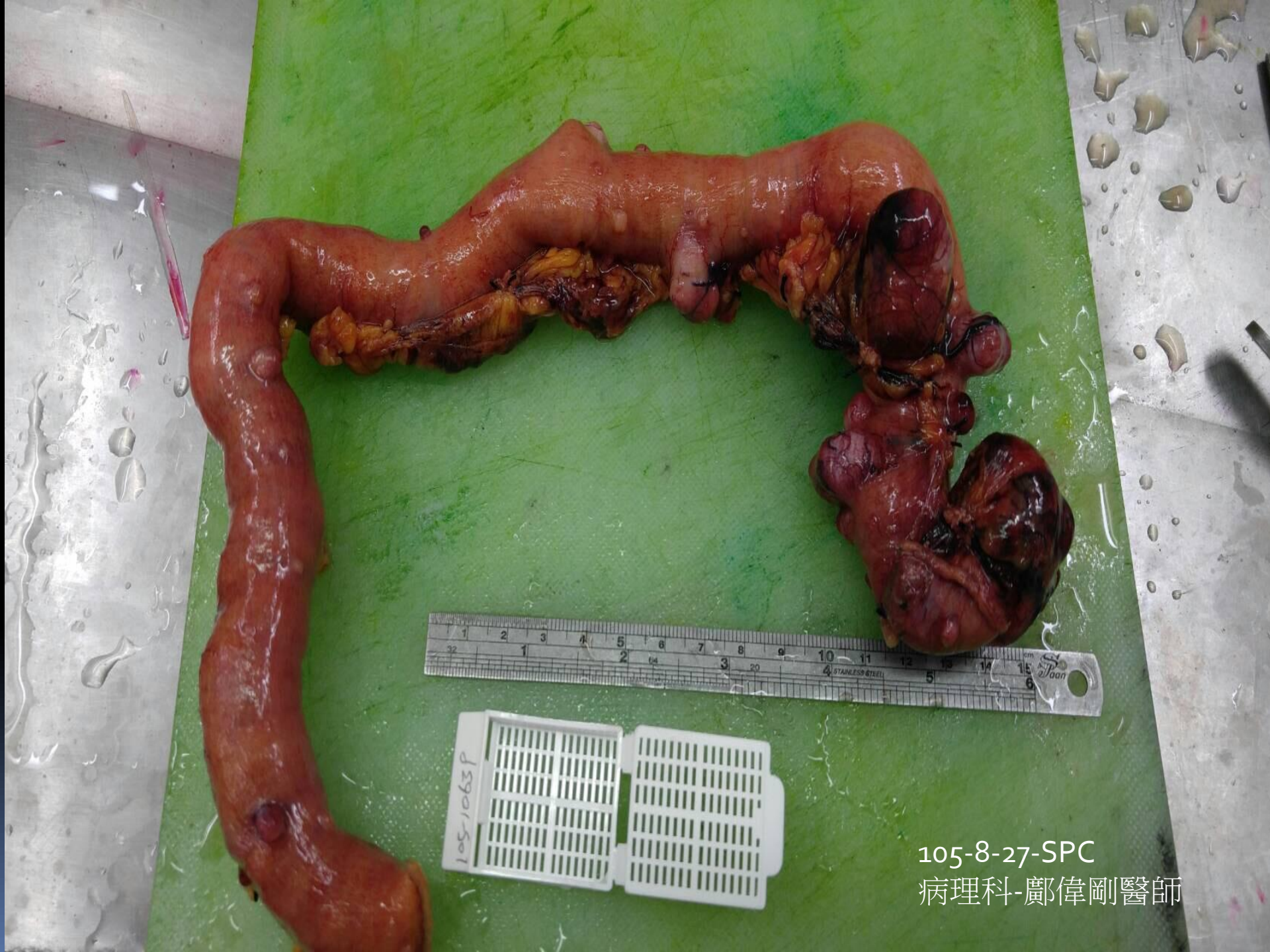
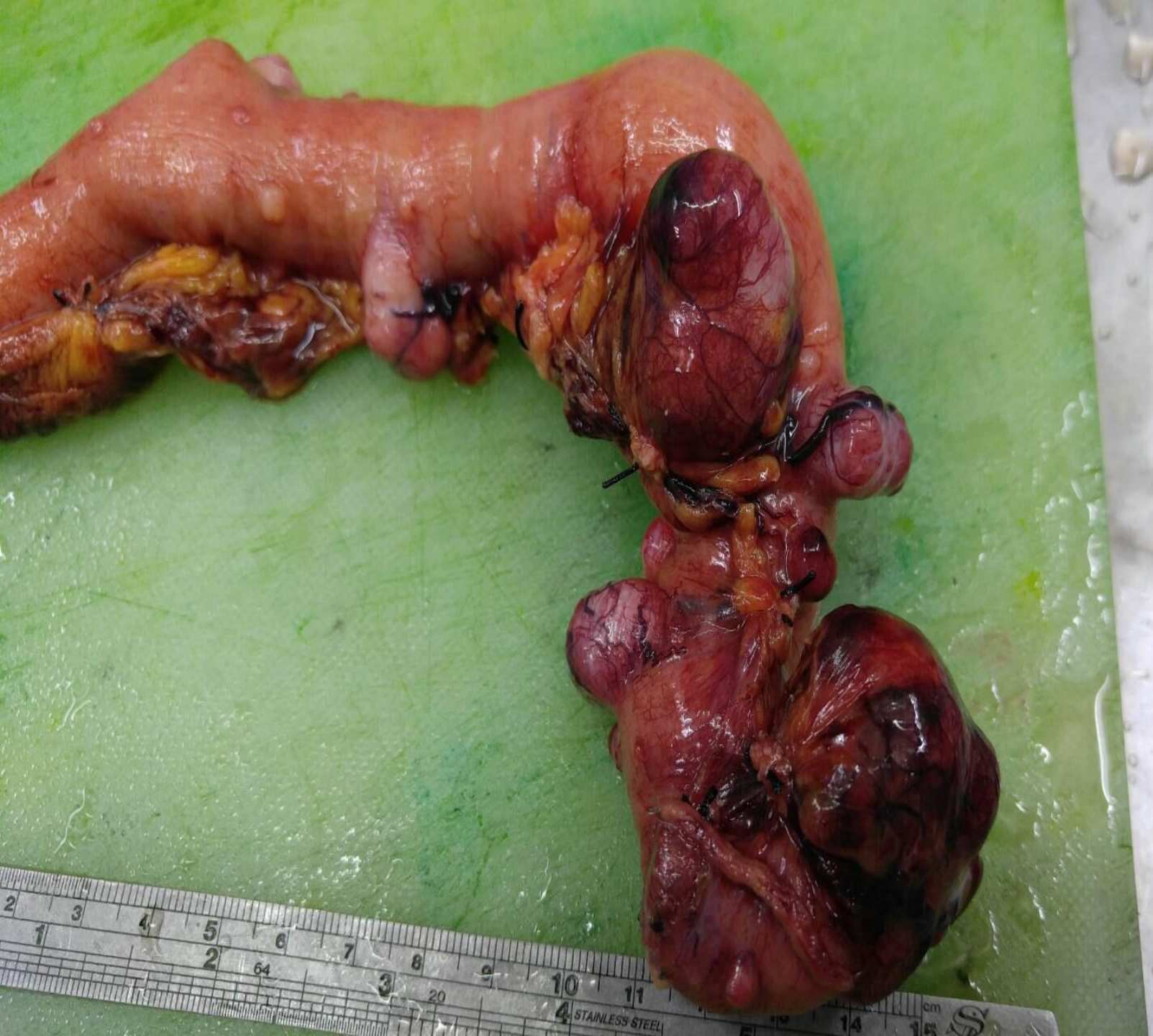
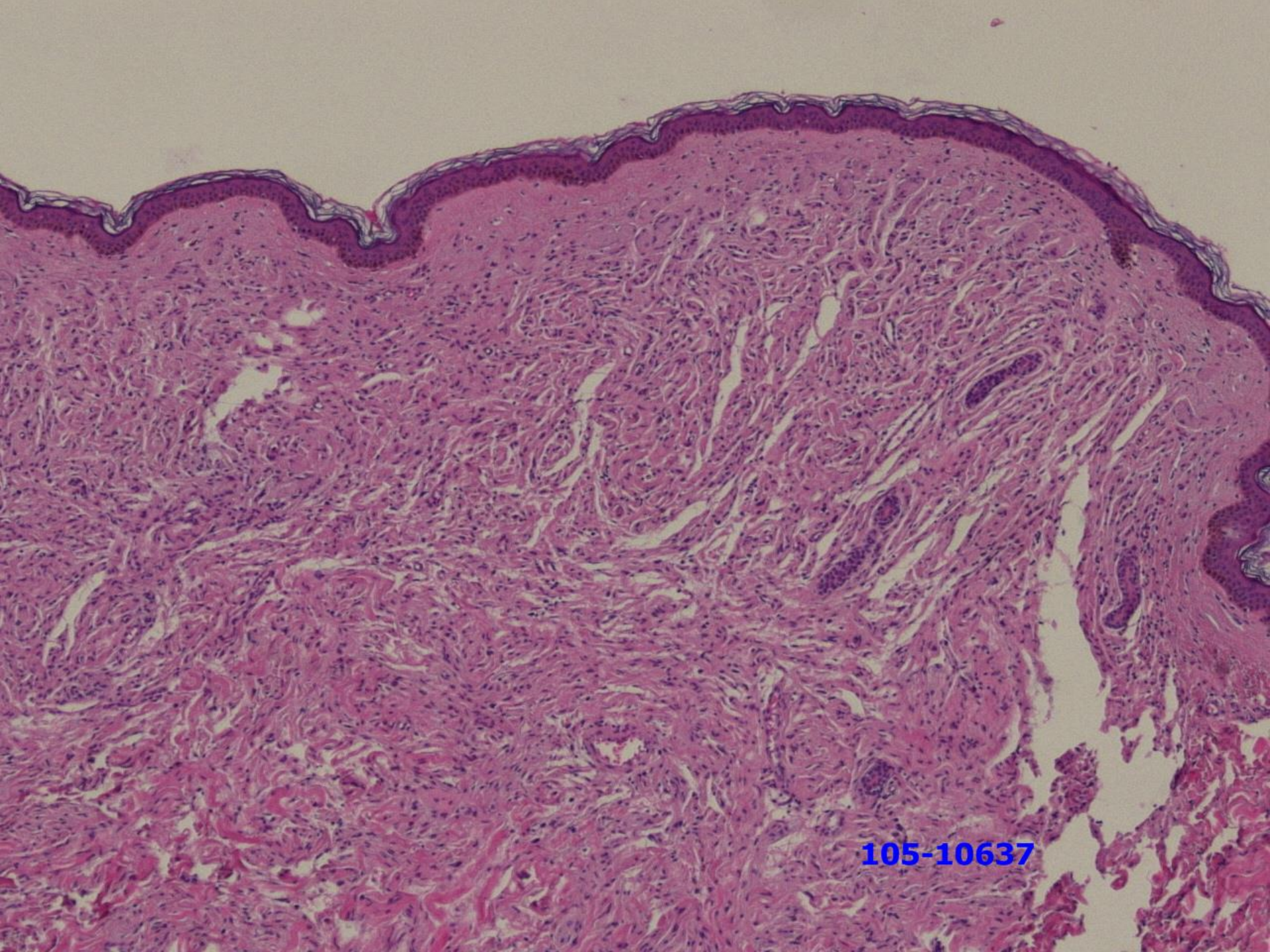
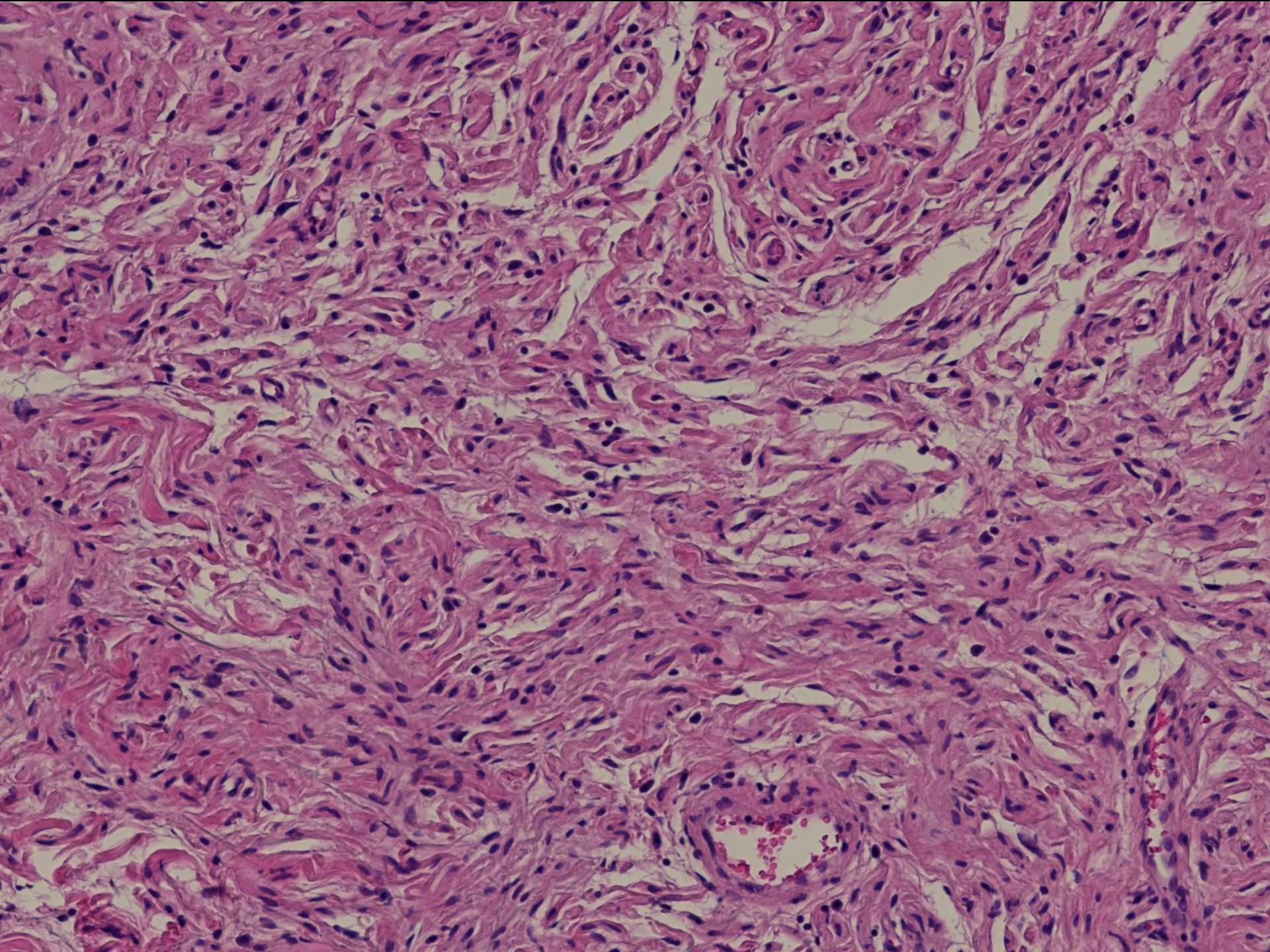
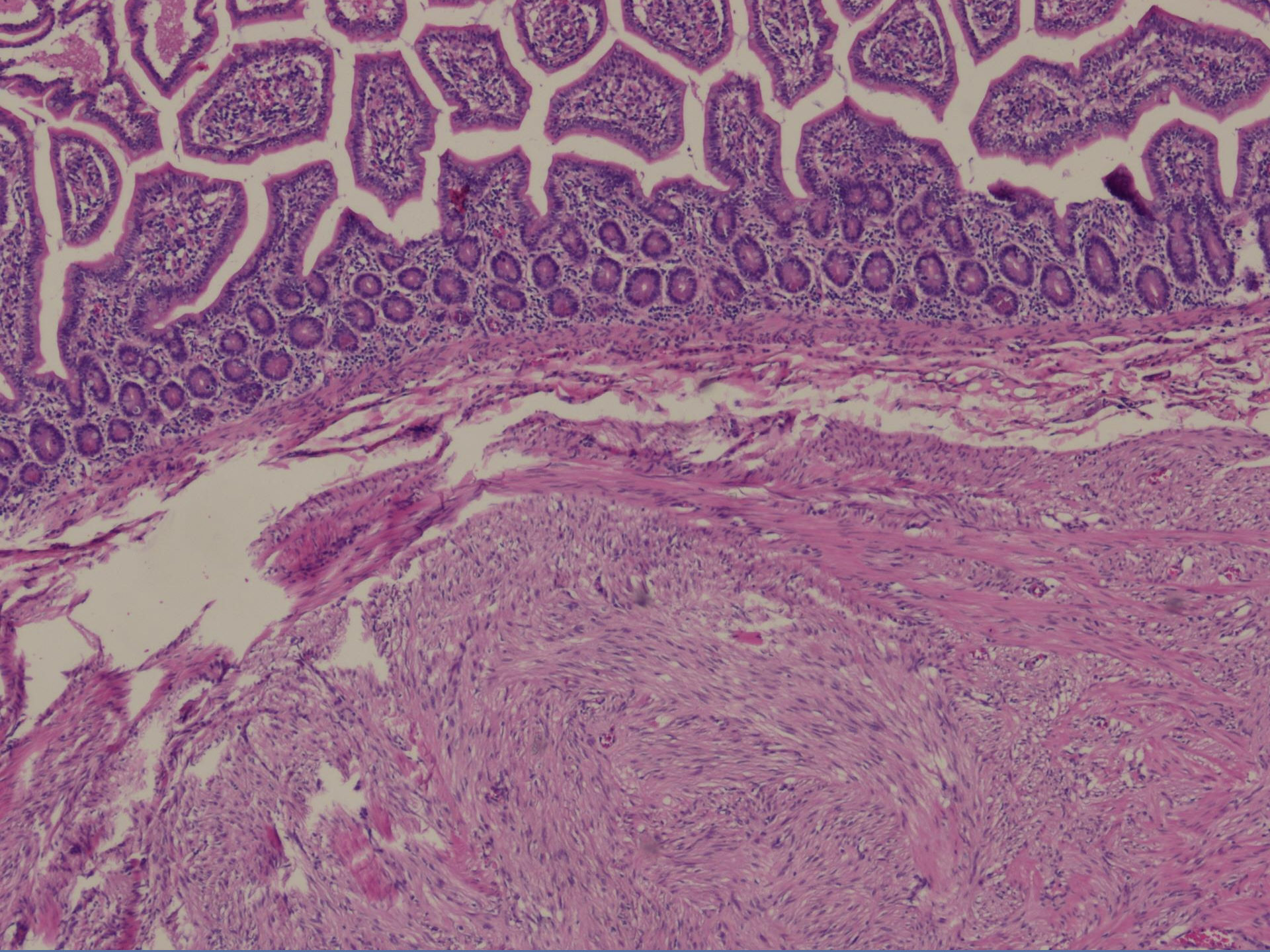

105-8-27-SPC
病理科-鄺偉剛醫師

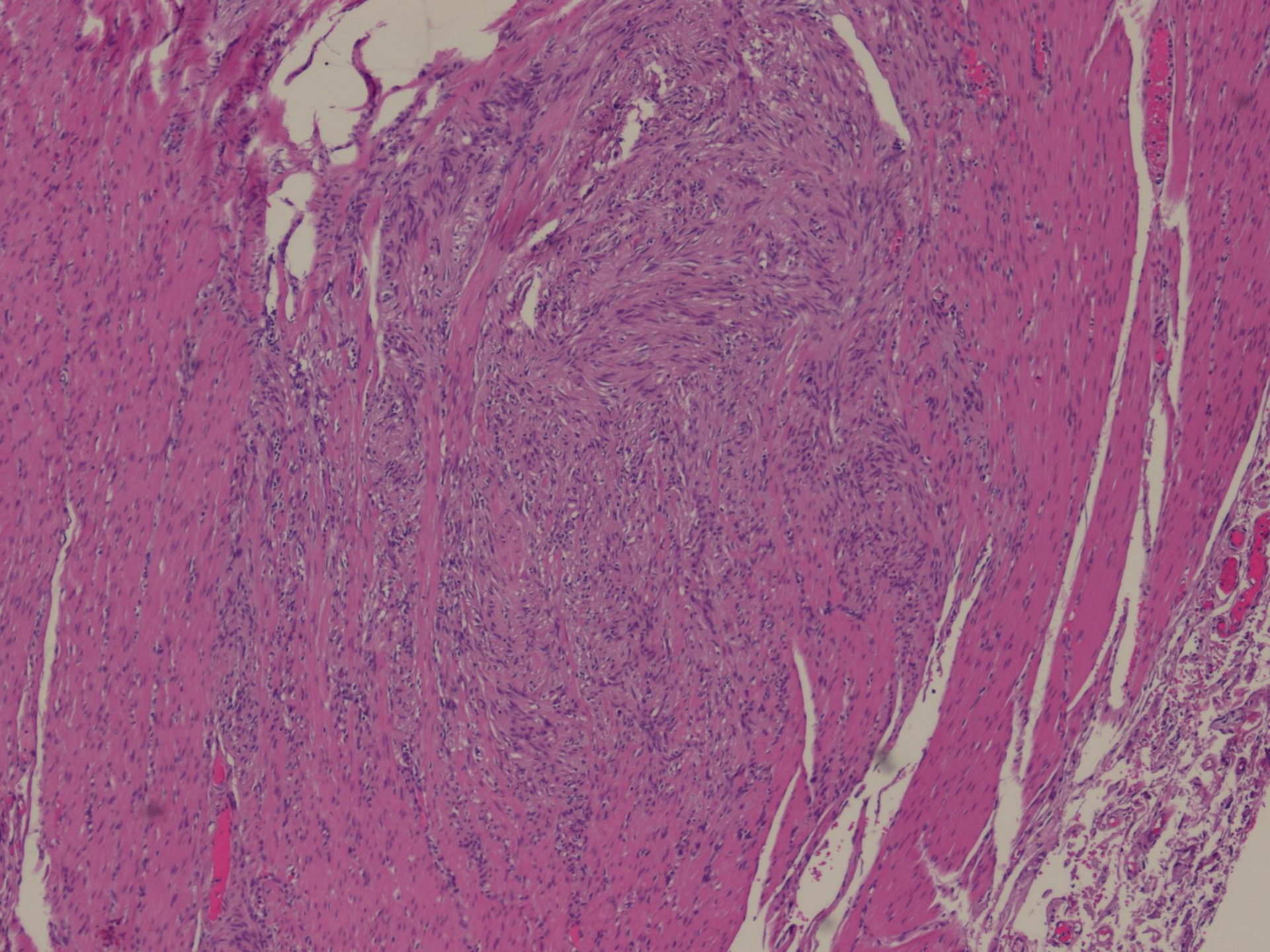


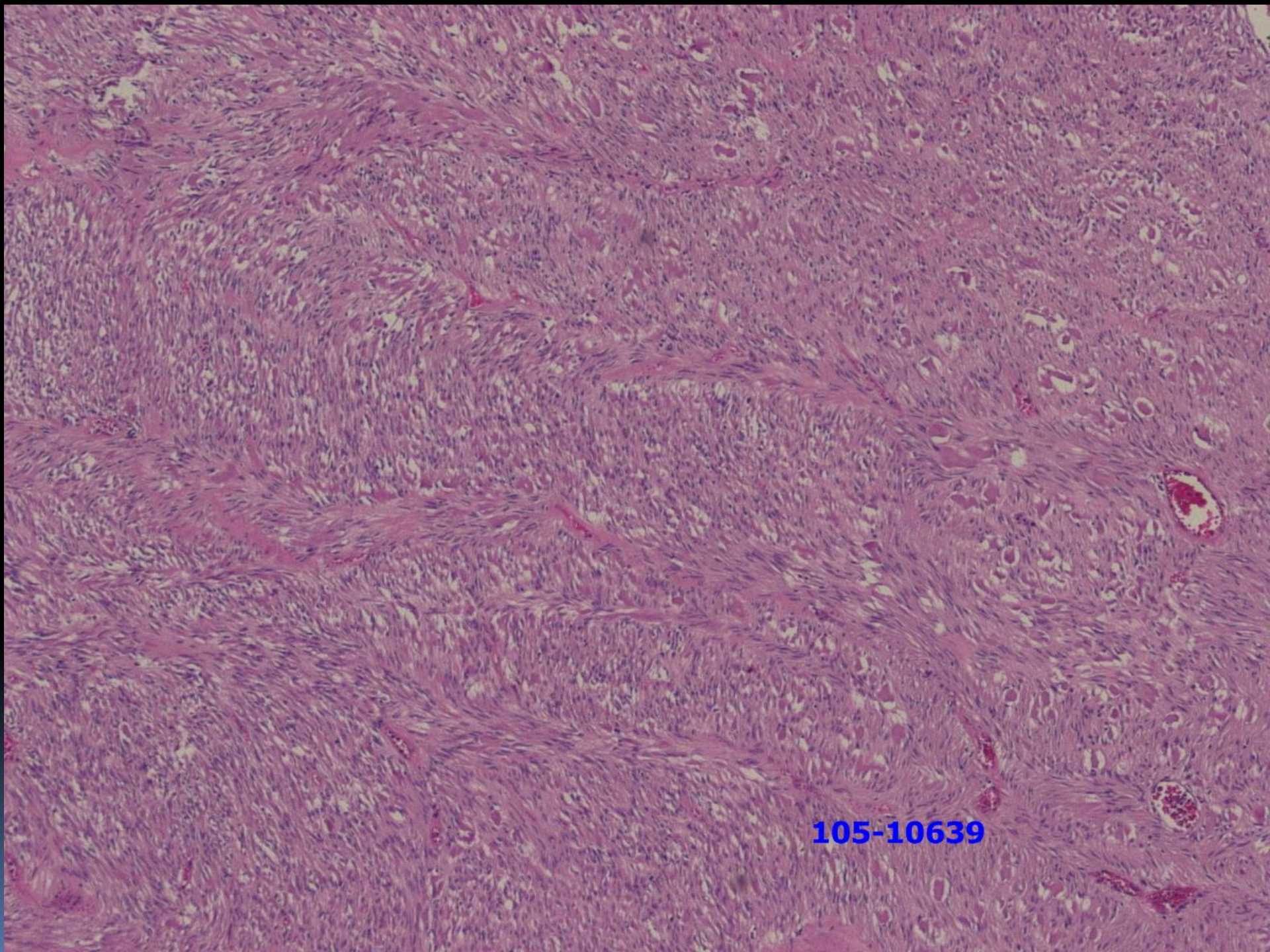
STAINLESS STEEL

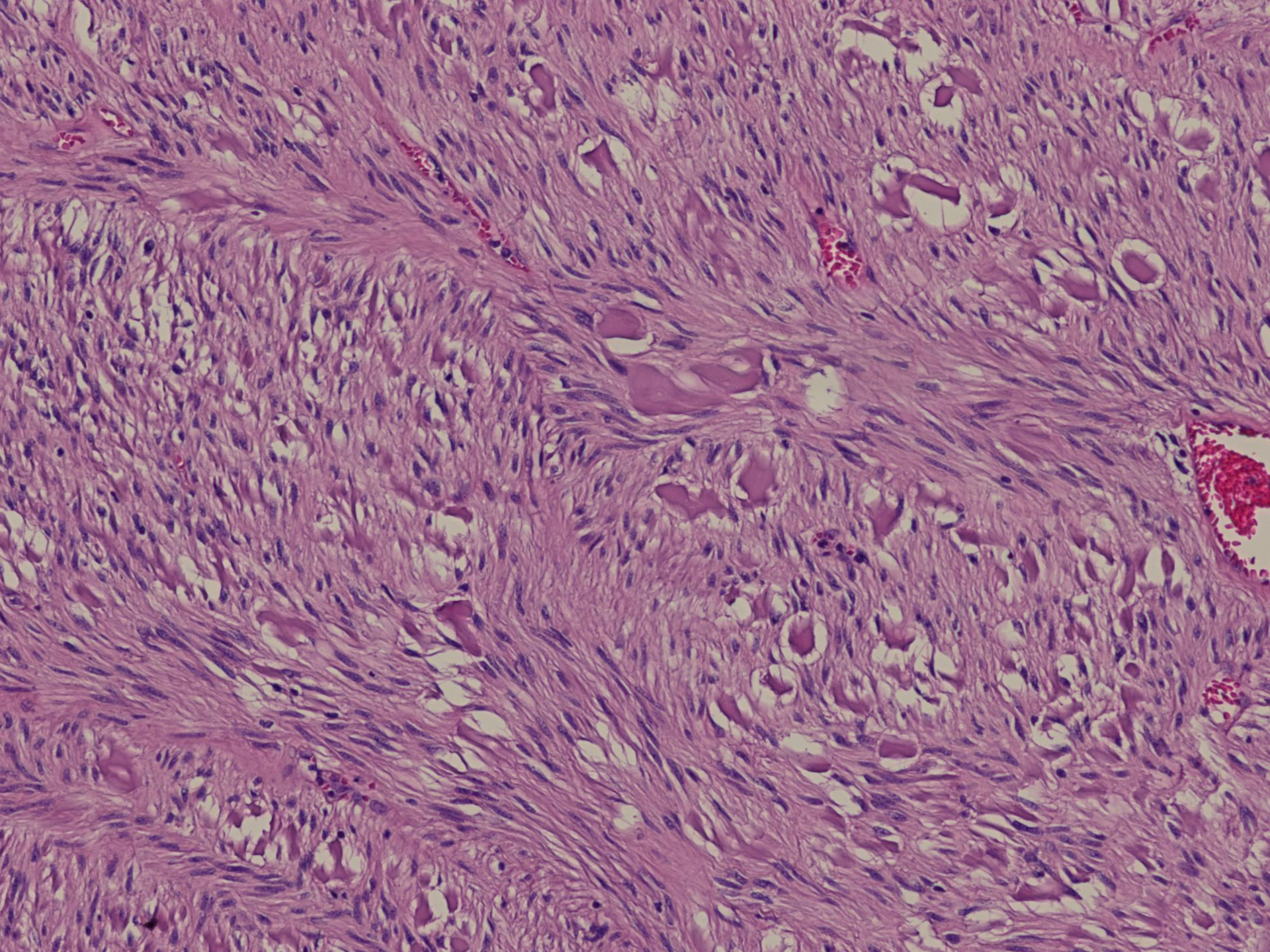

105-10637

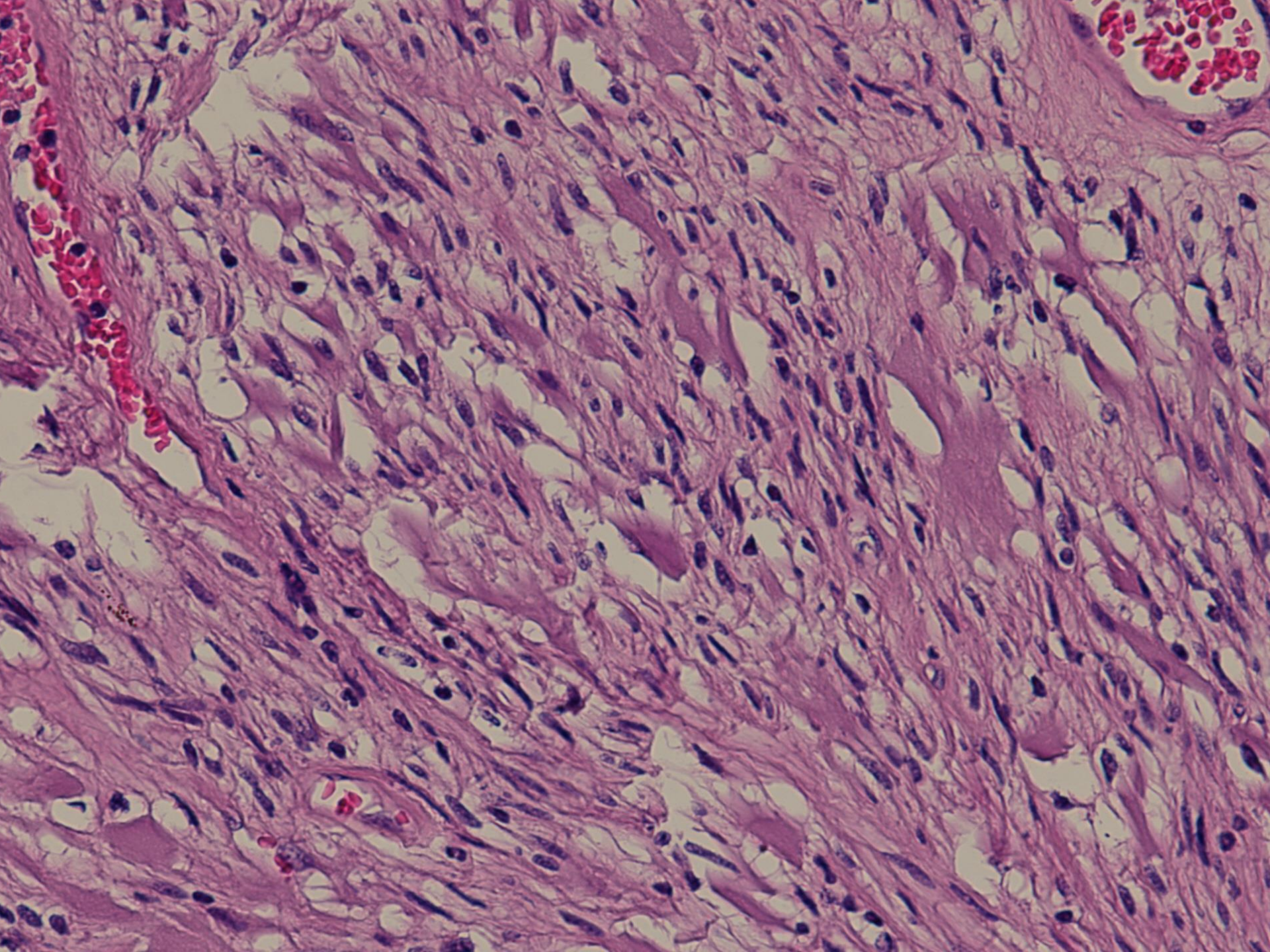


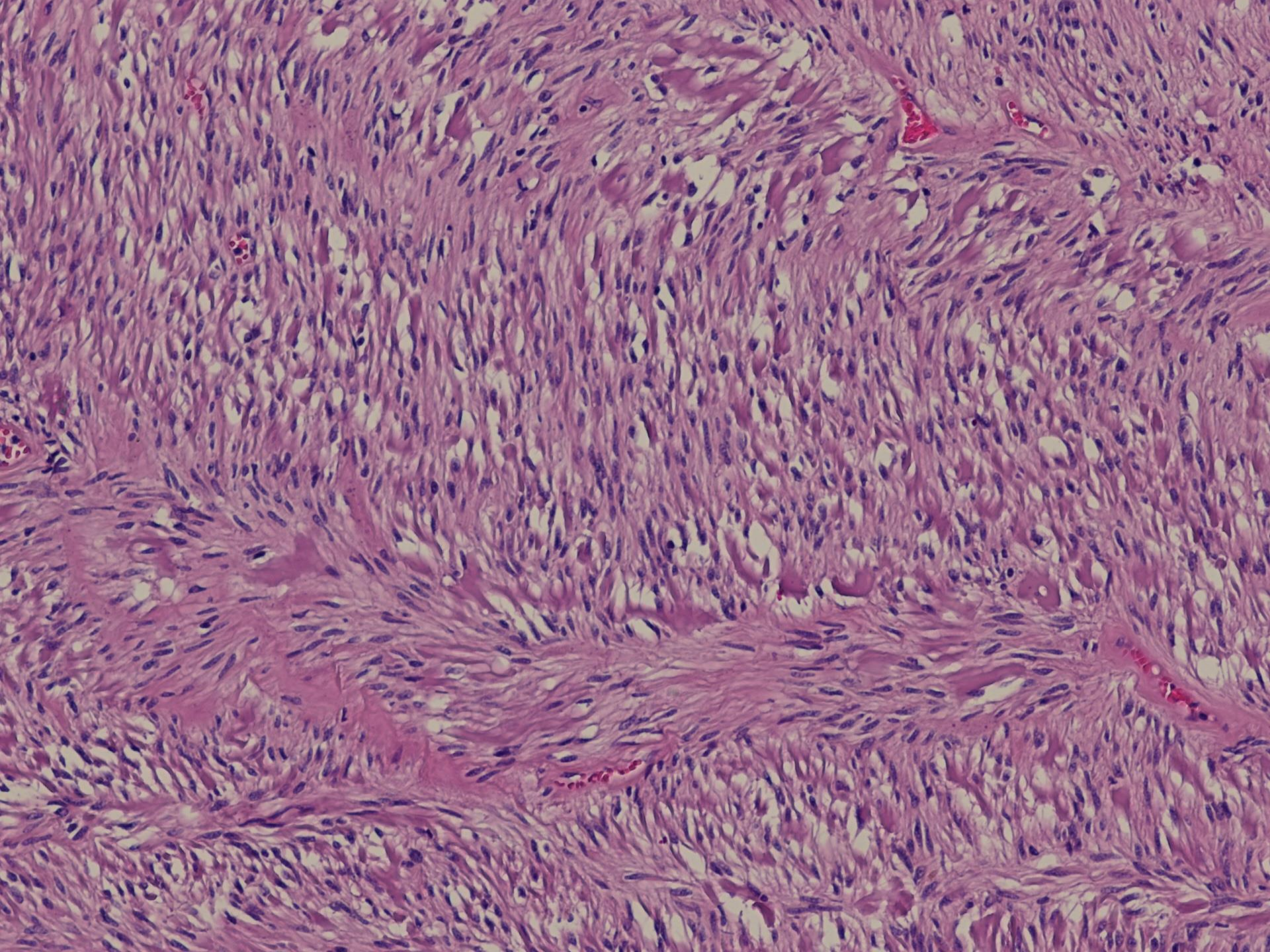


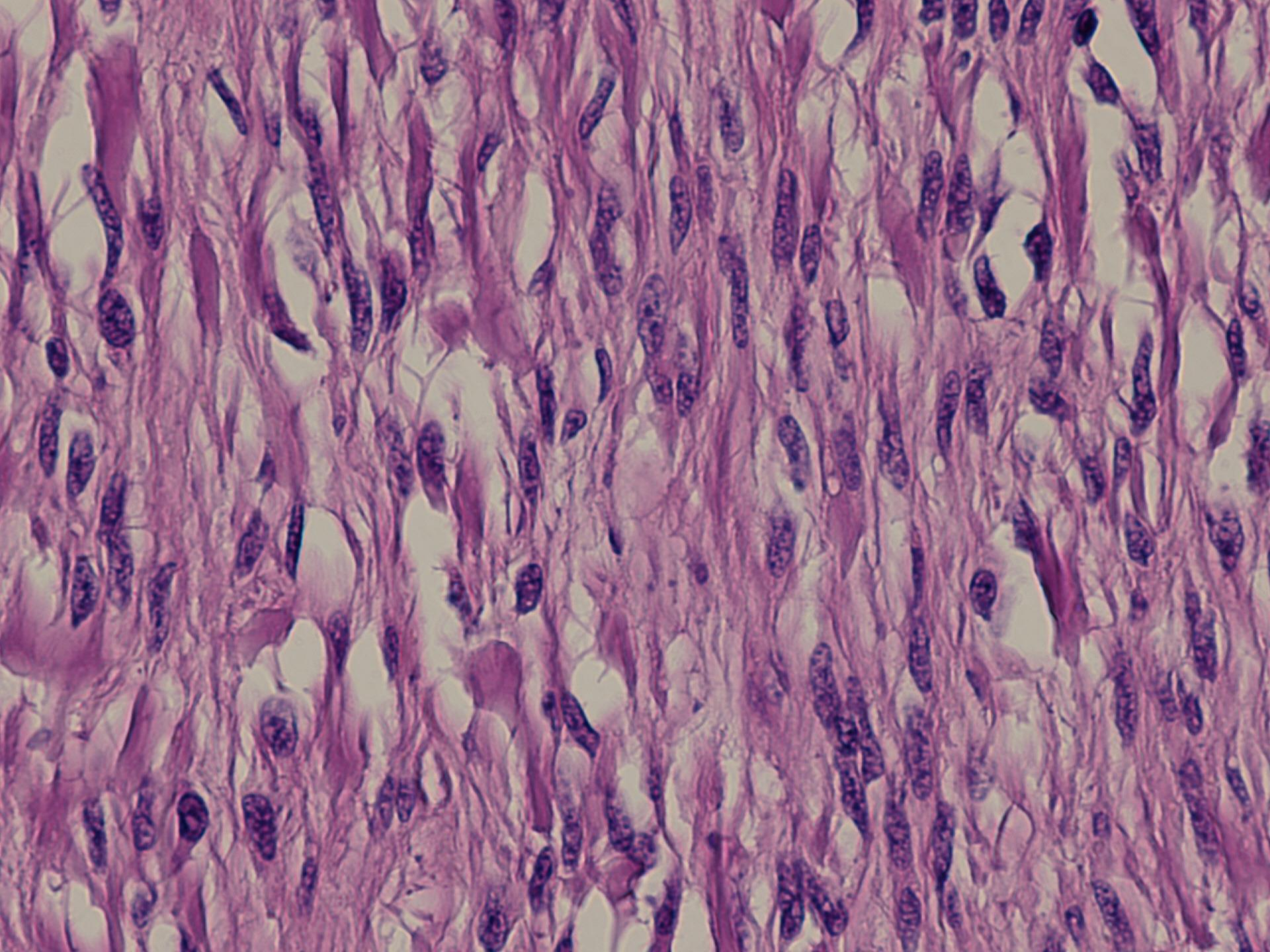


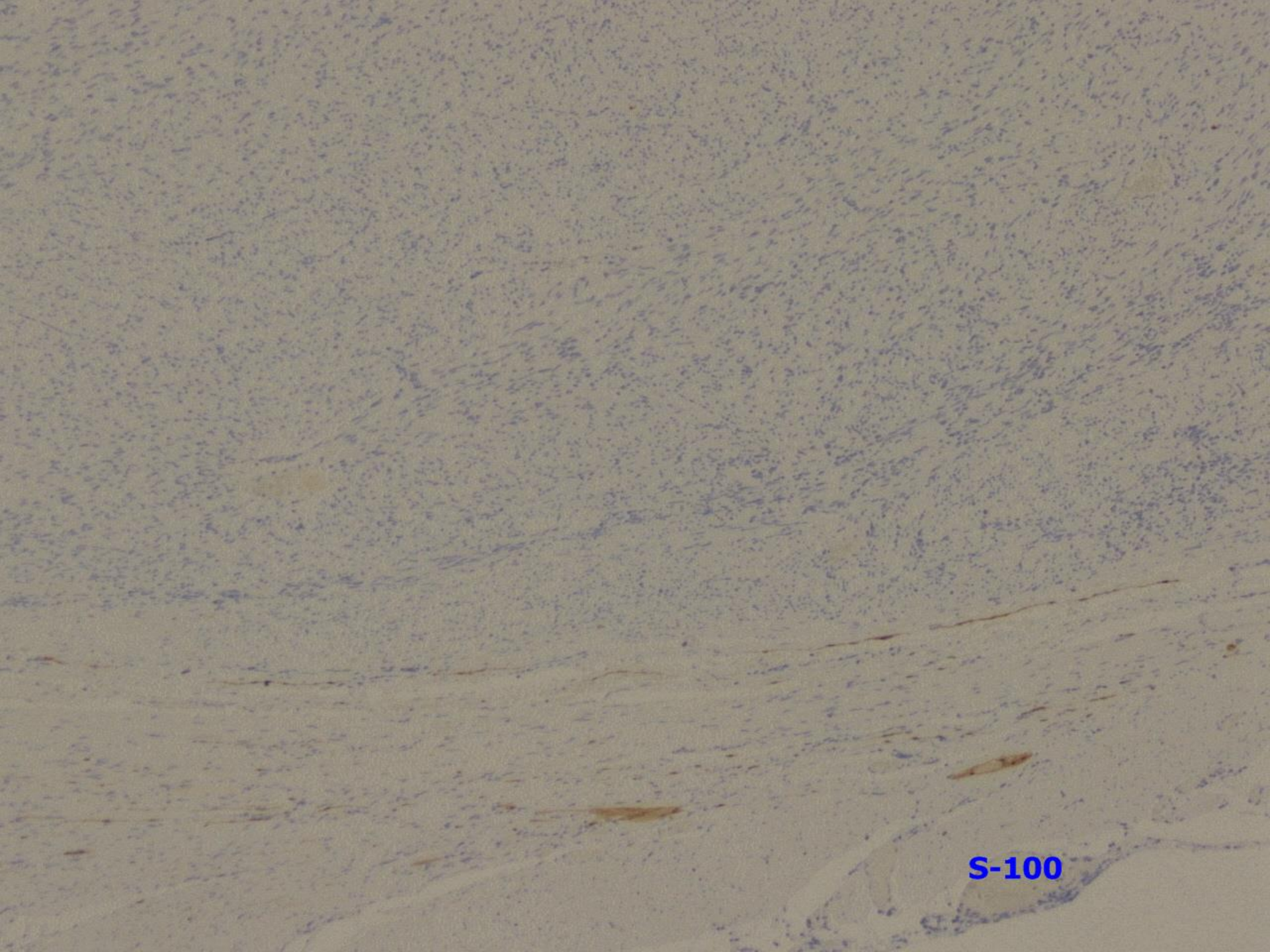

105-10639

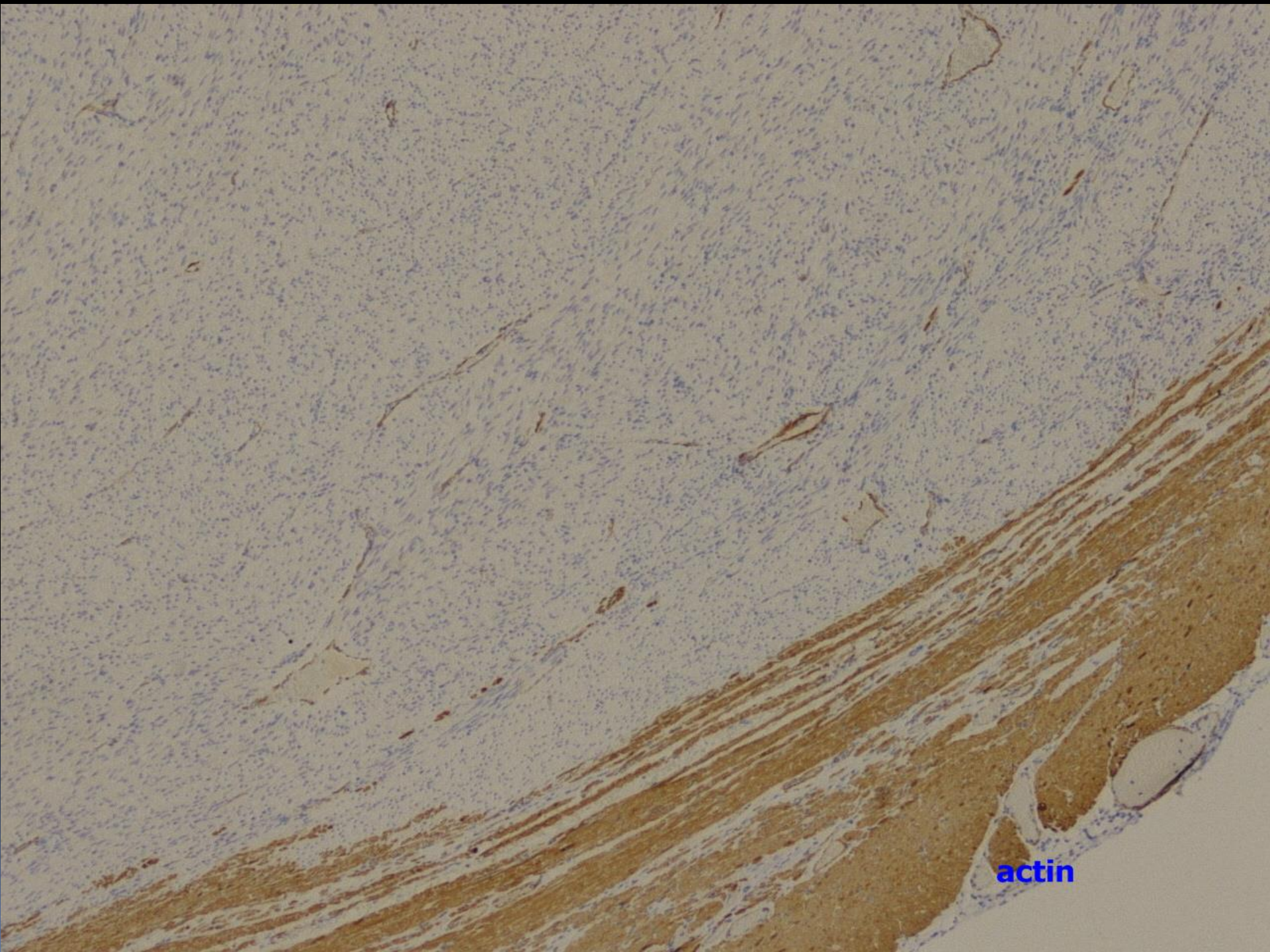


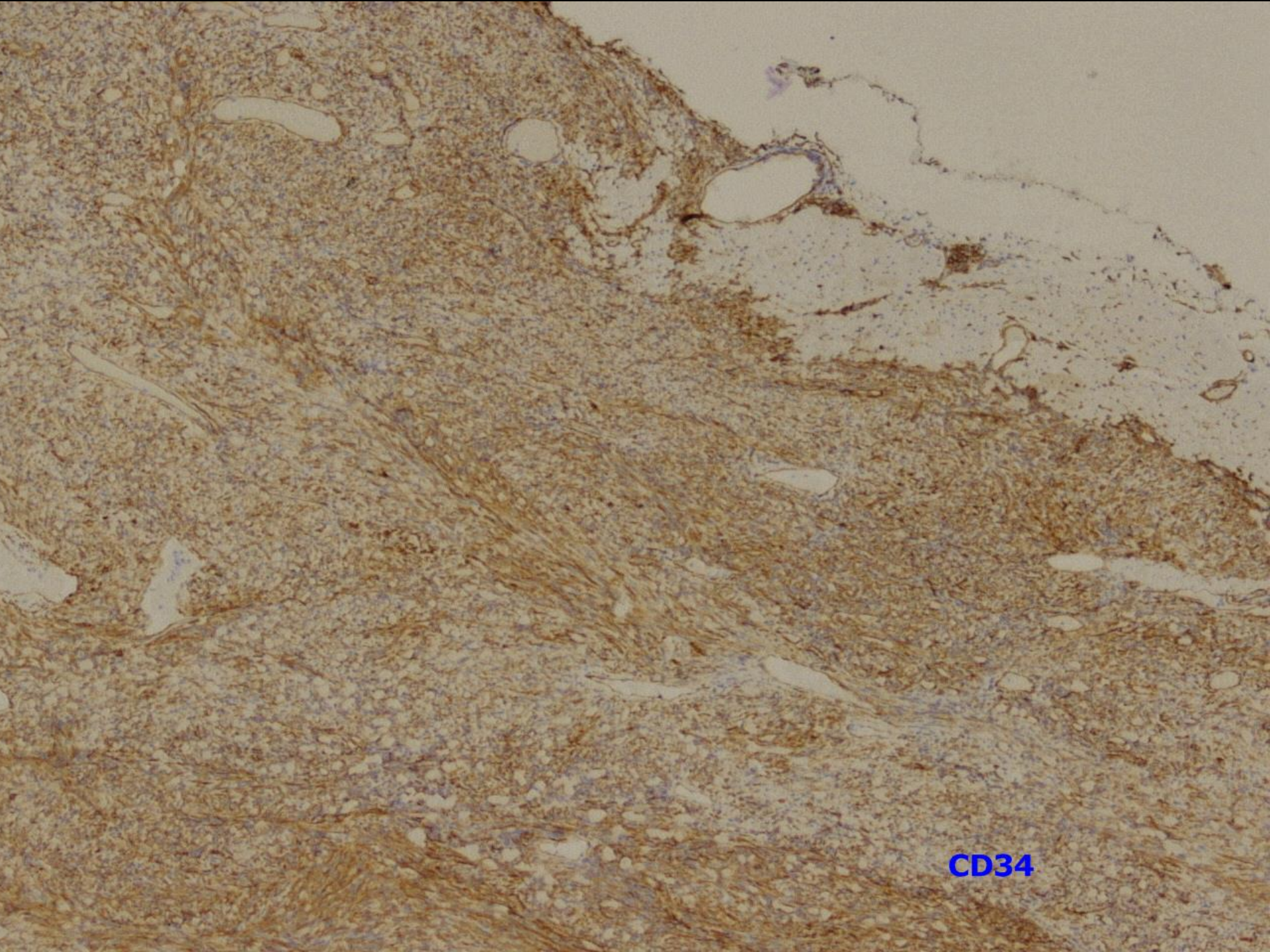


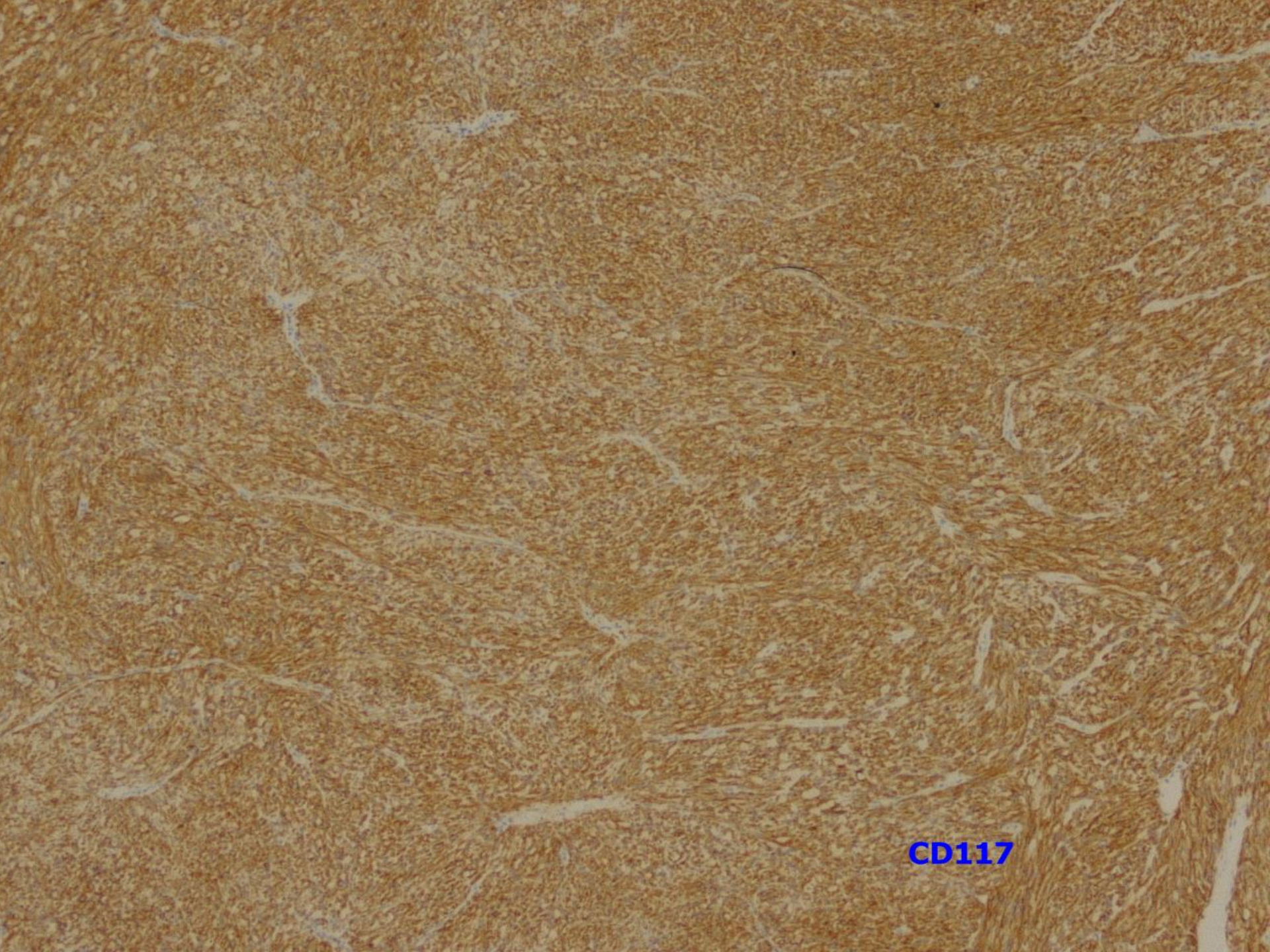


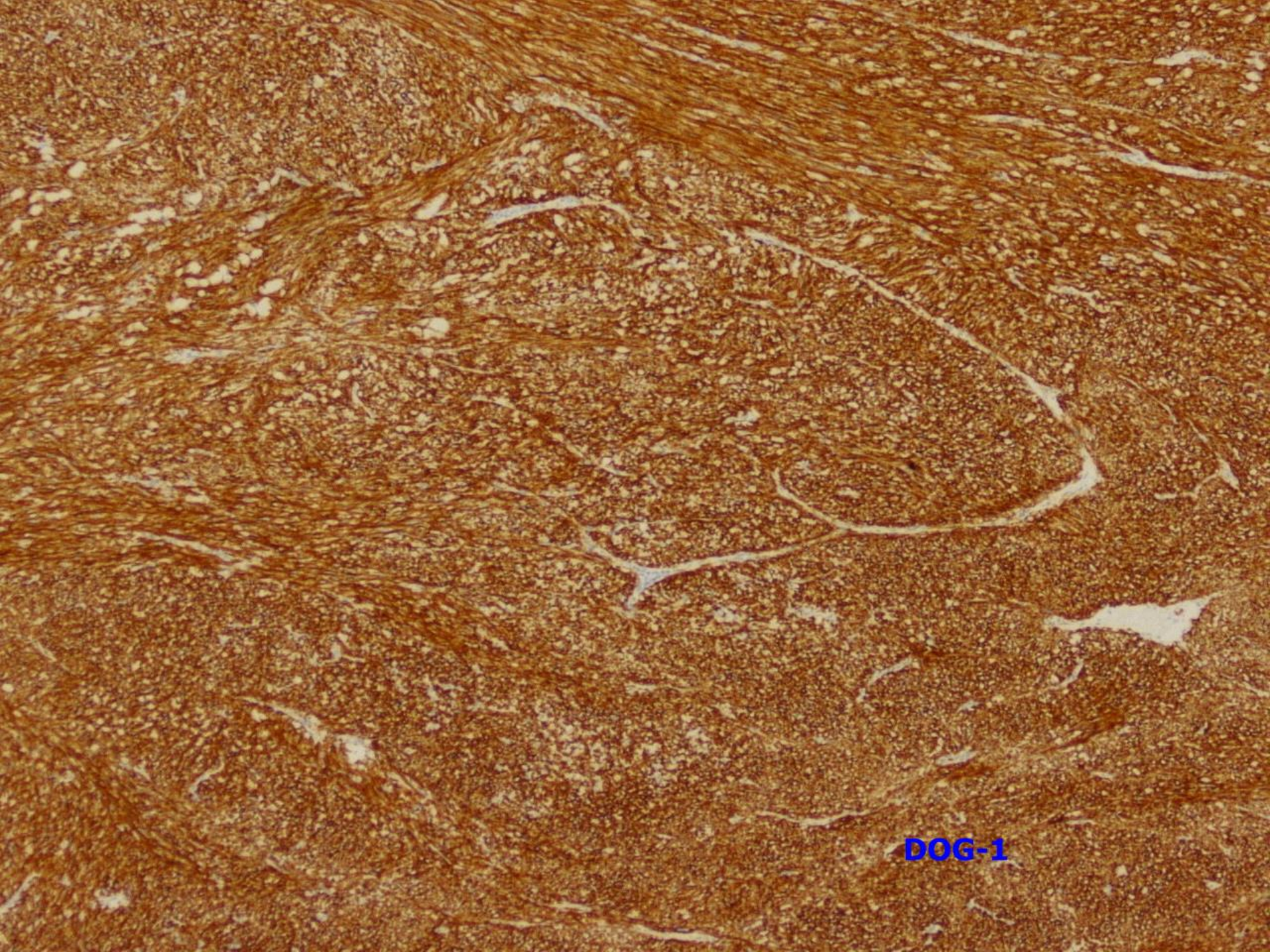


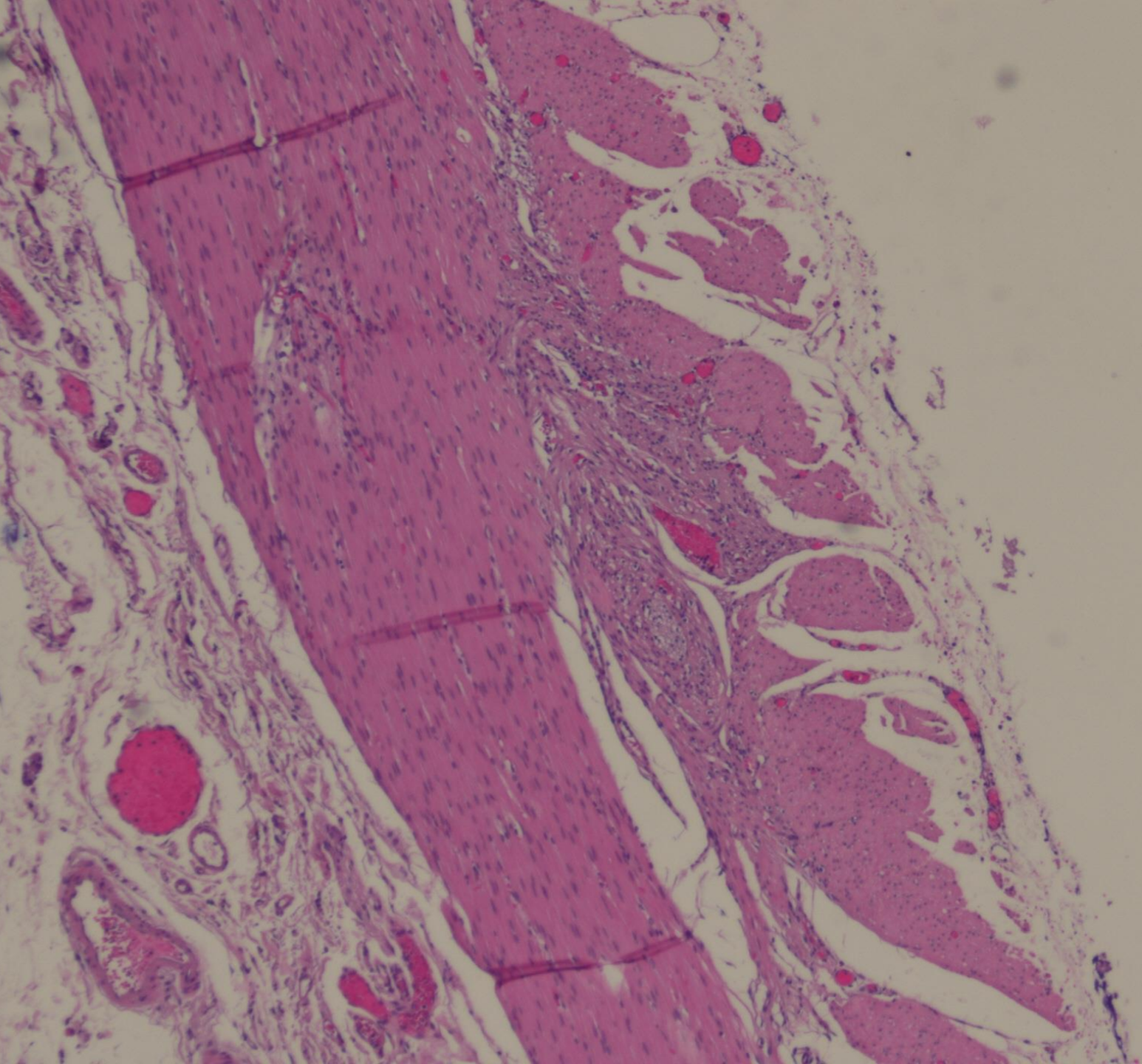

S-100

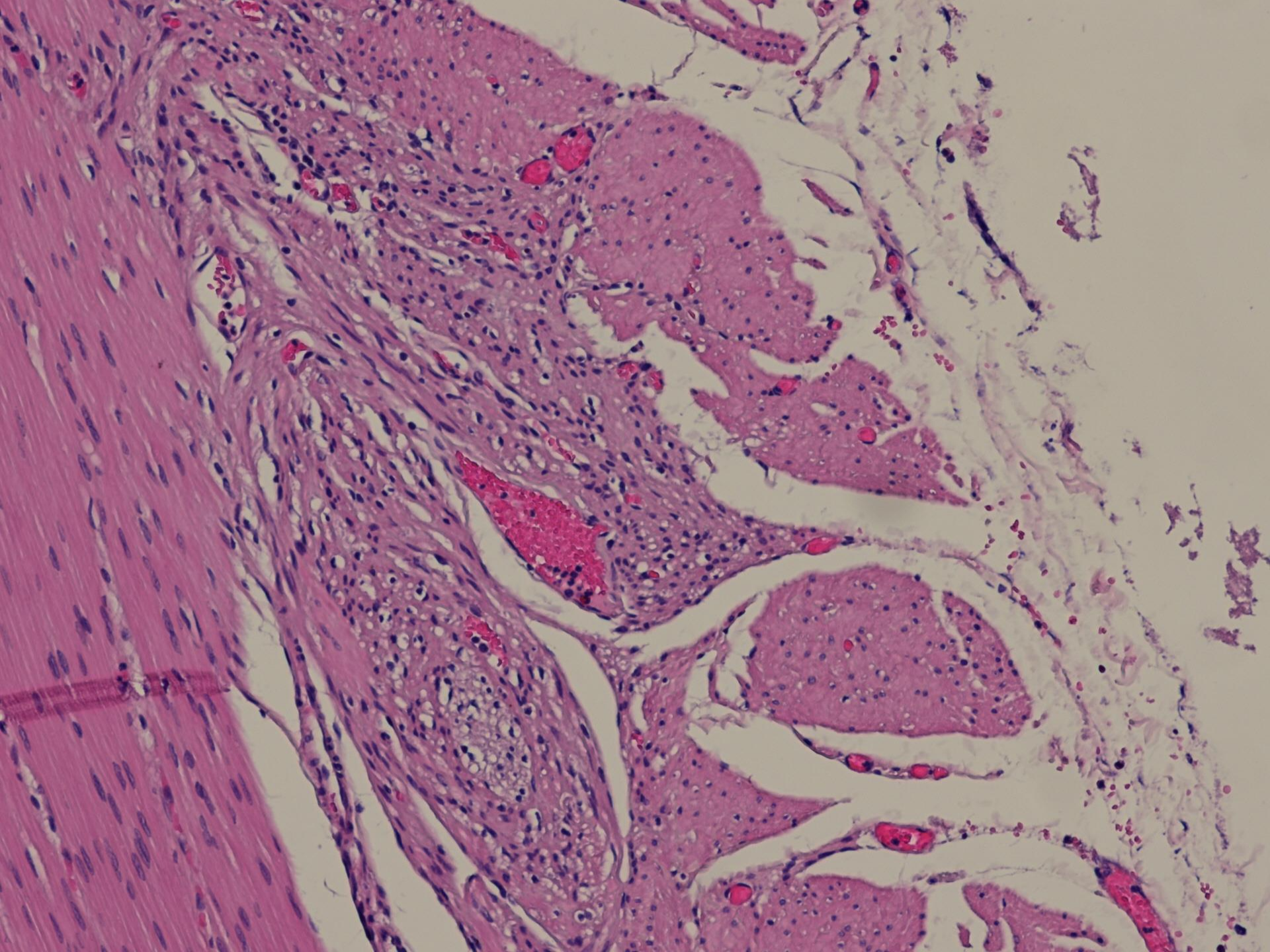

actin

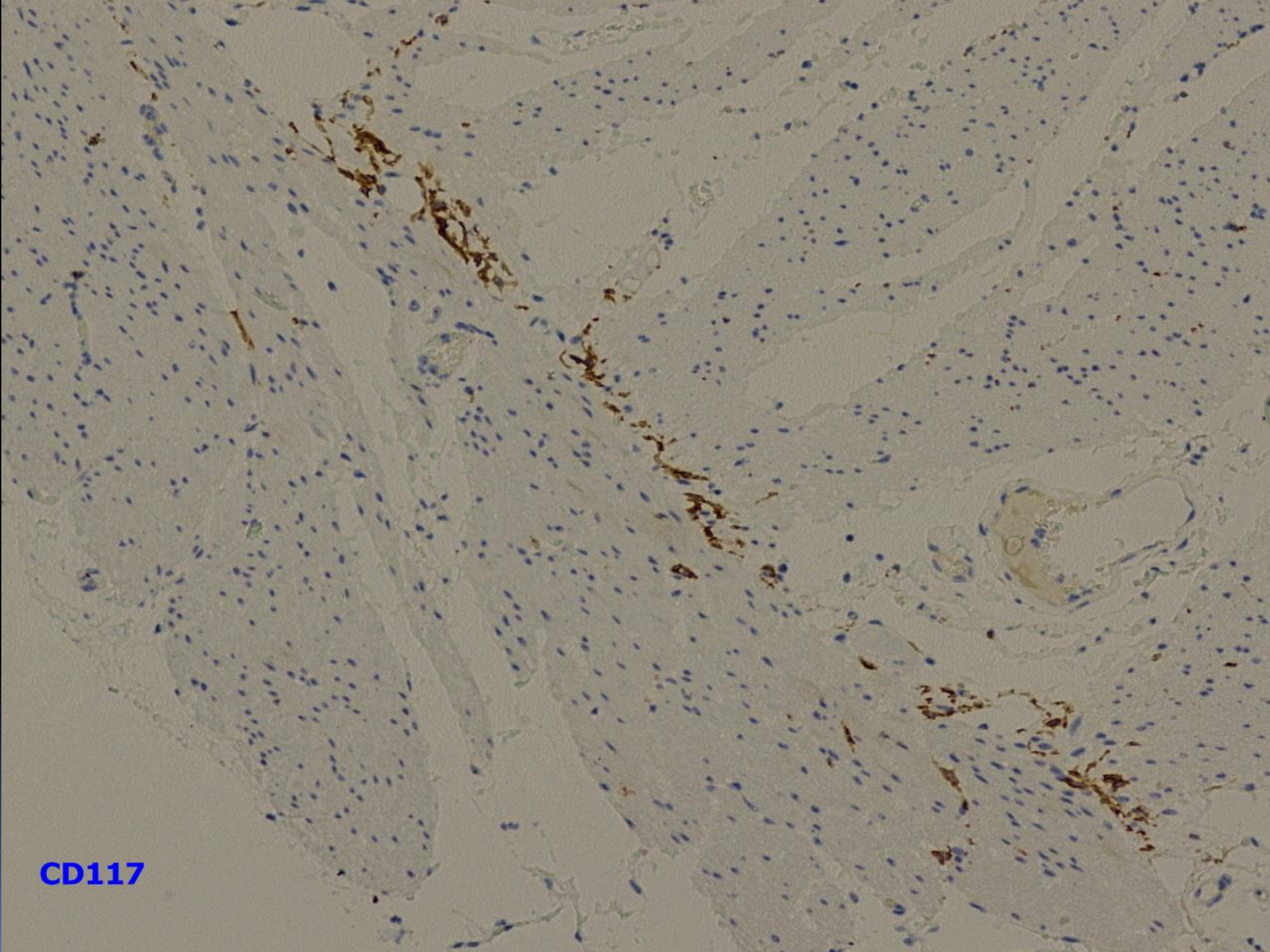

CD34

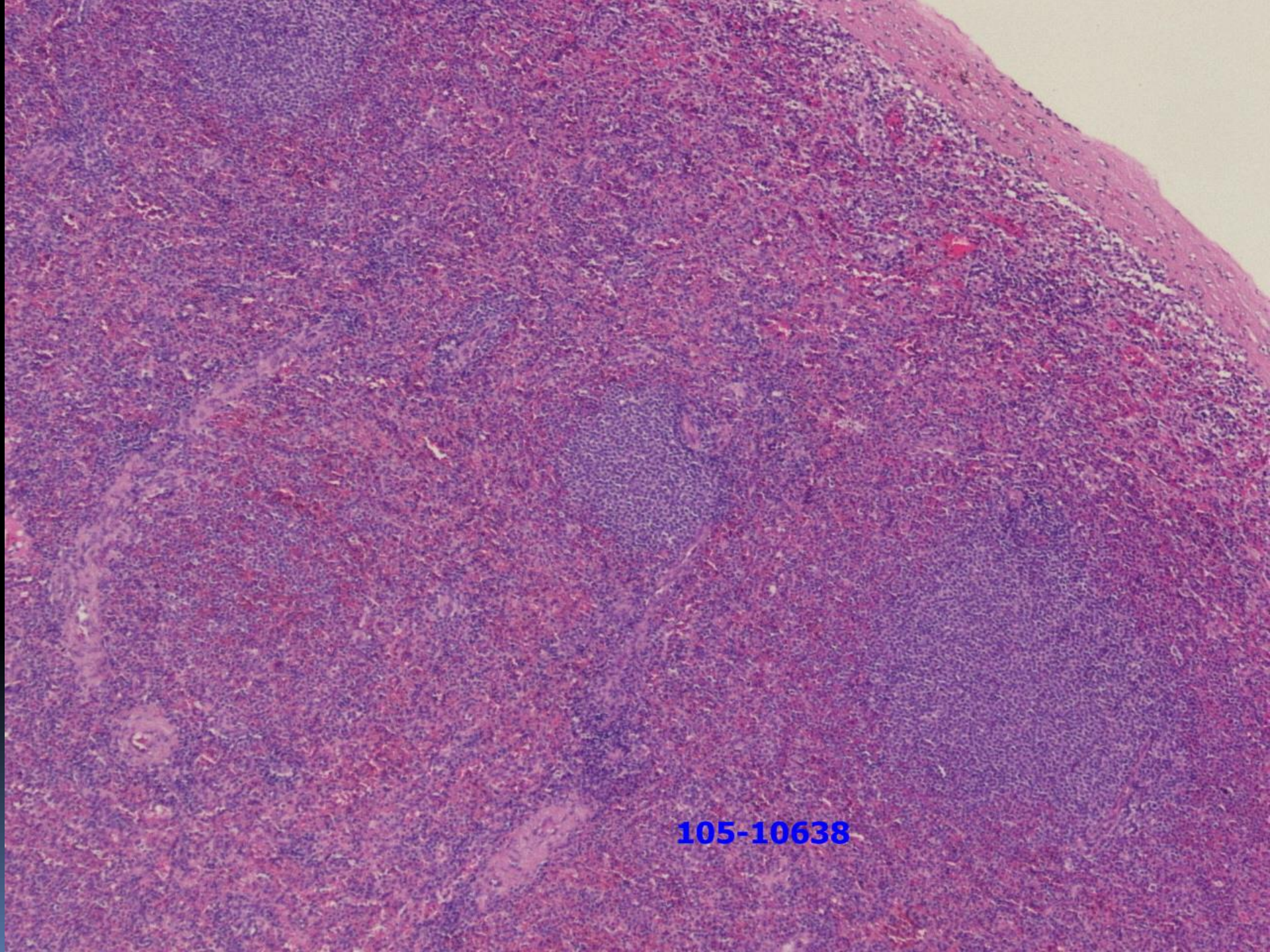

CD117


DOG-1






CD117


105-10638

Gastrointestinal stromal tumors in patients with neurofibromatosis 1

105-10639

Table 1. Guidelines for Risk Assessment of Primary Gastrointestinal Stromal Tumor (GIST)

Tumor Parameters		Risk of Progressive Disease# (%)			
Mitotic Rate	*Size*	*Gastric*	*Duodenum*	*Jejunum/Ileum*	*Rectum*
≤5 per 50 high-power fields (HPF)	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2 - ≤5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	>5 - ≤10 cm	Low (3.6%)	(Insufficient data)	Moderate (24%)	(Insufficient data)
	>10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
>5 per 50 HPF	≤2 cm	None##	(Insufficient data)	High##	High (54%)
	>2 - ≤5 cm	Moderate (16%)	High (50%)	High (73%)	High (52%)
	>5 - ≤10 cm	High (55%)	(Insufficient data)	High (85%)	(Insufficient data)
	>10 cm	High (86%)	High (86%)	High (90%)	High (71%)

Defined as metastasis or tumor-related death.
Denotes small number of cases.

Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs from the pre-imatinib era.[4-6,8]

- Gastrointestinal stromal tumors (GISTs), most commonly occur sporadically, but there seems to be some increased tendency for these tumors to develop in patients with neurofibromatosis 1 (NF1).

Am J Surg Pathol. 2006 Jan;30(1):90-6

- 45 patients who had NF1 and GIST.
- 26 F: 19 M (female predominance)
- median age of 49 y/o (10 years lower than the median age of GIST patients in general)
- A great majority of tumors occurred in the jejunum or ileum, with multiple tumors occurring in 28 cases.
- 10 patients had a duodenal
  1 had a gastric GIST
- Sporadic GIST //stomach(60%), jejunum & ileum (30%), duodenum (5%), rectum (<5%), elsewhere (2%))

S/S

- The most common presentations were gastrointestinal bleeding and anemia, and many patients had intermittent bleeding over several years

Micro

- The majority of the tumors were small (0.4-29 cm, median, 4 cm) and mitotically inactive; only 7 had mitotic activity >5/50 HPFs and 15 tumors were >5 cm

- Associated Cajal cell hyperplasia was common (10 cases: definite; 11 possible)

- The occurrence of multiple GISTs is notably common in NF1 pts, and it is very uncommon among pts with sporadic GISTs.
- It is important to distinguish NF1 pts with multiple GISTs from sporadic GIST pts with multiple metastatic nodules or familial GIST syndrome with innumerable and sometimes diffuse GISTs

Pathogenesis

- The pathogenesis of GISTs in NF1 is unclear.
- Its seems logical to assume that inactivation of the NF1 tumor suppressor pathway may play an alternative role in GIST pathogenesis

Molecular Genetics

- GISTs are specific KIT- or PDGFRA-signaling driven mesenchymal tumors
- All 16 tumors analyzed showed wild-type KIT exon 9, 11, 13, and 17 sequences, and PDGFRA exon 12 and 18 sequences (sporadic GISTs have a high frequency of such activating mutations)

- 21 GISTs in 7 NF1 patients found no KIT mutations
- 1/3 patients had KIT exon 11 point mutation
- Occasional KIT and PDGFRA mutations in NF1 GISTs

  →Random molecular events

- Lack of GIST –specific mutations suggests that the pathogenesis of GISTs in NF1 pats is different from that of KIT or PDGFRA-driven GISTs
- One possibility is that activation of the RAS pathway responsible for neurofibroma formation in NF1 also causes Cajal cell proliferation, ultimately leading to a GIST

Diagnosis:

Presence of nonsynonymous single-nucleotide polymorphism in exon 10 of PDGFRA.

Description:

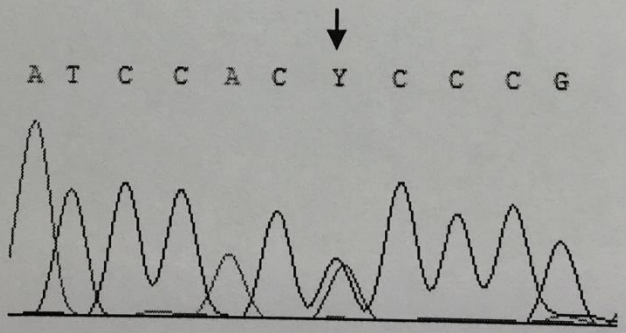
The tumor DNA, extracted from paraffin block section (105-10639E), was subjected to PCR amplification for the exons 9, 11, 13, and 17 of the c-kit gene and the exons 10, 12, 14, and 18 of the PDGFRA gene. These amplicons were then sequenced. The result shows p.Ser478Pro (c.1432T>C) in PDGFRA exon 10.

Note: This result is derived from a laboratory developed test. Therefore, the performance characteristics remains to be determined.

Tumor percentage:. not provided.

Analytic sensitivity: 25%

Reference mRNA sequence: KIT NM_000222.2, PDGFRA NM_006206.4



PDGFRA exon10

F/U

- 20 pts: alive and well after median f/u of 13.6 years
- 10 pts: died of unrelated causes (2 of them of other tumors known to be associated with NF1 (MPNST and unbiopsied brain tumor))
- 2 pts: alive the tumor status could not be ascertained
- 2 pts: died of peri-op or post-op complications

F/U

- 5 pts developed metastatic disease and died of tumor; all of these had a tumor >5 cm, mitotic rate >5/50 HPFs, or both; three of these tumors were located in the duodenum.
- 4 pts: dead of unknown cause
- 2 pts: lost of follow-up
- The presence of multiple small tumors was not associated with progressive disease

Summary

- Female
- Younger age
- Small intestine
- Often multiple
- Do not have KIT or PDGFRA mutations
- Favorable clinical behavior

rare in the duodenum (5%), rectum (3%), colon (1–2%), and esophagus (<1%). In some cases, they present as disseminated tumors without a known primary site, and a small number of GISTs may be primary in the omentum or mesenteries.

Regional Lymph Nodes. Nodal metastasis is very rare and virtually unheard of in GIST, especially if one adheres to its rigorous histologic verification. Surgeons generally agree that nodal dissection is not indicated for GIST. In the absence of information on regional lymph node status, N0/pN0 is appropriate; NX should not be used.

Metastastic Sites. Metastases include intra-abdominal soft tissue, liver, and distant metastases. Presence of any of these is designated M1. Distant metastases are relatively rare in GISTs, but they are increasingly detected with sophisticated radio-

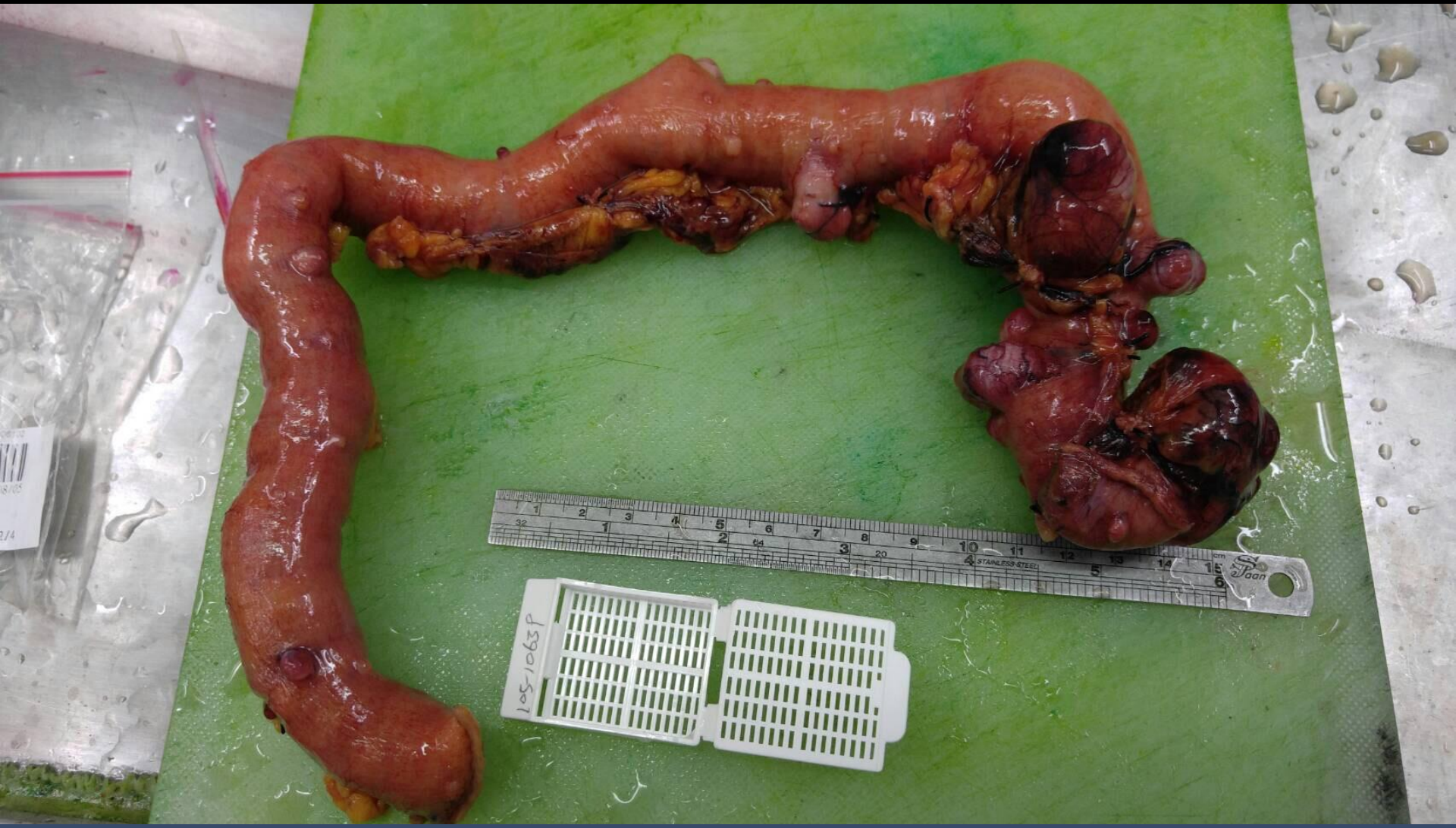

STAINLESS STEEL
Joan
105-10635P

Table 1. Guidelines for Risk Assessment of Primary Gastrointestinal Stromal Tumor (GIST)

Tumor Parameters		Risk of Progressive Disease# (%)			
Mitotic Rate	*Size*	*Gastric*	*Duodenum*	*Jejunum/Ileum*	*Rectum*
≤5 per 50 high-power fields (HPF)	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2 - ≤5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	>5 - ≤10 cm	Low (3.6%)	(Insufficient data)	Moderate (24%)	(Insufficient data)
	>10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
>5 per 50 HPF	≤2 cm	None##	(Insufficient data)	High##	High (54%)
	>2 - ≤5 cm	Moderate (16%)	High (50%)	High (73%)	High (52%)
	>5 - ≤10 cm	High (55%)	(Insufficient data)	High (85%)	(Insufficient data)
	>10 cm	High (86%)	High (86%)	High (90%)	High (71%)

Defined as metastasis or tumor-related death.
Denotes small number of cases.

Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs from the pre-imatinib era.[4-6,8]

- Most patients with long-term follow-up enjoyed a good prognosis; 2 died of other NF1-associated tumors (malignant peripheral nerve sheath tumors, brain tumor).
- None of the 16 tumors from 15 patients had a KIT exon 9, 11, 13, or 17 or PDGFRA exon 12 or 18 mutation as is typically seen in sporadic GISTs, indicating that GISTs in NF1 patients have a different pathogenesis than sporadic GISTs.