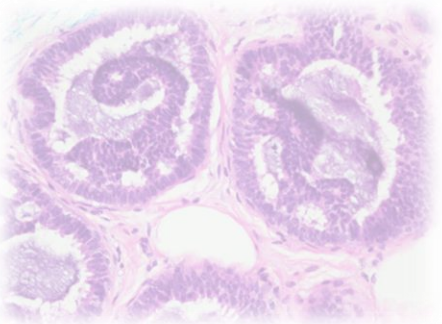
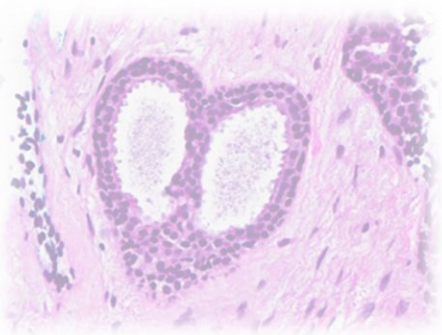
Additional pictures









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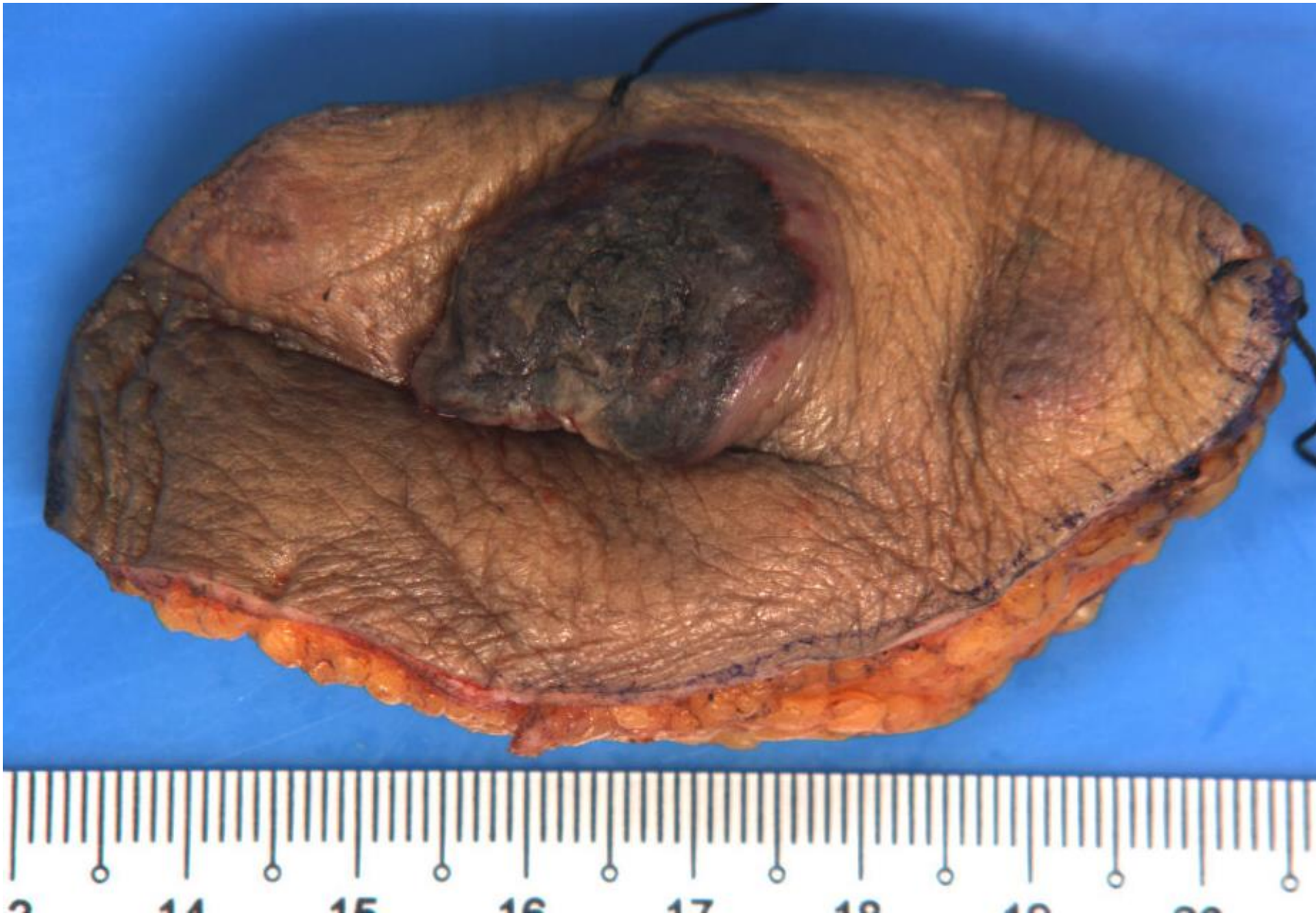
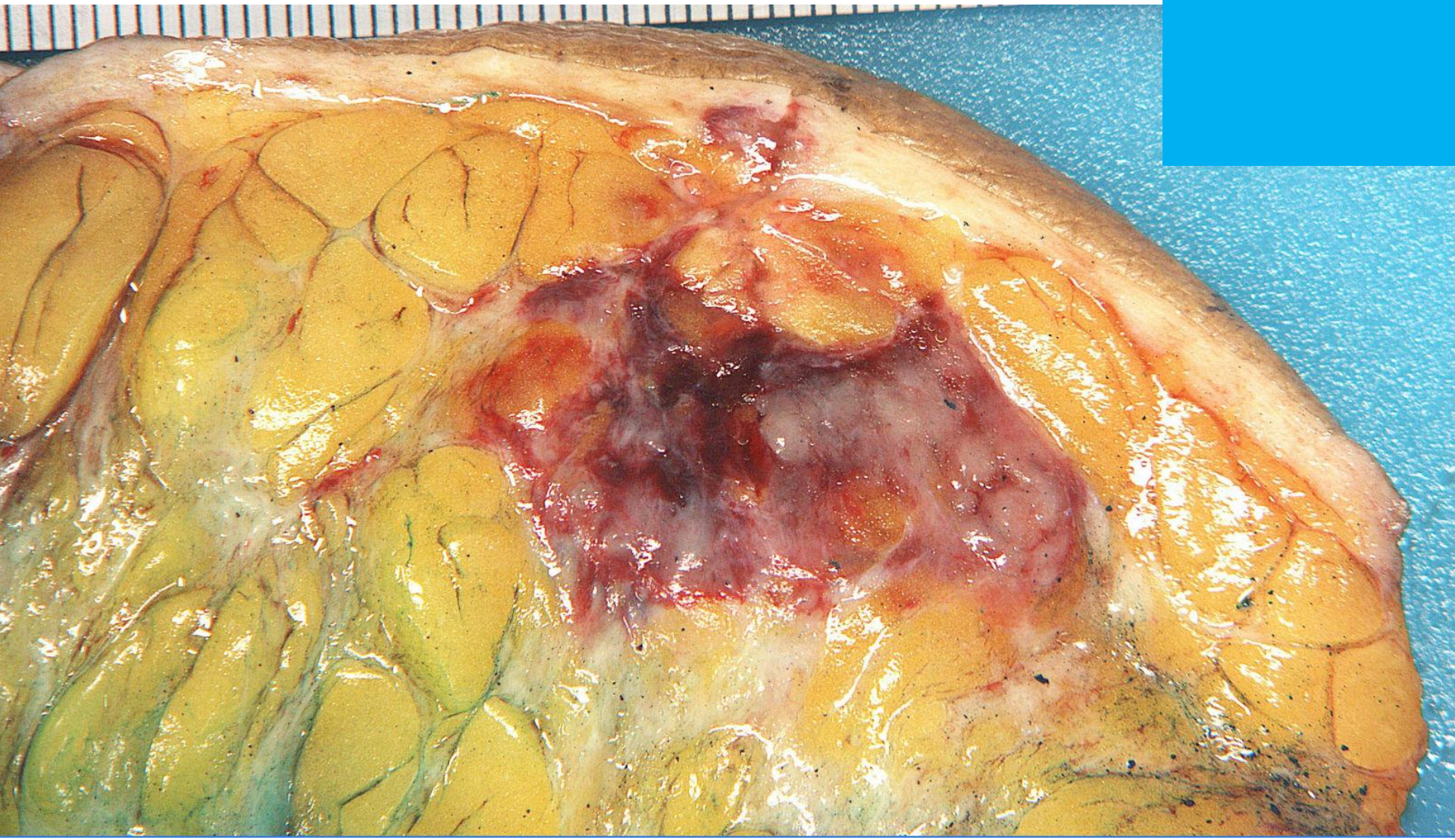




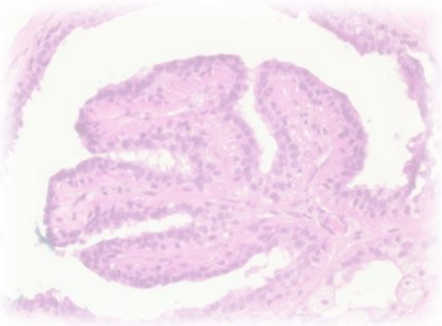
Immunohistochemistry

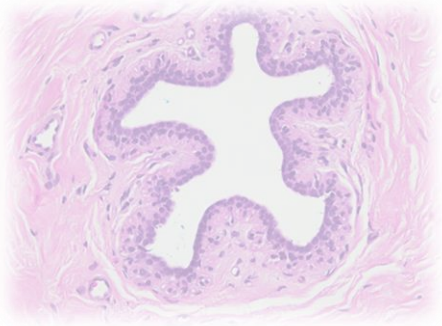
- Epithelial markers negative.
- Vascular endothelial markers positive ~
  - CD31, ERG, CD34, FLI1, D2-40

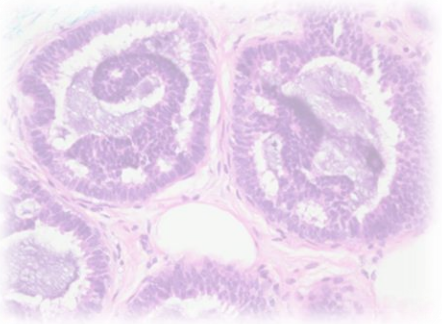
Diagnosis, case 29

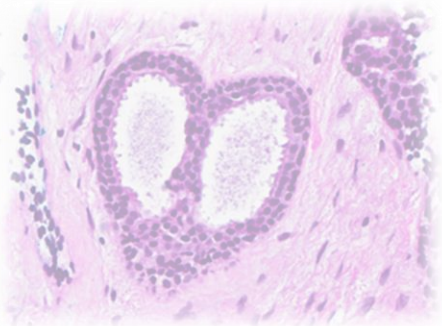
- Right breast mass:

  Epithelioid angiosarcoma.









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Vascular tumours

9120/0 Haemangioma NOS
- Perilobular haemangioma
- Venous haemangioma
- Cavernous haemangioma
- Capillary haemangioma

Angiomatosis
- Usual angiomatosis
- Capillary angiomatosis

9126/0 Atypical vascular lesion
- Lymphatic atypical vascular lesion, resembling lymphangioma
- Vascular atypical vascular lesion, resembling haemangioma or hobnail haemangioma

9120/3 Postradiation angiosarcoma
- Epithelioid angiosarcoma

9120/3 Angiosarcoma
- Epithelioid angiosarcoma

Postradiation angiosarcoma of the breast ~ definition

- Postradiation angiosarcoma of the breast is a malignant neoplasm occurring secondary to irradiation in the skin or breast parenchyma.

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Postradiation angiosarcoma of the breast

- **Localisation ~**
  - Occurs in the skin of the chest wall or scar of residual breast tissue in the irradiation field of previously treated breast carcinoma.
- **Clinical features ~**
  - Tumours arise in the radiation field with a mean latency period of 5–6 years, with rare cases presenting after a shorter latency period of 1–2 years.
  - They typically present as solitary or multiple cutaneous erythematous to violaceous patches, plaques, papules, or nodules.
  - Rarely, they may present as subtle skin thickening.
  - Angiosarcoma may also arise in the setting of chronic lymphoedema (Stewart–Treves syndrome).

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Postradiation angiosarcoma of the breast

- **Epidemiology** ~
  - Older patient age than primary angiosarcoma of the breast (at a median of 70 years vs 40 years).
- **Etiology** ~
  - Most commonly seen in the setting of breast-conserving surgery with radiation therapy.
  - Less frequently, it occurs in the setting of mastectomy and adjuvant radiation therapy.
  - Angiosarcoma is the most common radiation-induced sarcoma of the breast.

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Postradiation angiosarcoma of the breast

- **Pathogenesis ~**
  - The gene signature of angiosarcomas, which is distinct from those of other sarcoma types, is characterized by upregulation of vascular-specific receptor tyrosine kinases, including TIE1, KDR, TEK, and FLT1.
  - A subset of radiation-induced angiosarcomas harbour mutations in genes involved in the regulation of vascular growth factor tyrosine kinases, such as KDR (also known as VEGFR2), PLCG1, and PTPRB.
  - KDR and PLCG1 mutations are mutually exclusive; both genes are involved in the VEGFR2 signalling pathway.
  - Truncating mutations in PTPRB, a tyrosine phosphatase specific to vascular endothelium that inhibits angiogenesis, have been reported in 26% of angiosarcomas, all occurring in secondary or radiation-induced tumours.
  - An alternative mechanism of VEGFR activation in secondary angiosarcoma is the presence of FLT4 (also known as VEGFR3) gene amplifications at the 5q35 locus, which is coamplified with MYC in 5% of radiation-induced angiosarcomas.
  - FLT4 gene abnormalities are mutually exclusive with PLCG1/KDR mutations.

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Postradiation angiosarcoma of the breast

- **Immunohistochemistry** ~
  - Diffuse and strong immunoreactivity is seen with both CD31 and ERG, along with variable expression of CD34, FLI1, and podoplanin (D2-40) – a marker of lymphatic endothelium.
  - Focal keratin and rarely EMA expression can be seen, especially in epithelioid subtypes.
  - An outer layer of SMA-positive pericytic cells is often lacking around the lesional vessels.
  - Tumours also show strong nuclear expression of MYC, due to the consistent MYC gene amplifications.
  - Radiation-associated angiosarcomas may demonstrate loss of H3K27me3, whereas this marker is retained in the endothelial cells of benign and atypical vascular lesions.

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Postradiation angiosarcoma of the breast

- Angiosarcomas may be associated with preceding or synchronous postradiation atypical vascular lesions in the skin and subcutis of the breast.
- In challenging cases, immunohistochemistry or FISH can be performed, because postradiation atypical vascular lesions are MYC-negative.

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Postradiation angiosarcoma of the breast

- **Diagnostic molecular pathology ~**
  - High-level amplification of *MYC* at 8q24 is a consistent hallmark of radiation-induced and lymphoedema-associated angiosarcomas of the breast, present in > 90% of cases.
  - In contrast, radiation-induced angiosarcomas occurring at other sites and/or after radiotherapy for other disease types show a less frequent pattern of *MYC* amplification.
  - The high-level amplification of *MYC*, typically defined as > 100 copies of *MYC*, in the form of homogeneously staining regions or multiple focal amplicons by FISH, can be used as a powerful ancillary test in excluding challenging atypical vascular lesions.

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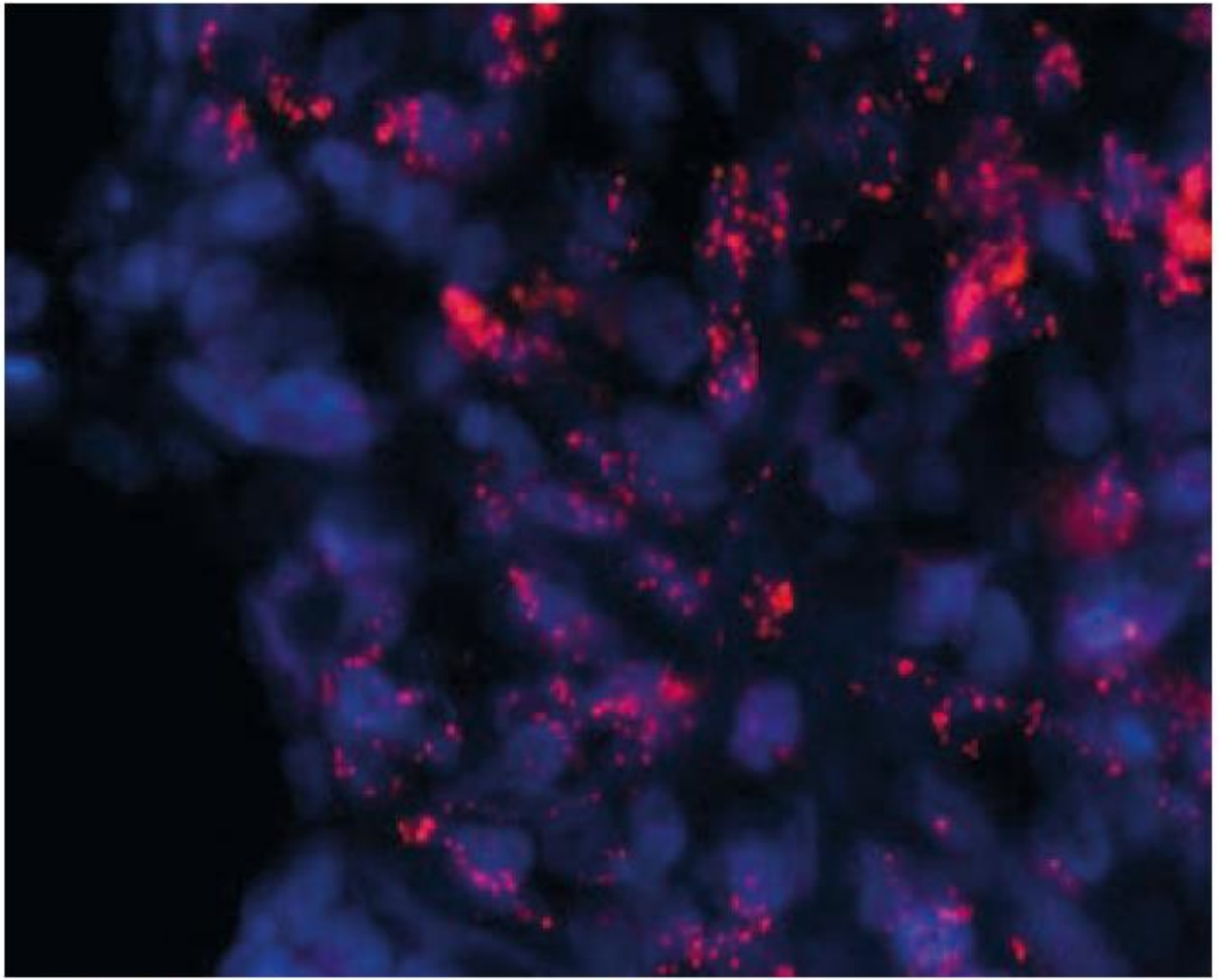

Fig. 5.XX Postradiation angiosarcoma. FISH showing a high level of *MYC* gene amplification (red signals) in the form of homogeneously staining regions.

Postradiation angiosarcoma of the breast

- **Essential**:
  - previous irradiation of the field, usually after a time interval of > 3 years;
  - predominantly dermal to subcutaneous growth, with rarer involvement of breast parenchyma;
  - infiltrative growth pattern, with dissection of adipose tissue and lobular stroma;
  - vasoformative growth with at least focal cytological atypia.
- **Desirable**:
  - MYC overexpression by immunohistochemistry;
  - MYC amplification by FISH.

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Postradiation angiosarcoma of the breast

- **Prognosis & Prediction** ~

High rate of locoregional recurrence, which occurred in about half of the cases in one study.

Multiple recurrences are common.

Common metastatic sites include the lungs, contralateral breast and skin, liver, and bone.

Axillary lymph node metastases are uncommon.

The median recurrence-free survival time is < 3 years and the median overall survival time < 5 years.

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Epithelioid angiosarcoma

- Solid appearance with sheets of large atypical epithelioid to polygonal cells with ovoid vesicular nuclei, large nucleoli, and relatively abundant cytoplasm.
- Because vasoformation can be limited, epithelioid angiosarcoma may be confused with carcinoma.
- There are often prominent mitotic figures and necrosis.

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Thank You

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