# Intrahepatic Cholangiocarcinomas Have Histologically and Immunophenotypically Distinct Small and Large Duct Pattern

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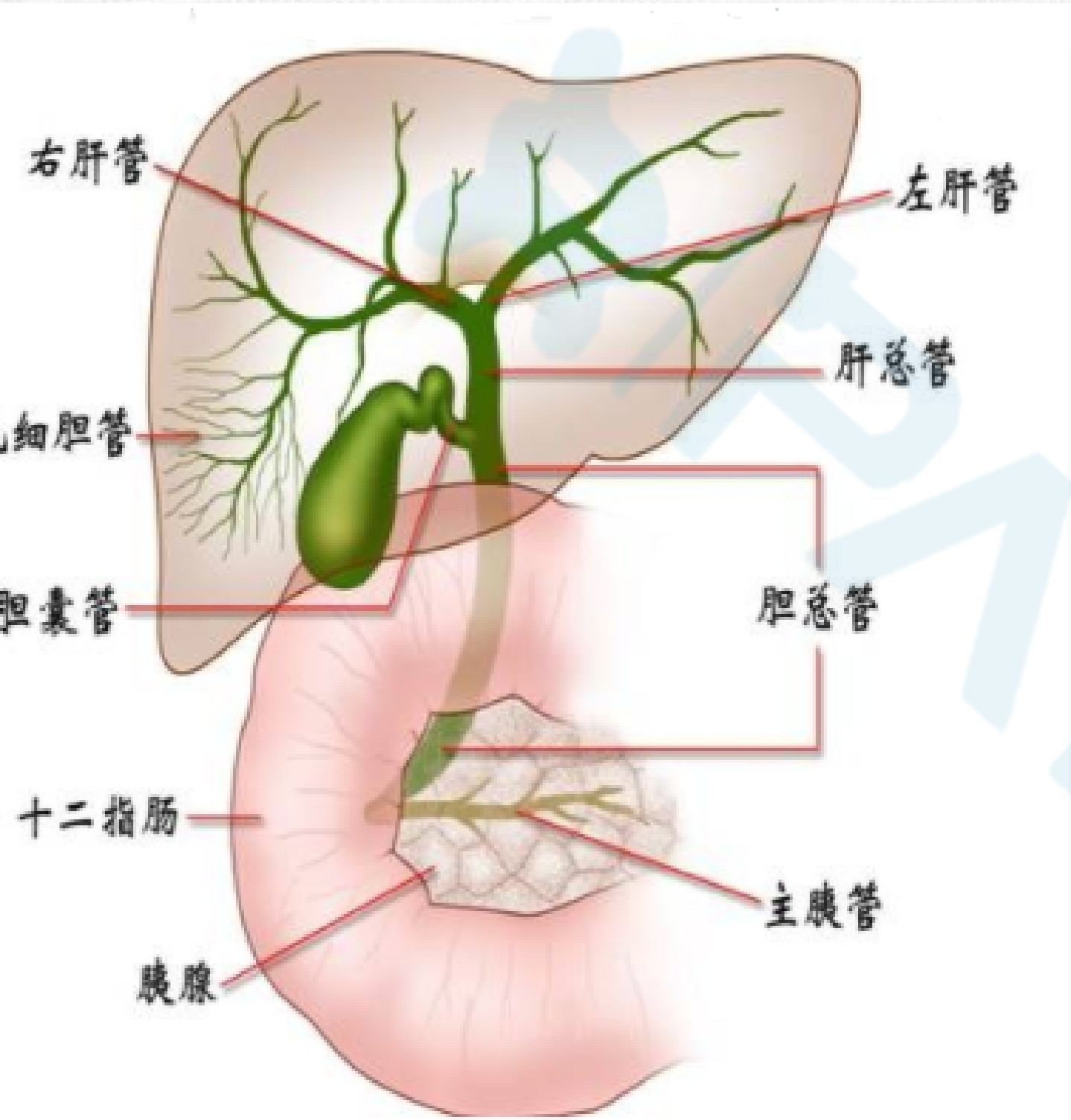
# 解剖学




肝左右肝管分别由左右半肝内的毛细胆管逐渐汇合而成，走出肝门之后即合成肝总管。

# 解剖学

- 胆管系统
  - 肝内胆管
    - 肝门部胆管（一级和二级分支肝内段）
    - 周围胆管（肝内胆管和二级分支以上）
  - 肝外胆管

# 肝内胆管细胞癌（Intrahepatic Cholangiocarcinomas, ICC）

定义：发生在二级胆管至小叶间胆管的原发性胆管细胞癌，约占胆管细胞癌的10%，在原发性肝脏恶性肿瘤中占5%-10%。

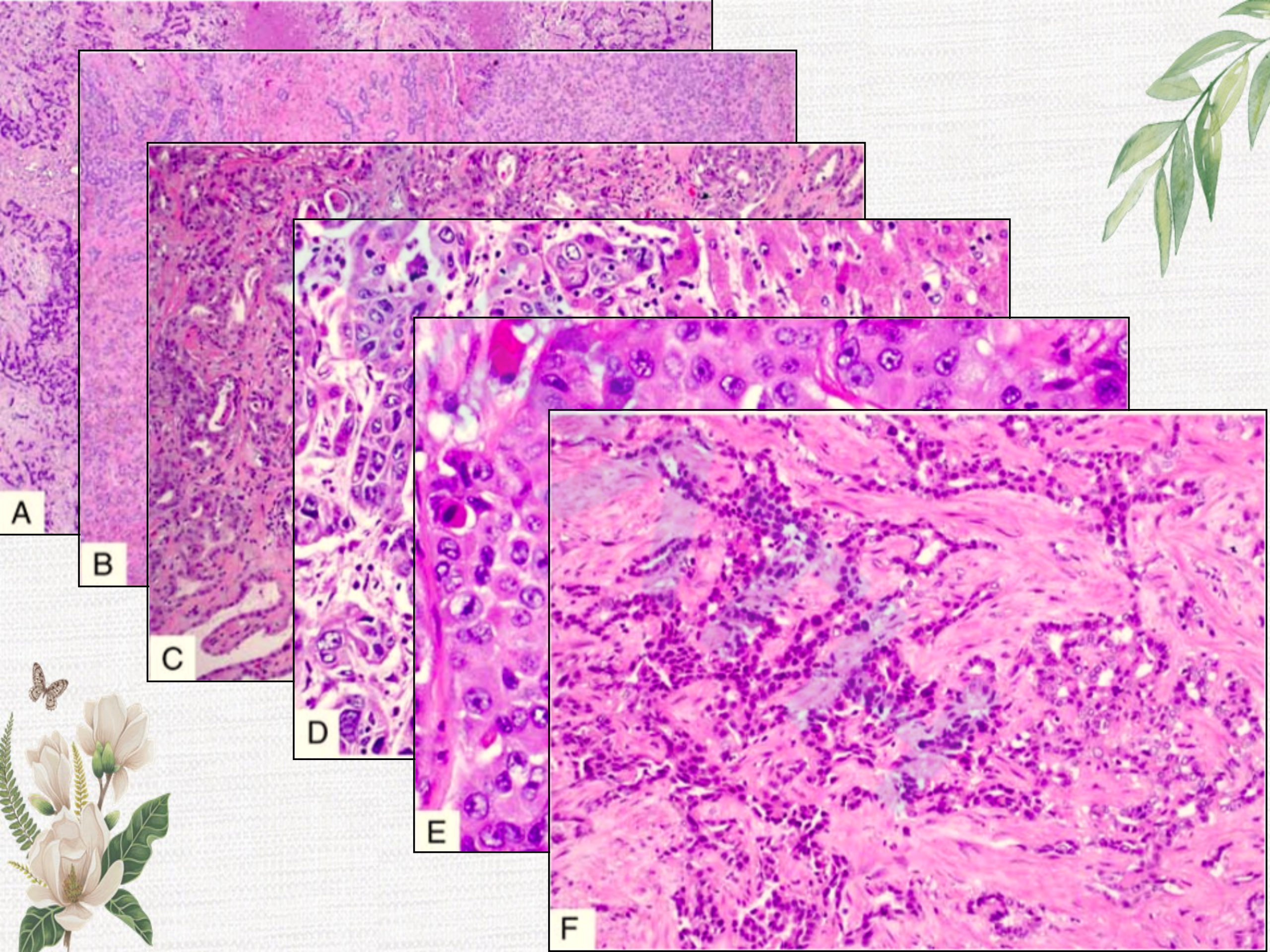
流行病学：多发生于60-70岁，男性稍多于女性，但无明显优势。

临床表现：缺乏典型的临床症状，可有腹痛、消化不良等非特异性症状。具有起病隐匿，发展迅速，恶性程高，预后不佳的特点。

# ICC

**病理特点：**依据肿瘤大体表现分为结节型、管周浸润型和管内型。其中结节型最多见，管内型外科手术切后预后好于其他类型。

镜下：大多数ICC为不同分化程度的腺癌，伴纤维间质反应。类似于肝门，肝外胆管或胰腺的腺癌。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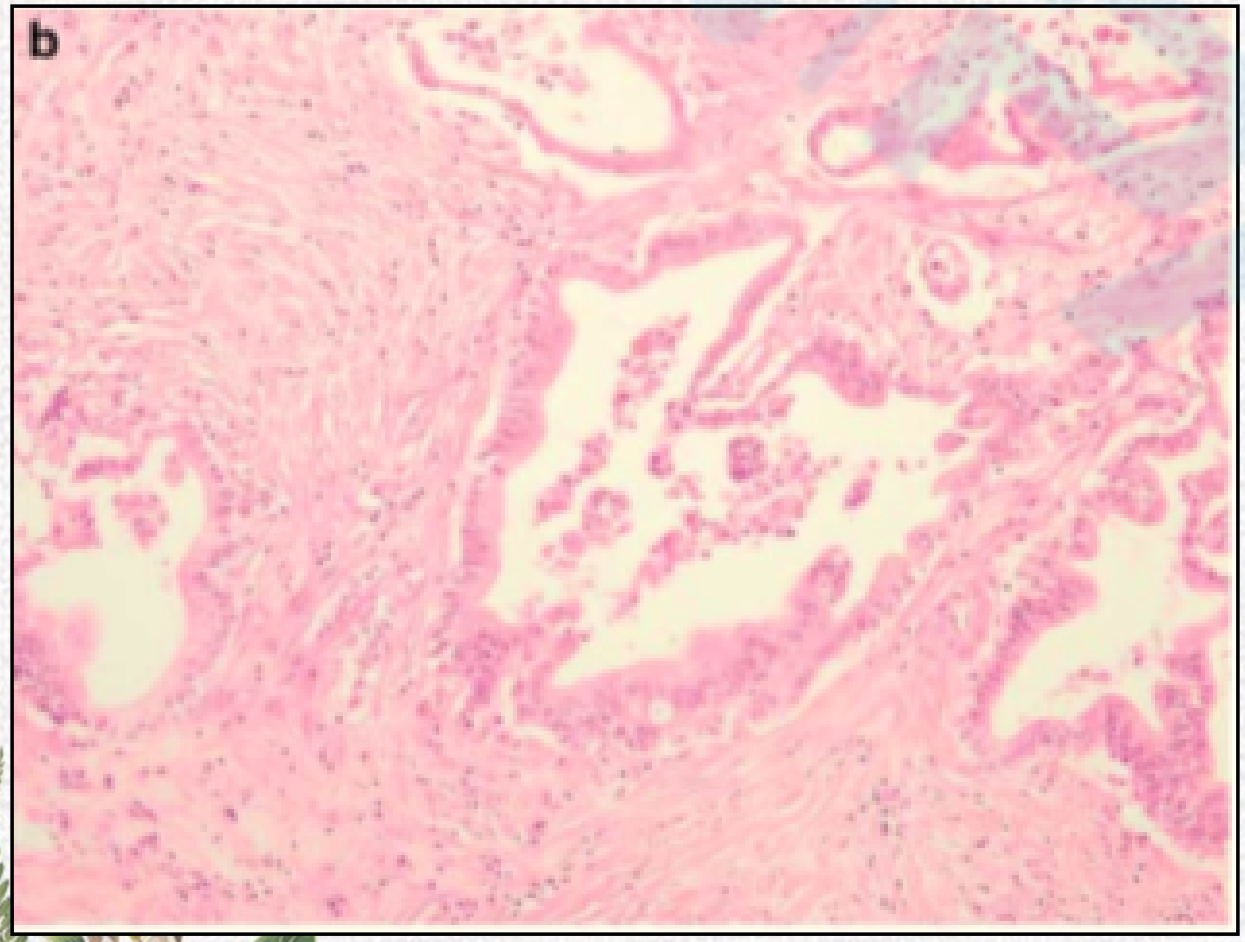
依据解剖结构分为：

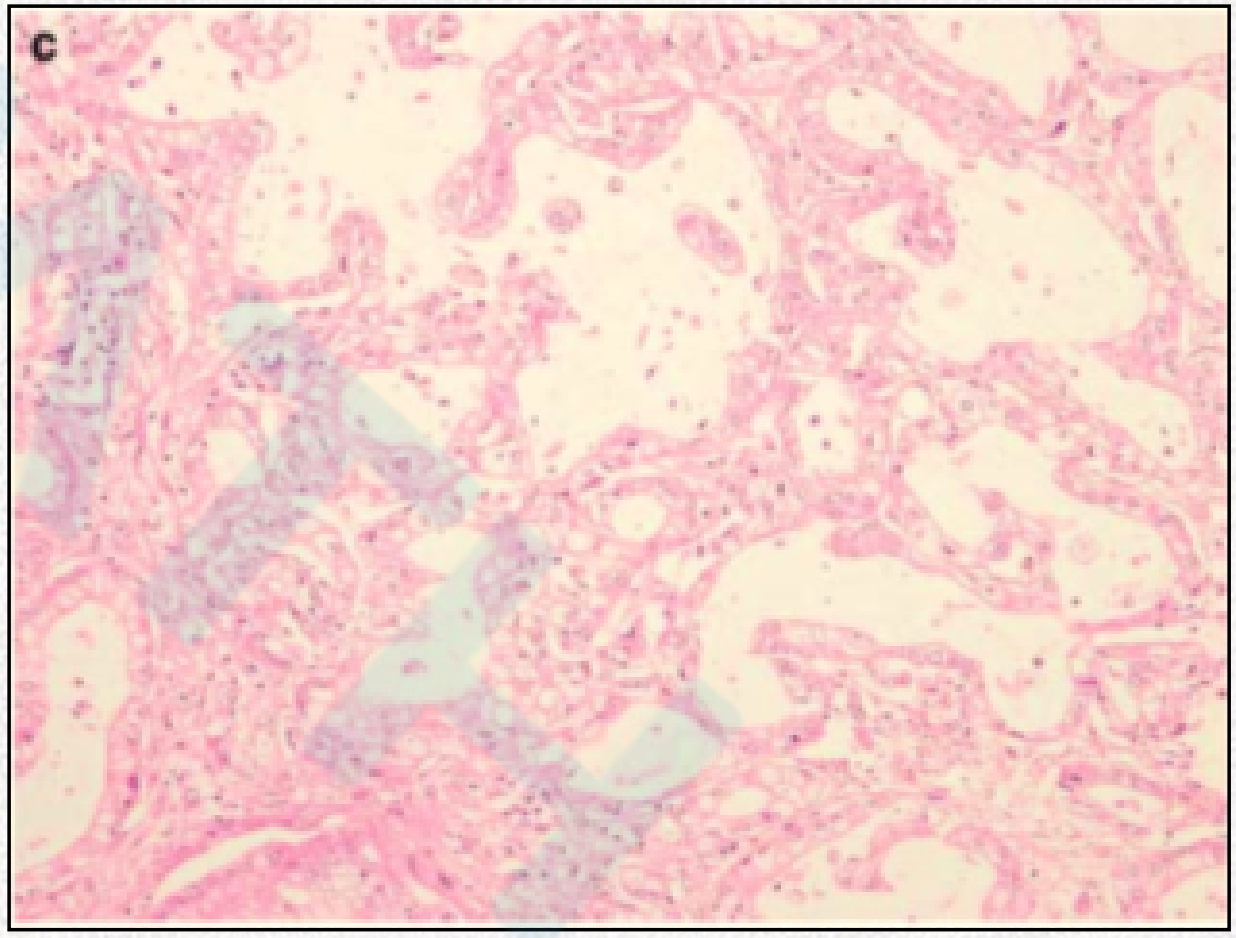
大管型（肝门型）ICC

小管型（周围型）ICC

# 大管型 ICC

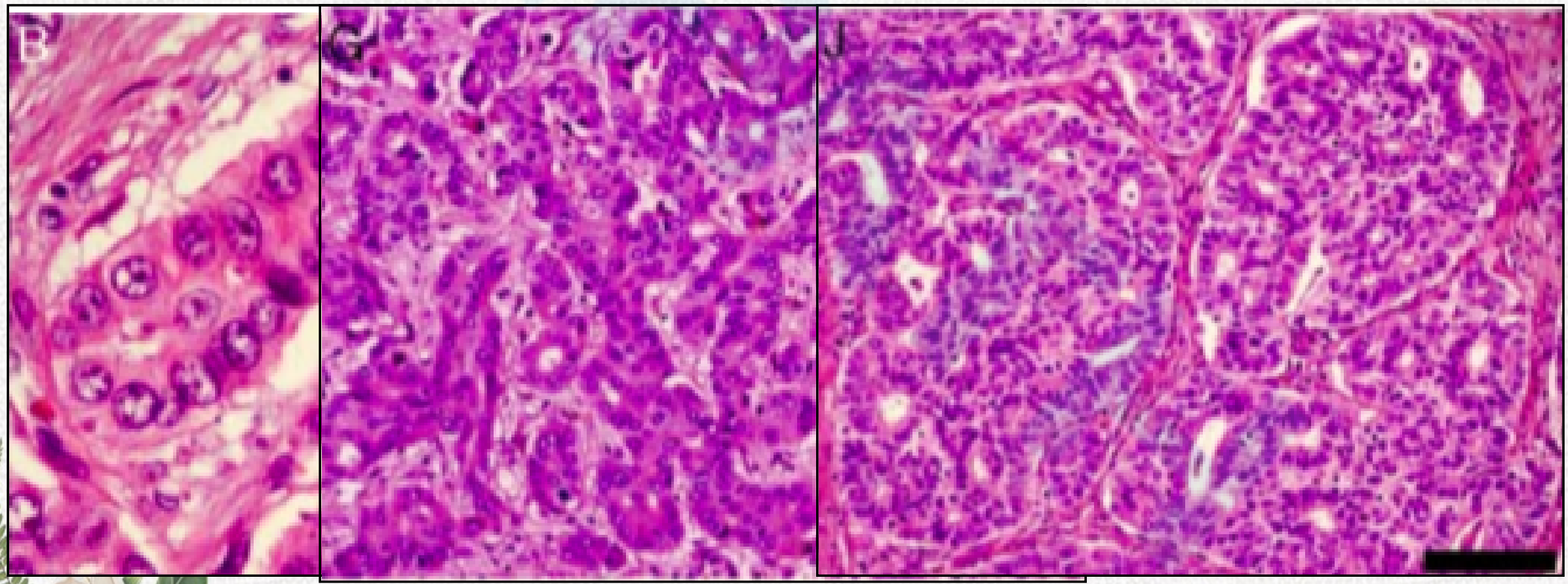
常起源于肝门部大胆管，由具有大导管或乳头状结构的富含黏液的柱状肿瘤细胞组成，并表现出浸润或扩张的生长模式。



# 小管型 ICC

起源于肝内导管周围腺体，由缺乏黏液的的立方体细胞组成，形成小的导管或管状结构，并形成分支状、筛状、乳头状等模式。



# 大管型 ICC *vs* 小管型 ICC

危险因素：大管型ICC：慢性胆道疾病（如：肝内胆管结石和原发性硬化性胆管炎）或胆管上皮内瘤变。

小管型ICC：与慢性肝炎或肝硬化相关

基因改变：大管型ICC：KRAS、SMAD4突变。

小管型ICC：IDH1/2、BAP1、FGFR2

# 材料 & 方法

**病例：**共184名临床上通过常规检查（包括临床表现、影像学改变、上、下消化道内窥镜检查和外科手术）确定患有ICC的患者。共分为4组：大管组（LD），小管组（SD1、SD2），IND组（不明确组）。

**方法：**免疫组化：HepPar1 、Arginase-1 、Glypican-3 、S100P 、 CD56、 CK19、CA19-9、CK7。

原位杂交：检测白蛋白RNA。

# 结论

**TABLE 1.** Clinical Characteristics

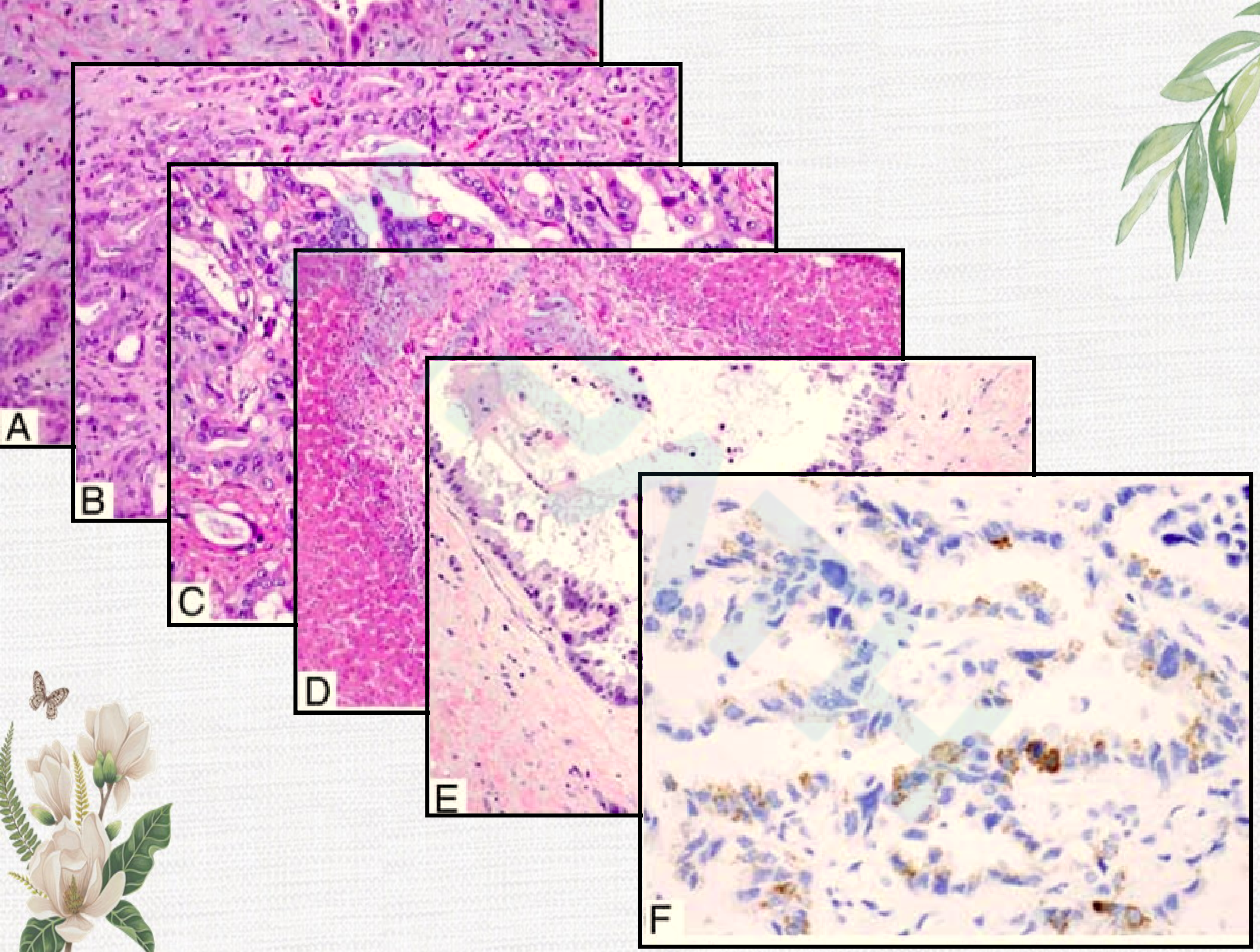
| Characteristic | Number Tested | N (%) |
|---|---|---|
| Age at diagnosis (median/IQR) (y) | 184 | 66 (57.75-74) |
| Sex | 184 | |
| Female | | 103 (0.56) |
| Male | | 81 (0.44) |
| Never | | 99 (0.54) |
| Frequent alcohol use | 183 | 16 (0.09) |
| Cirrhosis | 178 | 15 (0.08) |
| Steatosis | 184 | 6 (0.03) |
| Tumor size (median, IQR) | 183 | 6 (4-8.9) |
| Mass forming | 184 | 165 (0.90) |
| Periductal infiltrating | 182 | 17 (0.09) |
| Satellite nodules | 184 | 54 (0.29) |
| Associated with an intraductal neoplasm | 184 | 5 (0.03) |

HBV indicates hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range.

男：女=81:103，中位年龄66岁。 110例患者可得到血清学结果，肝炎患者占17%。吸烟占46%，酗酒患者为9%，肝硬化病人8%，自身免疫疾病患者占8%，脂肪变性占3%，原发性硬化性胆管炎比例为2%。

# 入组标准

**LD组：**肿瘤成分主要为由大的不规则浸润的腺体组成，腺体被覆柱状细胞，小灶出现的微乳头或小管样结构也纳入LD组。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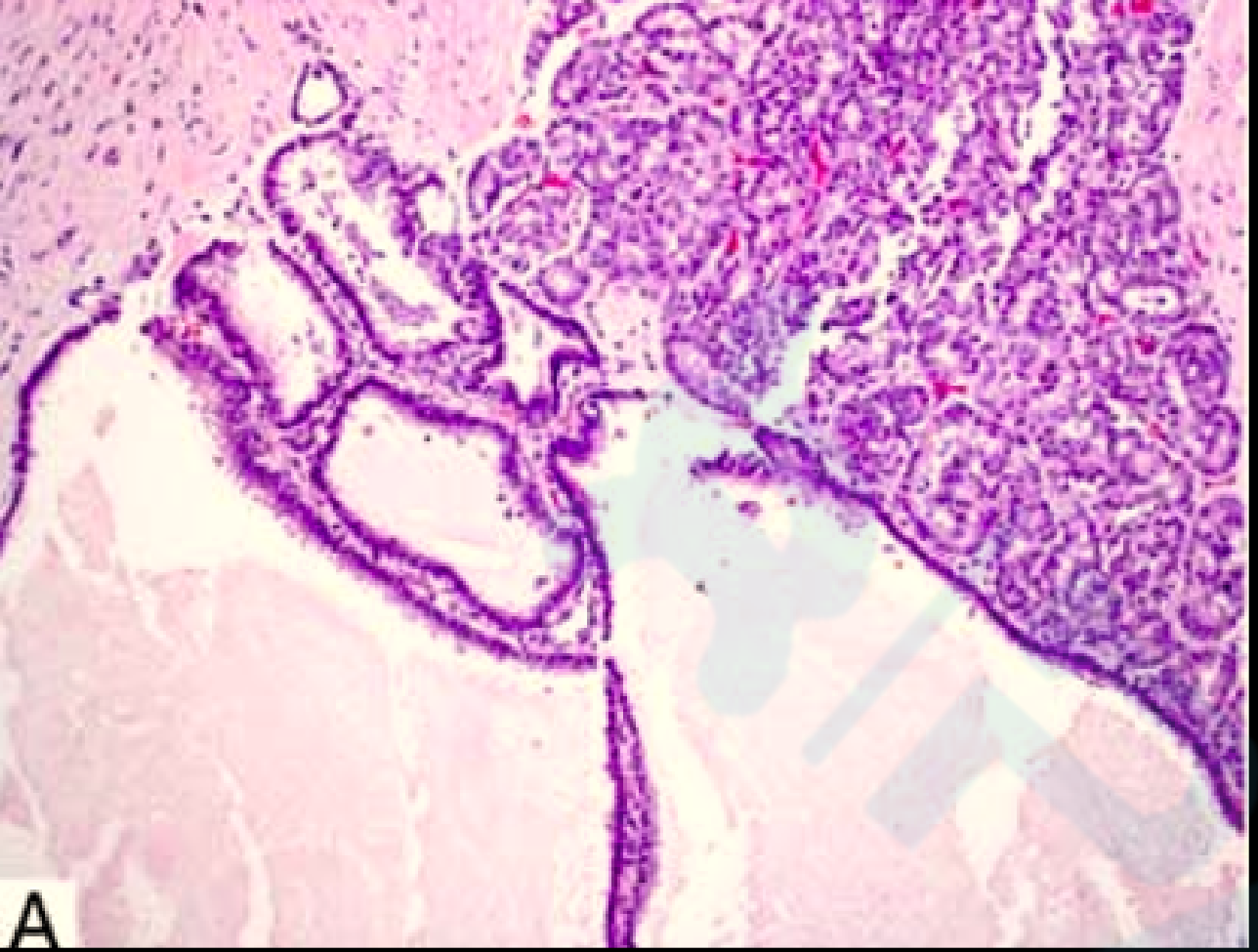
# 入组标准

**SD组：**肿瘤主要由小至中等大小和/或吻合异型腺体组成，腺体被覆立方体或多角形细胞。

**SD1：**主要由小至中等大小腺体组成。

**SD2：**主要由吻合腺体组成。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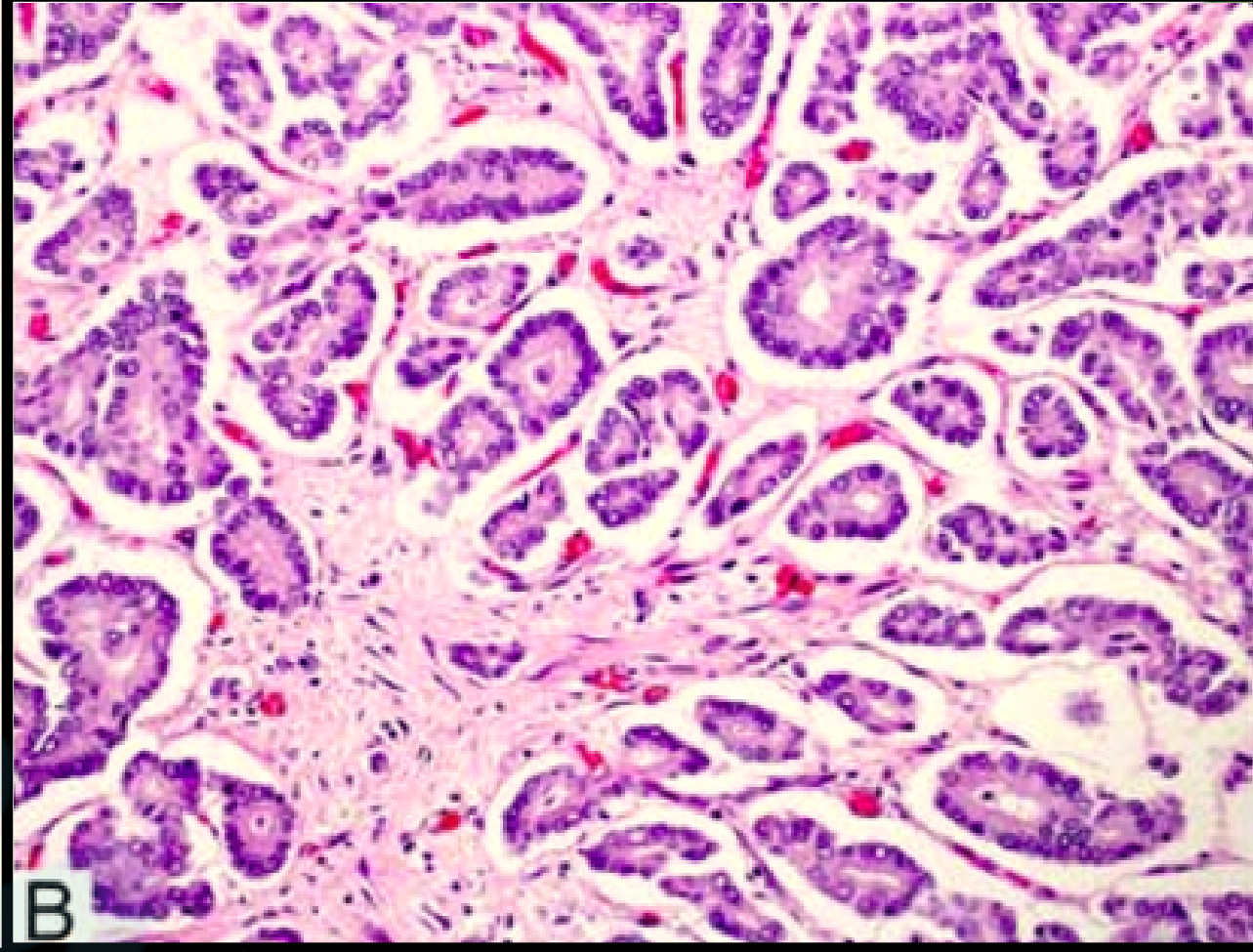
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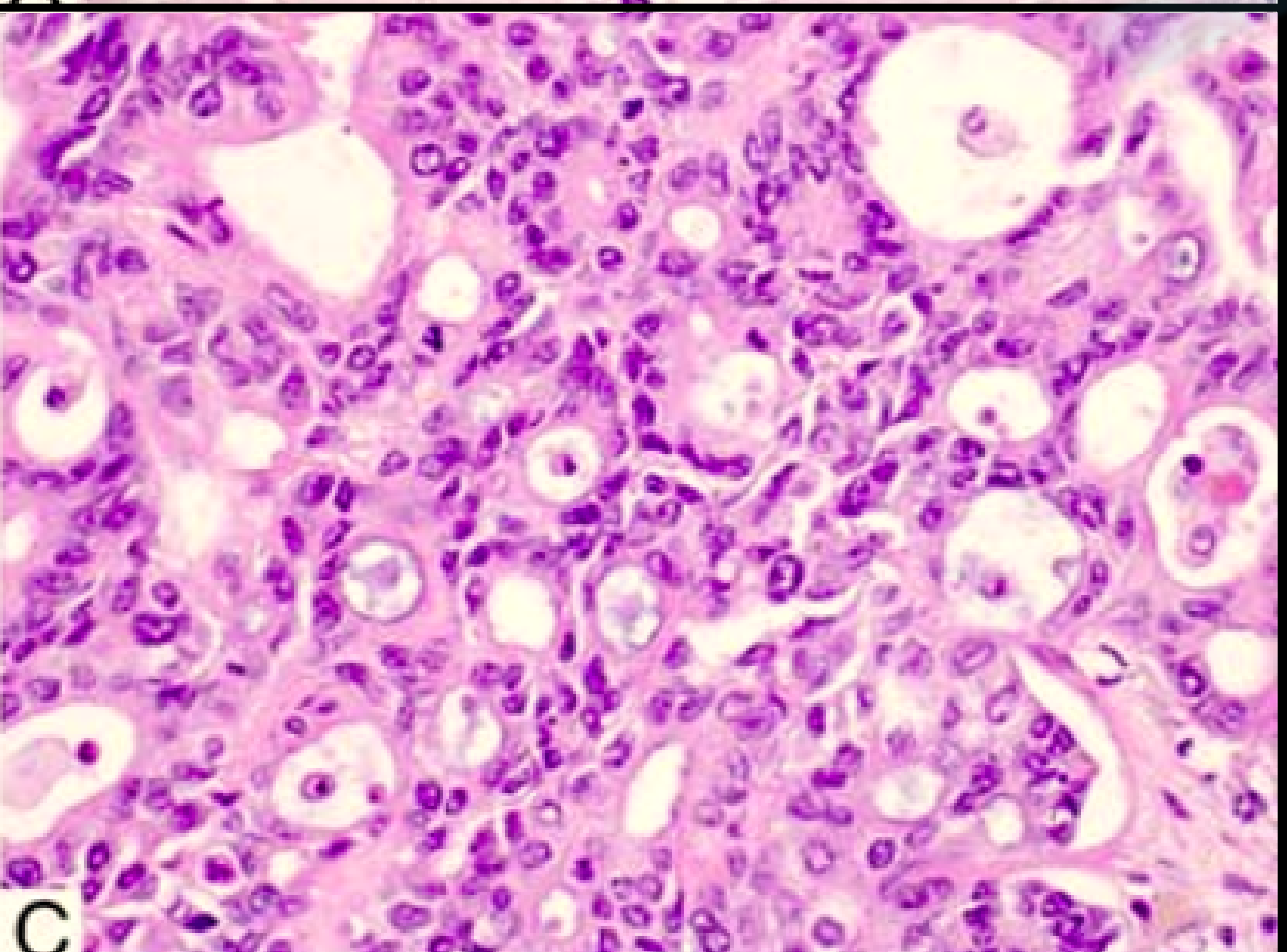
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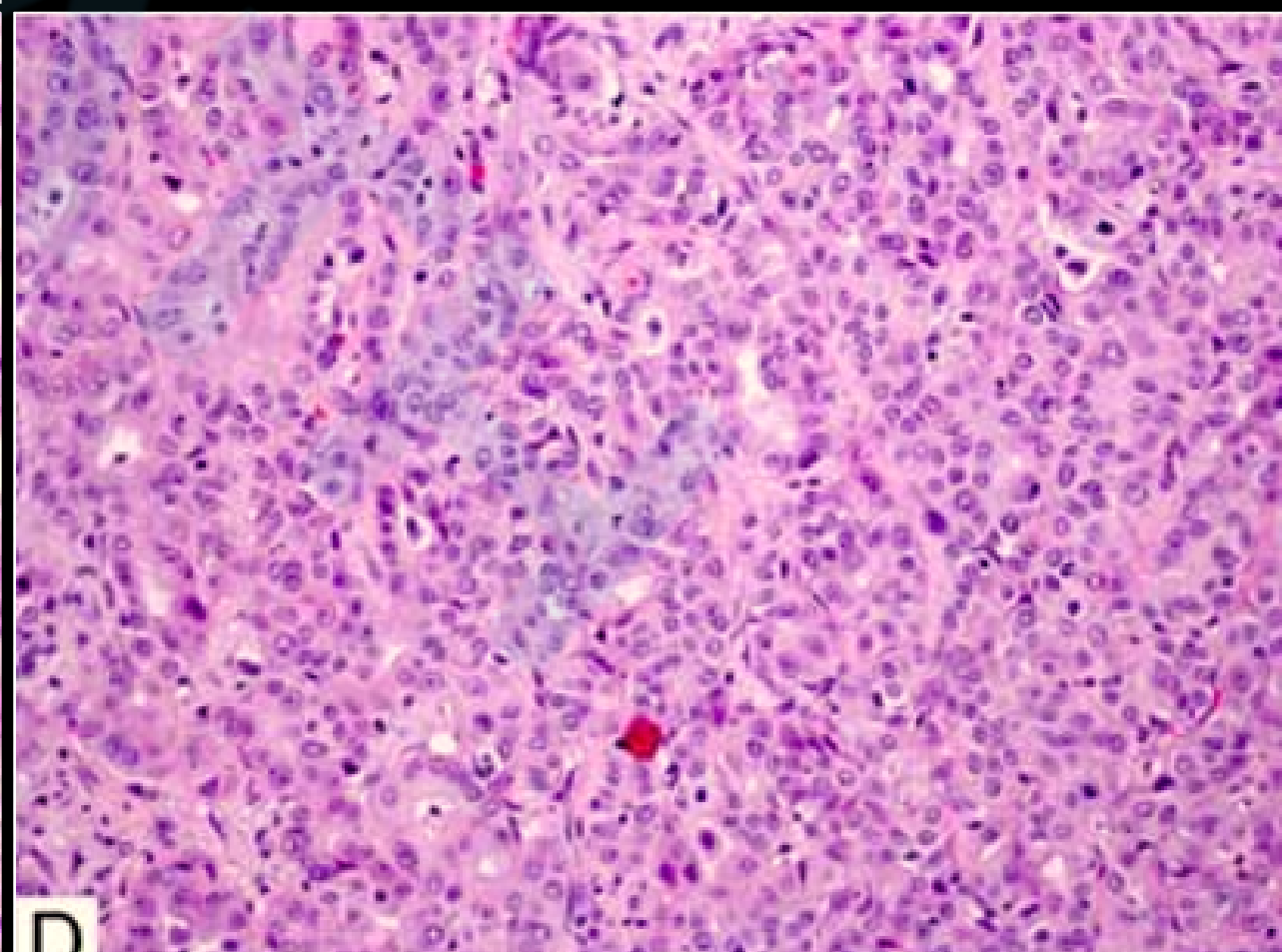
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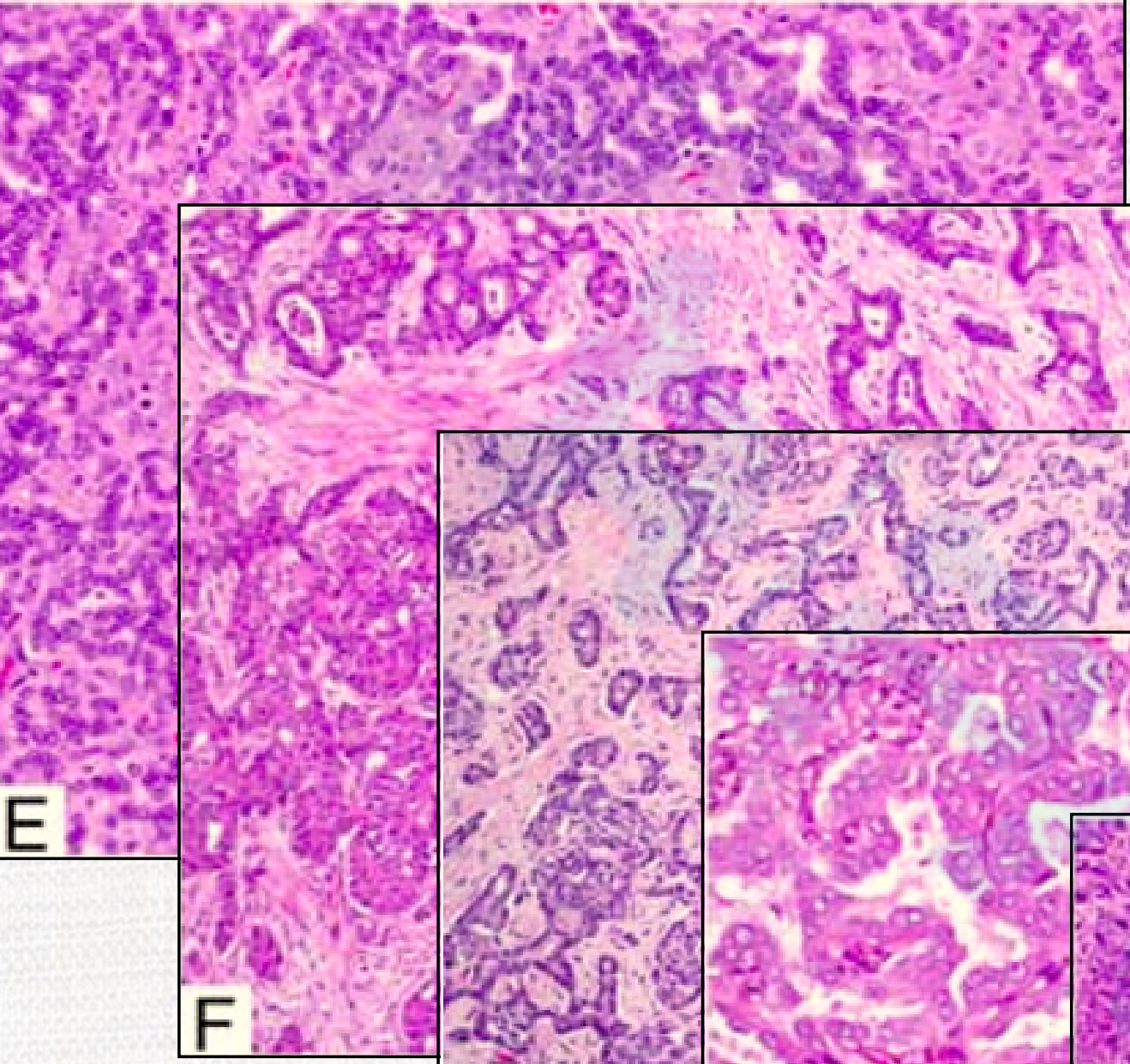
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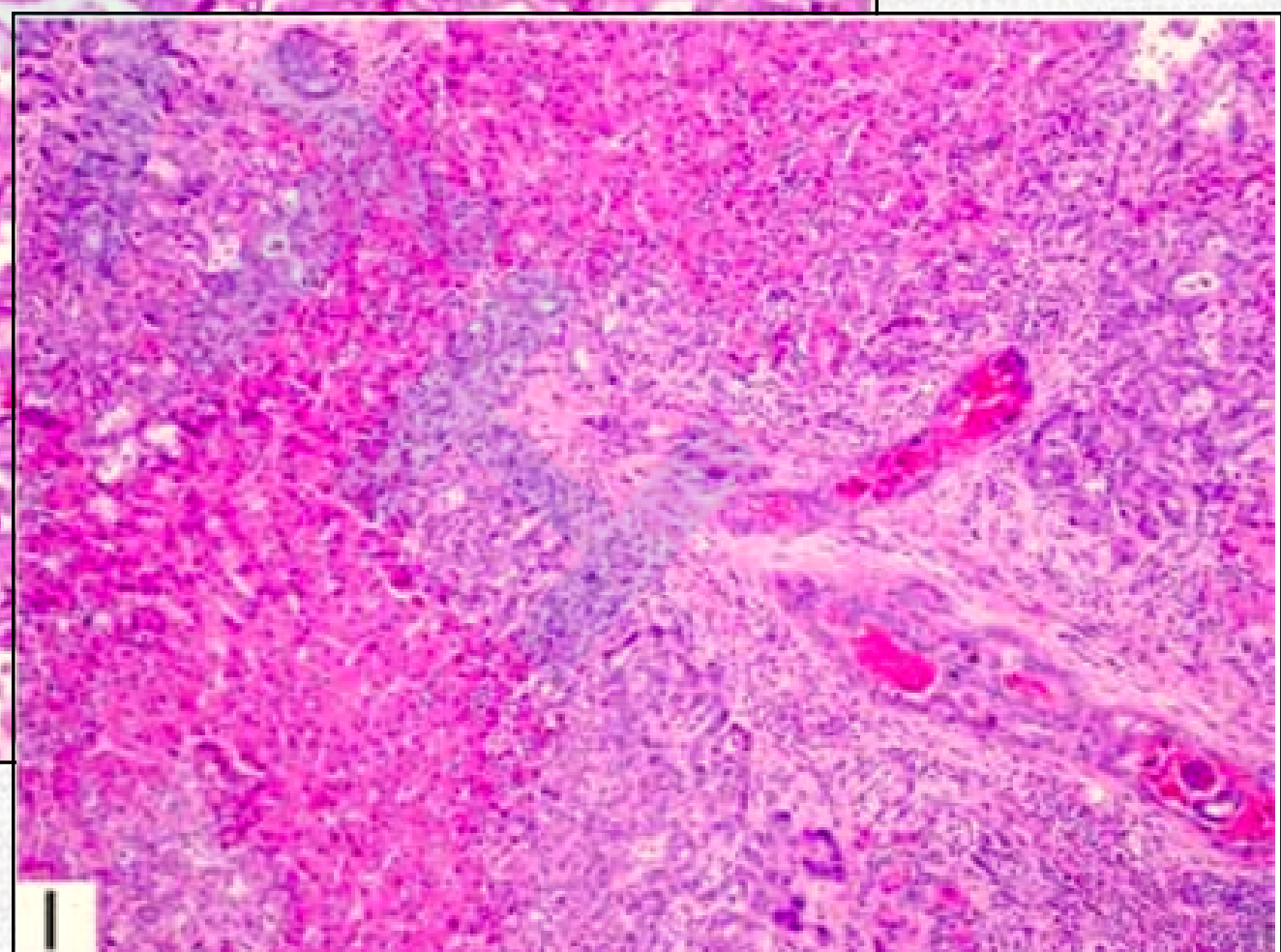
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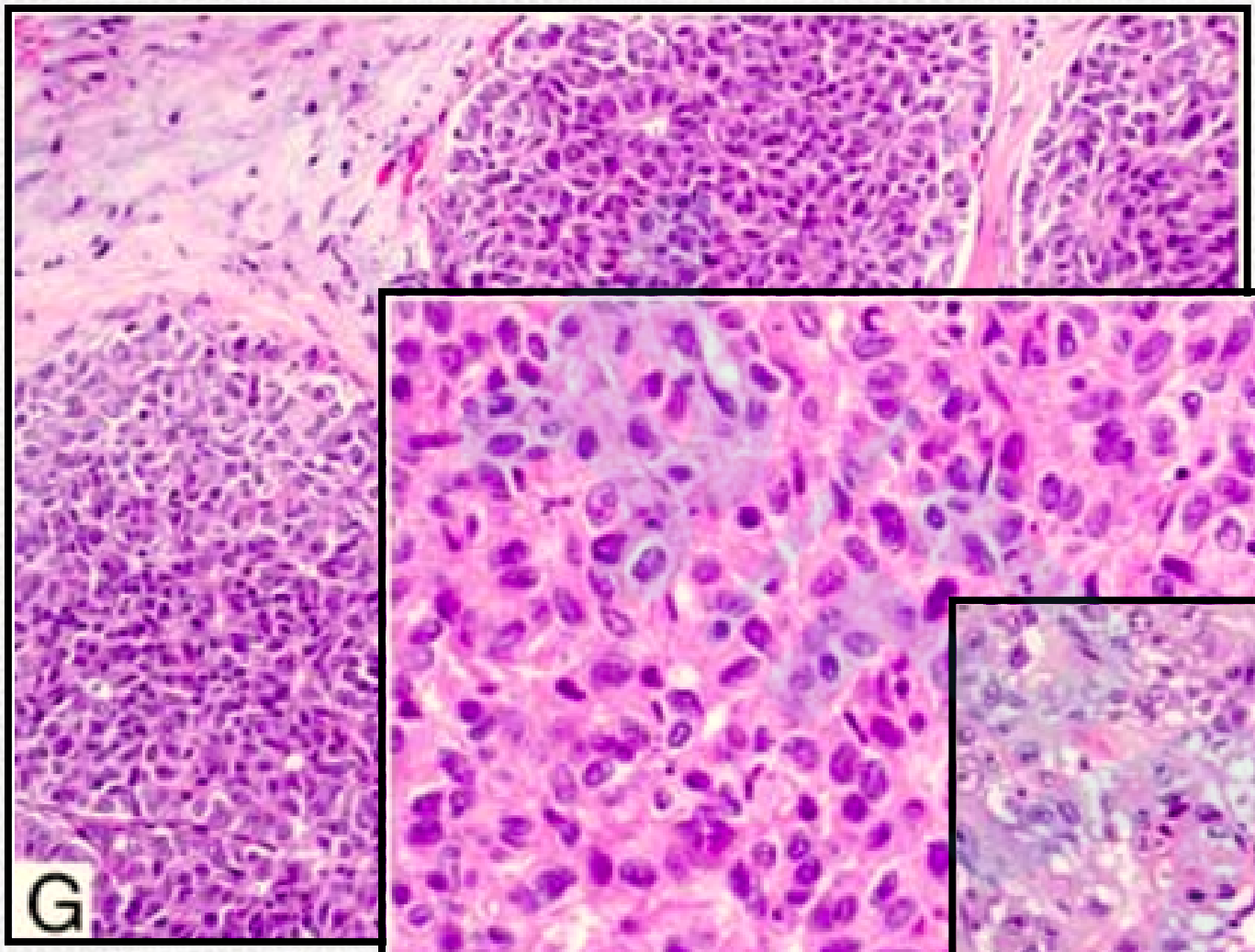
# 入组标准

**IND组：**形态无法纳入LD或SD组的病例。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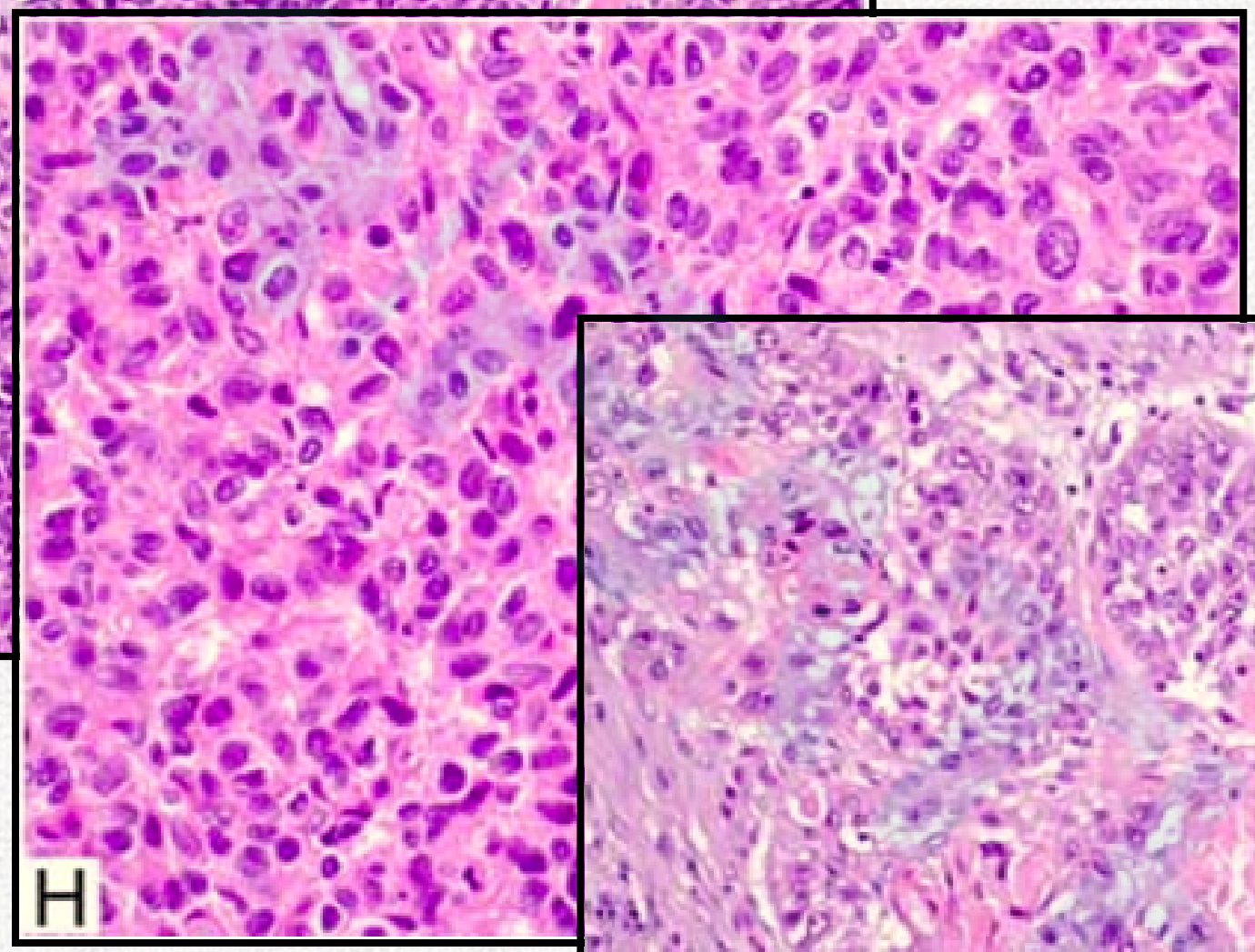
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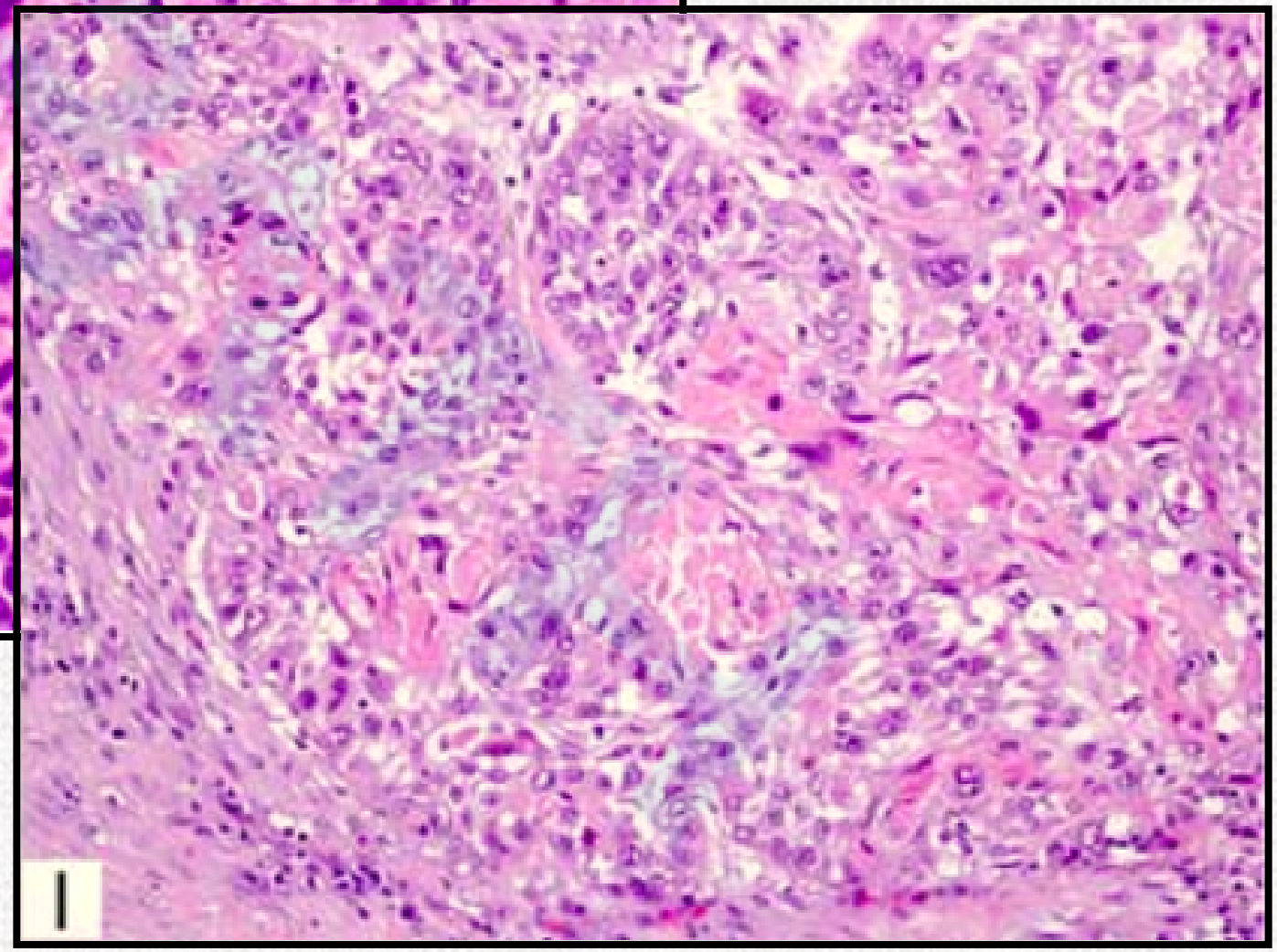
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# 结果

**TABLE 2.** Pathologic Features of Intrahepatic Cholangiocarcinoma by Histologic Type

| | n (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | SD1 (Tubular) (N = 45) | SD2 (Anastomosing) (N = 110) | LD Type (N = 14) | IND (N = 15) | Total (N | for SD | |
| Grade | | | | | | | |
| Low | 30 (0.67) | 82 (0.75) | 12 (0.86) | 4 (0.27) | 12 | | |
| High | 15 (0.33) | 28 (0.25) | 2 (0.14) | 11 (0.73) | 56 ( | | |
| Lymphovascular invasion | | | | | | | 1.000 |
| Negative | 35 (0.78) | 91 (0.83) | 12 (0.86) | 12 (0.8) | 150 (0.82) | | |
| Positive | 10 (0.22) | 19 (0.17) | 2 (0.14) | 3 (0.2) | 34 (0.18) | | |
| Perineural invasion | | | | | | 0.840 | **0.002** |
| Negative | 30 (0.71) | 73 (0.73) | 4 (0.29) | 9 (0.75) | 116 (0.69) | | |
| Positive | 12 (0.29) | 27 (0.27) | 10 (0.71) | 3 (0.25) | 52 (0.31) | | |
| Lymph node metastasis | | | | | | 1.000 | 0.498 |
| Negative | 17 (0.71) | 33 (0.72) | 7 (0.58) | 3 (0.43) | 60 (0.67) | | |
| Positive | 7 (0.29) | 13 (0.28) | 5 (0.42) | 4 (0.57) | 29 (0.33) | | |
| Mass forming | | | | | | | 0.174 |
| Negative | 5 (0.11) | 10 (0.09) | 3 (0.21) | 1 (0.07) | 19 ( | | |
| Positive | 40 (0.89) | 100 (0.91) | 11 (0.79) | 14 (0.93) | 1 | | |
| Periductal infiltrating | | | | | | | |
| Negative | 40 (0.93) | 100 (0.91) | 11 (0.79) | 14 (0.93) | 1 | | |
| Positive | 3 (0.07) | 10 (0.09) | 3 (0.21) | 1 (0.07) | 17 ( | | |
| Satellite nodules | | | | | | | 1.000 |
| Negative | 30 (0.67) | 80 (0.73) | 10 (0.71) | 10 (0.67) | 130 (0.71) | | |
| Positive | 15 (0.33) | 30 (0.27) | 4 (0.29) | 5 (0.33) | 54 (0.29) | | |
| Nodularity | | | | | | 0.368 | **0.019** |
| Negative | 30 (0.67) | 63 (0.58) | 13 (0.93) | 11 (0.73) | 117 (0.64) | | |
| Positive | 15 (0.33) | 45 (0.42) | 1 (0.07) | 4 (0.27) | 65 (0.36) | | |
| Zones of histologic patterns | | | | | | **0.003** | 0.572 |
| Negative | 36 (0.8) | 58 (0.54) | 10 (0.71) | 12 (0.8) | 116 (0.64) | | |
| Positive | 9 (0.2) | 50 (0.46) | 4 (0.29) | 3 (0.2) | 66 (0.36) | | |

LD组更容易出现神经侵犯

SD组结节状形态多见

# 结果

与LD组相比，SD组更容易出现肝样细胞、向周围浸润性生长以及硬化性间质

LD组细胞内、外黏液比SD组更多见

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Extracellular mucin | | | | | | 0.194 | **< 0.001** |
| Negative | 32 (0.71) | | | 11 (0.73) | 135 (0.74) | | |
| Positive | 13 (0.29) | 20 ( | ) | 4 (0.27) | 48 (0.26) | | |
| Intracellular mucin | | | | | | 0.757 | **< 0.001** |
| Negative | 42 (0.93) | 99 (0.91) | 3 ( | 15 (1) | 159 (0.87) | | |
| Positive | 3 (0.07) | 10 (0.09) | 11 (0.79) | 0 | 24 (0.13) | | |
| Hepatoid cytology | | | | | | 0.093 | **0.042** |
| Negative | 30 (0.67) | 88 (0.81) | 14 (1) | 10 (0.67) | 142 (0.78) | | |
| Positive | 15 (0.33) | 21 (0.19) | 0 | 5 (0.33) | 41 (0.22) | | |
| Infiltrative interface | | | | | | 0.291 | **< 0.001** |
| Negative | 8 (0.18) | 12 (0.11) | 10 (0.71) | 9 (0.6) | 39 (0.22) | | |
| Positive | 36 (0.82) | 96 (0.89) | 4 (0.29) | 6 (0.4) | 142 (0.78) | | |
| Stroma poor | | | | | | 0.231 | 0.706 |
| Negative | 35 (0.78) | 94 (0.86) | 11 (0.79) | 12 (0.8) | 152 (0.83) | | |
| Positive | 10 (0.22) | 15 (0.14) | 3 (0.21) | 3 (0.2) | 31 (0.17) | | |
| Desmoplastic stroma | | | | | | 0.453 | **0.001** |
| Negative | 37 (0.82) | 95 (0.87) | 6 (0.43) | 7 (0.47) | 145 (0.79) | | |
| Positive | 8 (0.18) | 14 (0.13) | 8 (0.57) | 8 (0.53) | 38 (0.21) | | |
| Sclerotic stroma | | | | | | 0.205 | **< 0.001** |
| Negative | 13 (0.29) | 21 (0.19) | 10 (0.71) | 9 (0.6) | 53 (0.29) | | |
| Positive | 32 (0.71) | 88 (0.81) | 4 (0.29) | 6 (0.4) | 130 (0.71) | | |
| Scar | | | | | | 0.288 | 0.265 |
| Negative | 24 (0.53) | 47 (0.43) | 9 (0.64) | 10 (0.67) | 90 (0.49) | | |
| Positive | 21 (0.47) | 62 (0.57) | 5 (0.36) | 5 (0.33) | 93 (0.51) | | |
| AJCC 8th ed. stage | | | | | | 0.830 | 0.296 |
| pT1 | 17 (0.38) | 42 (0.38) | 4 (0.29) | 6 (0.4) | 69 (0.38) | | |
| pT2 | 22 (0.49) | 53 (0.48) | 6 (0.43) | 7 (0.47) | 88 (0.48) | | |
| pT3 | 6 (0.13) | 13 (0.12) | 3 (0.21) | 2 (0.13) | 24 (0.13) | | |
| pT4 | 0 | 2 (0.02) | 1 (0.07) | 0 | 3 (0.02) | | |

Values in bold met the set threshold for statistical significance.

# 结论

LD组多见细胞内、外黏液；间质纤维化和神经侵犯。

SD组常见结节状形态；肿瘤向周围浸润性生长；硬化性间质和肝样细胞。

# 结果

**TABLE 3.** Staining Patterns for Histologic Subtypes

| | SD1 (Tubular) (N = 45) | SD2 (Anastomosing) (N = 110) | LD Type (N = 14) | Indeterminate (N = 15) | T (N = | | |
|---|---|---|---|---|---|---|---|
| $CK7^+$ $CK19^+$ $CD56^-$ | | | | | | | **0.001** |
| Negative | 20 (0.67) | 45 (0.59) | 1 (0.09) | 8 (0.73) | | | |
| Positive | 10 (0.33) | 31 (0.41) | 10 (0.91) | | | | |
| CA19-9 | | | | | | | |
| Negative | 27 (0.9) | 65 (0.87) | 3 (0.27) | | | | |
| Positive | 3 (0.1) | 10 (0.13) | 8 (0.73) | | | | |
| CD56 | | | | | | | |
| Negative | 21 (0.7) | 57 (0.75) | 11 (1) | 8 (0.73) | | | |
| Positive | 9 (0.3) | 19 (0.25) | 0 | 3 (0.27) | 31 (0.24) | | |
| Albumin ISH | | | | | | **0.018** | **0.001** |
| Negative | 14 (0.47) | 17 (0.22) | 9 (0.82) | 4 (0.36) | 44 (0.34) | | |
| Positive | 16 (0.53) | 59 (0.78) | 2 (0.18) | 7 (0.64) | 84 (0.66) | | |
| S100P | | | | | | 0.670 | 0.571 |
| Negative | 27 (0.96) | 68 (0.92) | 10 (0.91) | 10 (1) | 115 (0.93) | | |
| Positive | 1 (0.04) | 6 (0.08) | 1 (0.09) | 0 | 8 (0.07) | | |
| Mucicarmine (extracellular) | | | | | | 0.299 | **< 0.001** |
| Negative | 21 (0.72) | 62 (0.82) | 2 (0.18) | 9 (0.9) | 94 (0.75) | | |
| Positive | 8 (0.28) | 14 (0.18) | 9 (0.82) | 1 (0.1) | 32 (0.25) | | |
| Mucicarmine (intracellular) | | | | | | | 0.069 |
| Negative | 28 (0.97) | 69 (0.91) | 8 (0.73) | 10 ( | | | |
| Positive | 1 (0.03) | 7 (0.09) | 3 (0.27) | | | | |

Values in bold met the set threshold for statistical significance.
ISH indicates in situ hybridization.

LD组CA19-9
阳性更常见

（1）LD组白蛋白表达率更低
（2）SD1组与SD2组比较，SD2组白蛋白表达更多见

LD组细胞外MUC
阳性更多见

# 结果

**TABLE 4.** Staining Patterns for Selected Histologic Features

| | High Grade | Low Grade | *P* | Periductal Infiltrating Present | Periduct Infiltrati Absent | | | *P* | Albumin ISH Positive | Albumin ISH Negative | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CK7⁺ CK19⁺ CD56⁻ | | | 0.248 | | | 0.7 | | 0.581 | | | 0.451 |
| Negative | 49 (0.54) | 25 (0.66) | | 7 (0.54) | 66 (0.58) | | 26 (0.54) | 48 (0.6) | | 51 (0.61) | 23 (0.52) | |
| Positive | 41 (0.46) | 13 (0.34) | | 6 (0.46) | 47 (0.42) | | 22 (0.46) | 32 (0.4) | | 33 (0.39) | 21 (0.48) | |
| CA19-9 | | | 0.213 | | | **0.007** | | | 0.635 | | **<0.001** |
| Negative | 71 (0.8) | 34 (0.89) | | 6 (0.5) | 97 (0.86) | | 40 (0.85) | 65 (0.81) | | 76 (0.92) | 29 (0.66) | |
| Positive | 18 (0.2) | 4 (0.11) | | 6 (0.5) | 16 (0.14) | | 7 (0.15) | 15 (0.19) | | 7 (0.08) | 15 (0.34) | |
| CD56 | | | 0.179 | | | 1.000 | | | 0.834 | | | 0.831 |
| Negative | 65 (0.72) | 32 (0.84) | | 10 (0.77) | 86 (0.76) | | 37 (0.77) | 60 (0.75) | | | | |
| Positive | 25 (0.28) | 6 (0.16) | | 3 (0.23) | 27 (0.24) | | 11 (0.23) | 20 (0.25) | | | | |
| Albumin ISH | | | 0.839 | | | 0.759 | | | 0. | | | |
| Negative | 30 (0.33) | 14 (0.37) | | 5 (0.38) | 37 (0.33) | | 9 (0.19) | 35 (0.44) | | | | |
| Positive | 60 (0.67) | 24 (0.63) | | 8 (0.62) | 76 (0.67) | | 39 (0.81) | 45 (0.56) | | | | |
| S100P | | | 0.691 | | | 1.000 | | | 0.709 | | | 1.000 |
| Negative | 82 (0.94) | 33 (0.92) | | 12 (1) | 101 (0.93) | | 44 (0.96) | 71 (0.92) | | 76 (0.94) | 39 (0.9 | |
| Positive | 5 (0.06) | 3 (0.08) | | 0 | 8 (0.07) | | 2 (0.04) | 6 (0.08) | | 5 (0.06) | 3 (0.07) | |
| Mucicarmine (extracellular) | | | 0.370 | | | **0.038** | | | 0.405 | | | **<0.001** |
| Negative | 64 (0.72) | 30 (0.81) | | 6 (0.46) | 86 (0.77) | | 38 (0.79) | 56 (0.72) | | 71 (0.85) | 23 (0.55) | |
| Positive | 25 (0.28) | 7 (0.19) | | 7 (0.54) | 25 (0.23) | | 10 (0.21) | 22 (0.28) | | 13 (0.15) | 19 (0.45) | |
| Mucicarmine (intracellular) | | | 1.000 | | | 0.324 | | | 0.331 | | | 0.504 |
| Negative | 81 (0.91) | 34 (0.92) | | 11 (0.85) | 102 (0.92) | | 42 (0.88) | 73 (0.94) | | 78 (0.93) | 37 (0.88) | |
| Positive | 8 (0.09) | 3 (0.08) | | 2 (0.15) | 9 (0.08) | | 6 (0.12) | 5 (0.06) | | 6 (0.07) | 5 (0.12) | |

Values in bold met the set threshold for statistical significance.
CLC indicates cholangiocellular; ISH, in situ hybridization.

CA19-9表达与神经周侵犯相关

白蛋白阳性与细胞外MUC染色呈负相关

# 结论

LD组白蛋白表达阳性率低于SD组

LD组CA19-9阳性表达通常高于SD组

# 结果

**TABLE 5.** Univariate Cox Regression for RFS and DSS (n = 163*, 127 RFS Events, 95 DSS Events)

| Characteristic | RFS HR | RFS 95% CI | RFS *P* | DSS HR | DSS 95% CI | DSS *P* |
|---|---|---|---|---|---|---|
| Histologic subtype | | | 0.163 | | | 0.069 |
| SD1 | 1.29 | 0.85-1.97 | | 1.24 | 0.75-2.05 | |
| SD2 | 1.00 | Reference | | 1.00 | Reference | |
| LD type | 1.64 | 0.82-3.29 | | 1.98 | 0.94-4.18 | |
| IND type | 1.84 | 1.00-3.39 | | 2.18 | 1.16-4.07 | |
| Combined types: LD/IND | 1.63 | 1.02-2.61 | **0.043** | 1.98 | 1.21-3.25 | **0.007** |
| High grade (reference: low grade) | 1.13 | 0.78-1.64 | 0.517 | 0.93 | 0.60-1.45 | 0.756 |
| Periductal infiltrating type (reference: mass forming) | 2.73 | 1.55-4.80 | **0.001** | 3.58 | 2.01-6.39 | **< 0.001** |
| AJCC 8th edition T stage | | | **0.013** | | | **0.007** |
| pT1 | 1.00 | Reference | | 1.00 | Reference | |
| pT2 | 1.90 | 1.29-2.81 | | 2.15 | 1.36-3.38 | |
| pT3 | 1.37 | 0.76-2.47 | | 1.94 | 1.01-3.73 | |
| pT4 | 1.48 | 0.36-6.12 | | 1.02 | 0.14-7.47 | |

*Individuals were excluded if chemotherapy was received before resection, metastasis was present at the time of resection, or the resection was for recurrent disease.
Values in bold met the set threshold for statistical significance.
CI indicates confidence interval; HR, hazard ratio.

# 结果

**TABLE 6.** Multiple Cox Regression for RFS and DSS (n = 163*, 127 RFS Events, 95 DSS Events)

| Characteristic | RFS HR | RFS 95% CI | RFS *P* | DSS HR | DSS 95% CI | DSS *P* |
|---|---|---|---|---|---|---|
| Periductal infiltrating type (reference: mass forming) | 2.31 | 1.29-4.16 | **0.010** | 2.65 | 1.43-4.90 | **0.004** |
| LD type/IND (reference: small duct type) | 1.54 | 0.94-2.53 | 0.103 | 1.70 | 1.00-2.89 | 0.060 |
| AJCC 8th edition T stage | | | **0.012** | | | **0.012** |
| pT1 | 1.00 | Reference | | 1.00 | Reference | |
| pT2 | 1.92 | 1.30-2.84 | | 2.11 | 1.33-3.34 | |
| pT3 | 1.26 | 0.70-2.28 | | 1.73 | 0.90-3.35 | |
| pT4 | 1.65 | 0.40-6.86 | | 1.18 | 0.16-8.67 | |

Model: Gross type+AJCC 8th Edition T Stage+Histologic subtype.

*Individuals were excluded if chemotherapy was received before resection, metastasis was present at the time of resection, or the resection was for recurrent disease.

Values in bold met the set threshold for statistical significance.

CI indicates confidence interval; HR, hazard ratio.

# 结论

无法证实LD组与SD组预后差异

AJCC（第8版）pT分期及导管周浸润可作为预后的独立预测因素

# 讨论

（1）LD组：北美人群发病率较低，与原发性硬化性胆管炎相关。形态与肝外胆道肿瘤类似，常可见黏液，缺乏白蛋白表达。

（2）SD组：本课题中最多见的肿瘤类型，肿瘤主要由小管或吻合的小导管组成，也可见黏液，白蛋白杂交阳性多见。可通过白蛋白原位杂交方法区分LD与SD。

（3）目前无法通过临床或生物学角度进一步区分SD组亚型（SD1，SD2）

（4）试验结果显示LD与SD预后并无明显差异，但通过识别LD与SD形态学的差异，将来能够进一步研究这两种亚型不同的形态与生物和遗传特征的相关性。

# 谢谢