

Deęişen Bronkioloalveoler Karsinom Kavramı

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Adenokarsinom WHO 2004

- Asiner tip
- Papiller tip
- Bronkioloalveoler tip
 - Nonmüsinöz
 - Müsinöz
 - Mikst
- Müsin üreten solid tip
- Varyantlar
 - Fötal adenokarsinom
 - Müsinöz (kolloidal) karsinom
 - Müsinöz kistadenokarsinom
 - Taşlı yüzük hücreli karsinom
 - Berrak hücreli adenokarsinom

Moleküler biyolojinin ve teknolojinin geliřimi

BAK ve EGFR üzerindeki alıřmalar

Subtiplerin önem kazanmasına

- Tirozinkinaz inhibitörleri adenokarsinomda etkili
- En etkili alt tipin ise **bronkioloalveoler karsinom (BAK)**

Kaira K, Naito T, Takahashi T, et al. Pooled analysis of the reports of erlotinib after failure of gefitinib for non-small cell lung cancer. Lung Cancer 2010; 68(1):99-104

Wislez M, Antoine M, Pradere M, et al. Non-mucinous and mucinous subtypes of adenocarcinoma with bronchioloalveolar carcinoma features differ by biomarker expression and in the response to gefitinib. Lung Cancer 2009 ;68 (2):185-191.

- 62 BAK vakasını müsinöz-nonmüsinöz olarak gruplamış
- Tüm demografik dataların incelenmesinde, klinik ve evre ile tedavi cevabının ilişkili olmadığı, sadece **müsinöz tipin** önemli olduğu görülmüş
- Müsinöz tipte TKİ cevabı **saptanmamış**
- Müsinöz tip tümörlerde **EGFR mutasyonu daha nadir**

- Müsinöz tip BAK nonmüsinöze göre daha kısa yaşam süresi ile ortaya çıkmakta
- SWOG SO126 ve IFCT0401 faz II çalışması ile gösterilmiş

Nonmüsinöz tip daha çok solid nodül, müsinöz tip pnömonik infiltrasyon ile karakterize

- Hirsch FR, Varella-Garcia M, McCoy J, et al. Increased epidermal growth factor receptor gene copy number detected by fluorescence in situ hybridization associates with increased sensitivity to gefitinib in patients with bronchioloalveolar carcinoma subtypes: a Southwest Oncology Group Study. J Clin Oncol. 2005;23(28):6838-45.
- Cadranel J, Quoix E, Debove P, et al. IFCT0401 trial: phase II study of gefitinib administered as first line treatment in non resectable adenocarcinoma with bronchioloalveolar carcinoma features (ADC-BAC): final results on efficacy and survival. Proceedings of the ASCO annual meeting. Part I. J Clin Oncol 2007;25.
- Wislez M, Antoine M, Poulot V, et al. IFCT0401- bio phase trial: gefitinib administrated as 1 st line in non resectable adenocarcinoma with bronchioloalveolar carcinoma features (ADC-BAC) predictive biomarkers of efficacy and survival. Proceedings of the ASCO annual meeting proceedings, Part I. J Clin Oncol 2008:26.

- Son yıllarda yapılan çalışmalar müsinöz ve nonmüsinöz tipin farklı tümörler olduğunu düşündürmekte

- Wislez M, Antoine M, Poulot V, et al. IFCT0401- bio phase trial: gefitinib administrated as 1st line in non resectable adenocarcinoma with bronchioloalveolar carcinoma features (ADC-BAC) predictive biomarkers of efficacy and survival. Proceedings of the ASCO annual meeting proceedings, Part I. J Clin Oncol 2008:26.
- Yousem SA, Beasley MB. Bronchioloalveolar Carcinoma: A Review of Current Concepts and Evolving Issues. Arch of Path and Lab Med 2007; 131(7): 1027-1032.

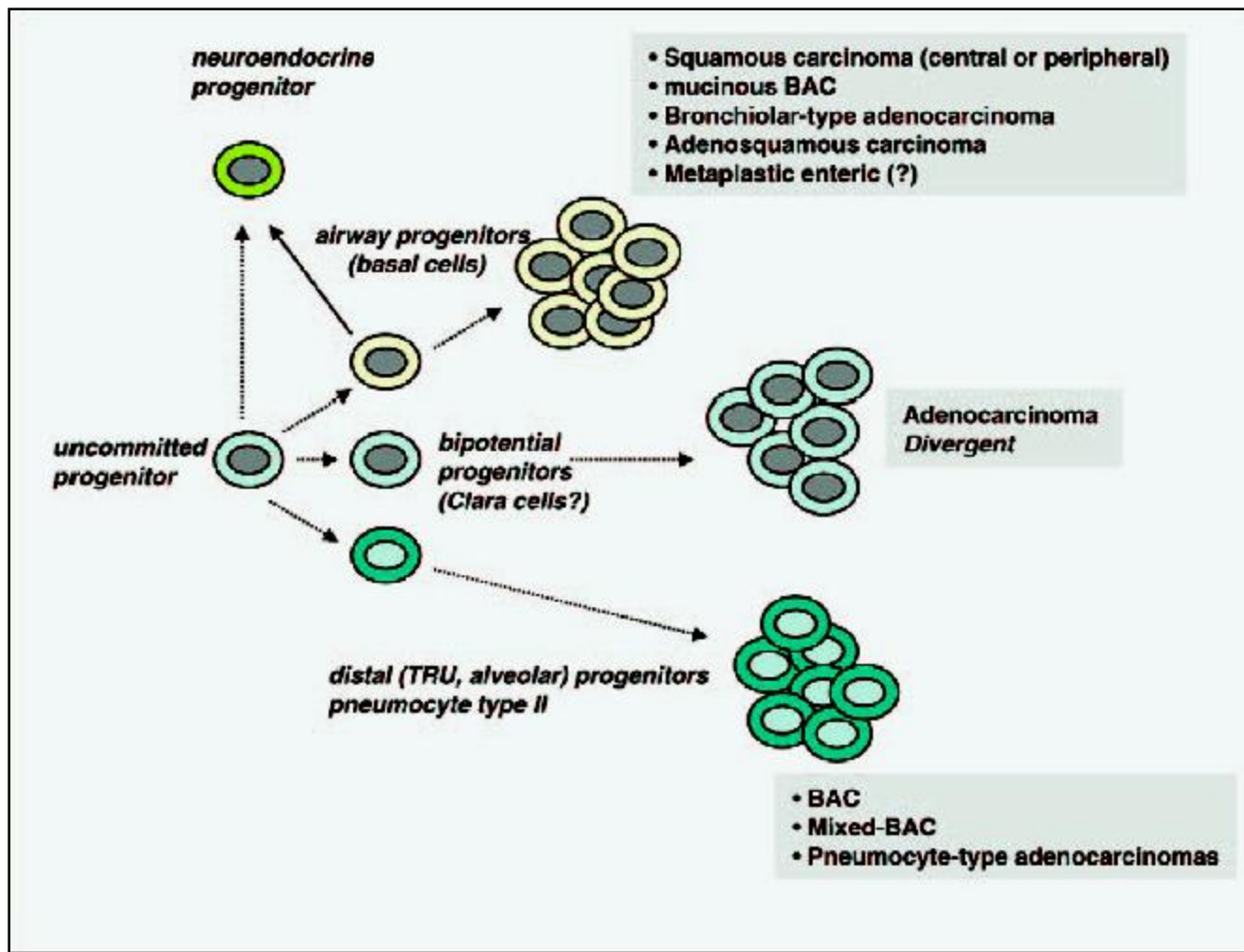
Adenokarsinomlar arasında

Papiller	(%37)
Asiner	(%30)
Solid	(%25)
Bronkioloalveoler	(%7)
Pür BAK	yok

Inamura K, Ninomiya H, Ishikawa Y, et al. Is the Epidermal Growth Factor Receptor Status in Lung Cancers Reflected in Clinicopathologic Features? Arch of Path and Lab Med 2010; 134 (1): 66-72.

- Genotip-fenotip bağlantısı araştırılmış
- Bronkioloalveoler component,
- Mikropapiller pattern
- Hobnail tip
- EGFR mutasyonları **daha sık**

- Papiller tipte exon 19
 - Non müsinöz BAK exon 20
 - Adenokarsinom k-ras
 - Solid tipte mutasyon yok
-
- YENİ BİR MODEL



Chilosi et al 2010

Neden yeni bir sınıflandırma ??

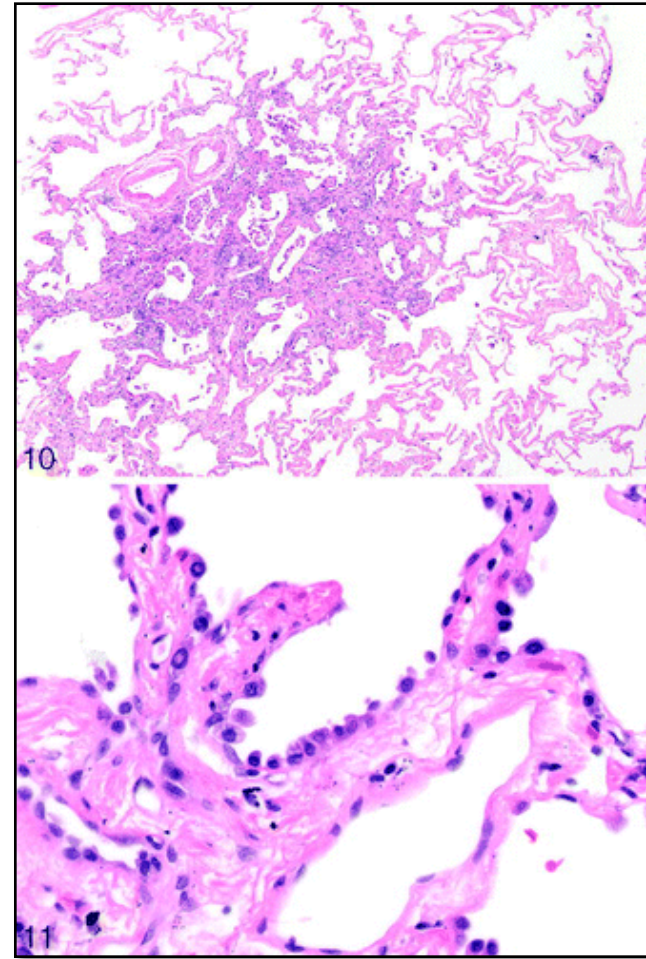
- Adenokarsinom artıyor
- Sigara içen ve içmeyenlerde; farklı klinik, morfolojik ve moleküler özellikler
- Erken yakalanan vakalar artıyor, VATS!
- Tedavi seçenekleri farklılaştı-EGFR
- İnsitu ve erken invazif karsinom kavramları tartışılmaya başlandı
- Mikst adenokarsinom subjektif ve anlamsız hale geldi

Adenokarsinomda önerilen yeni sınıflama IASLC/ATS/ERS 2010

Preinvazif lezyonlar	İnvazif tümörler	Varyantlar
<p>*Atipik adenomatöz hiperplazi</p> <p>*İnsitu adenoka (eski BAK) müsinöz nonmüsinöz</p> <p>Minimal invazif Adenoka</p> <p>•5 mm>lepidik •%10 > invazyon</p>	<p>Lepidik baskın (nonmüsinöz BAK)</p> <p>Asiner</p> <p>Papiller</p> <p>Mikropapiller baskın</p> <p>Solid baskın</p>	<p>Lepidik paternli müsinöz adenoka (Müsinöz BAK)</p> <p>Müsinöz kistadenokarsinom</p> <p>Kolloidal adenokarsinom</p> <p>Fötal adenokarsinom (Düşük-yüksek derece)</p> <p>Enterik adenokarsinom</p>

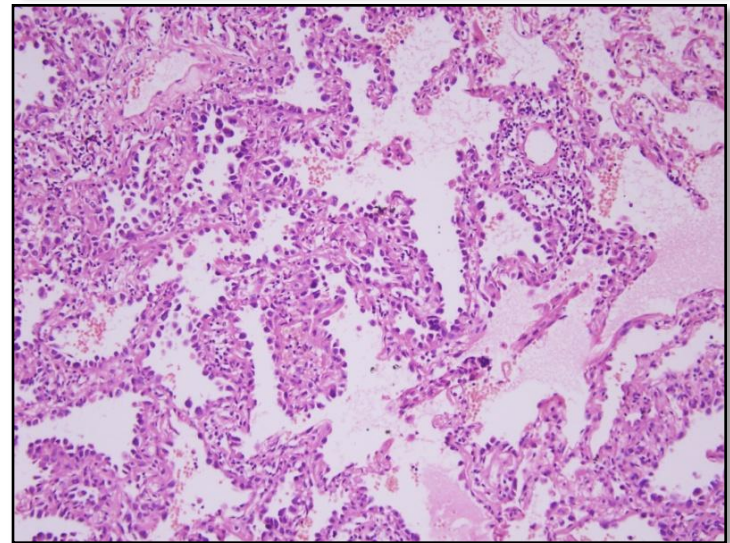
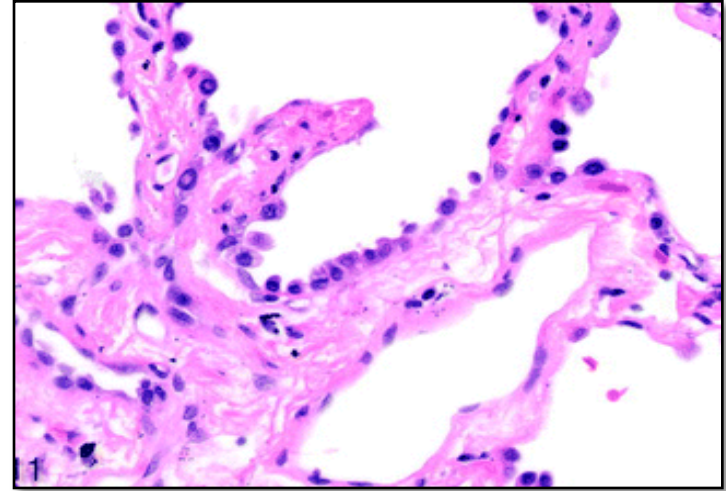
Atipik adenomatöz hiperplazi-AAH (1)

- Lokalize
- Küçük (Genellikle 0,5 cm den küçük)
- Hafif-orta atipik Tip II pnömosit ve/veya Klara hücre proliferasyonu
- Hücreler alveolleri veya bronşioelleri döşeyecek
- Hücreler arası boşluklar (gap) var
- Yuvarlak, kübik, alçak silendrik, kabara çivisi (peg) biçimli hücreler
- Sık intranükleer inklüzyonlar



Atipik adenomatöz hiperplazi (2)

- AAH ve AIS geçişebilir
- Düşük-yüksek dereceli AAH önerilmemiş
- Hücreler daha sık sıralanmış
- Hiperselülarite, üst üste binme
- Kaba kromatin, belirgin nukleolus
- Gerçek papilla, çit şeklinde dizilim
- Tümör hücre yüksekliğinde artış ve çevreye uzanım
- 1-2 özellik AAH
- 3 den fazla BAK *Minami 2009*
- **AAH 5 mm< BAK 10 mm>**



Adenokarsinoma in situ-AIS

Non müsinöz ve/veya Müsinöz

- Lokalize-küçük (3cm↓)
- Lepidik patern
- Stromal,vasküler, plevral invazyon yok
- Papiller,mikropapiller, intraalveoler tm hüç yok
- Non müsinöz/Tip II pnömosit veya Klara hüç.
Ayırım önerilmiyor!
- Müsinöz / Yüksek kolumnar,sitoplazmik müsin

Minimal invazif adenokarsinom-MIA

Non müsinöz ve/veya Müsinöz

- Küçük (3cm_↓) , soliter, lepidik, adenokarsinom
- Bir odakta 5mm_↓ invazyon
- Genellikle non müsinöz, bazan müsinöz
- Birden fazla tm varsa senkron olduğu kabul edilirse kullanılabilir!

Minimal invazif adenokarsinom-MIA

Non müsinöz ve/veya Müsinöz (2)

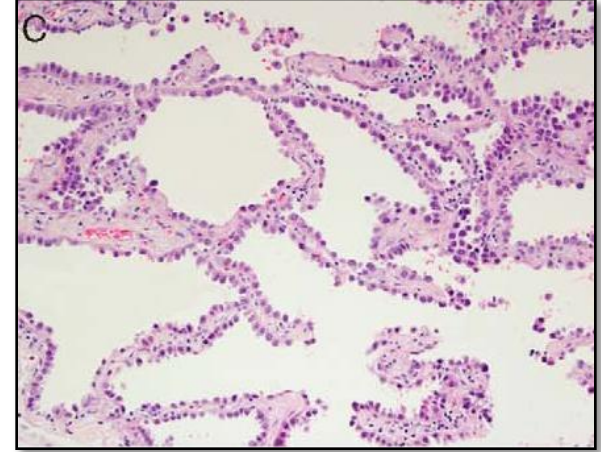
- İnvazif komponent

- Lepidik dışında- asiner, papiller, mikropapiller, solid
- İnvazyon miyofibroblastik stromada
- Lenfatik, vasküler, plevral invazyon yok
- Tümör nekrozu yok

- Multipl mikroinvazyon varsa en büyük invazif alanın büyük boyu ölçülecek
- 5mm↓ olacak
- Toplam alınmayacak!
- Ölçülemiyorsa nonlepidik invazif alanın tümör büyüklüğüne oranı hesaplanacak!

Lepidik predominant adenokarsinoma-LPA- (Nonmüsinöz BAK)

- Klara hücreleri ve tip II pnömosit kökenli
- Kübik-kolumnar, eozinofilik ya da berrak sitoplazmalı, vakuoler olabilir
- Tip II pnömosit diferansiyasyonunda eozinofilik intranükleer inklüzyonlar görülebilir
- Klara hücre diferansiyasyonunda apikal çıkıntılar ve PAS pozitif granüller görülebilir
- Tiplerin klinik ve prognostik önemi yok!

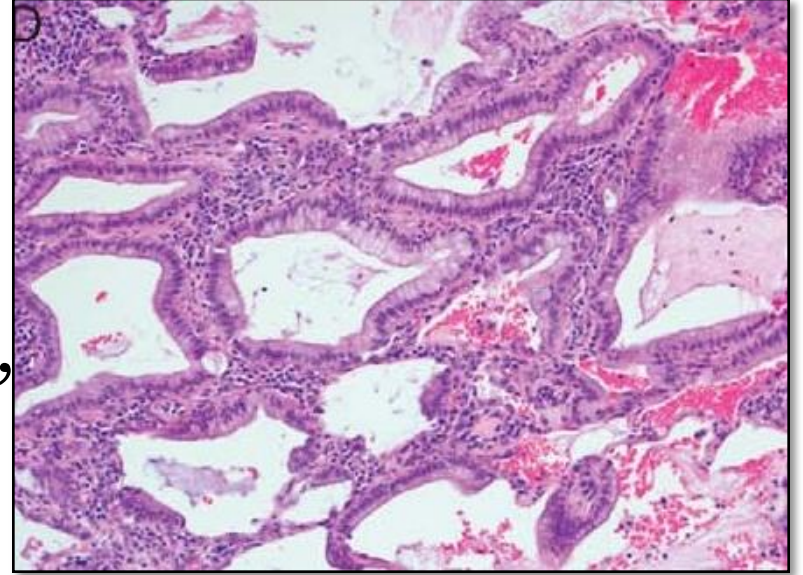


Lepidik predominant adenokarsinoma-LPA- (Nonmüsinöz BAK) (2)

- En az bir odakta 5mm[↑] invazyon
- Lenfatik, vasküler, plevral invazyon
- Nekroz var!
- LPA Lepidik baskın müsinöz invazif adenoca için kullanılmayacak!
- İHK konvansiyonel adeno Ca gibi; CK7 ve TTF-1 pozitif, CK20 negatif

Müsinöz BAK AIS veya MIA

- Yüksek silendrik hücreler, nukleuslar bazalde, bol apikal sitoplazmik müsin
- Alveoler septumlarda parsiyel tutulum var
- Stromal, vasküler, plevral invazyon yok-AIS
- İnvazyon 5mm ↓-MIA
- İHK CK7, CK 20 pozitif, TTF-1 negatif. Müsinöz akciğer karsinomlarında görülebilen cdx-2 negatif, % 20 müsin pozitif



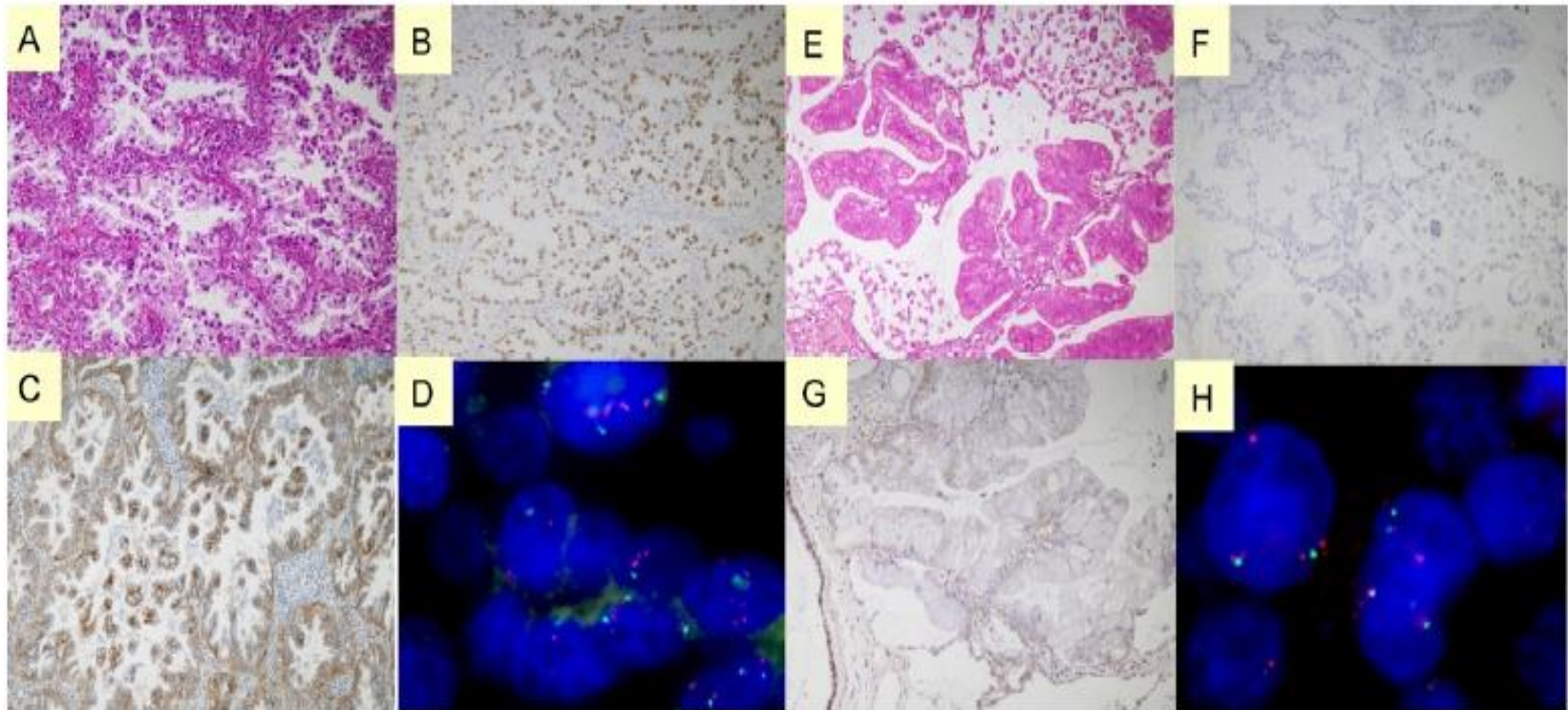
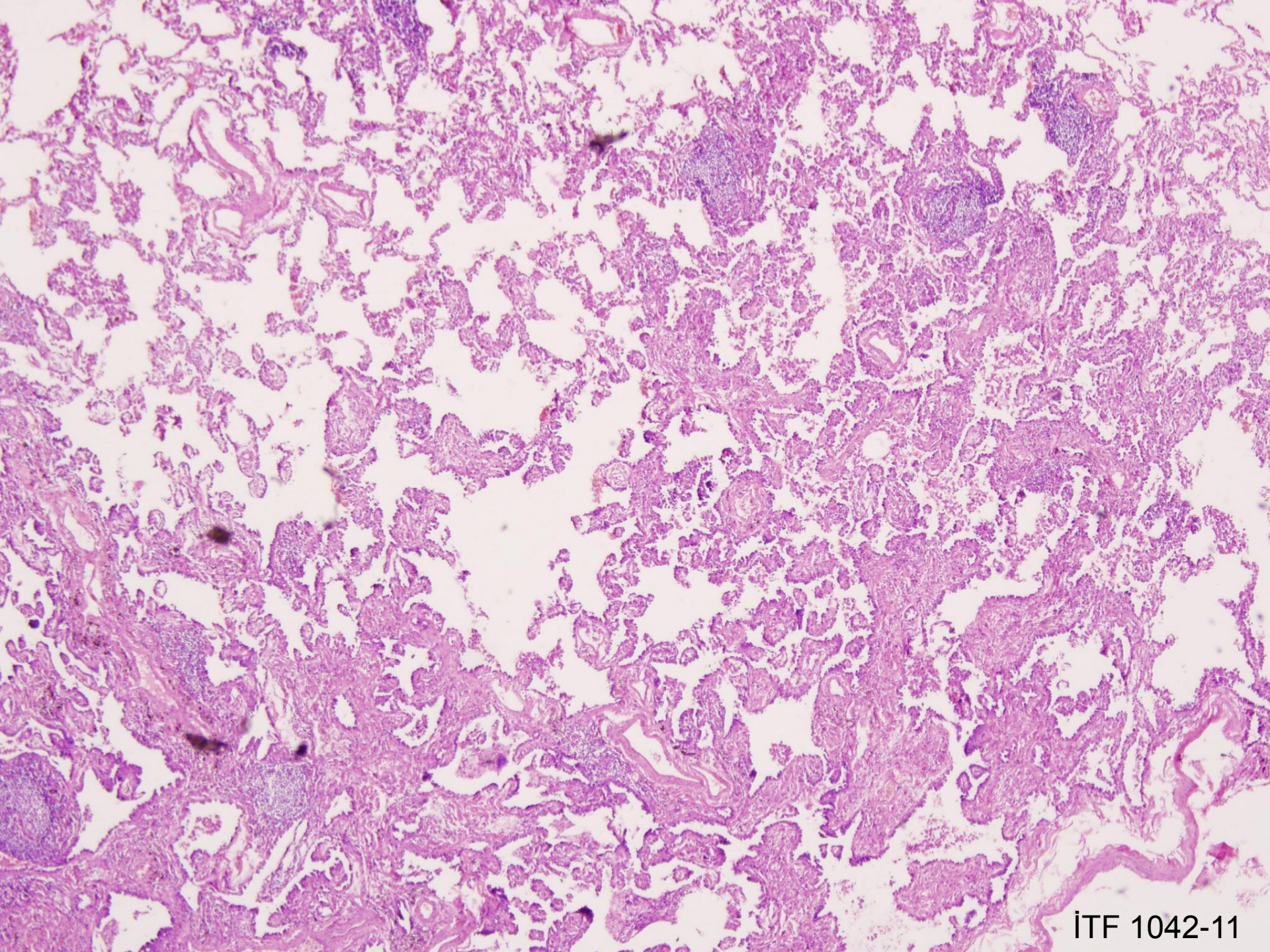


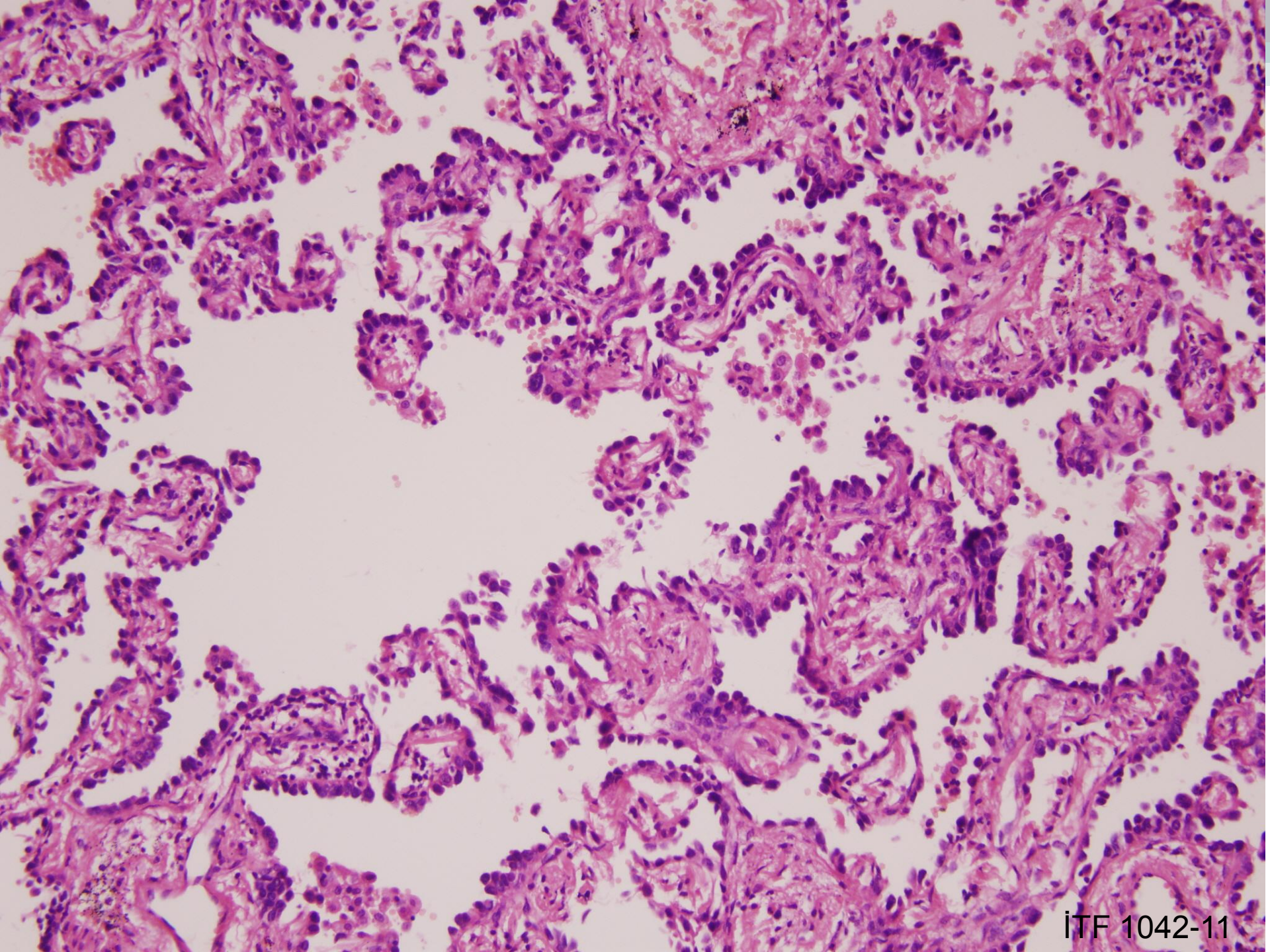
Fig. 1. TTF-1, EGFR expression and EGFR copy number in non-mucinous and mucinous subtype. As described in Section 2, ADC-BAC variants were classified into non-mucinous or mucinous cytological types on the basis of hematoxylin and eosin staining of slides (panel A and E, respectively). For non-mucinous (A-D) and mucinous (E-H) subtype, illustration of TTF-1 (B, positive score and F, negative score) and EGFR (C, score of 400 and G score of 60) expression assessed by immunohistochemistry and EGFR copy number (G, polysomy and H, disomy) by fluorescent in situ hybridization is shown.

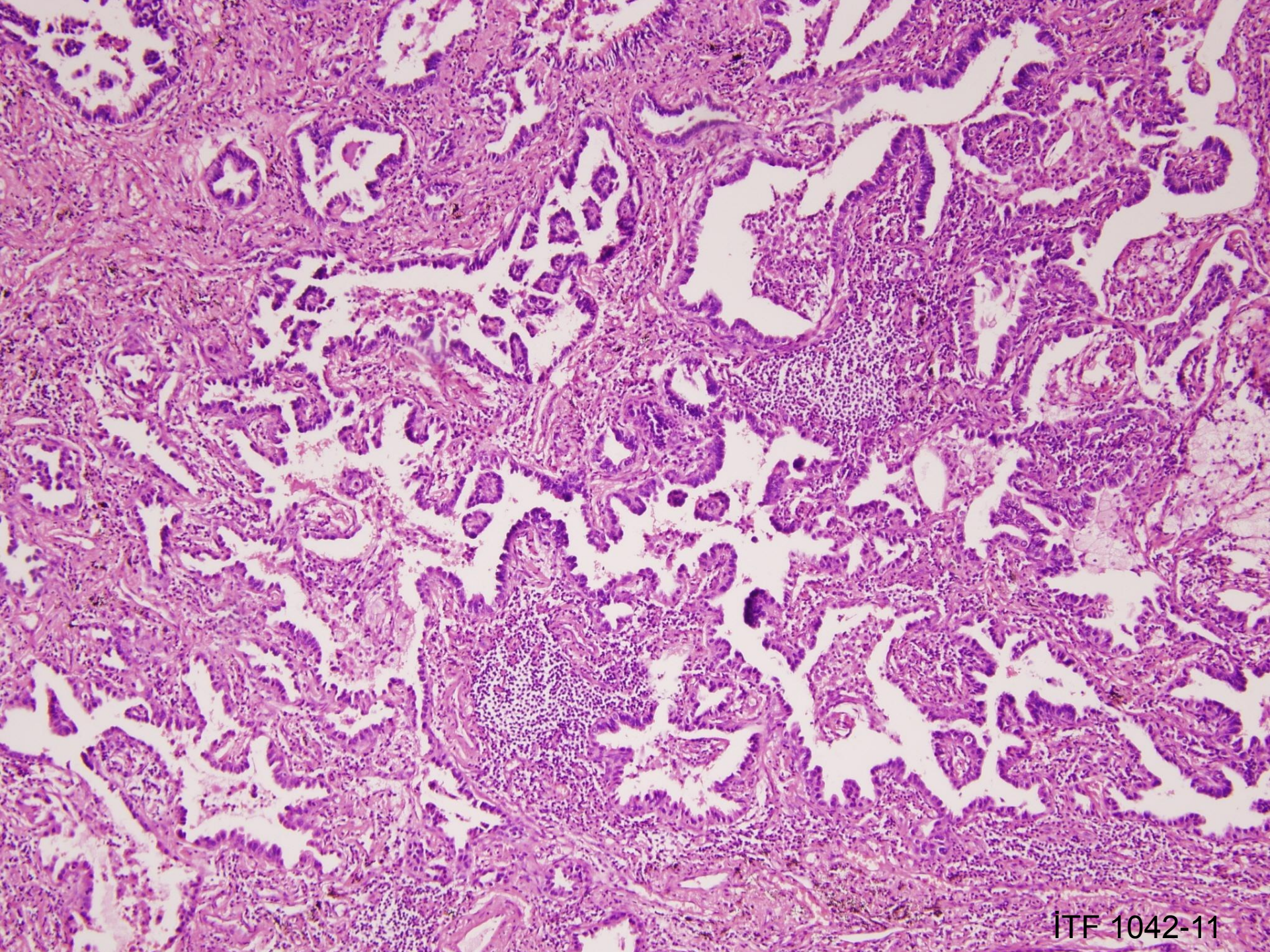
Non müsinöz
TTF-1 ve EGFR pozitif

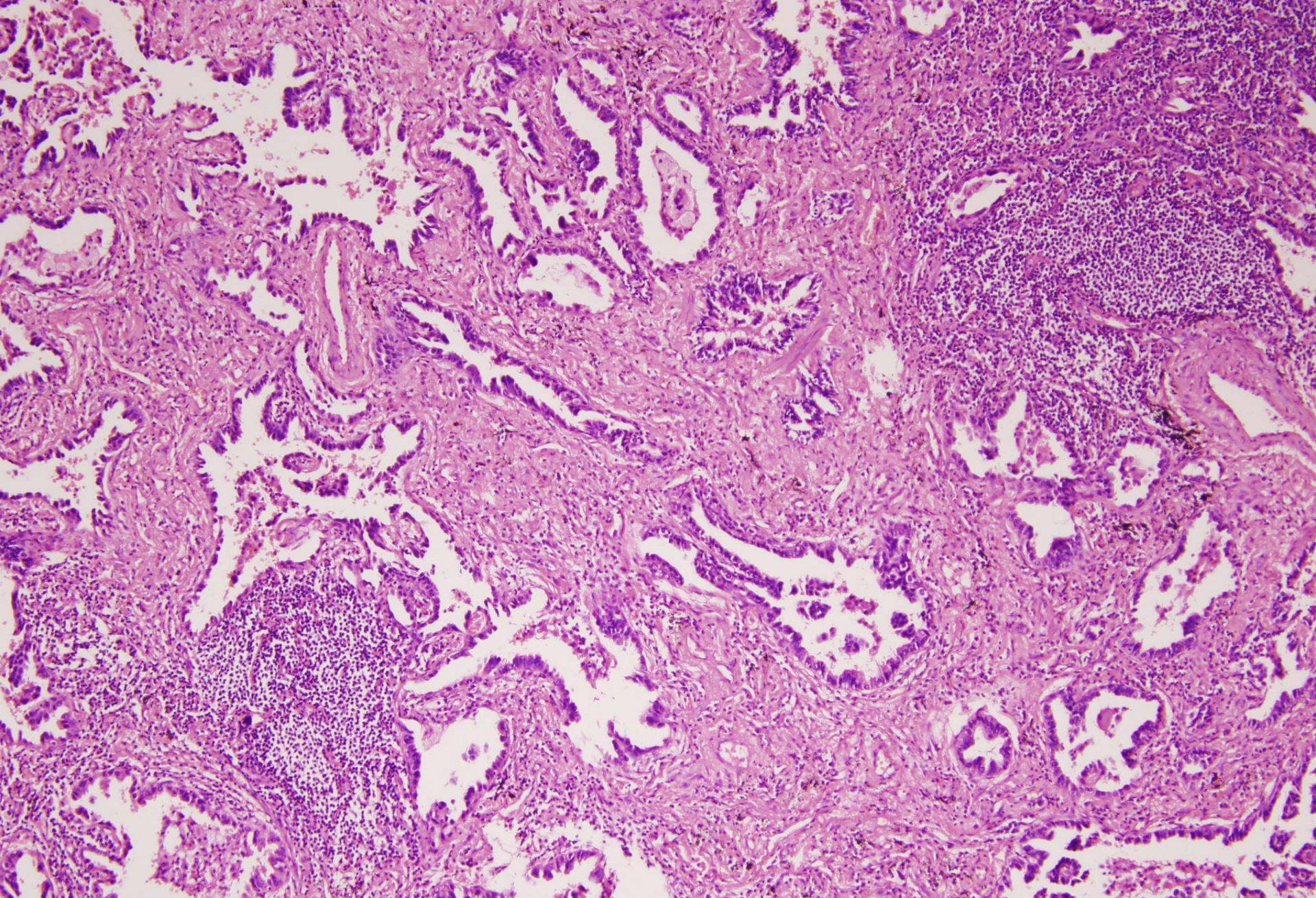
Müsinöz
TTF-1 ve EGFR negatif



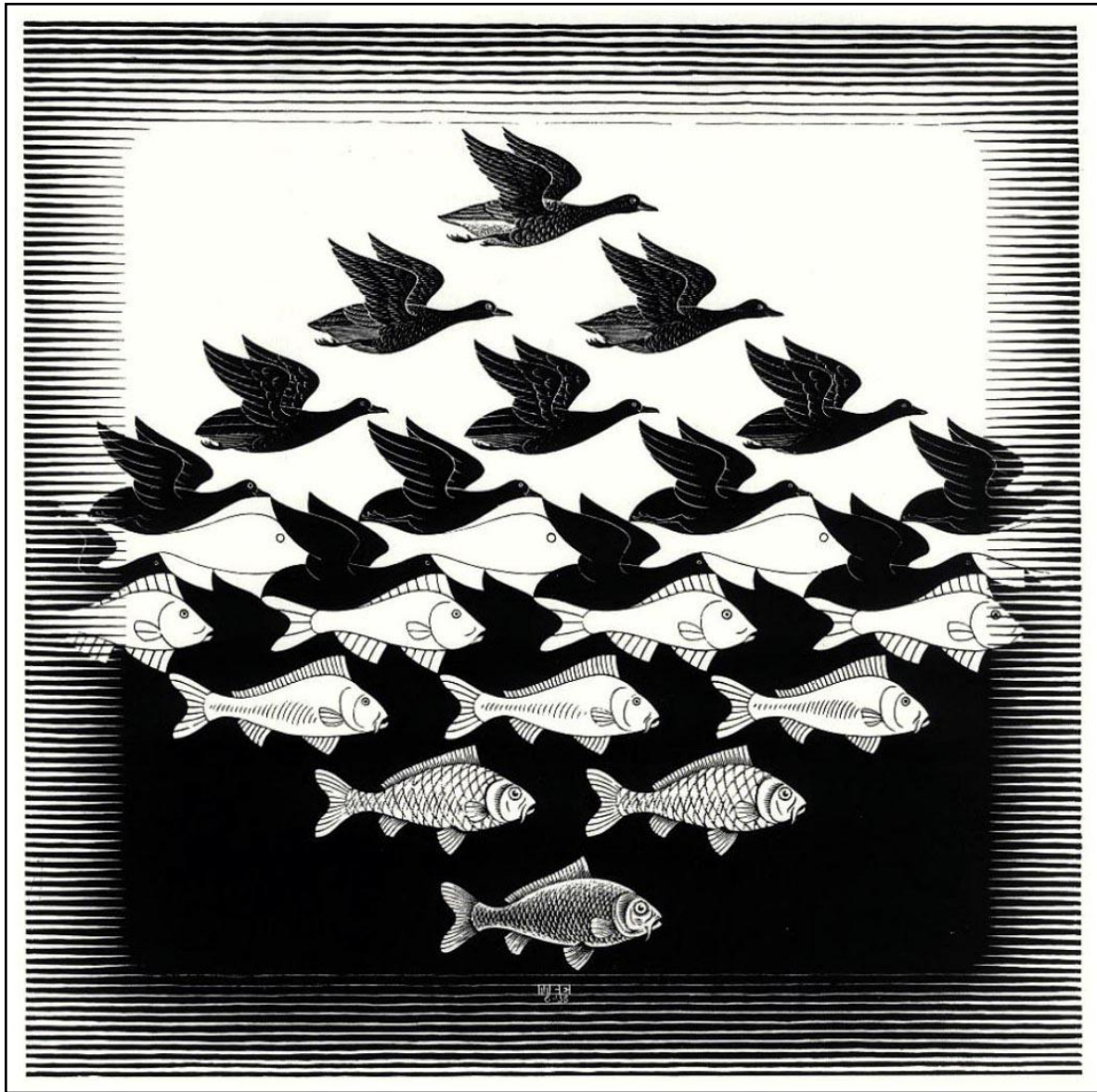
ITF 1042-11



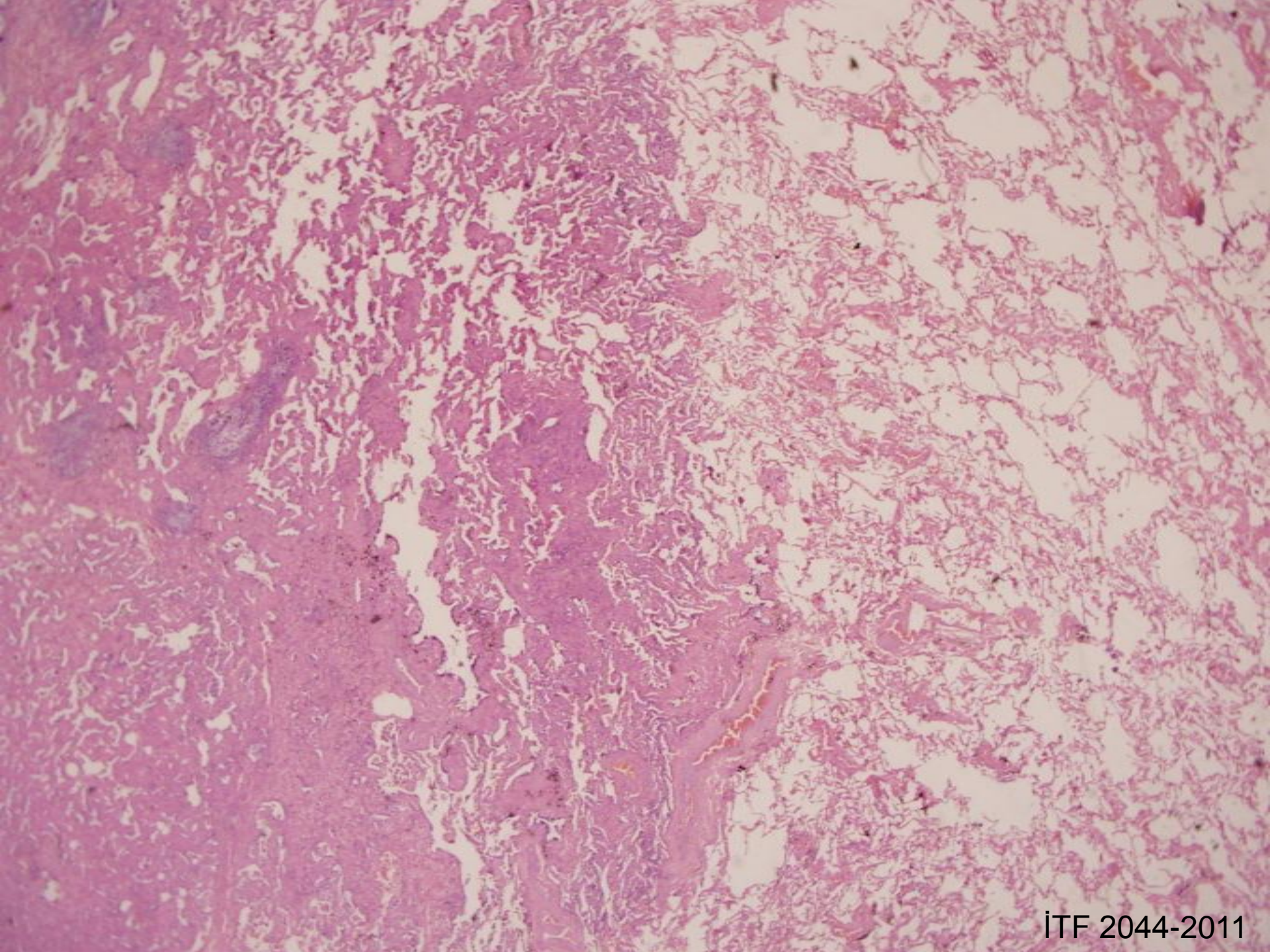


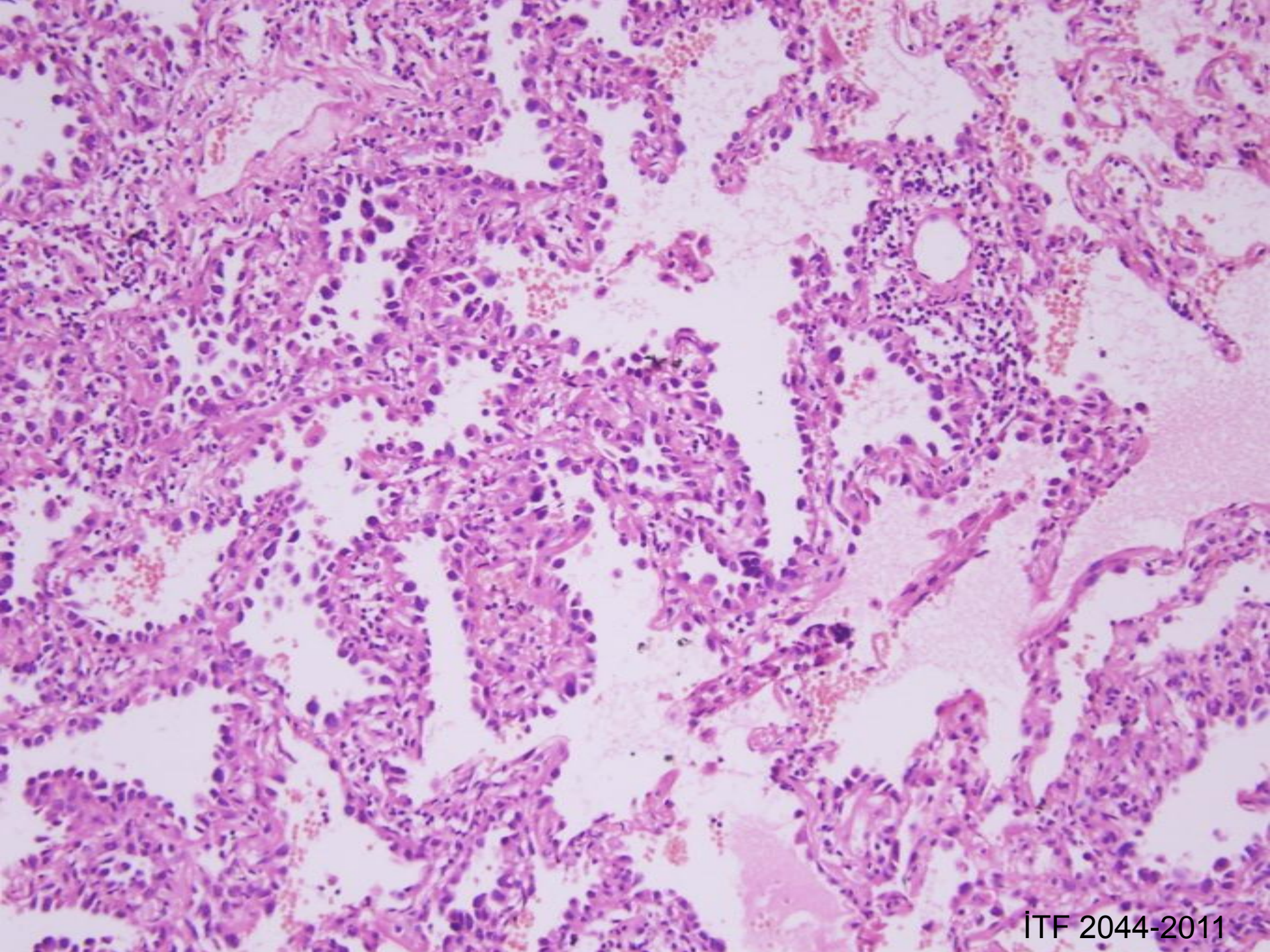


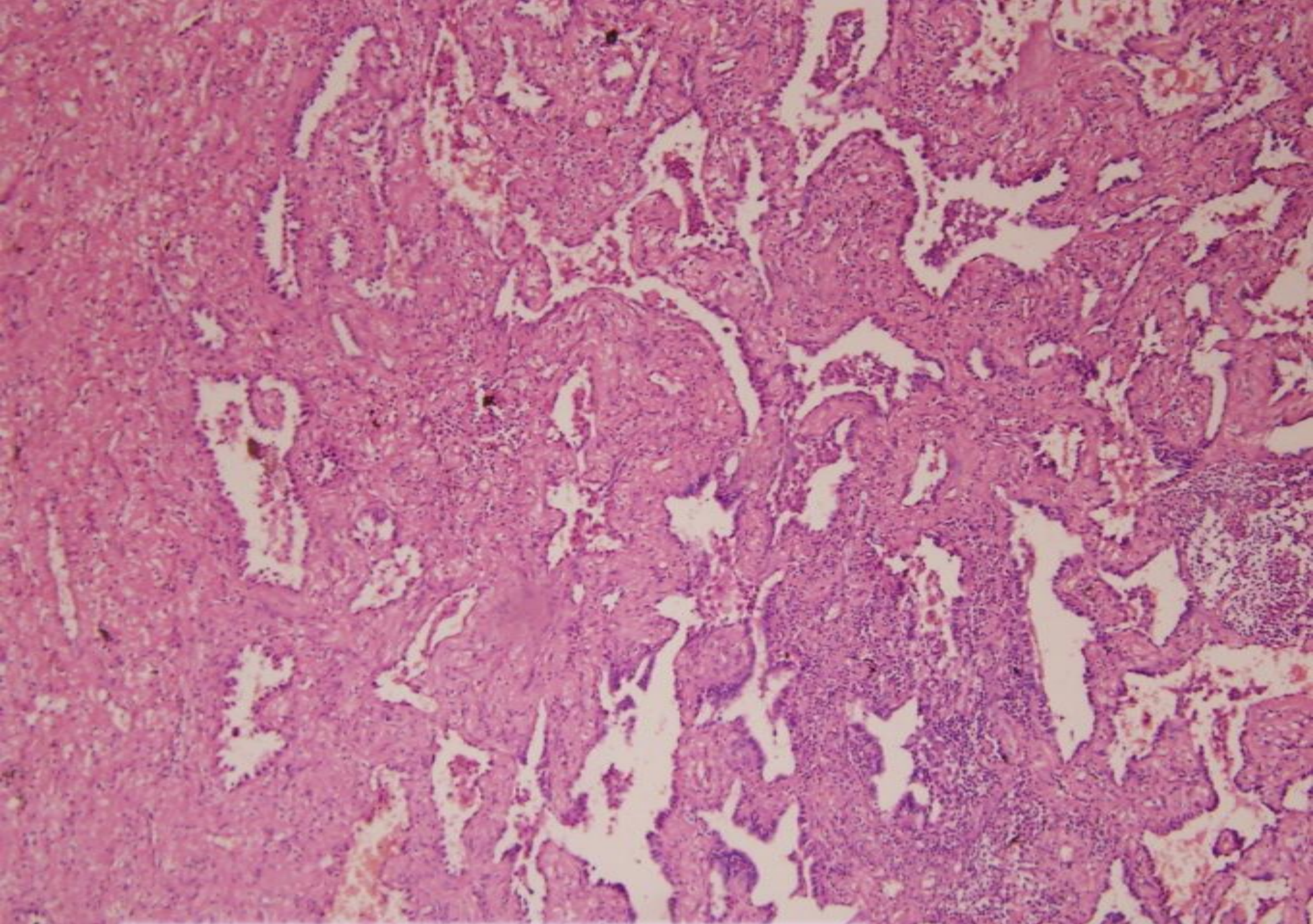
Minimal invazif adenokarsinom-lepidik baskın -non müsinöz



Escher

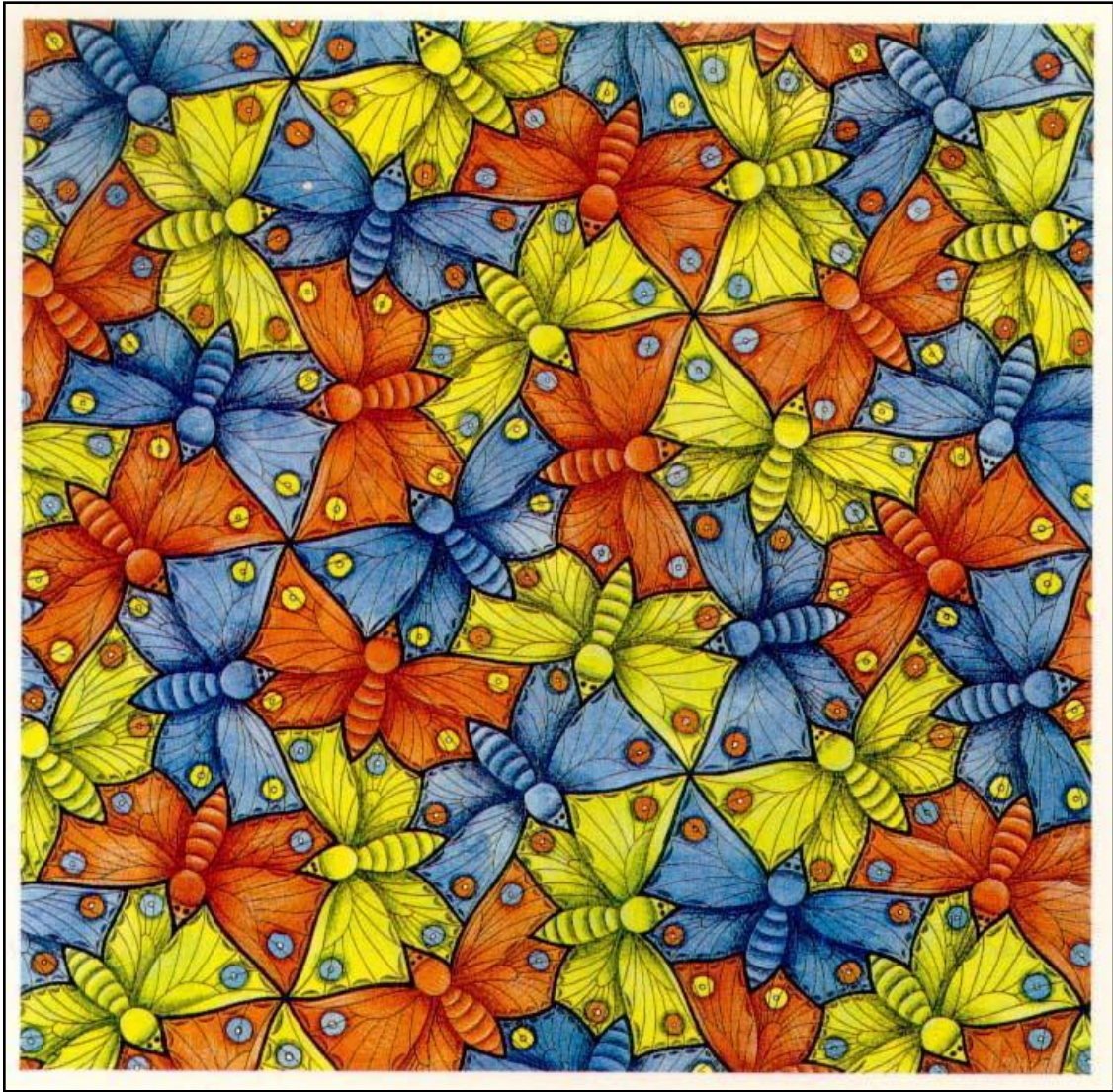




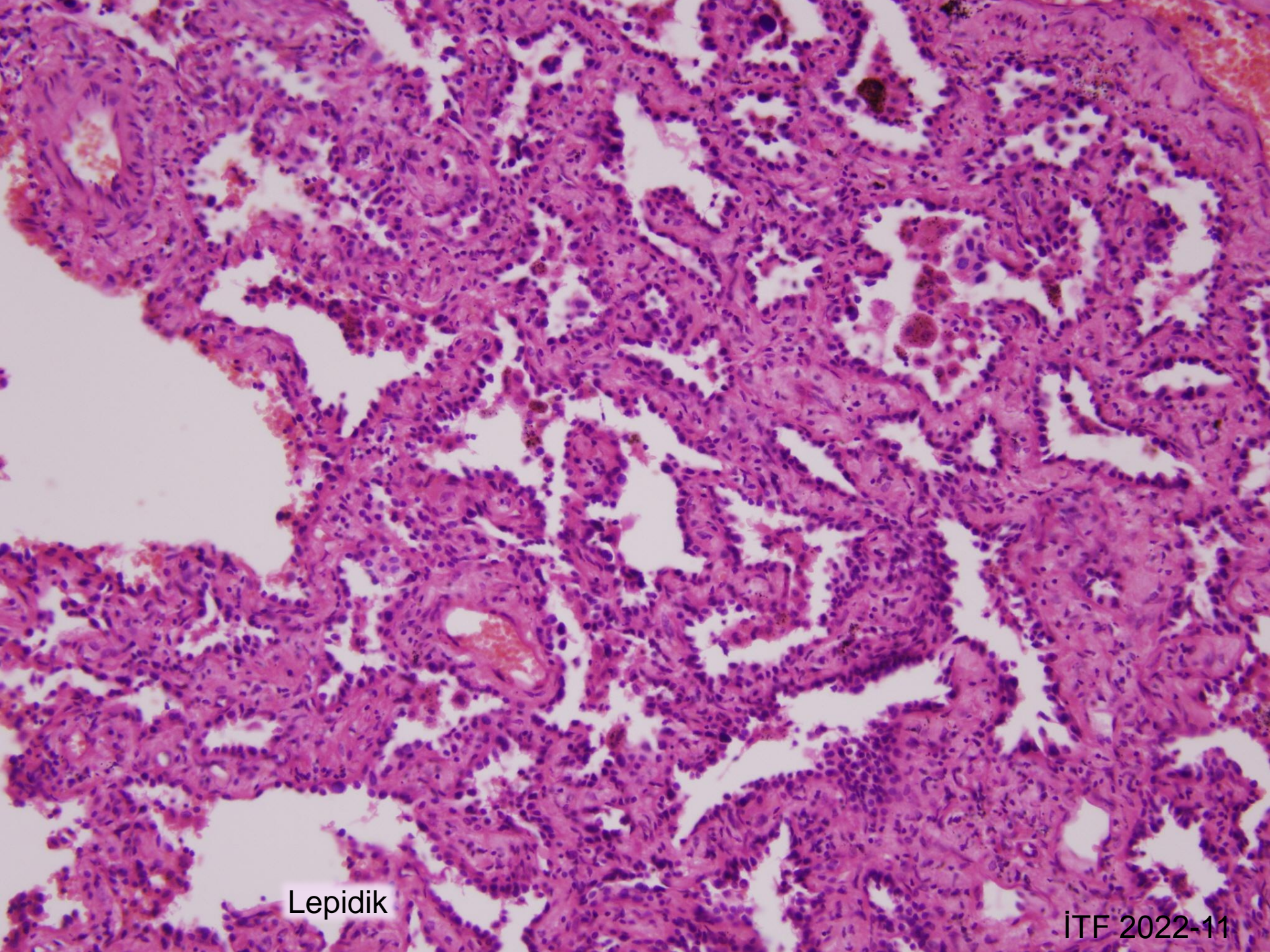


İnvazif adenokarsinom-lepidik baskın-non müsinöz

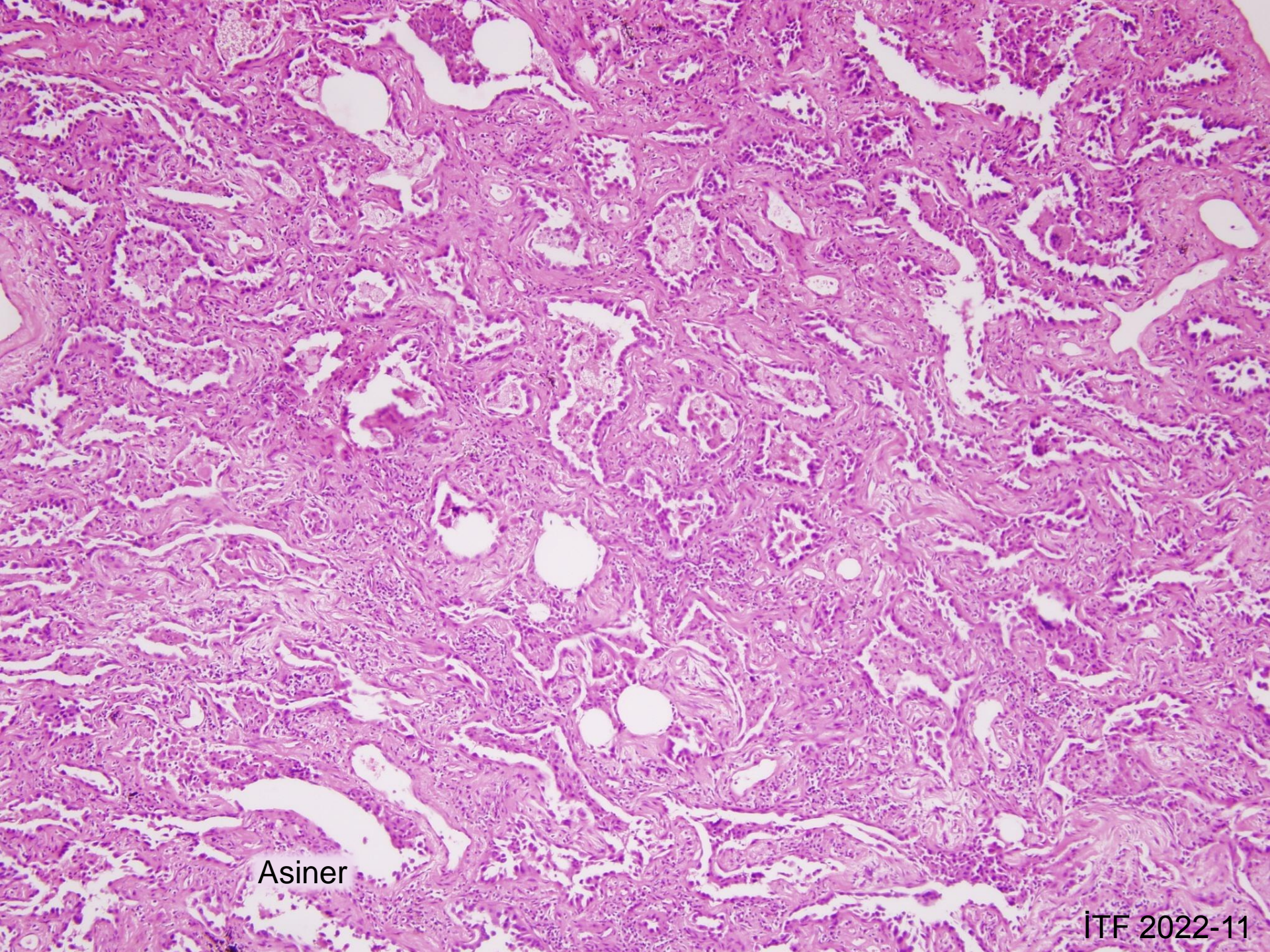
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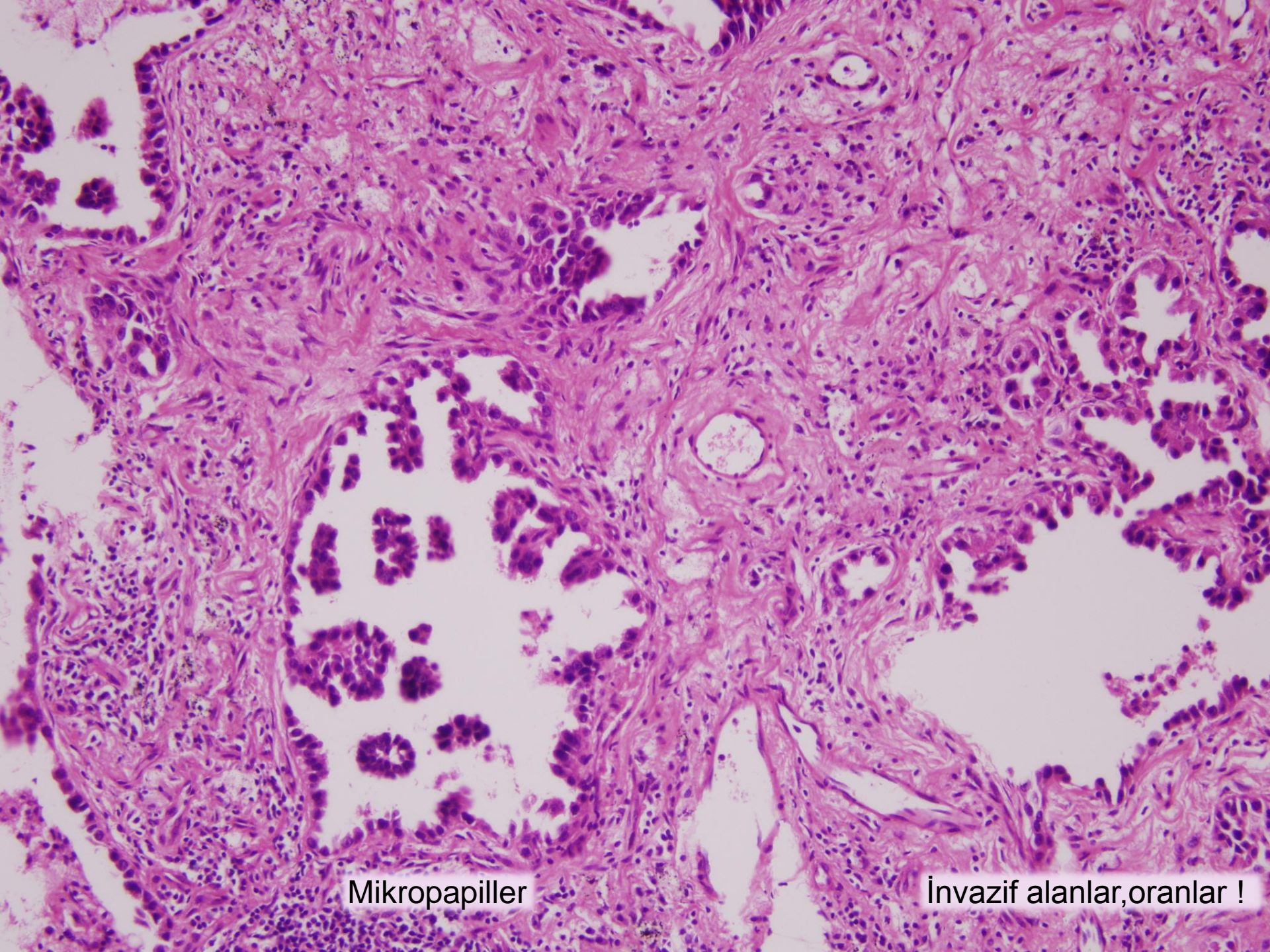


Lepidik



Asiner

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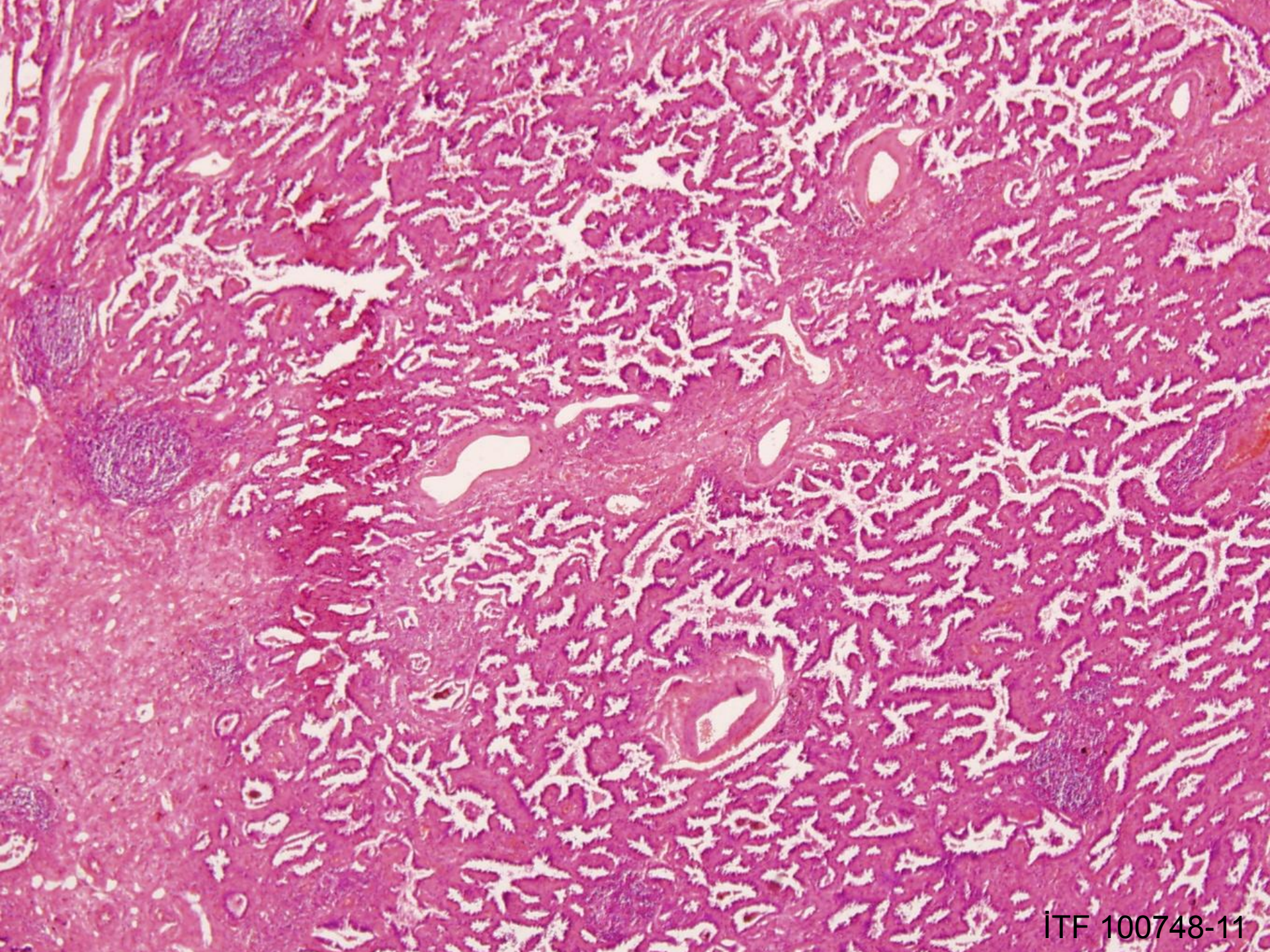


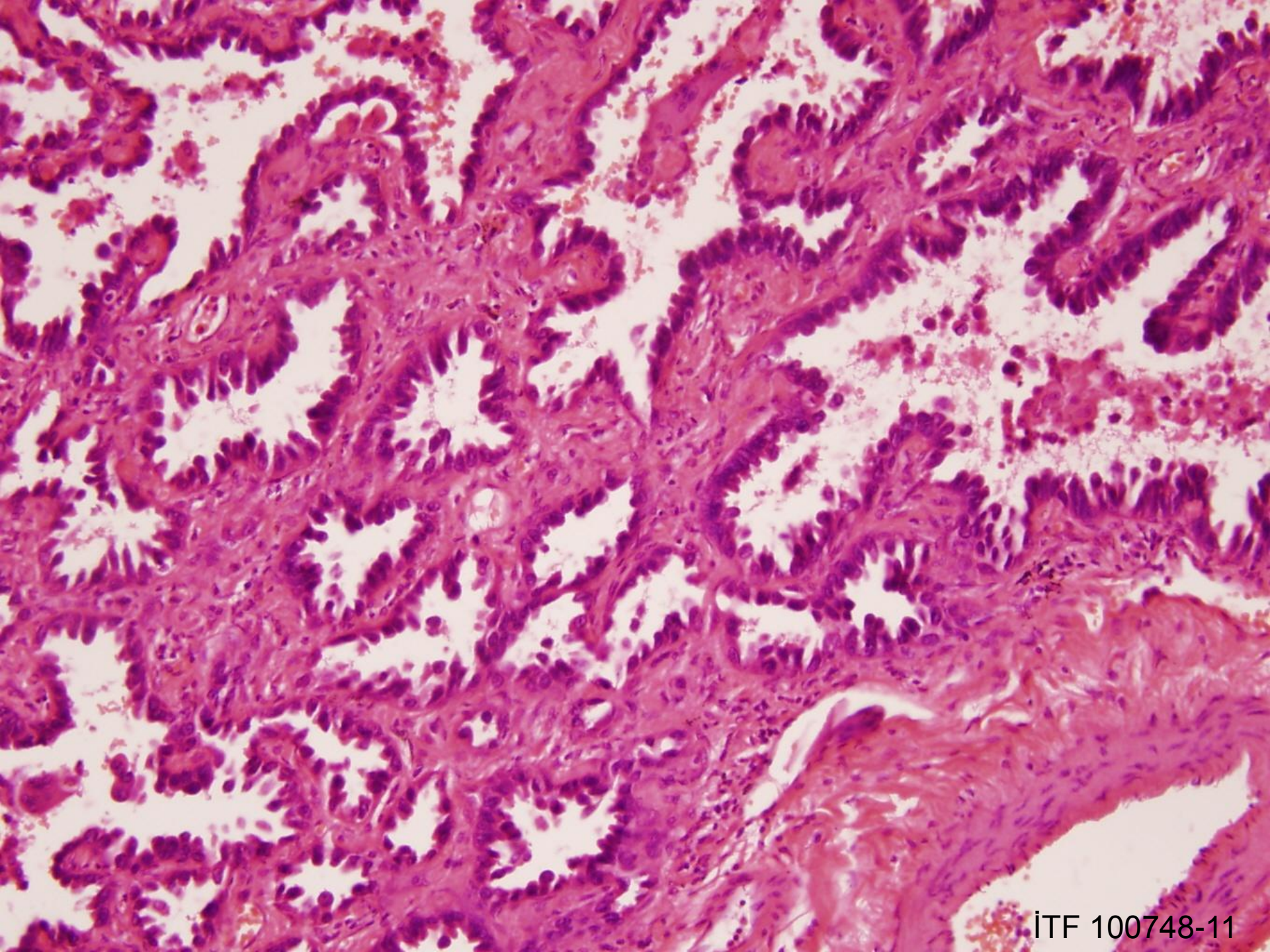
Mikropapiller

İnvazif alanlar, oranlar !



Escher

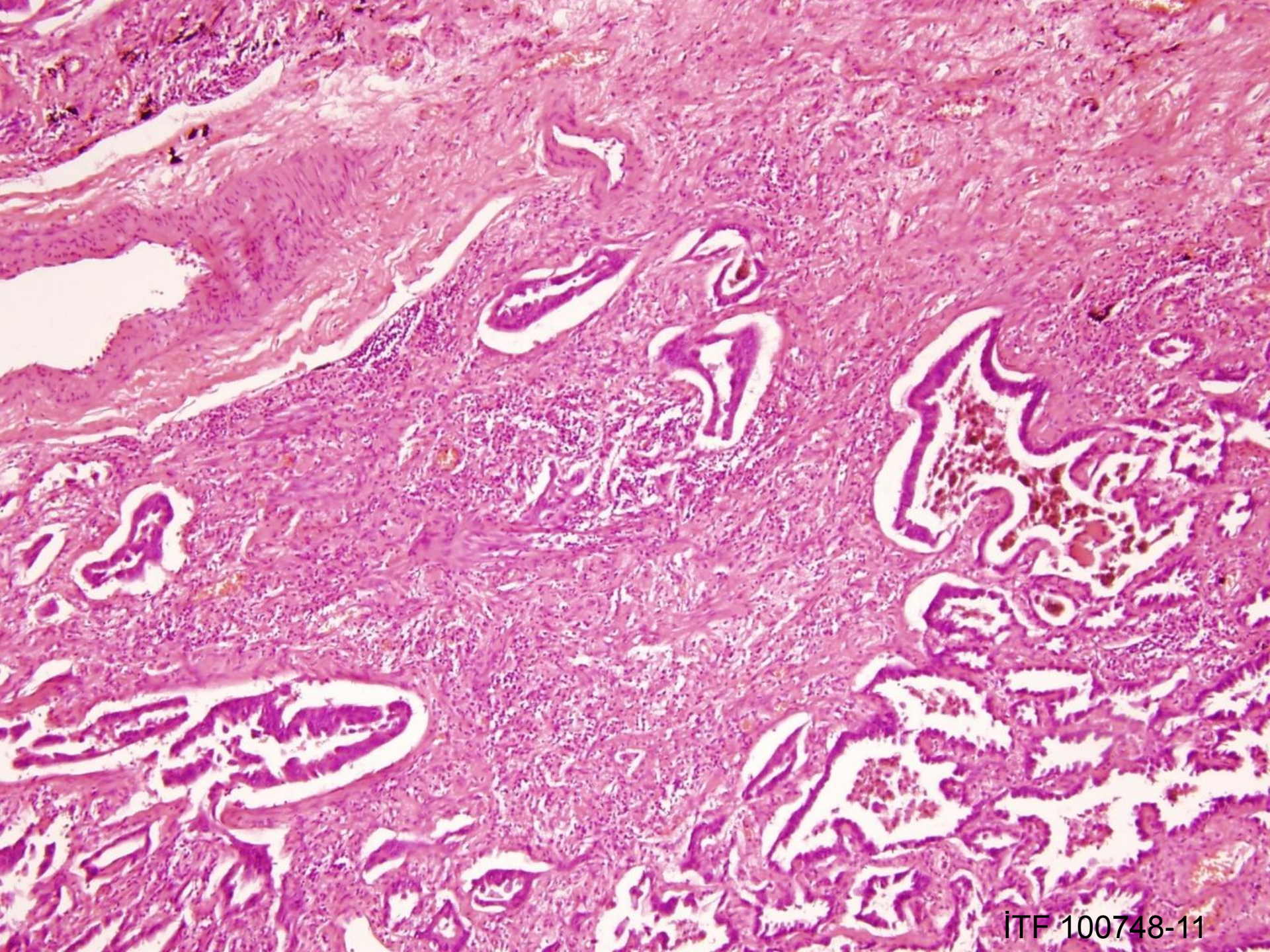


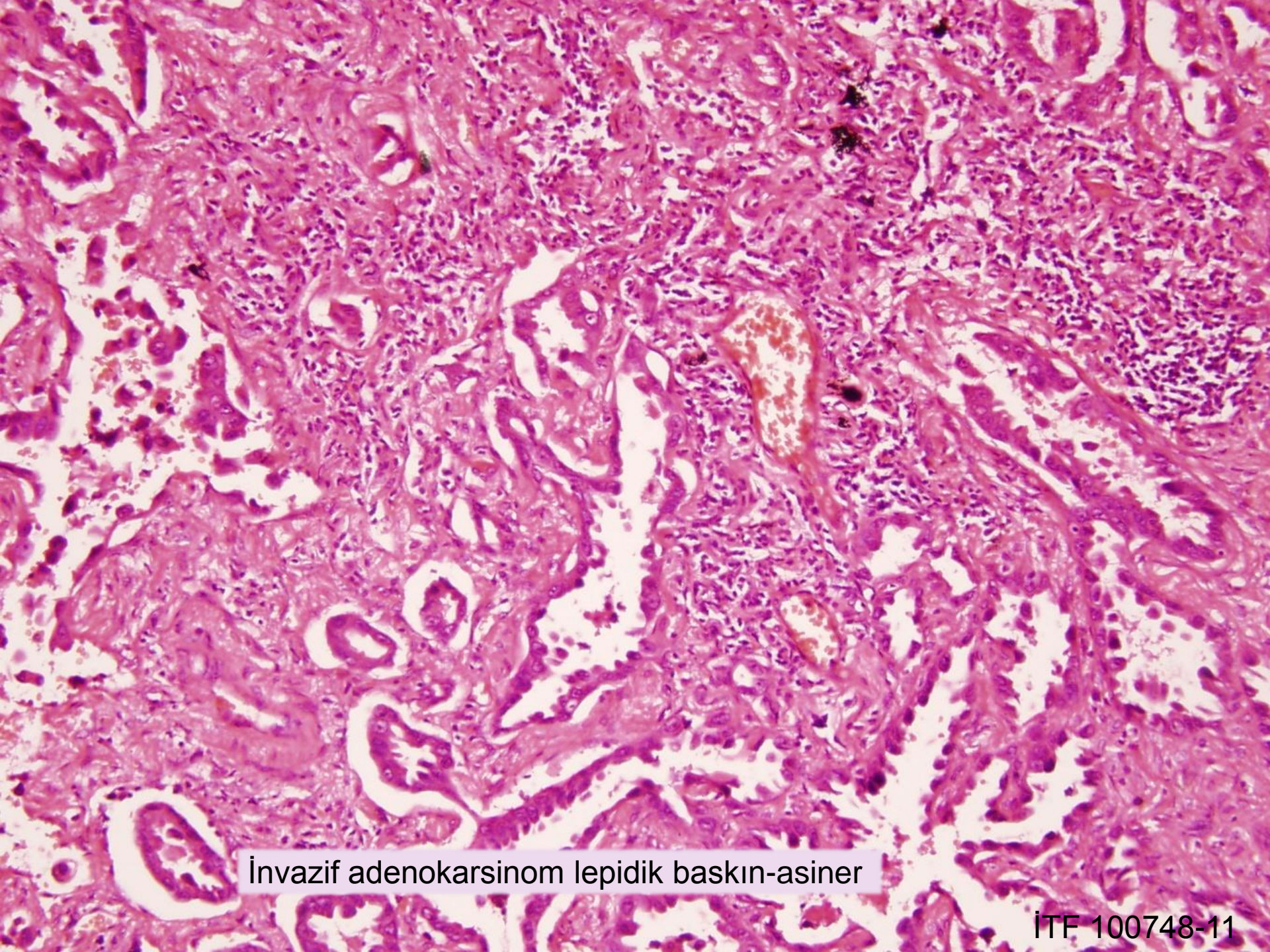




Invazyon??

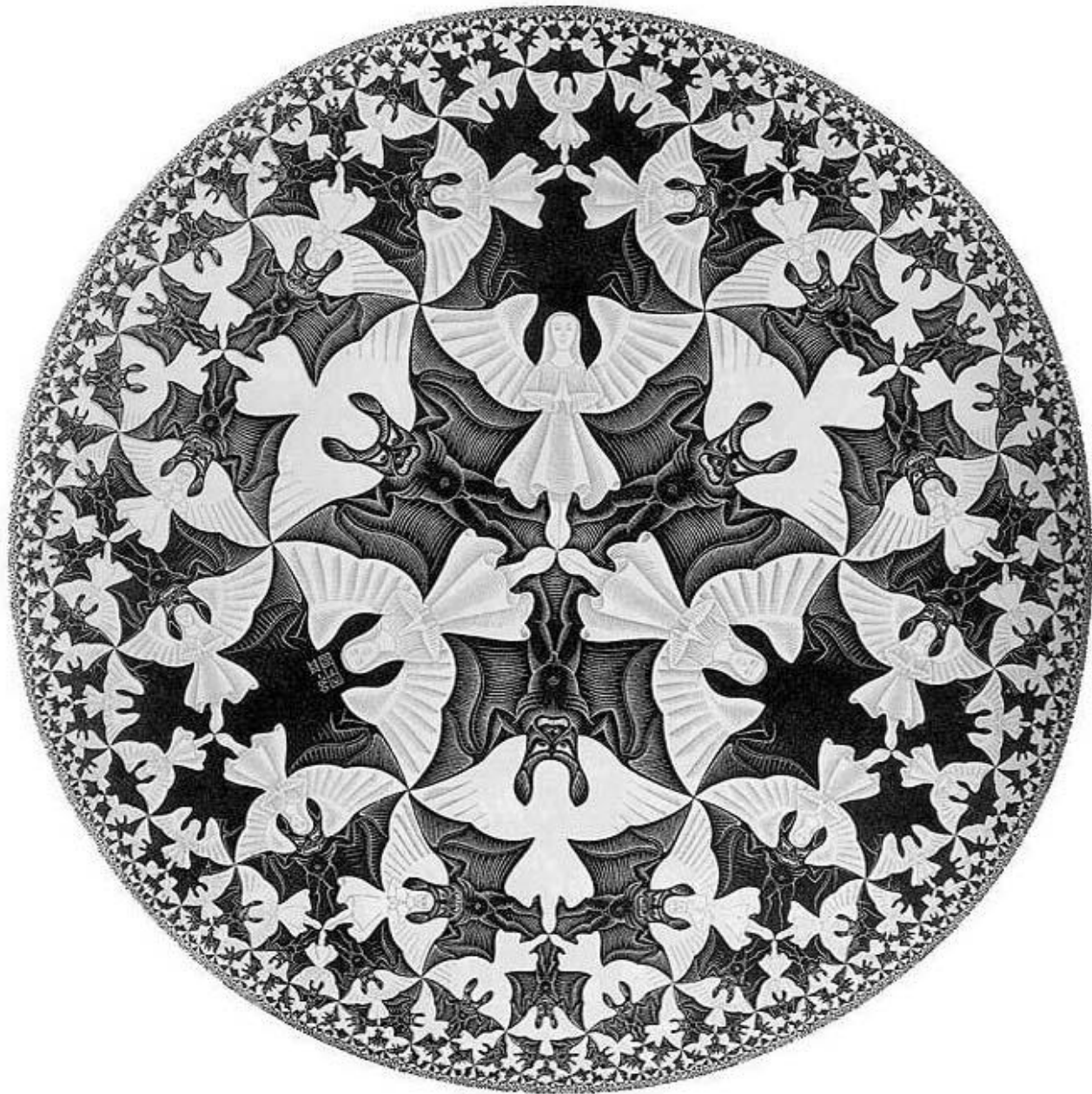
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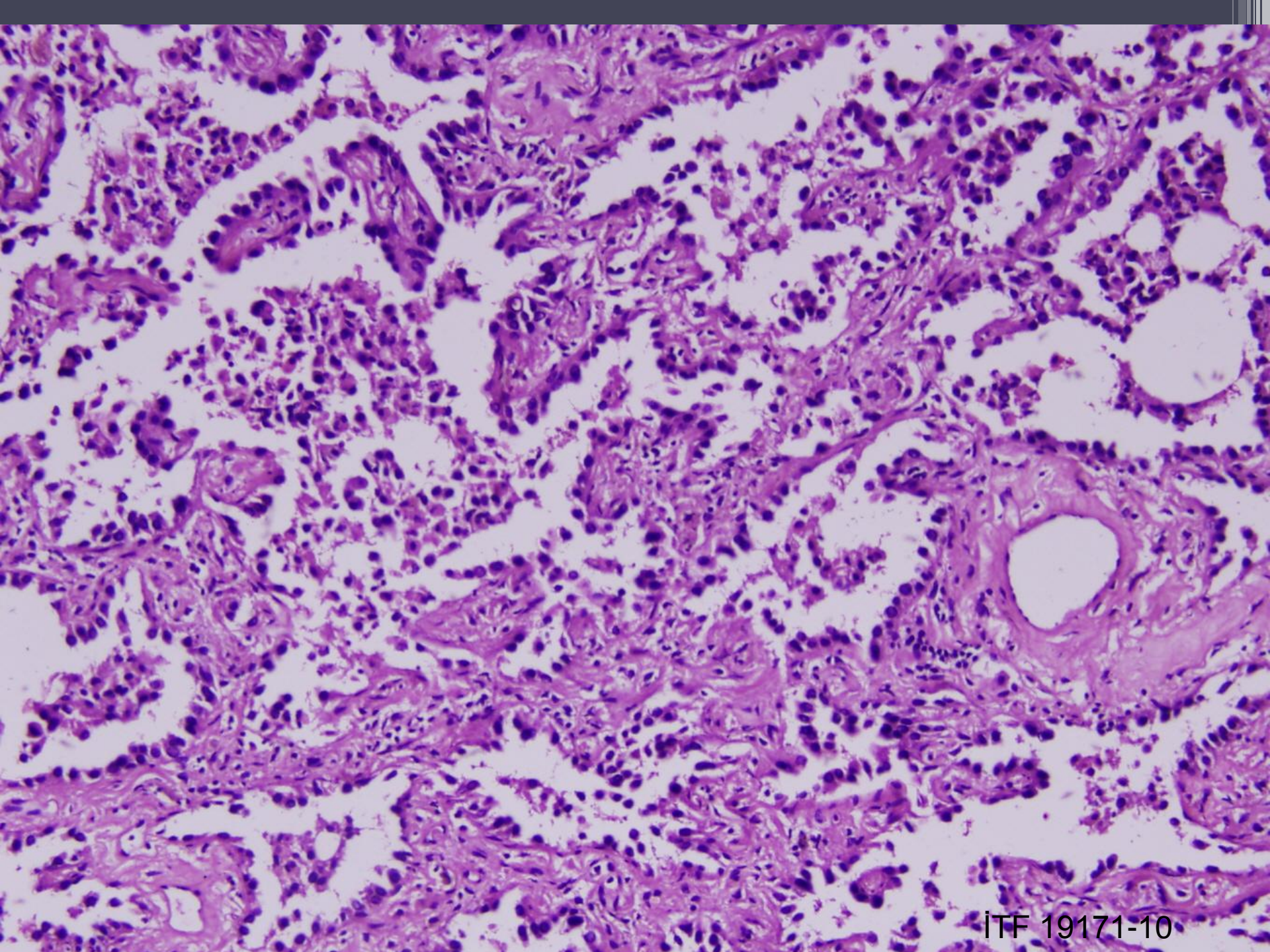


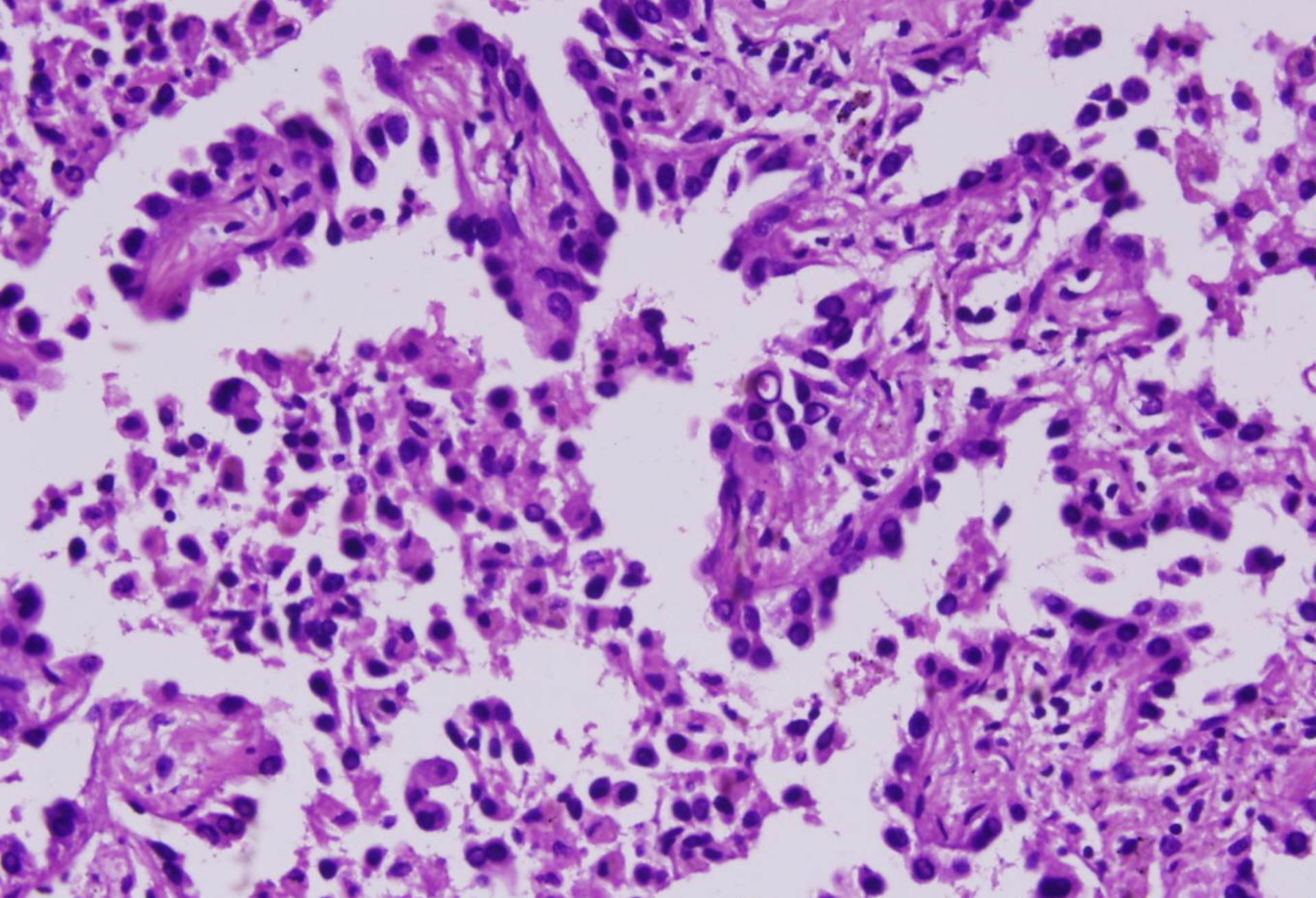
İnvazif adenokarsinom lepidik baskın-asiner

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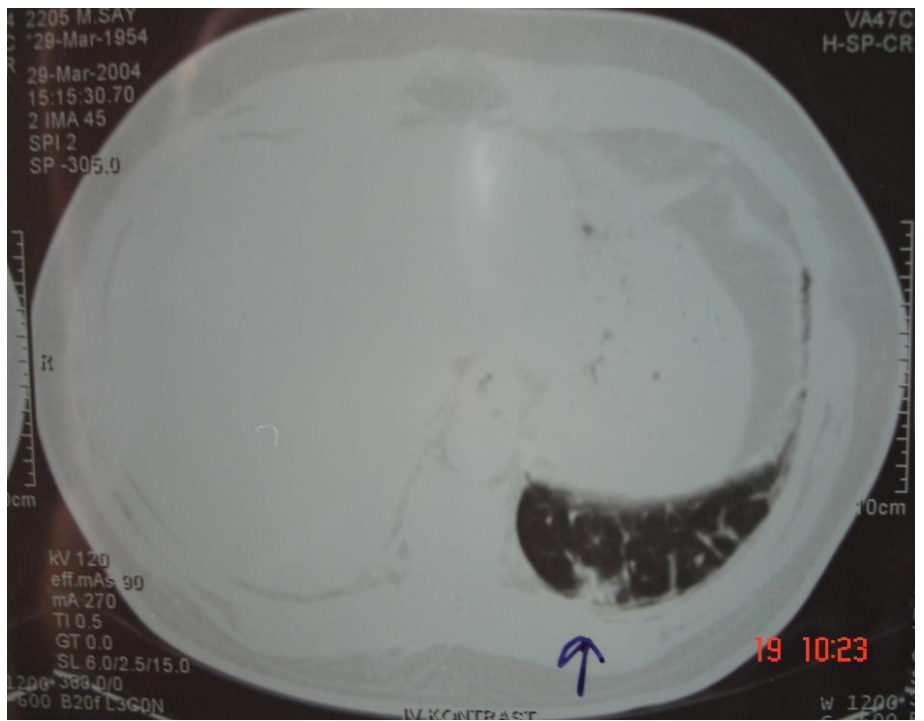
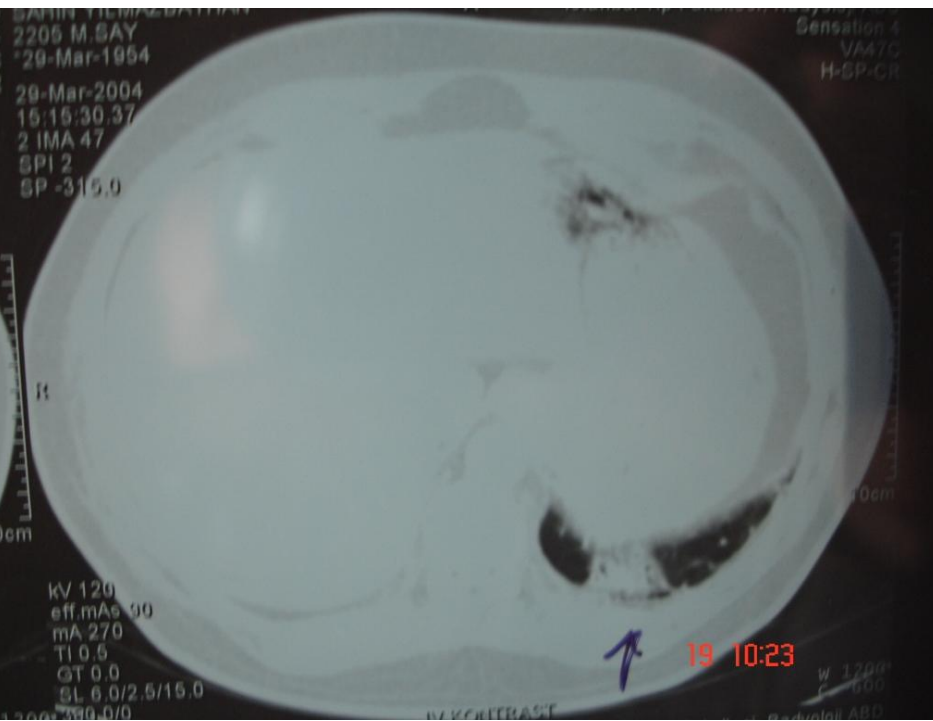


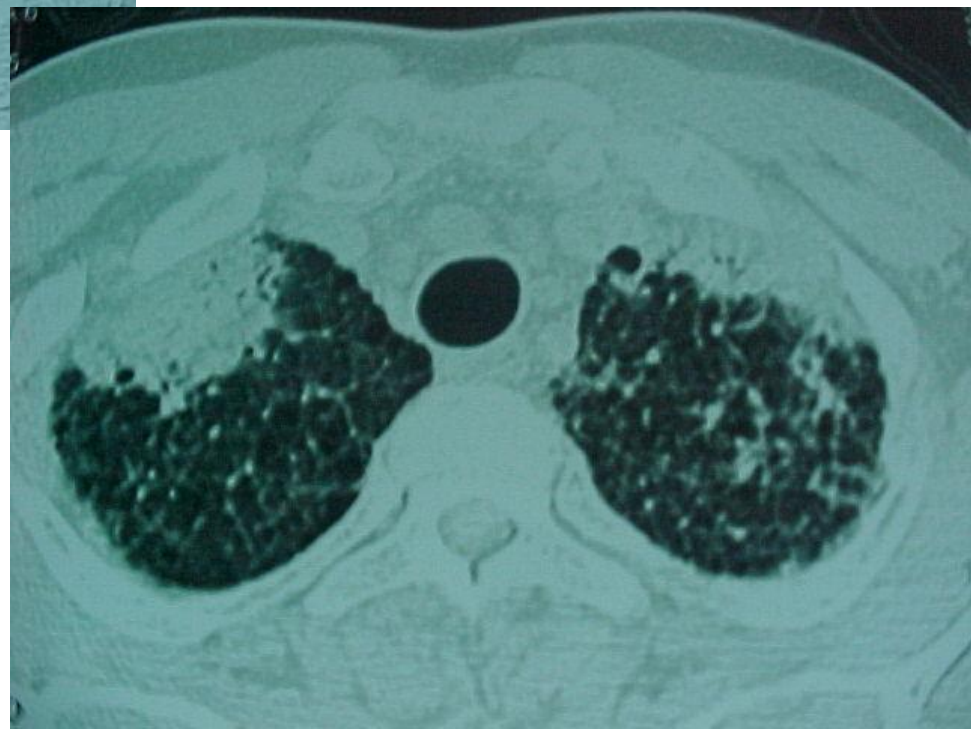
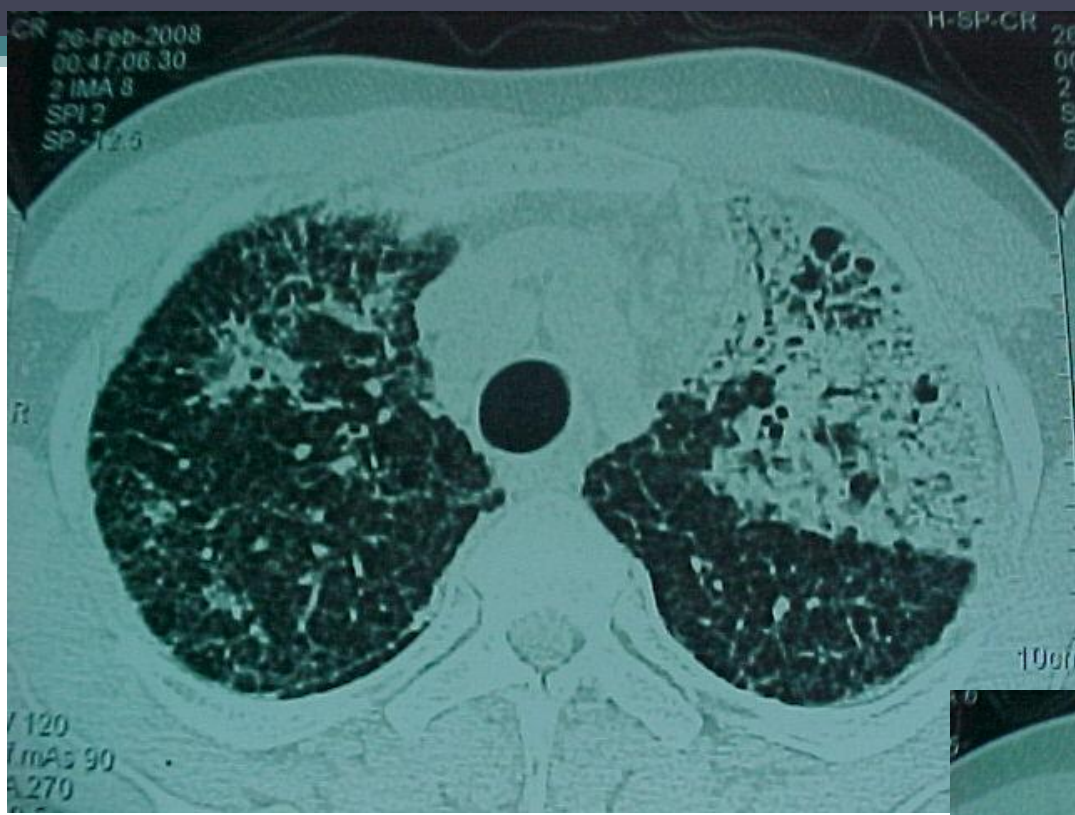
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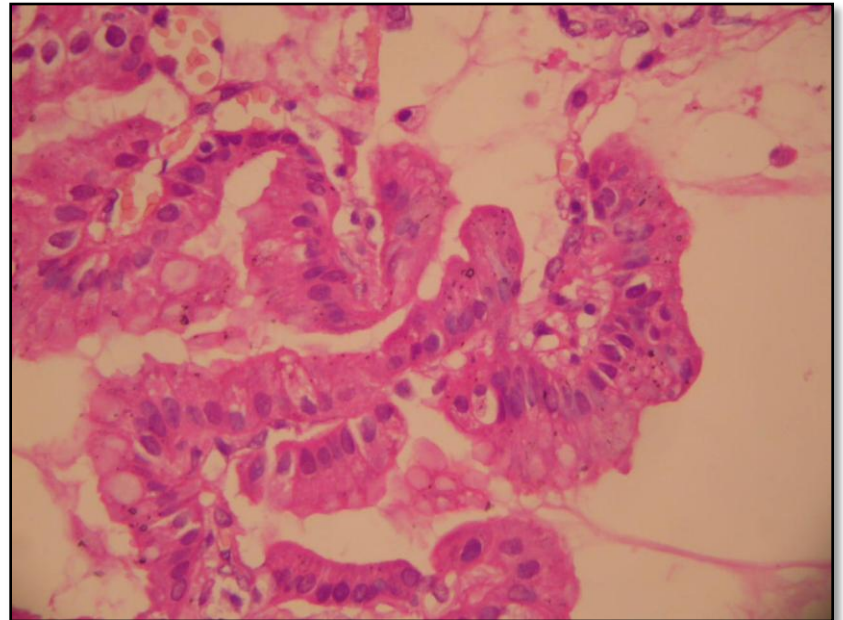
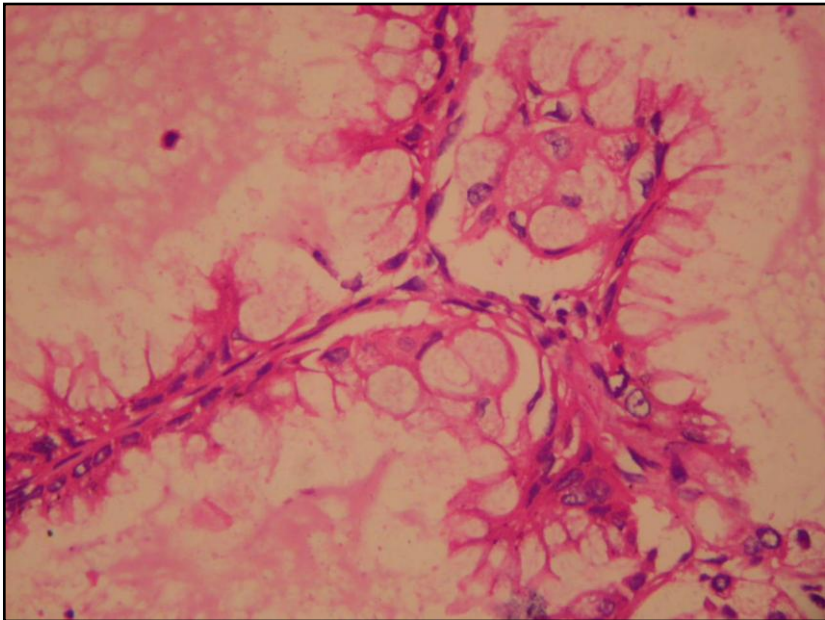
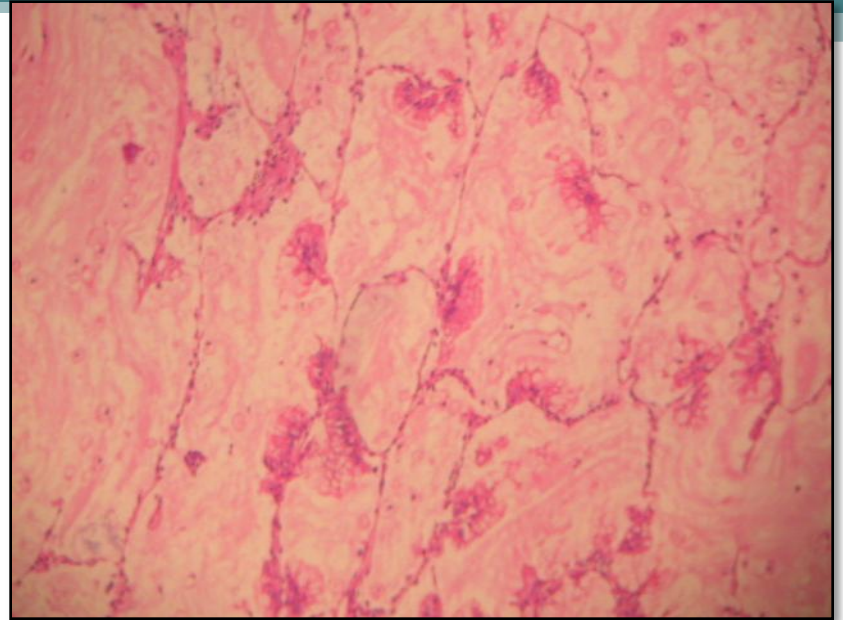
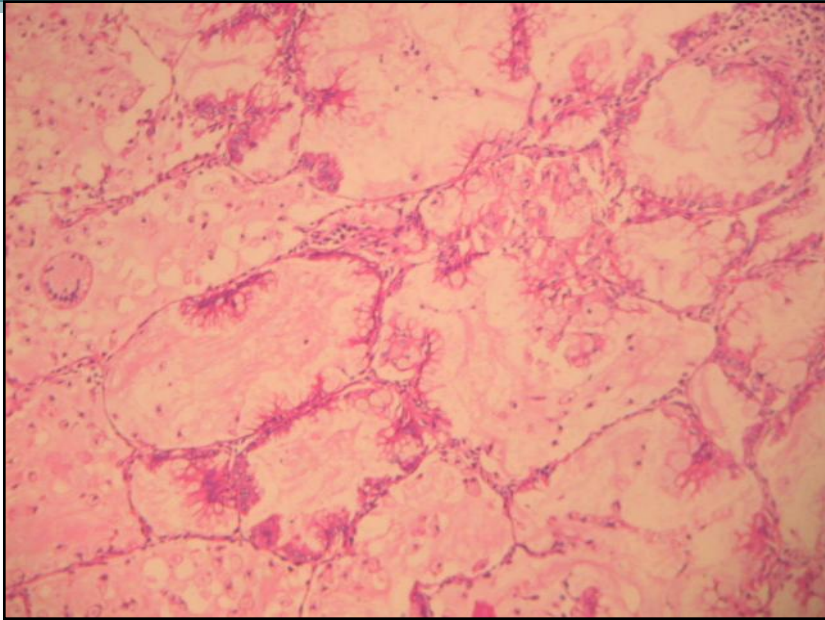


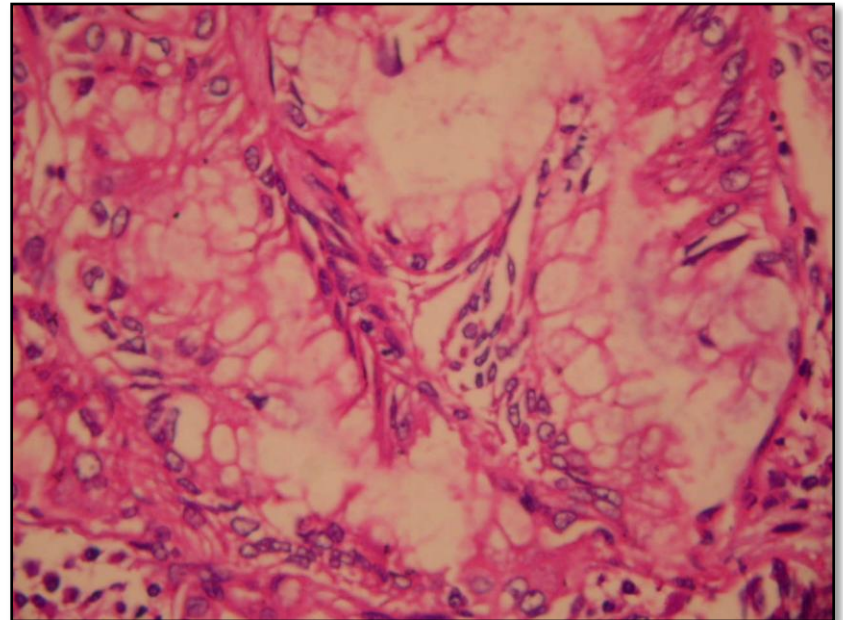
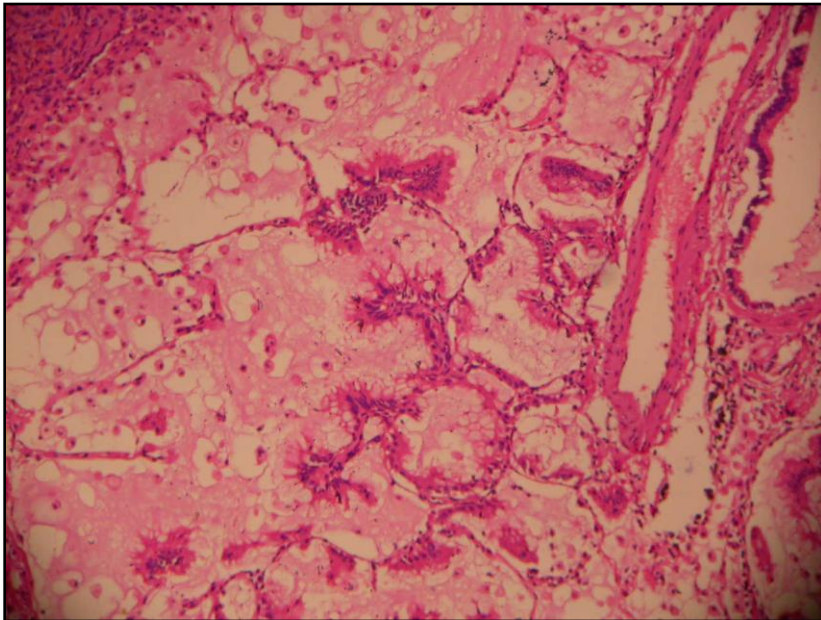
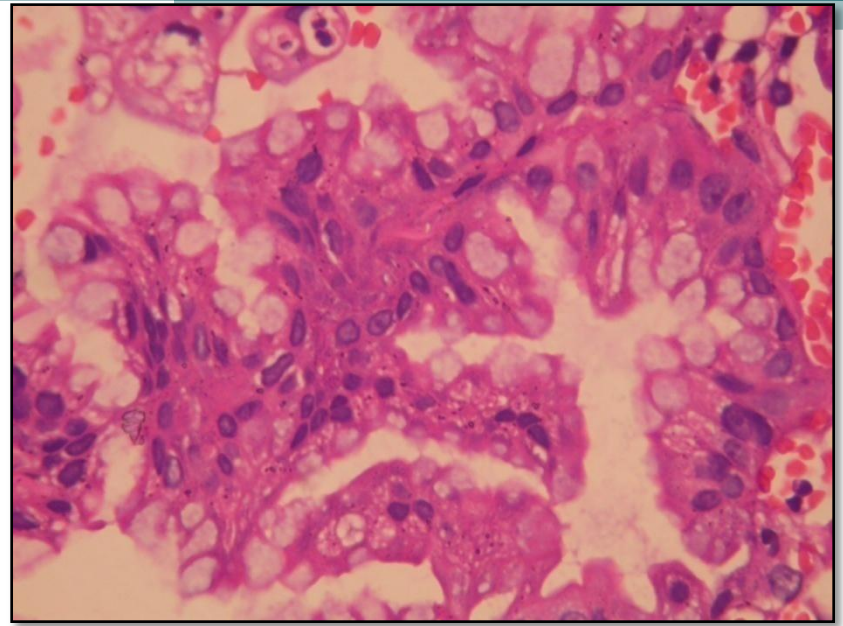
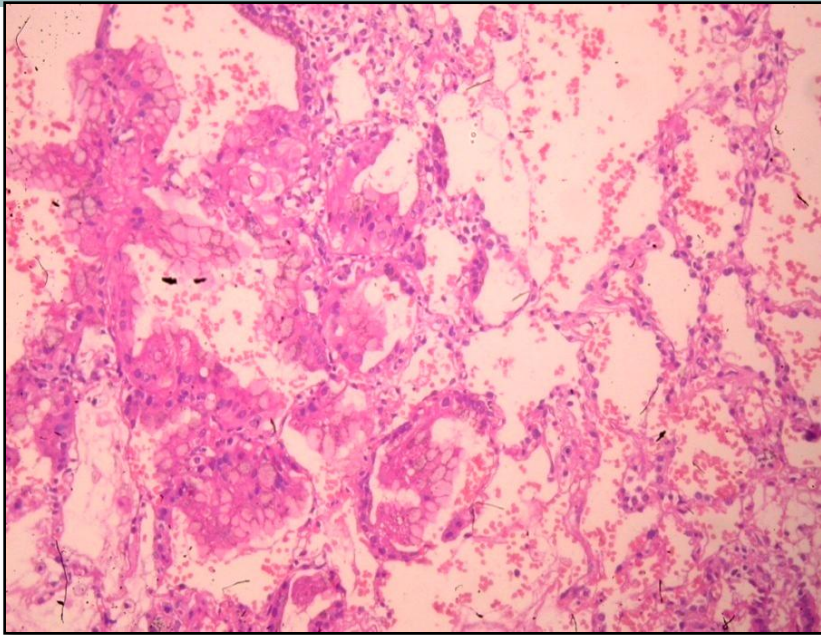


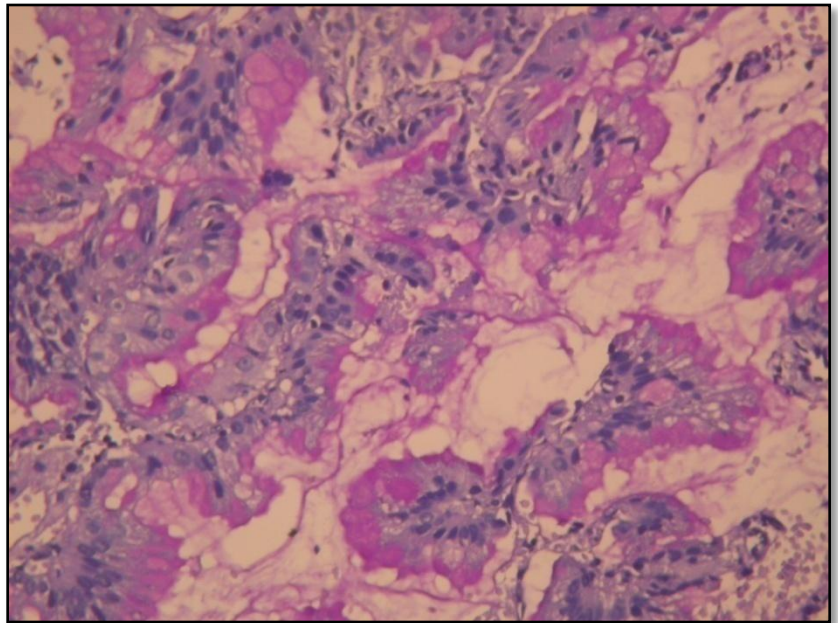
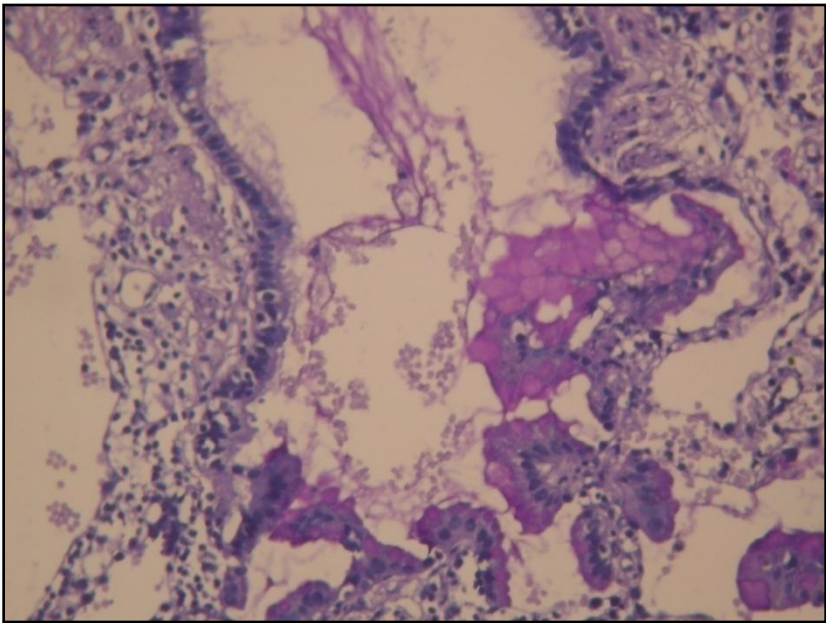
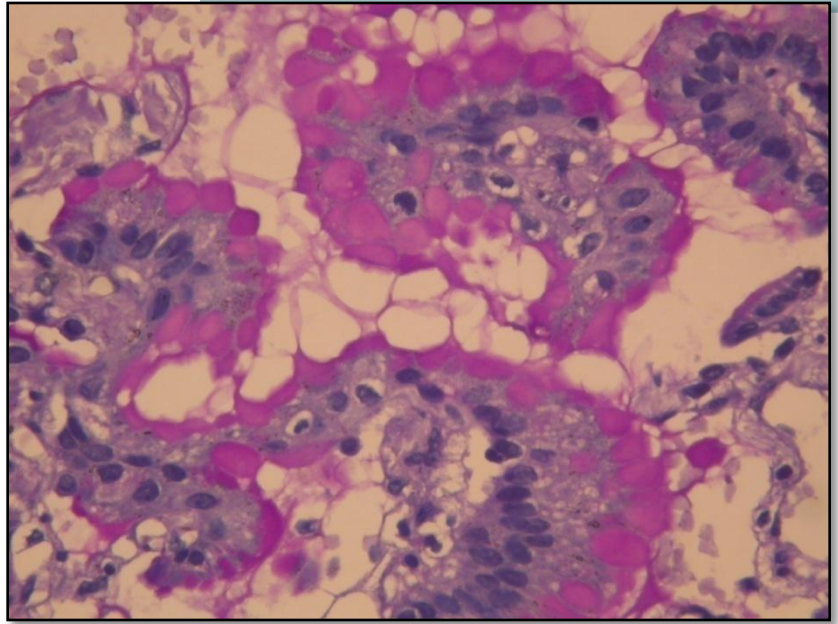
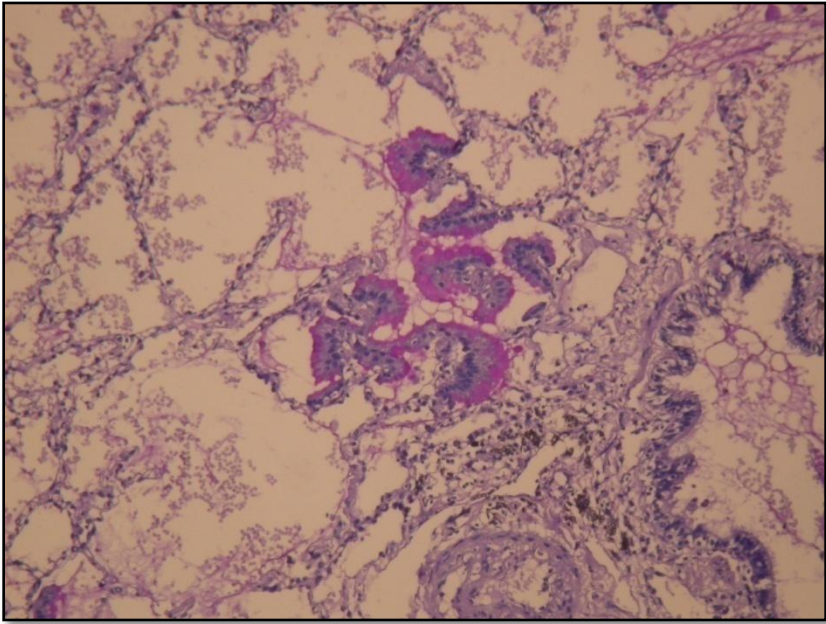
İntraalveoler hücreler invazyon???

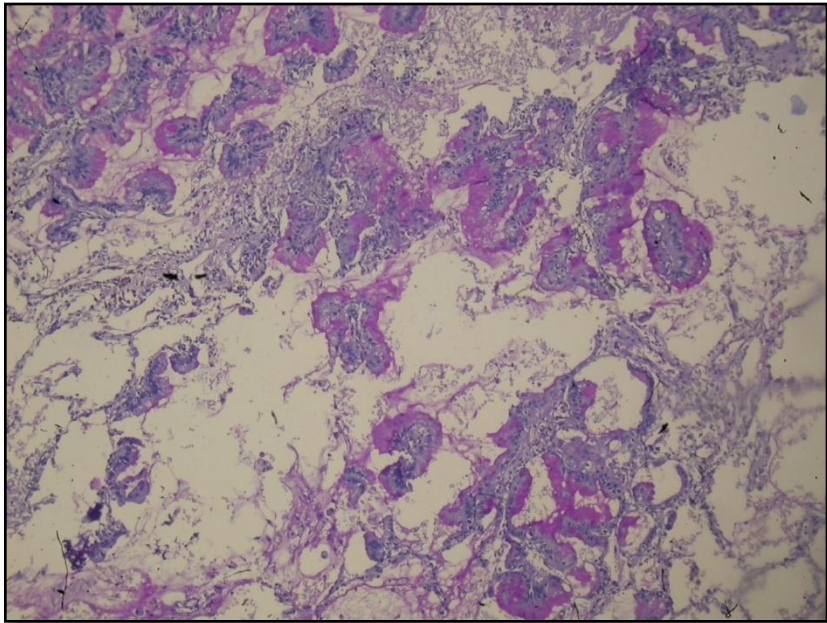
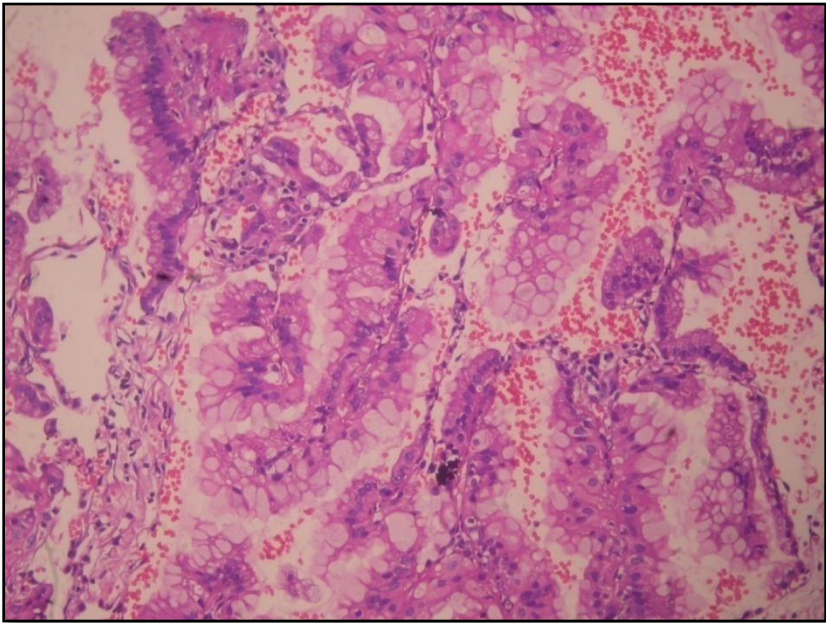
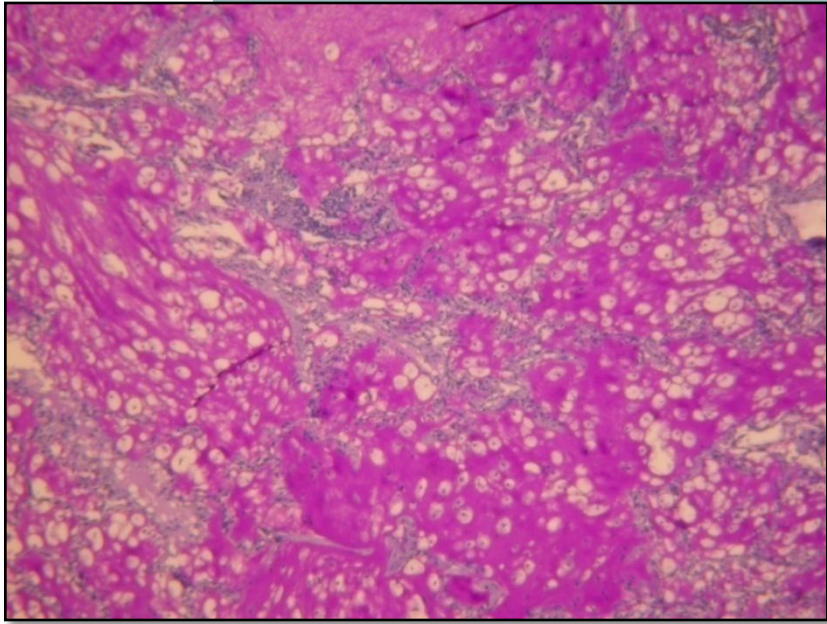
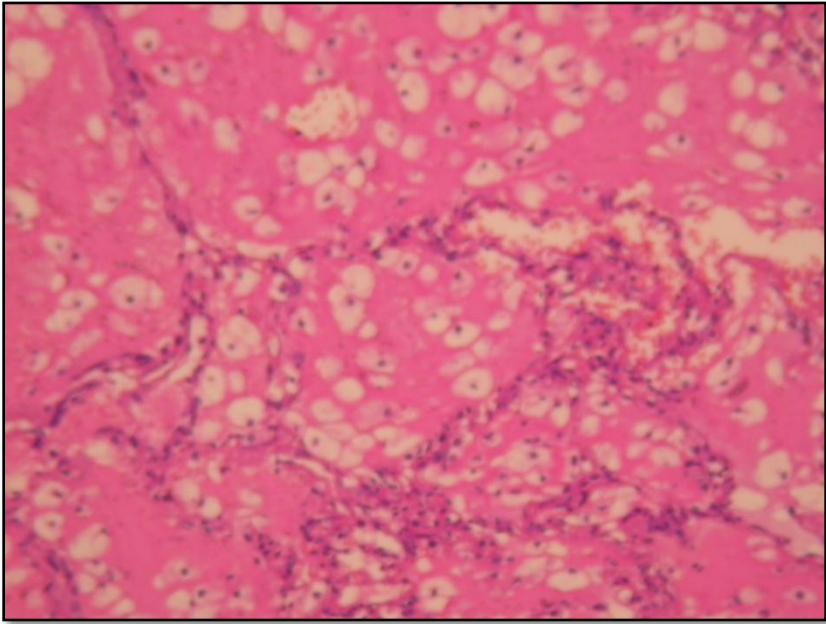


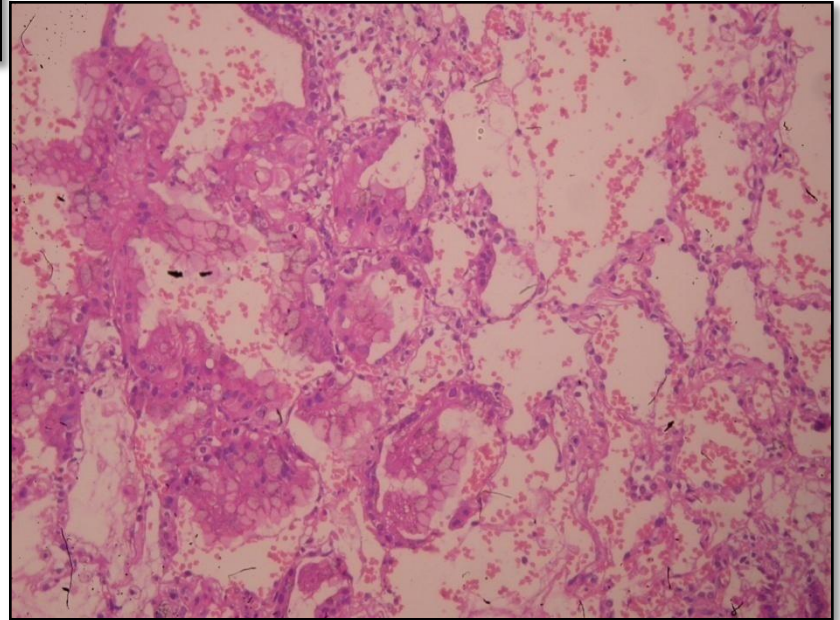
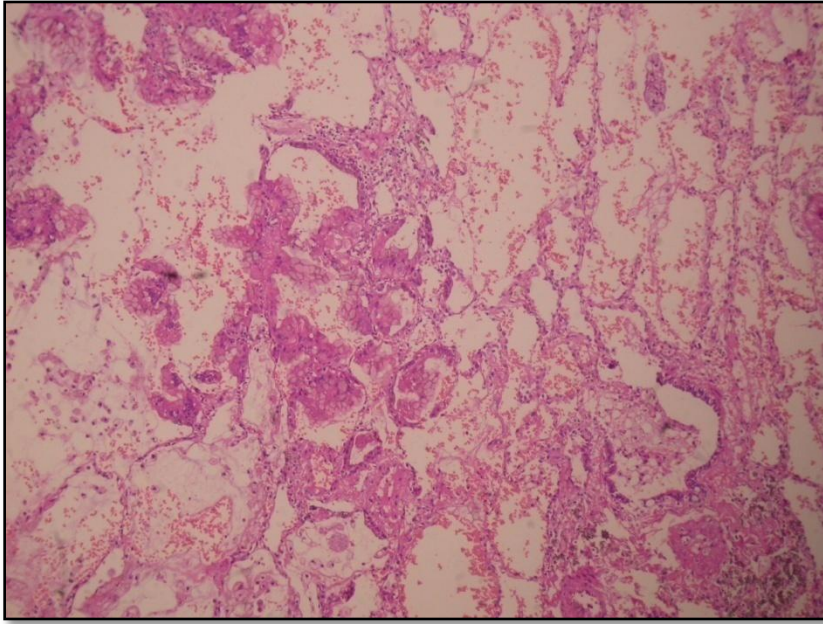




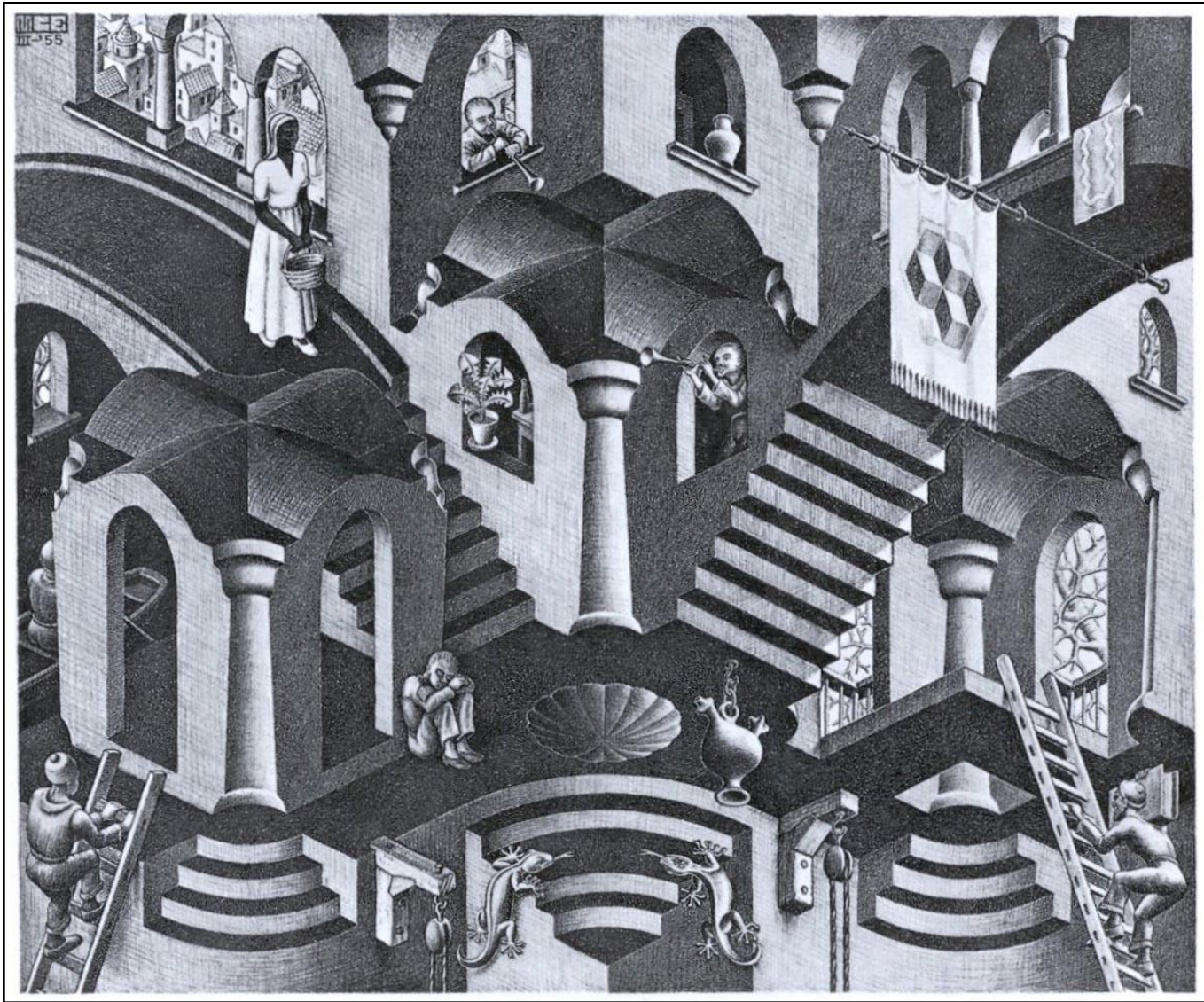




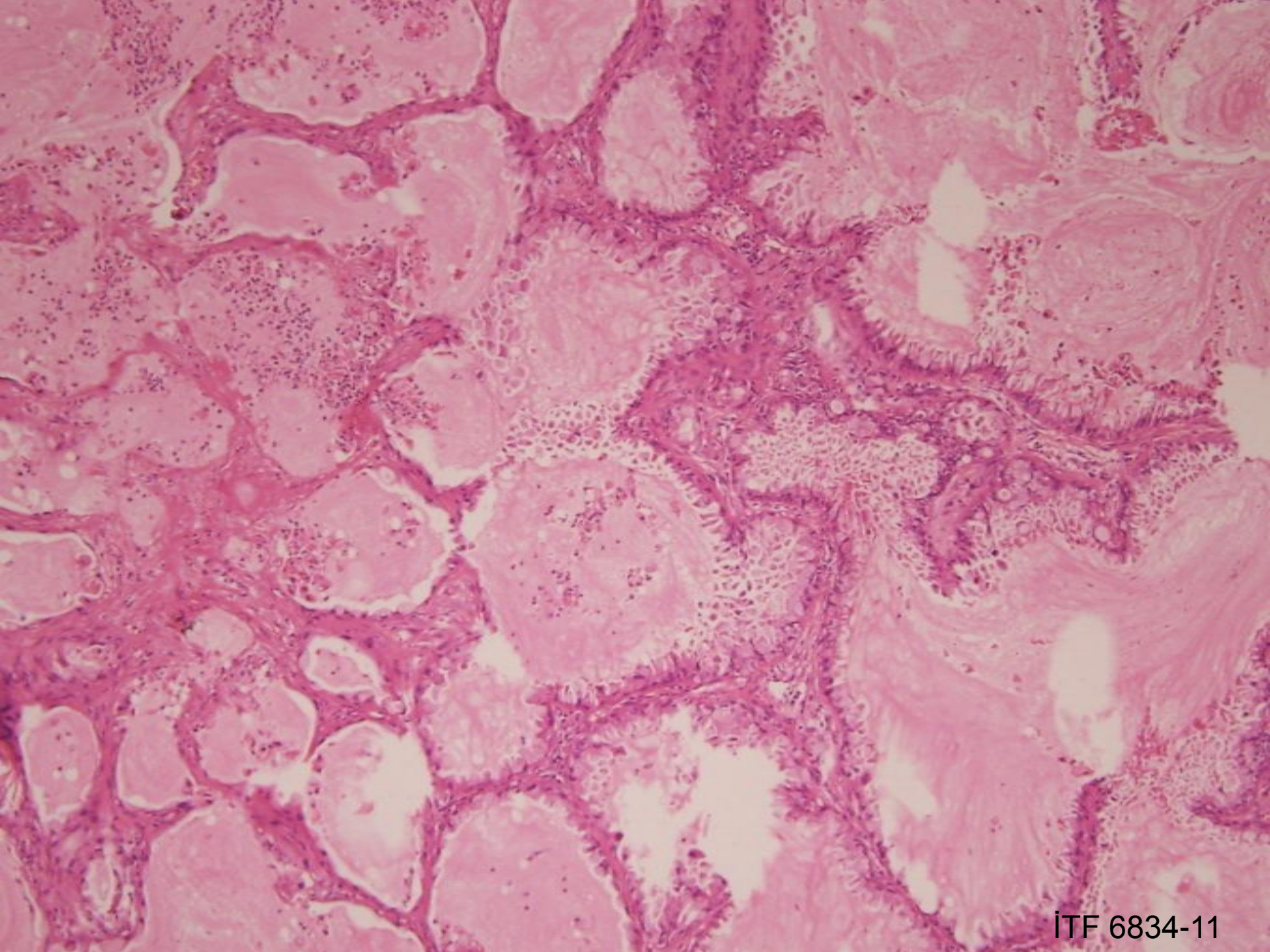


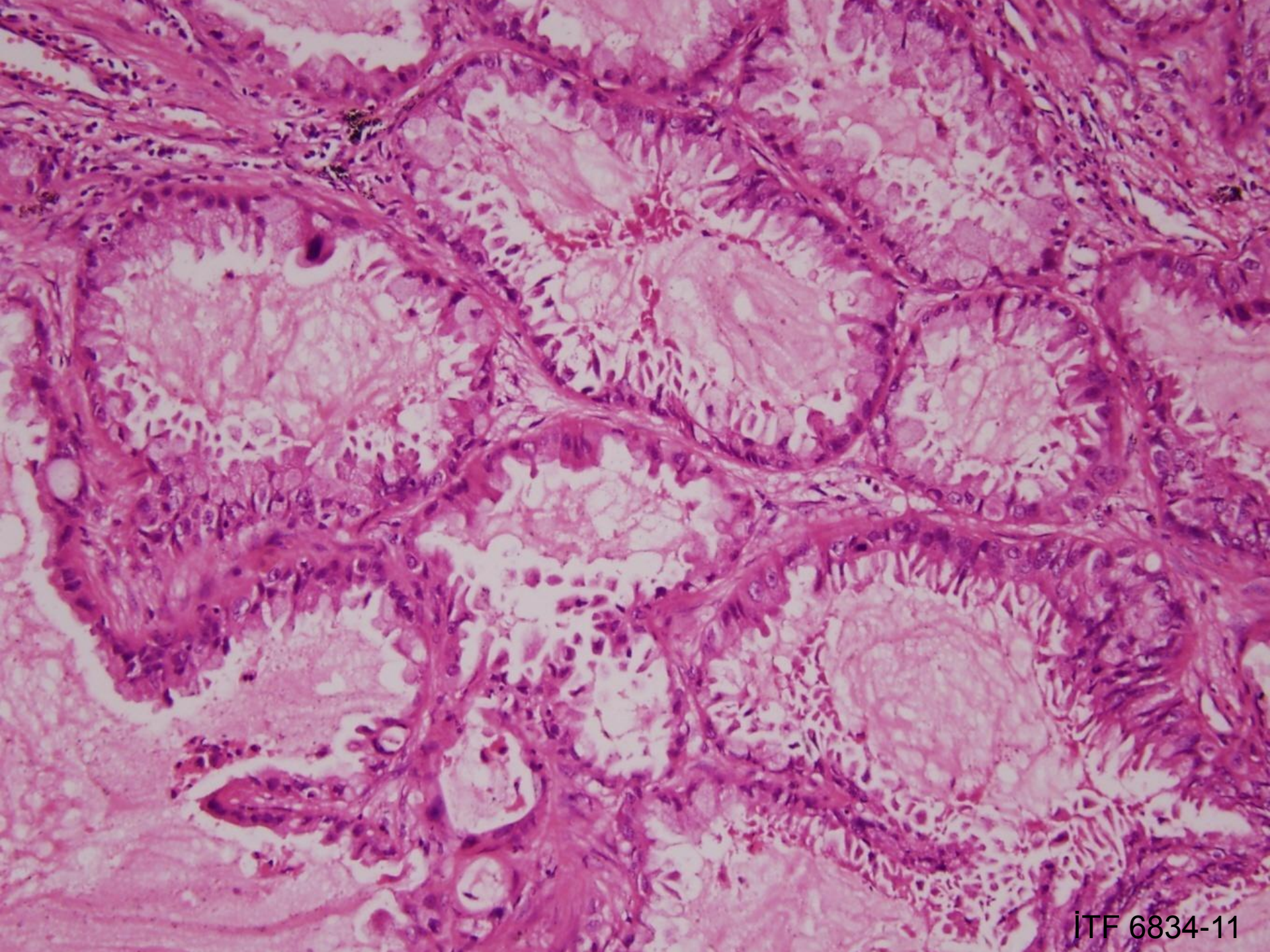


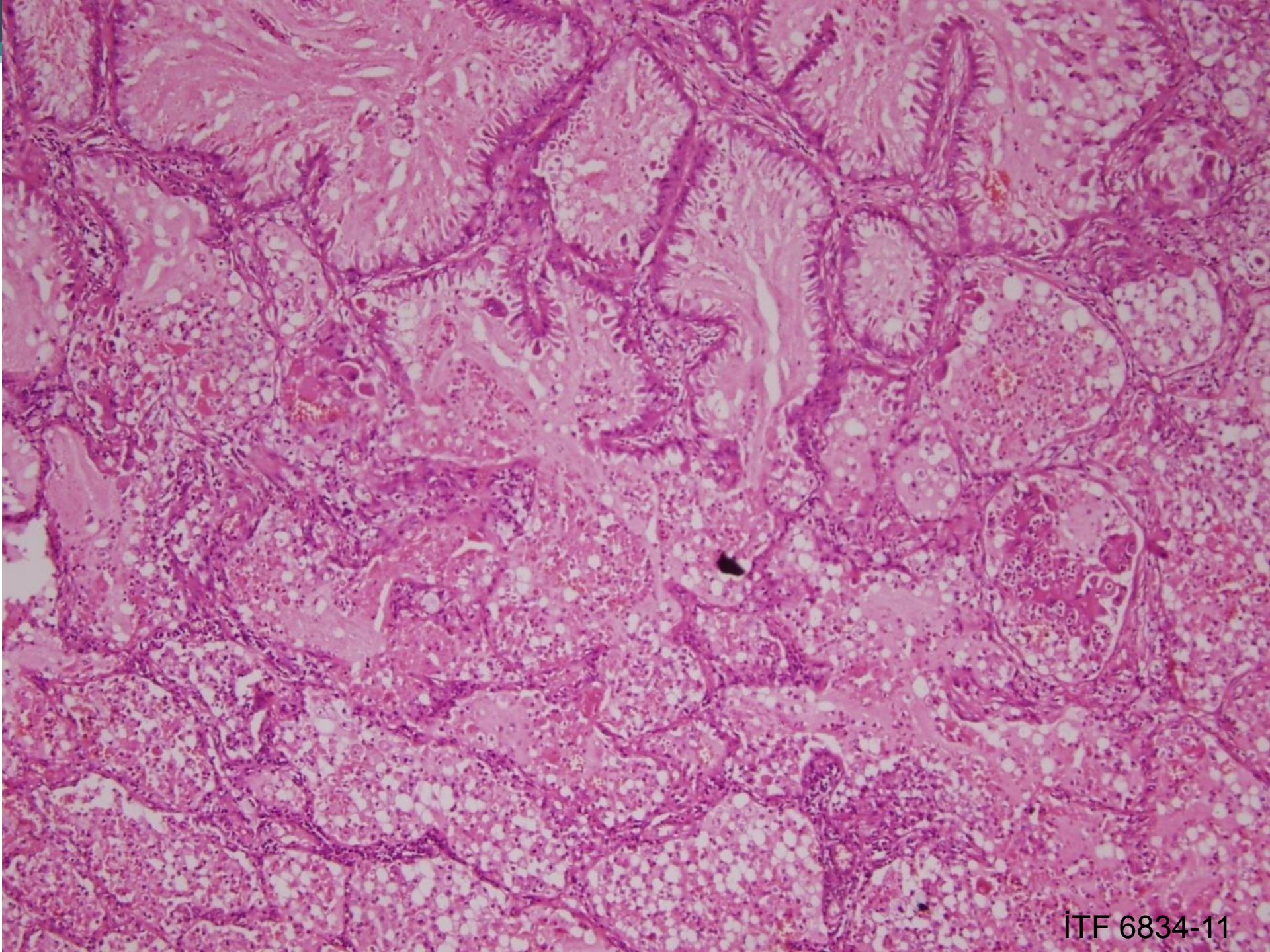
İn situ ???? müsinöz

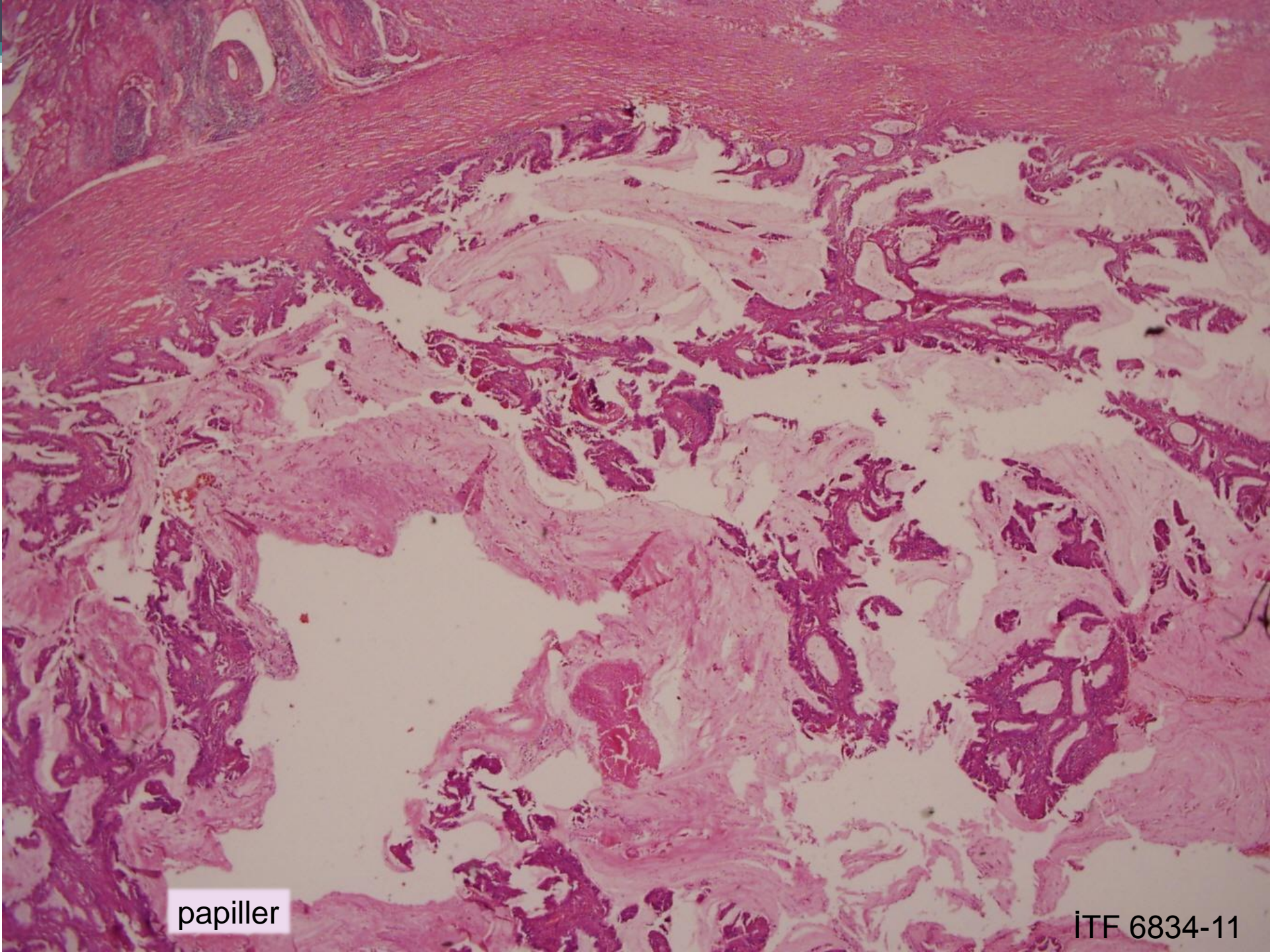


Escher



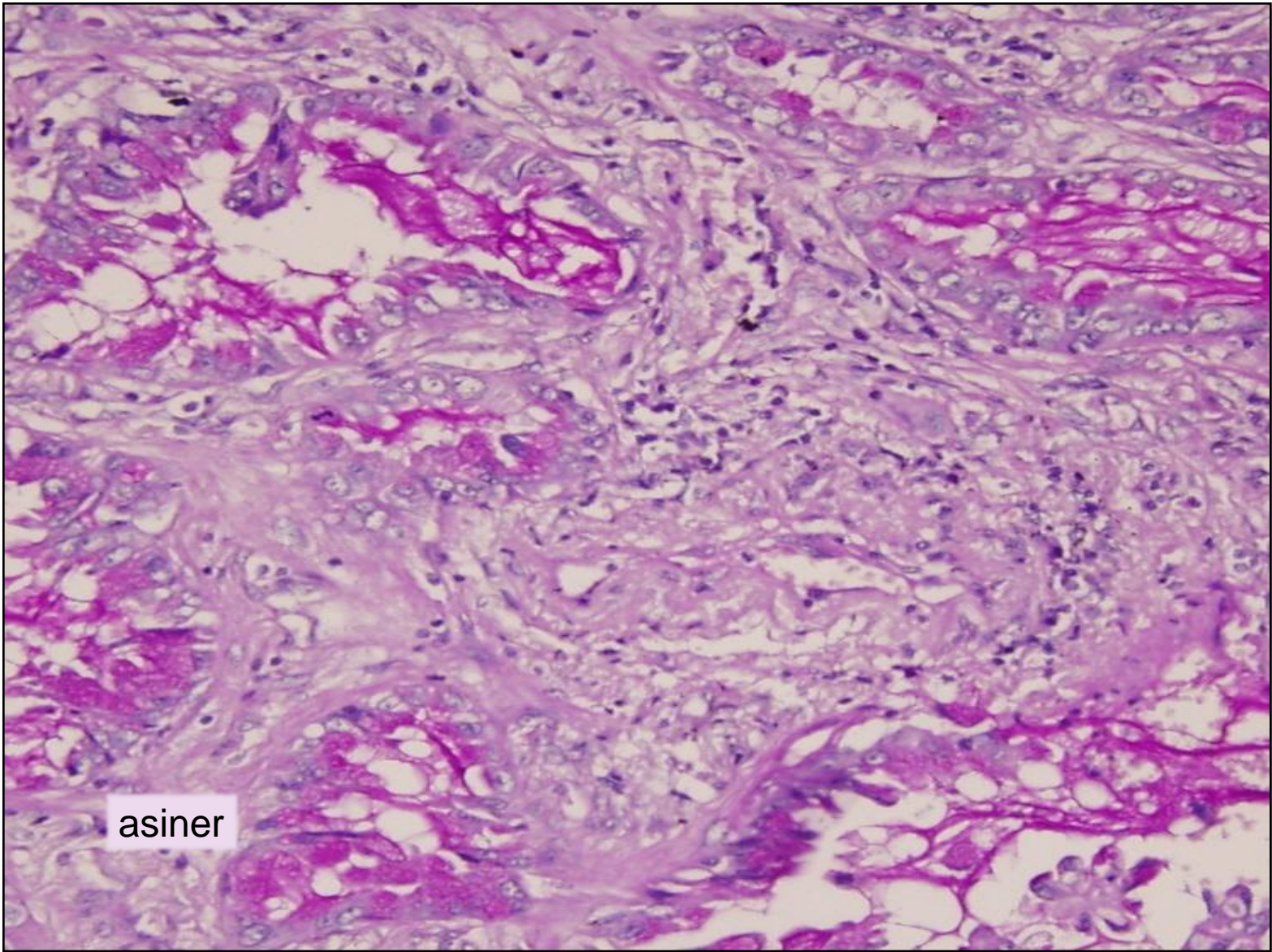




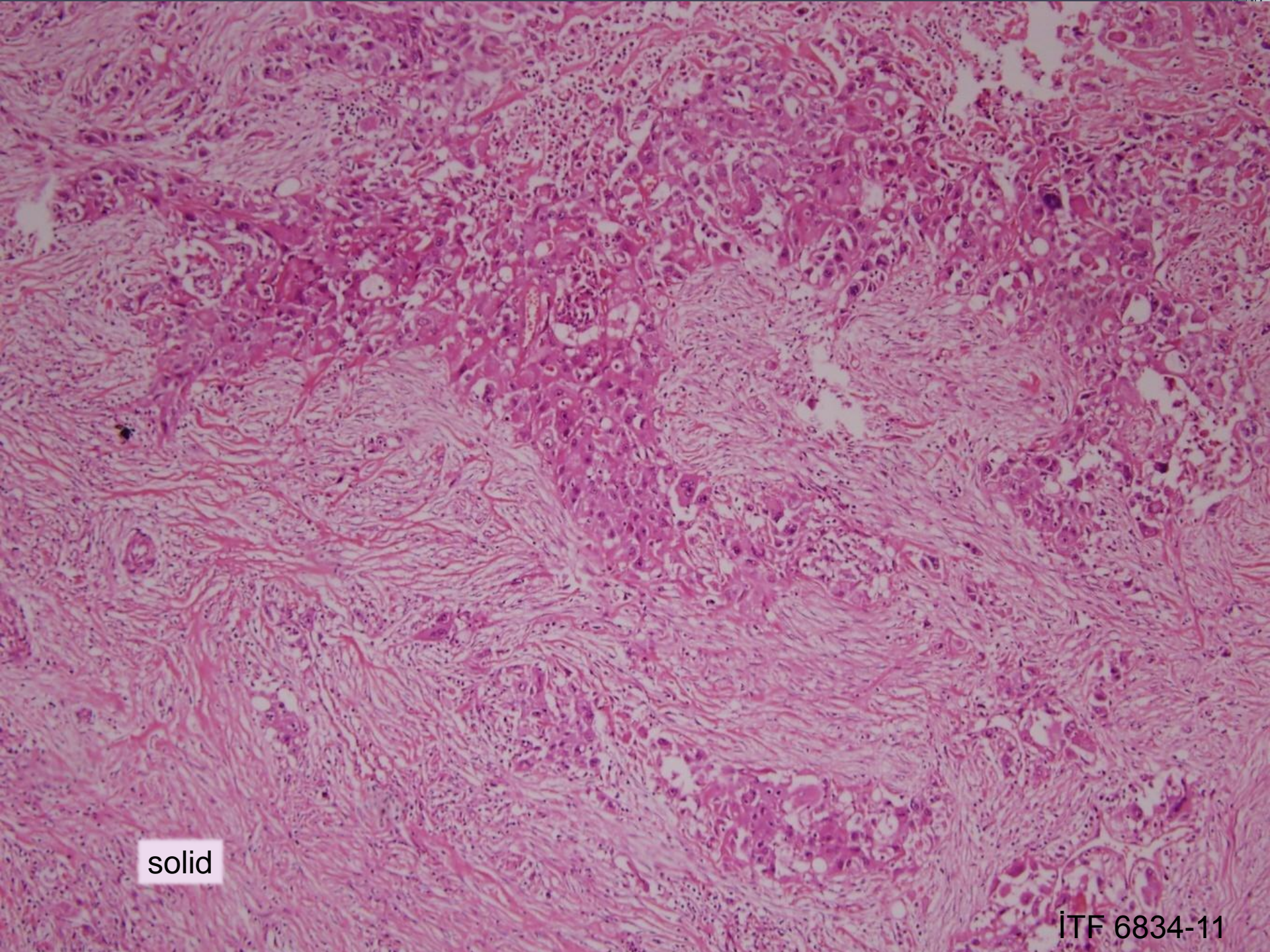


papiller

ITF 6834-11

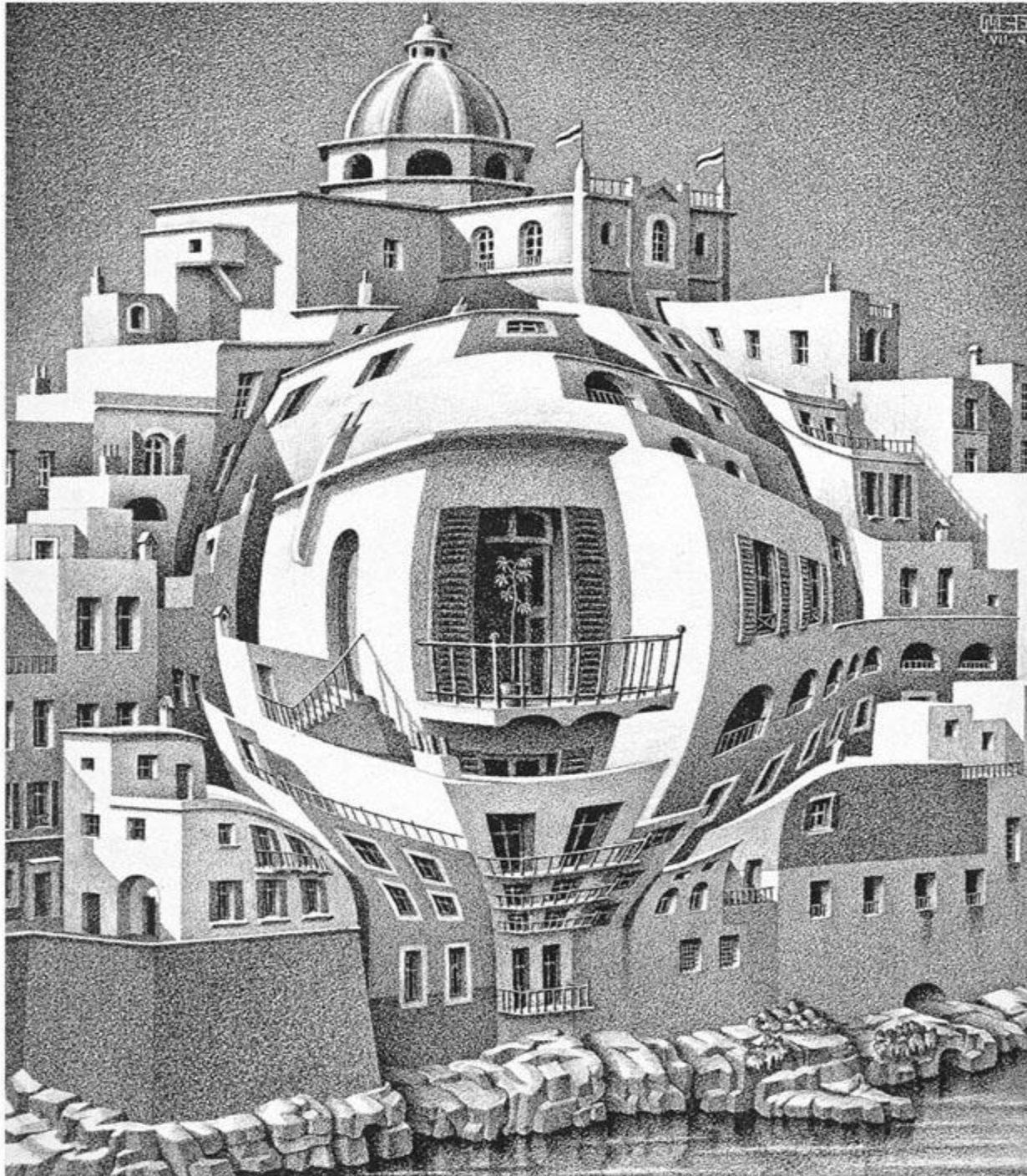


asiner

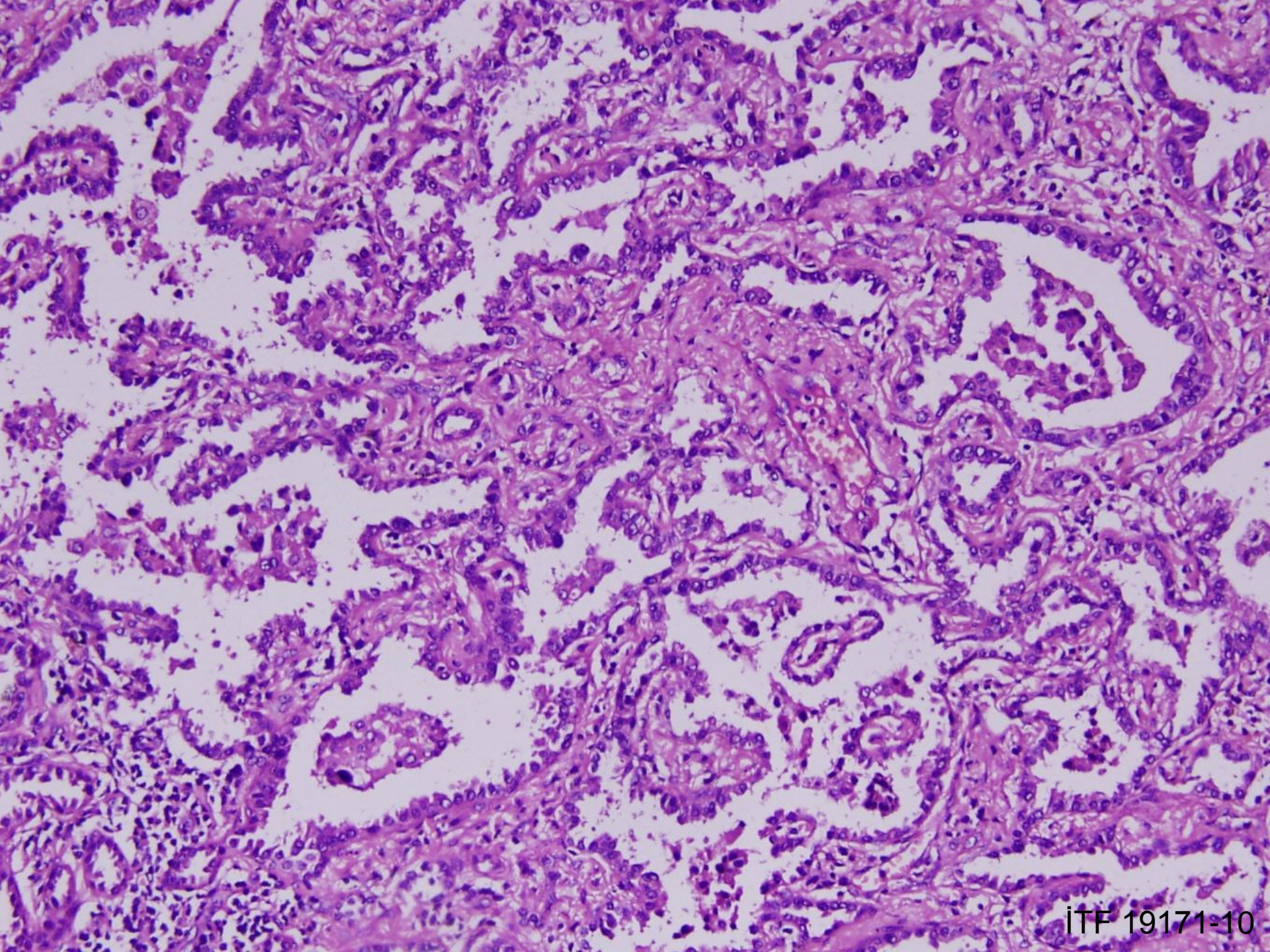


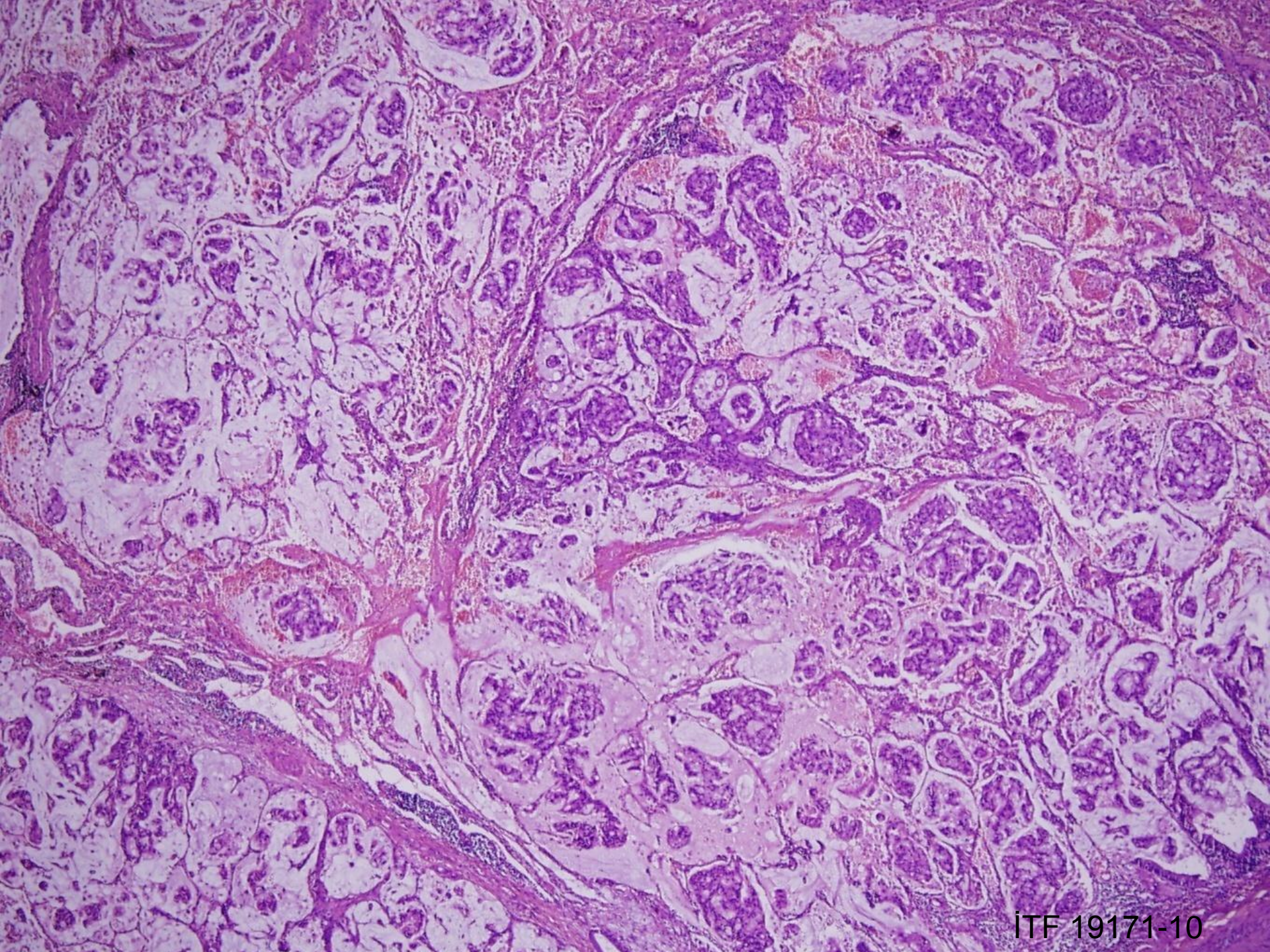
solid

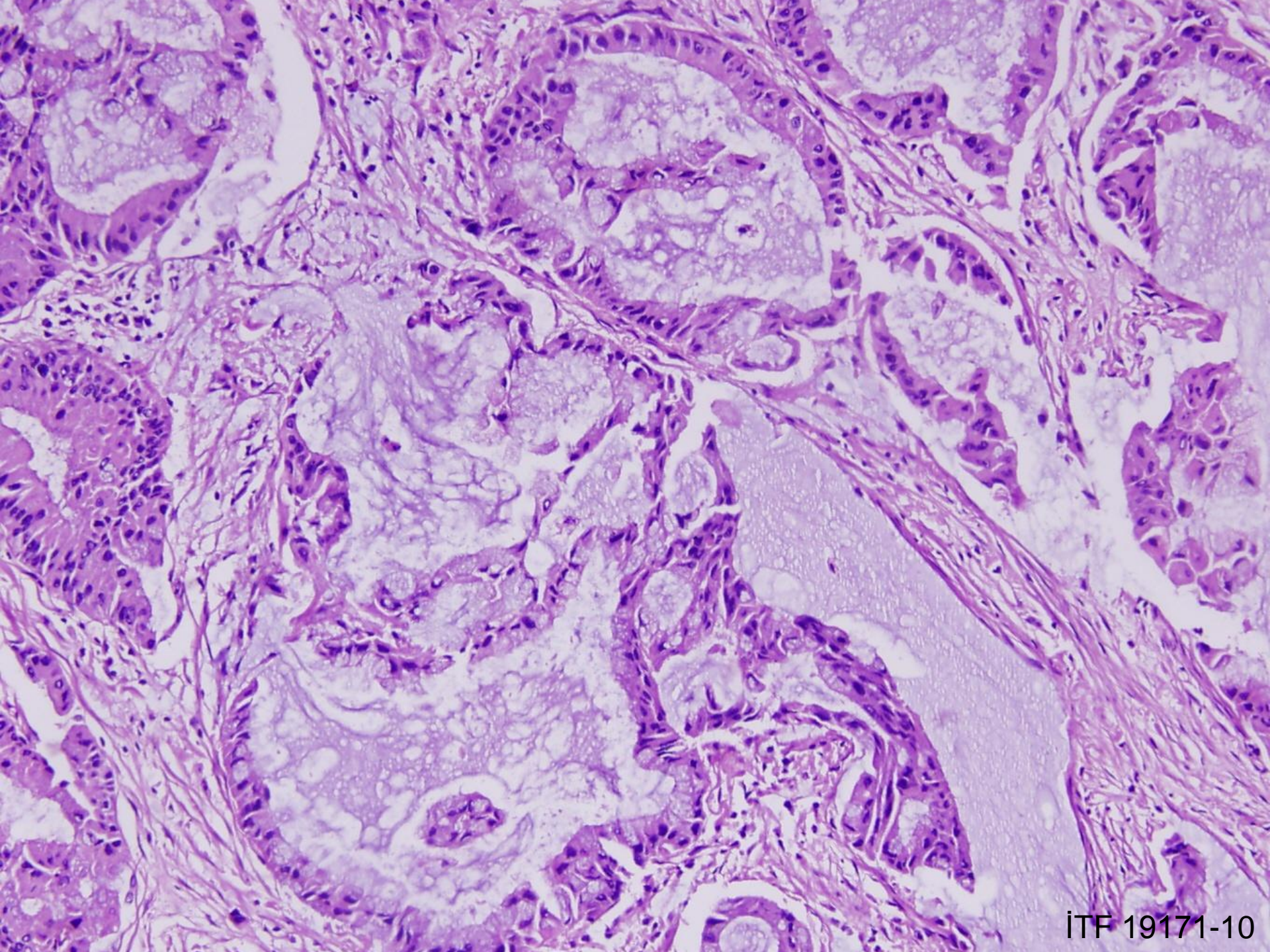
ITF 6834-11



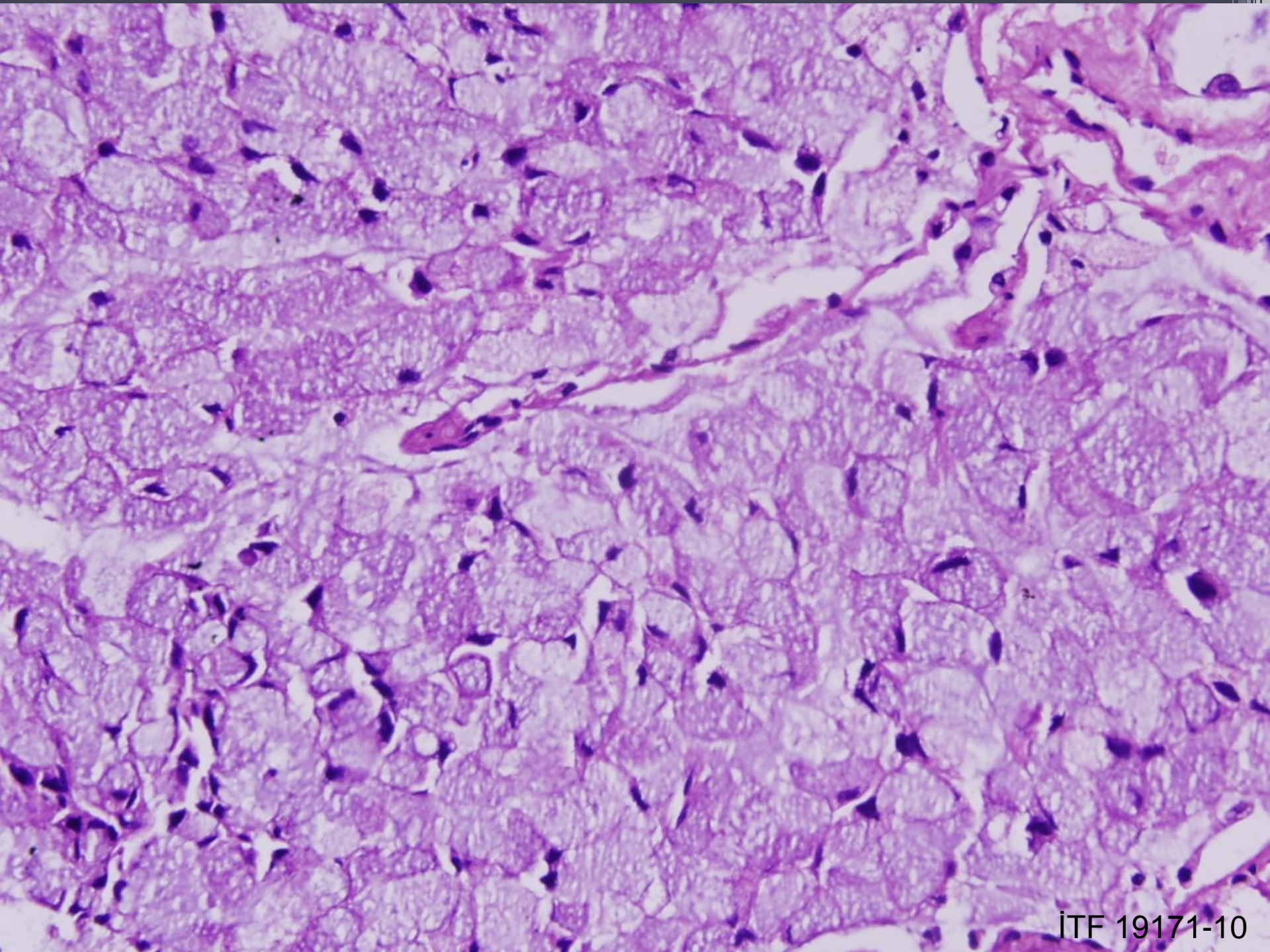
Escher



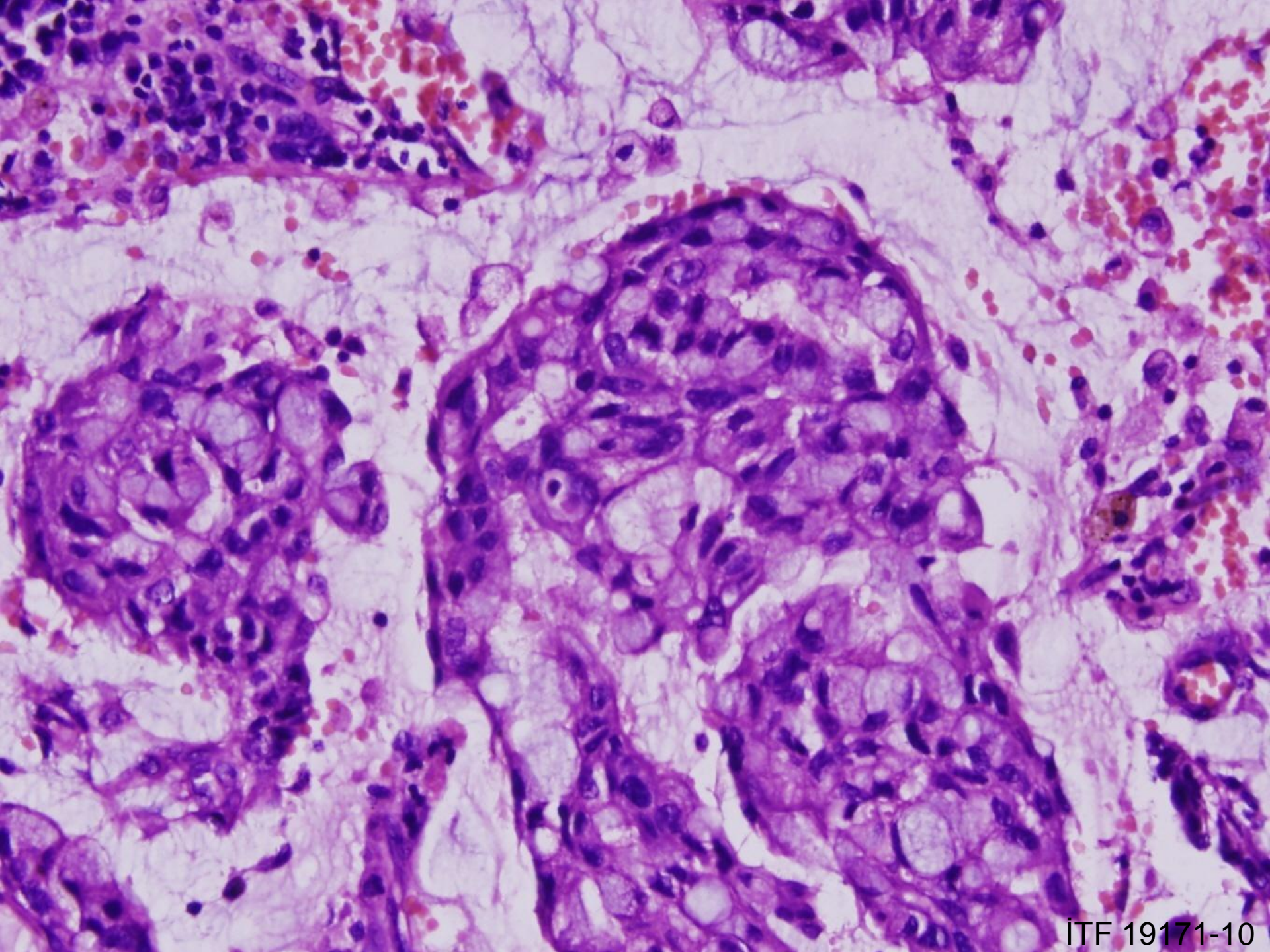




ITF 19171-10



ITF 19171-10





AKCİĞER ADENOKARSİNOMLARI ÇOK HETEROJEN!!

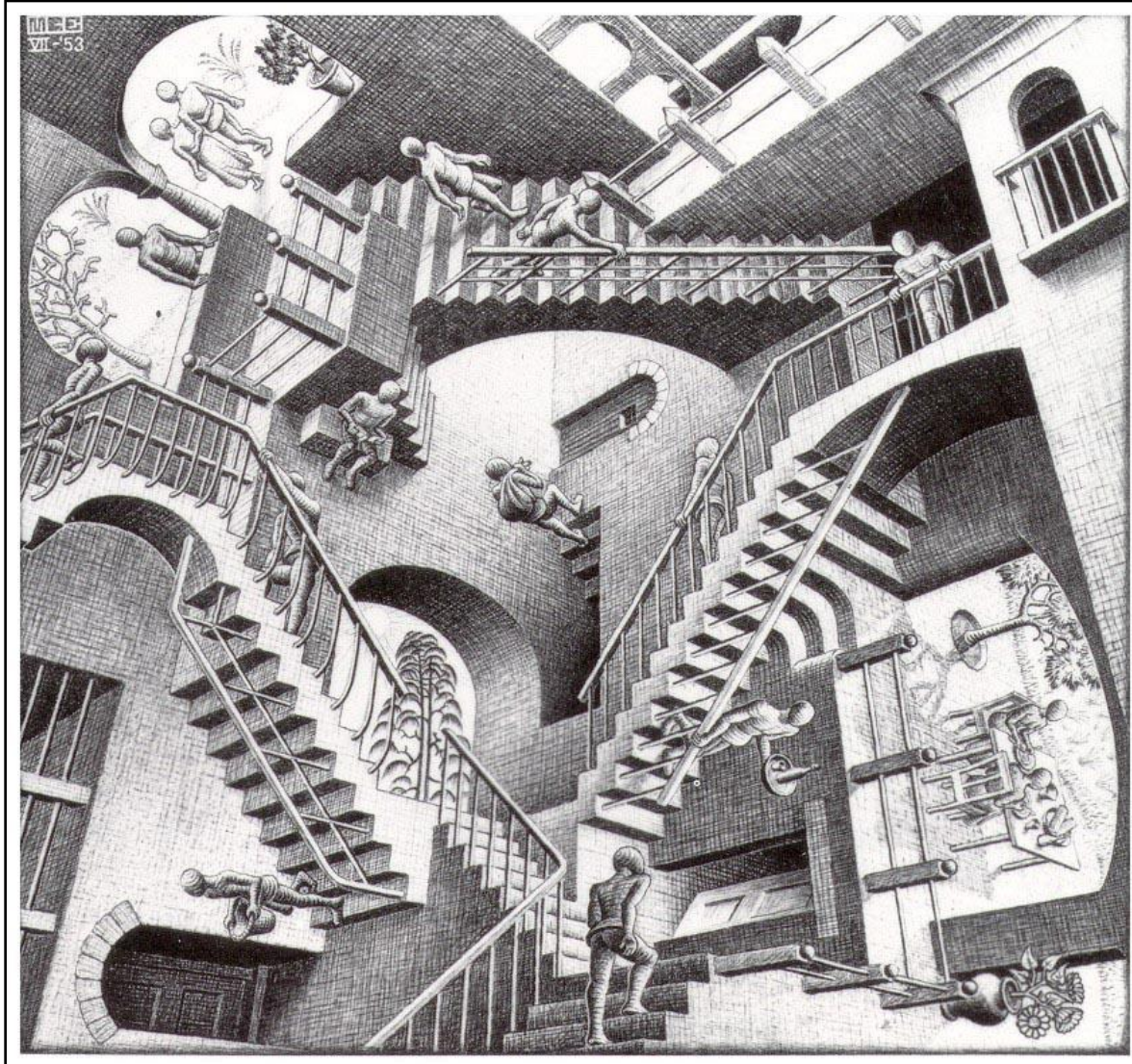
Sonuç olarak;

- BAK parçalandı
 - İnsitu adeno
 - Minimal invazif adeno
 - Lepidik paternli invazif adeno
- İnsitu adenoka boyut önemli
 - Eski BAK
 - $3\text{cm} > \text{tm}$
- Mikroinvazif eklendi
 - $5\text{mm} < \text{lepidik}$

- Mikst tip kalktı
 - Üstün patternle adlandırılacak
 - Oranlar yazılacak
 - %5-10 katılan komponent belirtilecek
 - Müsinöz-nonmüsinöz çok nadir, %10 iki komponent varsa “mikst müsinöz-nonmüsinöz adenoCA” denebilir!
- Mikropapiller adenoka
 - Mikrovasküler kor içermeyen papilla **Prognoz kötü**
- Eski müsinöz BAK
 - İn situ müsinöz (çok nadir)
 - Müsinöz adenokarsinom lepidik patternli

- Lepidik patternli müsinöz BAK
 - En sık kras
 - Multifokalite
- Berrak ve taşlı yüzük kalktı
- Enterik adenoca geldi
 - CK20 +, CDx2 +, TTF-1 –
 - CK7 -, surkatan apop A-, villin+, muc2+
 - GIS tm met dışlanmalı

Teşekkür ederim...



Escher