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Prognostic Implication of Histopathologic Indicators in Salivary Duct Carcinoma

Proposal of a Novel Histologic Risk Stratification Model

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Salivary Duct Carcinoma

- **Dedinition**
  - Aggressive epithelial malignancy resembling high-grade mammary ductal carcinoma
  - De novo or as the outcome of a malignant component of carcinoma ex pleomorphic adenoma
- **ICD-O** code 8500/3
- **Epidemiology**
  - Accounts for as many as 10% of all salivary gland malignancies
  - Distinct male predilection
  - Elderly individuals,with peak incidence in the sixth and seventh decades of life

Salivary Duct Carcinoma

- **Localization**
  - Most tumours arise from the parotid gland
- **Histopathology**
  - A striking resemblance to high-grade ductal carcinoma of the breast
  - Apocrine,oncocytoid,and characterized by abundant cytoplasm and large pleomorphic nuclei with coarse chromatin and prominent nucleoli,mitotic figures are easily identifiable
  - Sarcomatoid,mucin-rich,invasive micropapllary,and oncocytic cacinomas

Salivary Duct Carcinoma

- **Immunophenotype**
  - Positive　EMA　CK　CEA AR（70%）　HER2　（25-30%）
  - Negative　ER　PR　S-100
- **Genetic prfile**
  - HER2 gene amplification is seen in as many as 25% of cases
  - *PLAG*1and/or *HMGA2* rearrangements are identified in most cases of SDC ex pleomorphic adenoma

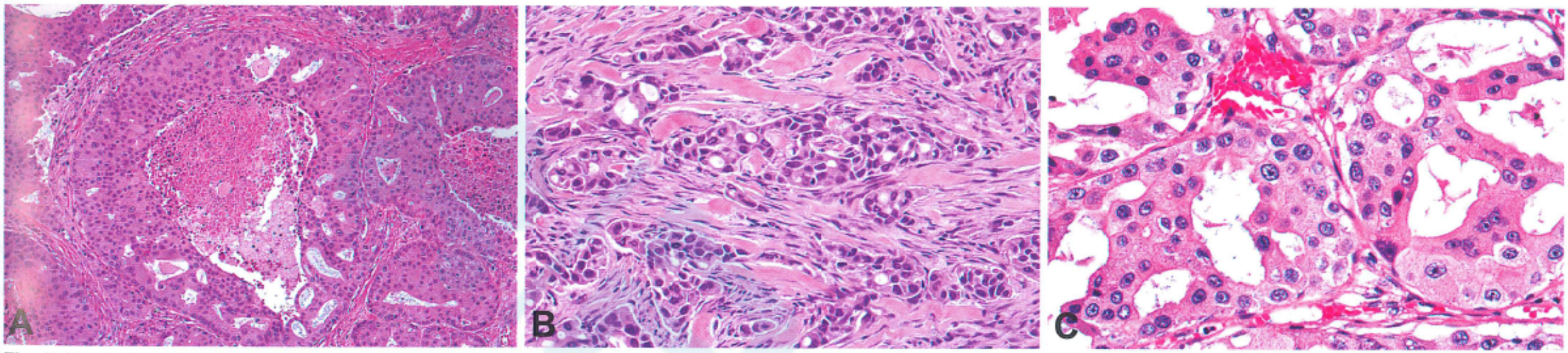


Fig. 7.18 Salivary duct carcinoma. **A** The intraductal component consists of cribriform structures with so-called Roman-bridge architecture; note that the central portion of the ductal cell nests undergoes comedonecrosis. **B** The invasive component consists of irregular glands and cords of cells that elicit a prominent desmoplastic reaction. **C** Carcinoma cells exhibit large pleomorphic nuclei with coarse chromatin and prominent nucleoli; the cytoplasm is abundant and granularly eosinophilic.

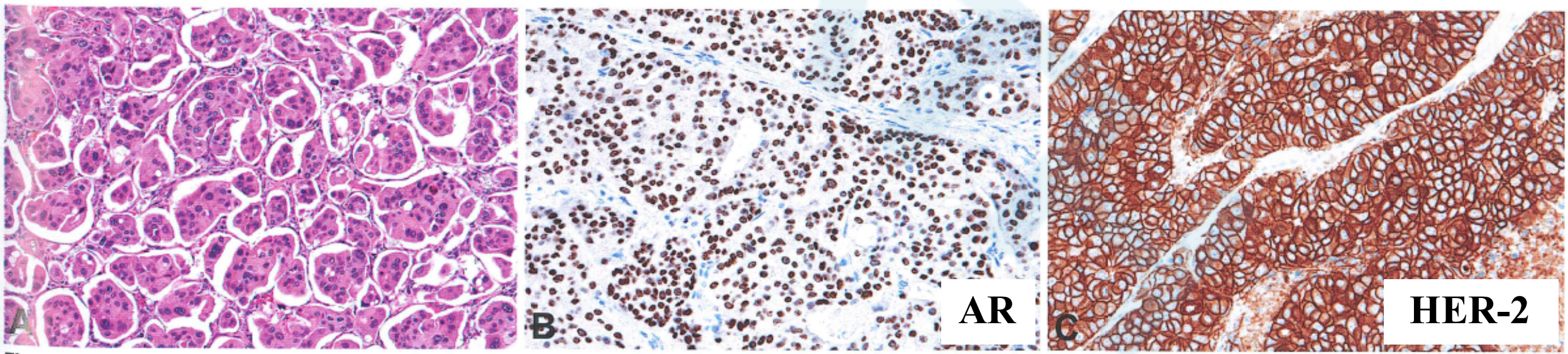


Fig. 7.19 Salivary duct carcinoma. **A** Invasive micropapillary variant. Morula-like small cell clusters without fibrovascular cores, surrounded by a clear space. **B** Carcinoma cells show a diffuse nuclear immunopositivity for androgen receptor. **C** Diffuse and strong membranous immunostaining for ERBB2/HER2.

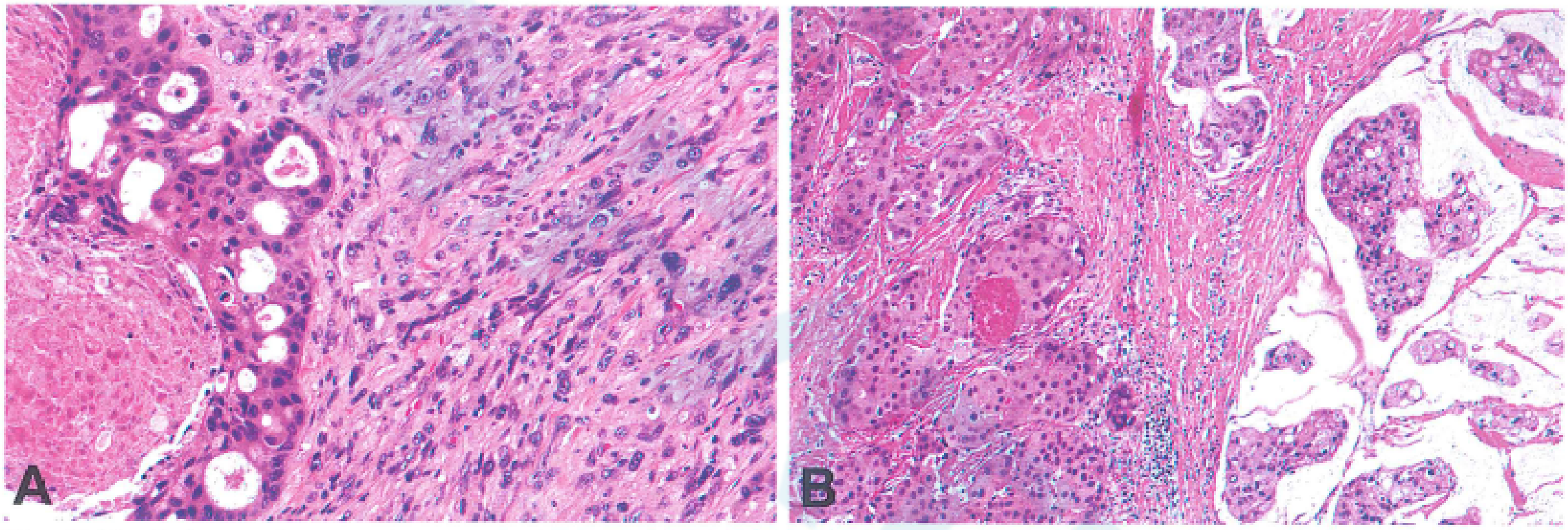


Fig. 7.20 Salivary duct carcinoma **A** Sarcomatoid variant. Biphasic neoplasm with both conventional salivary duct carcinoma (left) and sarcomatoid elements with a fascicular pattern of atypical spindle cells (right). **B** Mucin-rich variant. Mucin lakes containing islands of carcinoma cells (right) in addition to the conventional salivary duct carcinoma component (left).

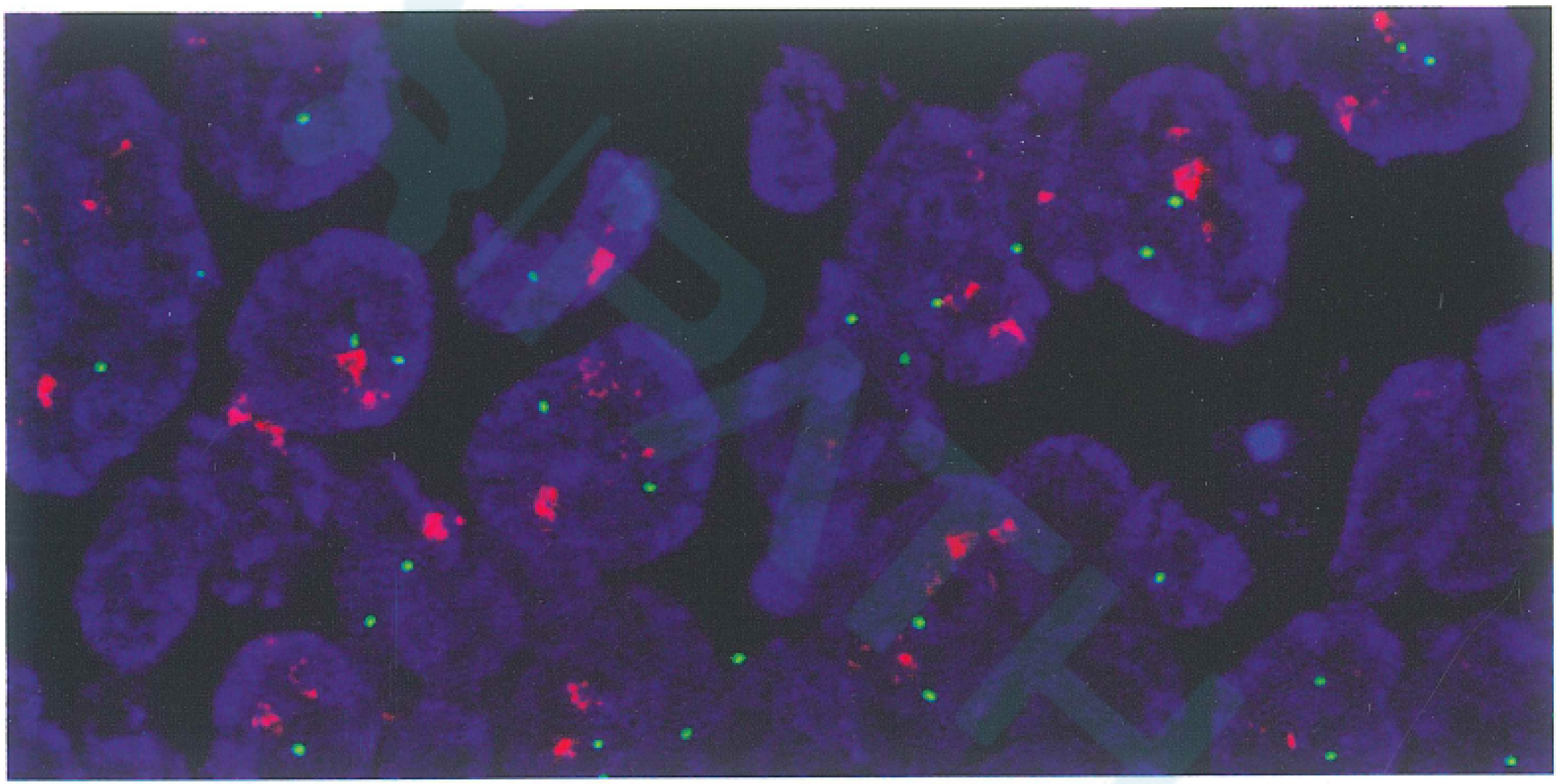


Fig. 7.21 Salivary duct carcinoma. FISH analysis is positive for *ERBB2* (also called *HER2*) gene amplification, showing numerous red signals (*ERBB2*) versus a normal number of green signals (centromere 17).

Salivary Duct Carcinoma

- **Standard treatment**
  - Surgical resection through radiation therapy and conventional chemotherapy
  - Recent advances in molecular targeted therapy
    - Targeting human epidermal growth factor receptor 2 (HER2) with trastuzumab
    - Combined androgens Blockers target androgen receptor
- **Prognosis and predictive factors**
  - Frequent local recurrence and regional lymph node and distant metastasis
    - 55-65% have died of disease,usually within 5 years

Nottingham Histologic Grade

Table 2.06 Semiqualitative method for assessing histological grade in breast tumours {585}

Feature	Score
Tubule and gland formation	
Majority of tumour (> 75%)	1
Moderate degree (10–75%)	2
Little or none (< 10%)	3
Nuclear pleomorphism	
Small, regular, uniform cells	1
Moderate increase in size and variability	2
Marked variation	3
Mitotic count	
Dependent on microscope field area[a]	1–3
Total score	**Final grading**
Add the scores for gland formation, nuclear polymorphism, and mitotic count:	
3–5	Grade 1
6 or 7	Grade 2
8 or 9	Grade 3

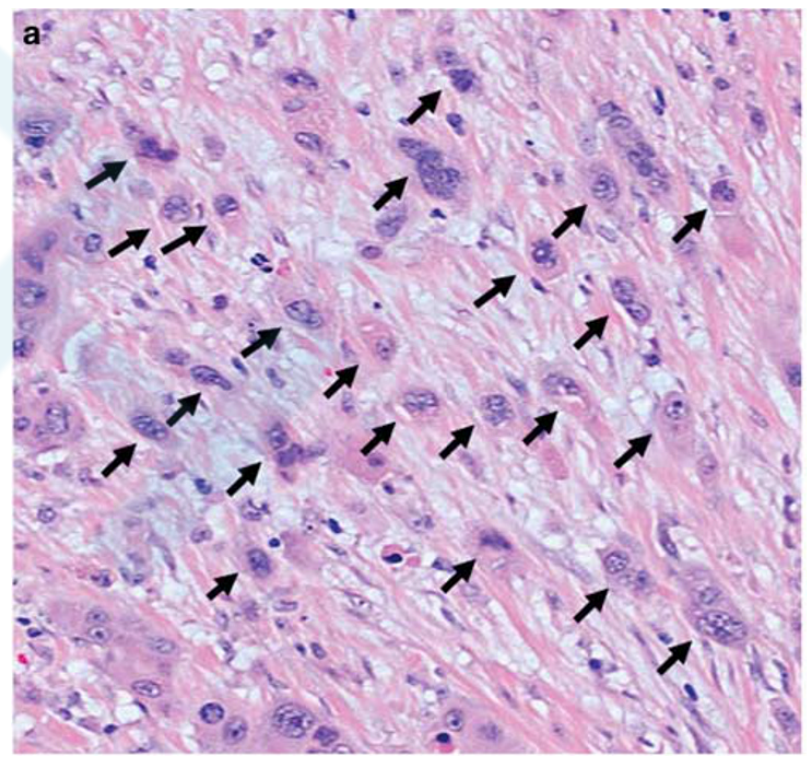
2019 WHO Classification of Tumours Breast Tumours – 5th edition

Nottingham Histologic Grade

- **The mitotic count was determined in 10 fields with a ×40 objective lens (HPF) (field diameter 0.55 mm)**
  - ⩽8 mitoses 1
  - 9 to 17 mitoses 2
  - ⩾18 mitoses 3

Tumor Budding

- Based on the recommendation of the International Tumor Budding Consensus Conference
- Single cells or clusters of up to 4 cells at the invasive margin
- H&E staining using a ×20 objective lens and assessed in the highest hotspot at the invasive front
- Three-tier system
  - 0–4 buds—low budding (Bd 1)
  - 5–9 buds—intermediate budding (Bd 2)
  - 10 or more buds—high budding (Bd 3)

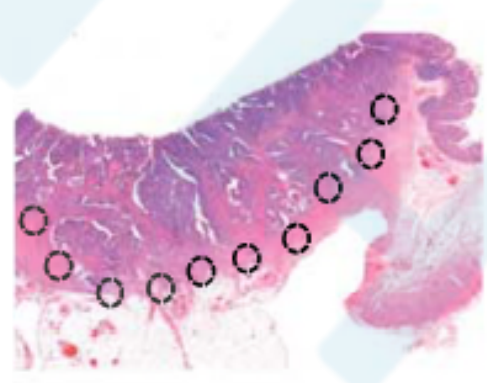


1 **Define the field (specimen) area for the 20x objective lens of your microscope based on the eyepiece field number (FN) diameter**

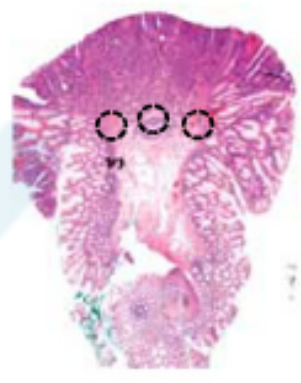
Objective magnification: 20		
Eyepiece FN Diameter (mm)	Specimen Area (mm2)	Normalization Factor
18	0.636	0.810
19	0.709	0.903
20	0.785	1.000
21	0.866	1.103
22	0.950	1.210
23	1.039	1.323
24	1.131	1.440
25	1.227	1.563
26	1.327	1.690

2 **Select the H&E slide with greatest degree of budding at the invasive front**

3 **Scan 10 individual fields at medium power (10x objective) to identify the "hotspot" at the invasive front**



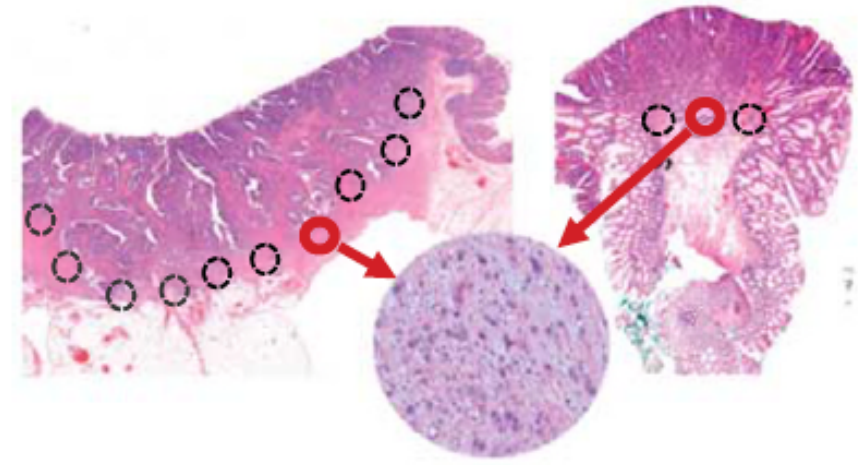
For surgical resection specimens, scan 10 fields



For pT1 endoscopic resections (usually <10 fields available), scan all

Modern Pathology (2017) 30, 1299–1311

4 **Count tumor buds in the selected "hotspot" (20x objective)**



Selected hotspot indicated in red

5 **Divide the bud count by the normalization factor (figure 2) to determine the tumor bud count per 0.785mm²**

Select the budding [Bd] category based on bud count and indicate the absolute count per 0.785mm² (see reporting example)

Tumor bud count per 0.785 mm² = Bud count (20x objective) / Normalization factor*

Bd1 (low):	0-4 buds	per 0.785 mm²
Bd2 (intermediate):	5-9 buds	
Bd3 (high):	≥10 buds	

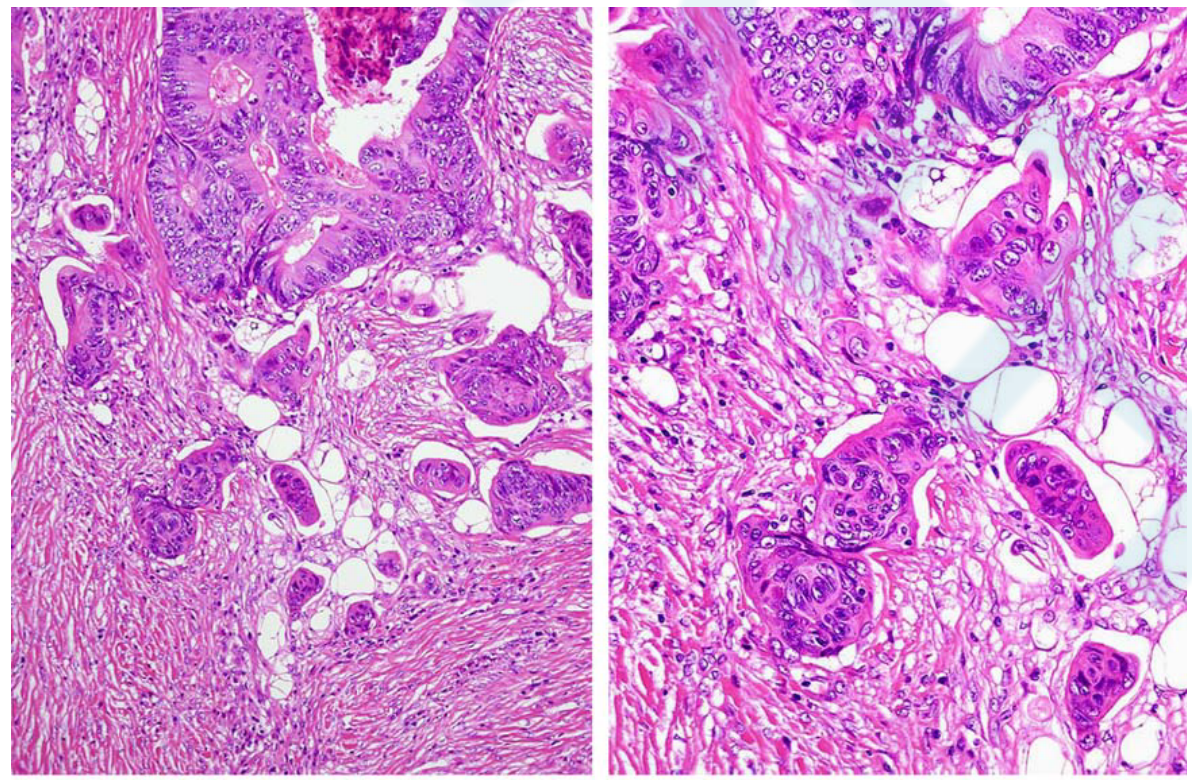
Reporting example:
Tumor budding: Bd3 (high), count 14 (per 0.785 mm²)

Figure 4 Procedure proposed by the ITBCC 2016 for reporting tumor budding in colorectal cancer in daily diagnostic practice.

Modern Pathology (2017) 30, 1299–1311

Poorly Differentiated Cluster (PDC)

- Cancer cell cluster composed of ⩾5 cancer cells lacking a gland-like structure
- The counting and grading methods were the same as for tumor budding



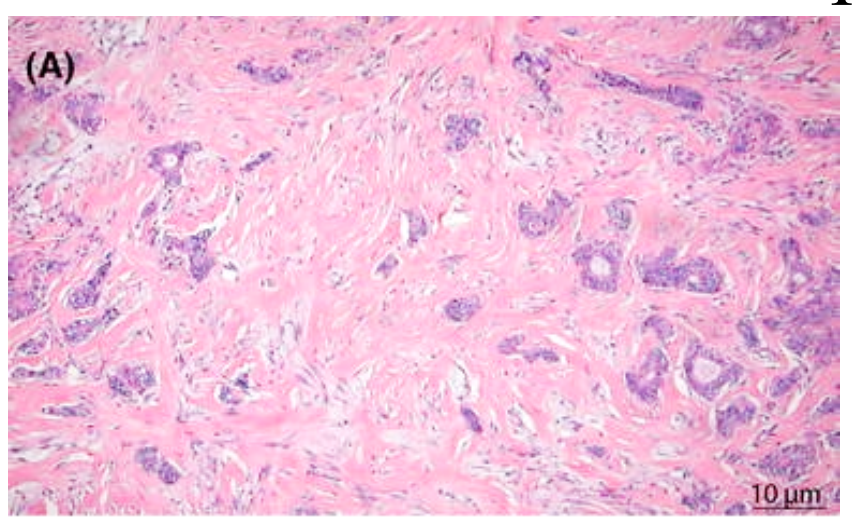
Am J Surg Pathol Volume 36, Number 2, February 2012

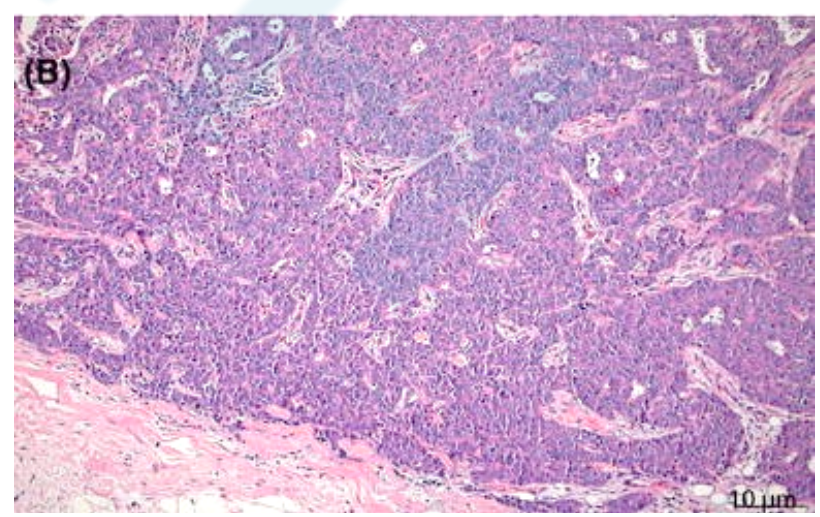
Tumor Budding and PDC

- Tumor budding is reported to be a promising adverse prognostic indicator in many organs, including the colon, esophagus, breast, skin, stomach, and pancreas
- PDC is also a poor prognosticator

Tumor-stroma Ratio

- Assessed using a ×10 objective lens in the most stroma-abundant area
  - stroma-low　stroma percentage ⩽50%
  - stroma-high　stroma percentage >50%
- Stroma-rich tumors were associated with poor prognosis and an increased risk of relapse





Breast Cancer Res Treat. 2011;125:687–696.

BACKGROUND

- The number of studies with histologic assessments of SDC is limited, largely due to the rarity of this entity
- Performed an analysis of the association between various histomorphologic parameters and the clinical outcome
- Developing a histologic risk stratification model that predicts the prognosis of SDC patients

MATERIALS AND METHODS

- **Patient Selection**
  - 151 patients with SDC diagnosed and treated at 7 institutions between 1992 and 2014
- **The Evaluation of Histologic Factors**
  - **Nuclear size and pleomorphism, mitotic count, and tubule formation**
  - High mitotic counts were defined as ⩾30 mitoses in 10HPF
    - SDC exhibited more pronounced nuclear atypia and had more mitoses

MATERIALS AND METHODS

- **The Evaluation of Histologic Factors**
  - **Lymphatic and vascular invasion**
    - H&E staining
    - Elastica van Gieson (EVG) and D2-40 immunohistochemical staining
  - **Noncomedo necrosis**
    - Coagulative tumor necrosis in the invasive component imparting an infarcted appearance

MATERIALS AND METHODS

- **The Evaluation of Histologic Factors**
  - **The evaluation of tumor budding**
    - Low tumor budding grade 1 cases
    - High tumor budding grades 2 and 3 cases
  - **Poorly differentiated cluster (PDC)**
- **Statistical Analyses**
  - Univariate and multivariate Cox proportional hazards models
  - Kaplan-Meier product-limit method

TABLE 1. Patient and Tumor Characteristics (N = 151)

Characteristics	n (%)
Age (y)	
< 65	84 (55.6)
≥ 65	67 (44.4)
Sex	
Male	127 (84.1)
Female	24 (15.9)
T classification	
1	13 (8.6)
2	39 (25.8)
3	30 (19.9)
4	69 (45.7)
N classification	
0	71 (47.0)
1	9 (6.0)
2	71 (47.0)
M classification	
0	142 (94.0)
1	9 (6.0)
Primary tumor site	
Parotid gland	117 (77.5)
Submandibular gland	30 (19.9)
Others	4 (2.6)
Histologic origin	
De novo	57 (37.7)
Ex pleomorphic adenoma	89 (58.9)
Unknown	5 (3.3)

RESULTS

- The median follow-up period of survivors was 3.4 years (range, 0.04 to 19.0 y)
  - 3-year OS was 68.5% (95% CI, 60.1%-75.5%)
  - 3-year PFS was 34.3% (95% CI, 26.7%-42.1%)

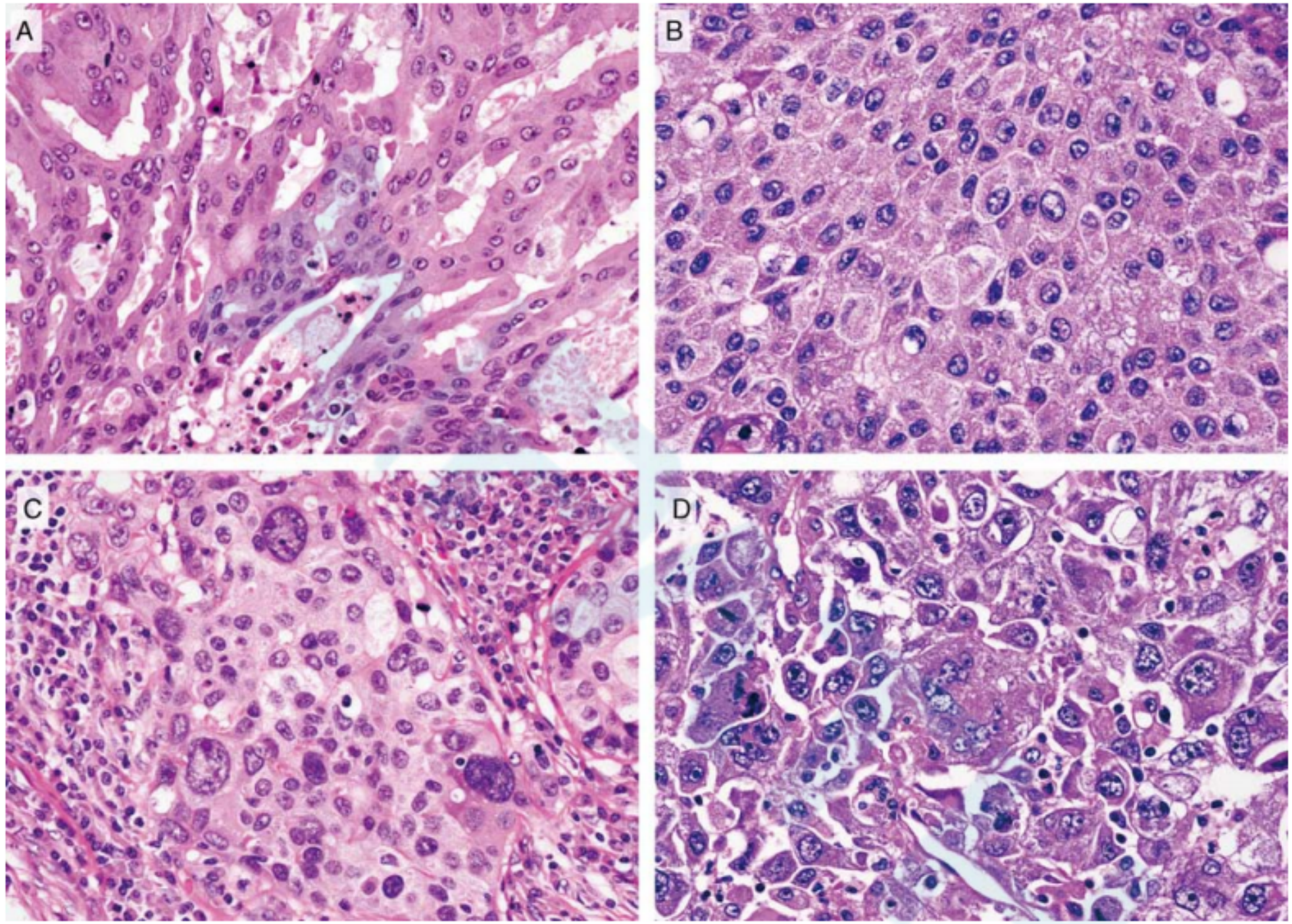
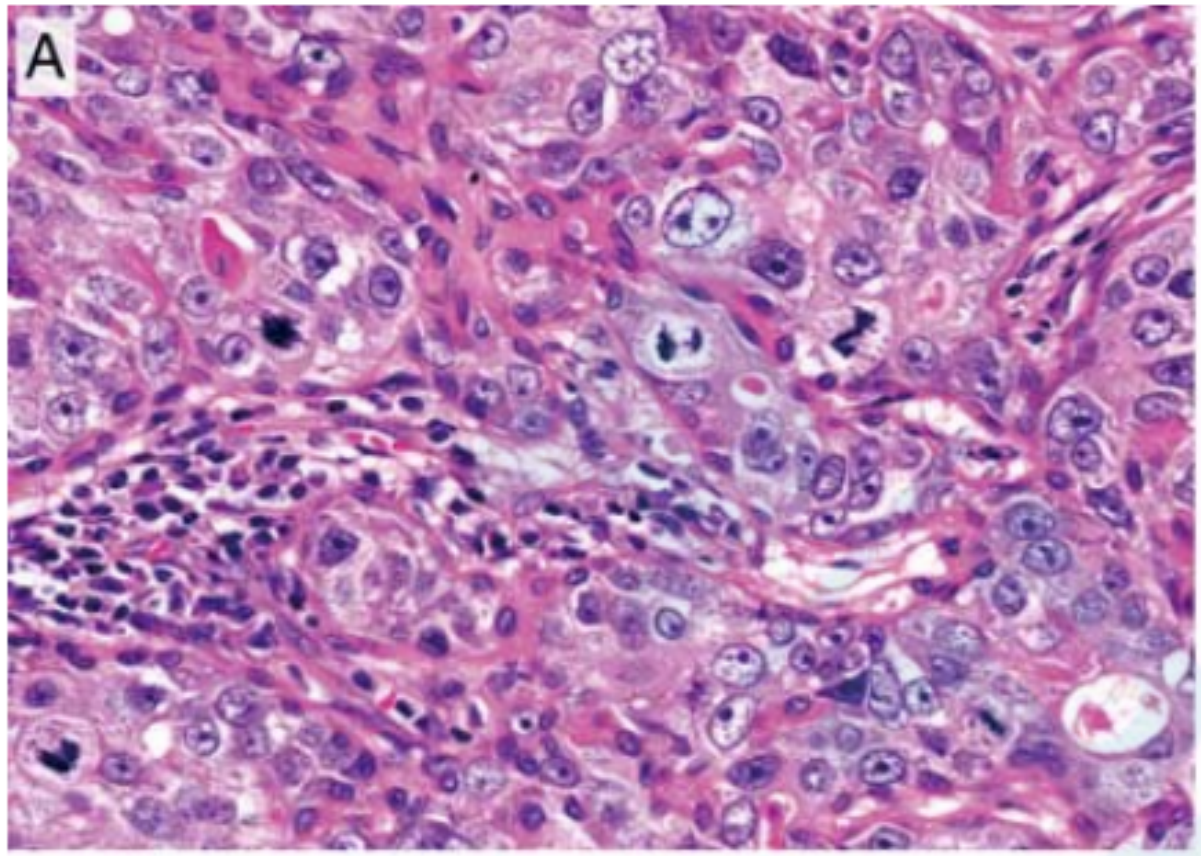
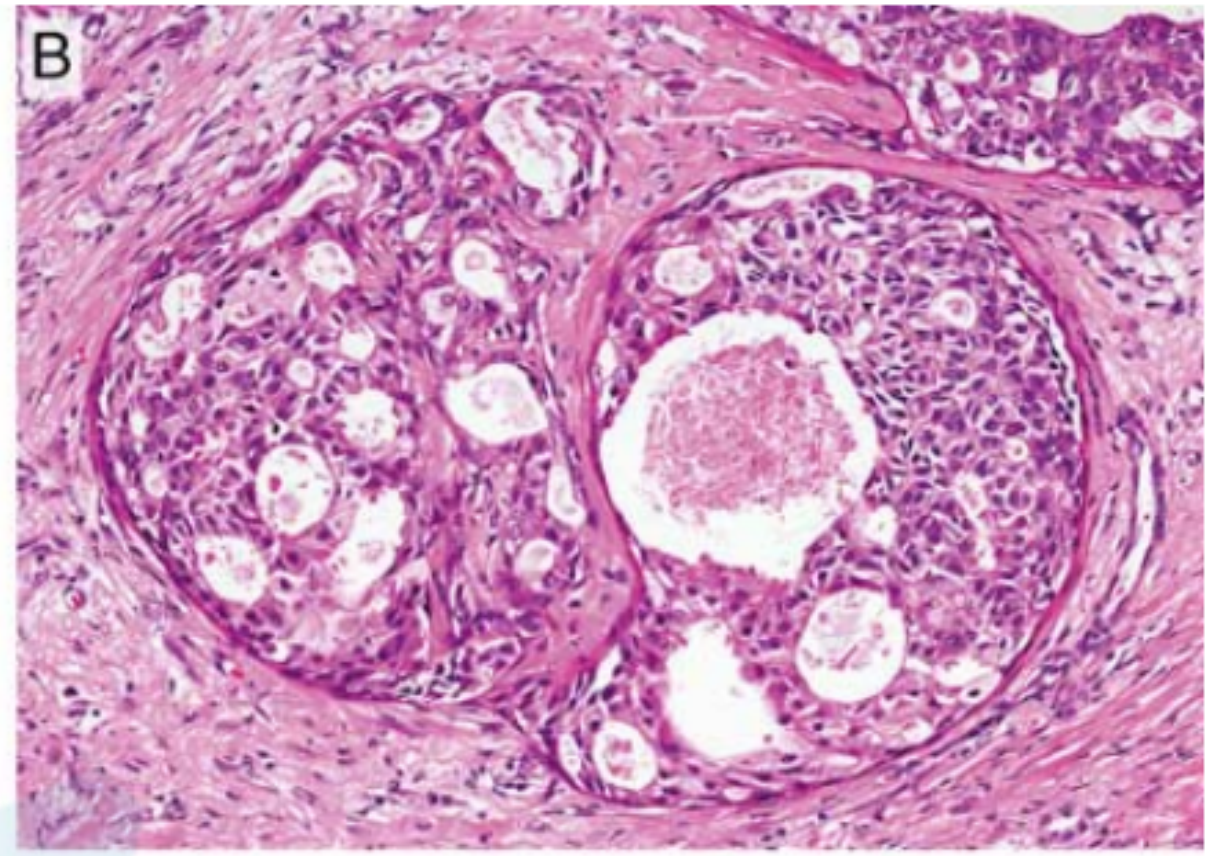


FIGURE 1. Evaluation of prominent nuclear pleomorphism in SDC. A and B, SDC cases without prominent nuclear pleomorphism.Although the tumor cells have larger nuclei accompanied by conspicuous nucleoli in comparison to normal salivary duct epithelial cells, the variation in the size and shape is minimal (A) or slight (B). C and D, SDC cases with prominent nuclear pleomorphism. Tumor cells containing extremely large pleomorphic nuclei are scattered but others have relatively small monotonous nuclei (C). All tumor cells vary in size and shape. Bizarre nuclei and atypical mitoses are also present (D).


A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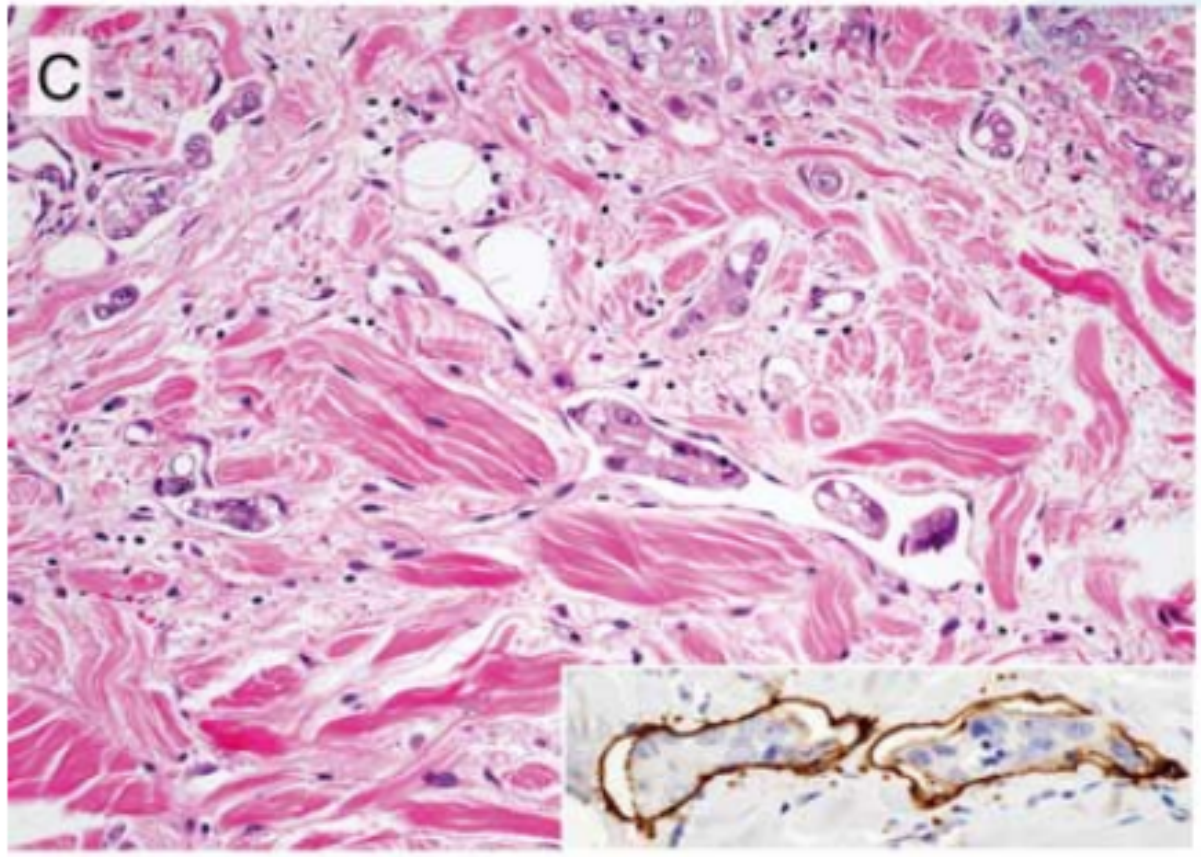
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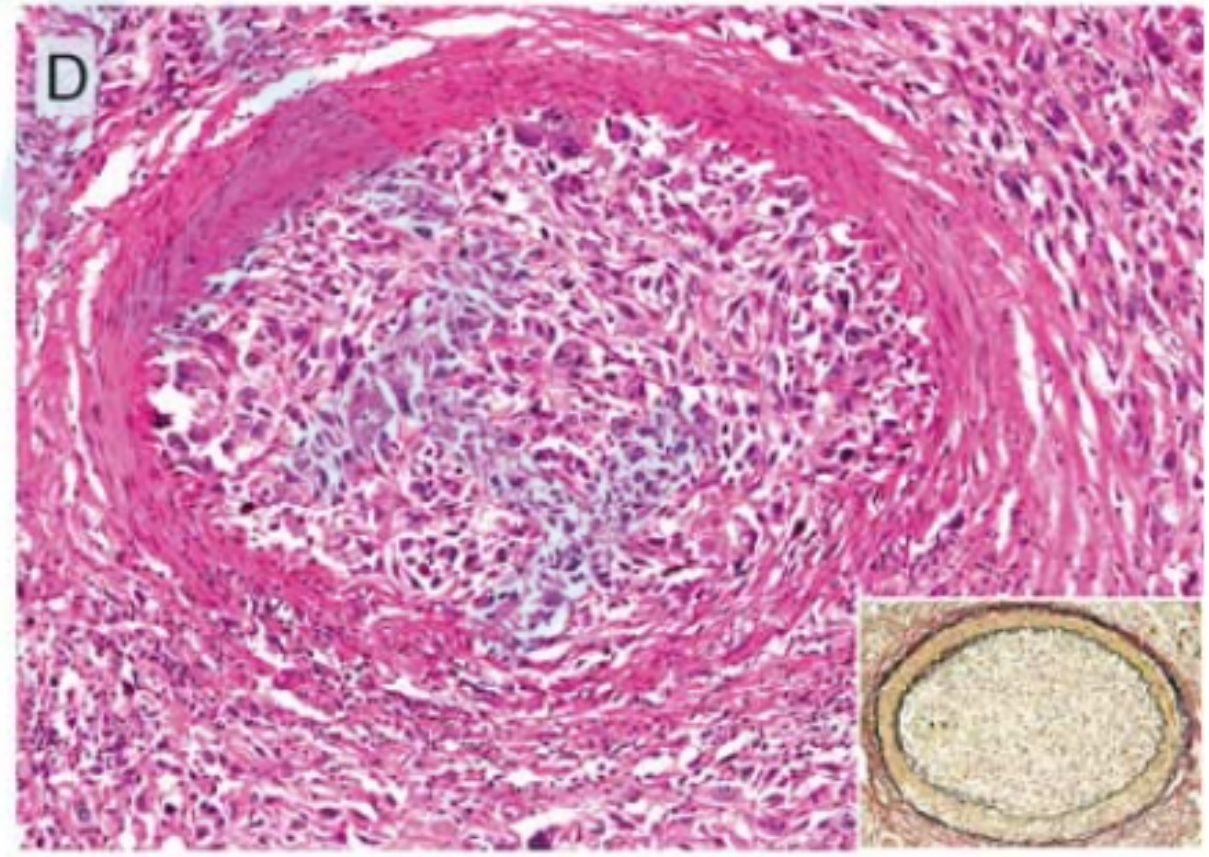
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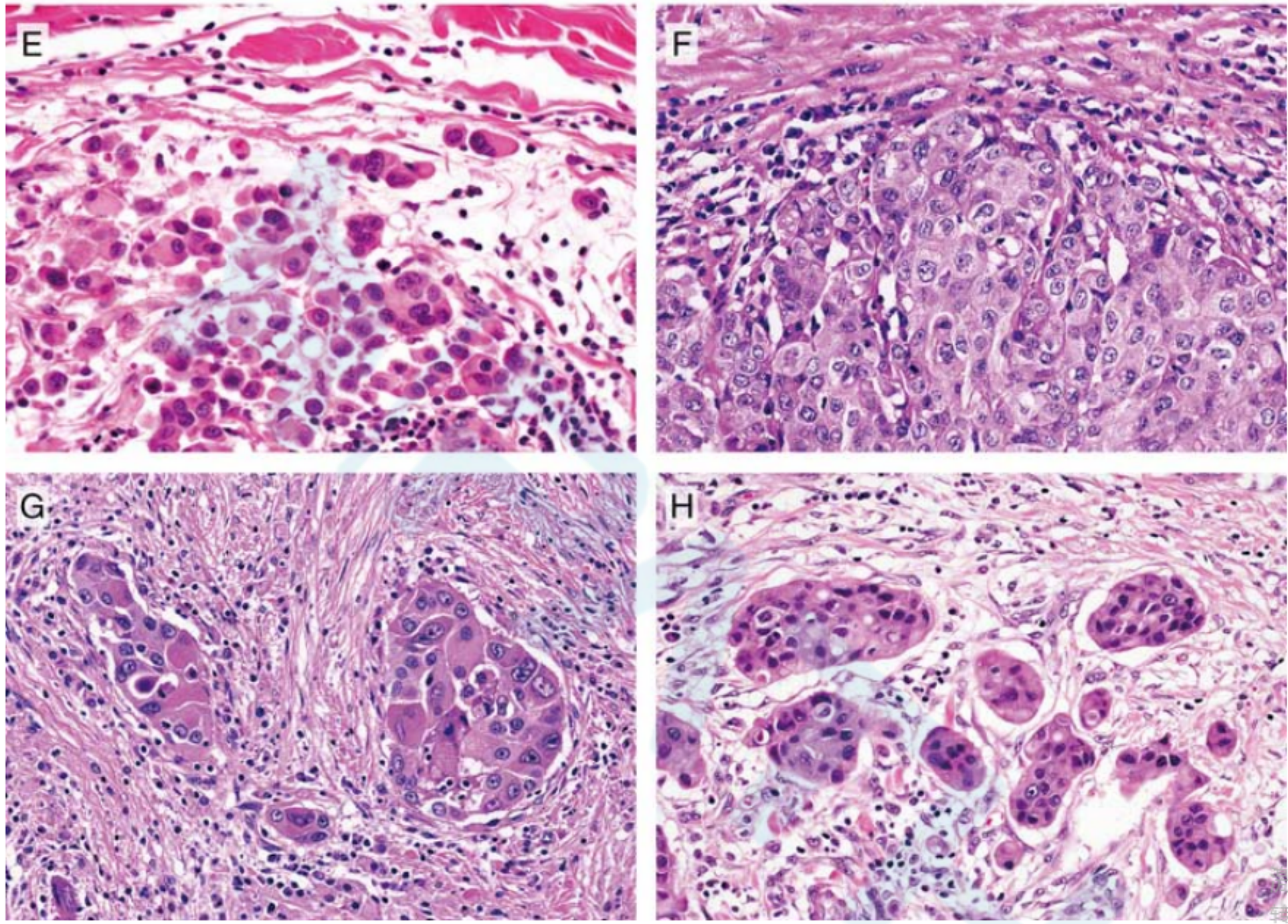


FIGURE 2. Various histologic parameters in SDC. A, Brisk mitotic activity. B, Intraductal pattern consisting of large ductal structures with a cribriform formation. C, Lymphatic invasion (inset: D2-40 immunohistochemistry). D, Vascular invasion (inset: EVG staining). E, High tumor budding. F–H, Varying degrees of PDCs in SDC. F, The invasive front is irregular, but no PDCs are found. G, Three PDCs are identified in this high-power view. PDCs of ⩽ 5 in a hotspot was regarded as low PDC. H, SDC categorized as high PDC. A few tumor buddings are also noted

TABLE 2. Univariate and Multivariate Analyses of Factors Associated With Clinical Outcomes (N = 151)

		OS						PFS					
		Univariate Analysis			Multivariate Analysis			Univariate Analysis			Multivariate Analysis		
Histopathologic Parameters	**n (%)**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Prominent nuclear pleomorphism													
Absent	50 (33.1)	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference
Present	101 (66.9)	2.21	1.28-3.82	0.004*	2.06	1.16-3.66	0.013*	1.81	1.17-2.80	0.007*	1.75	1.09-2.79	0.019*
Mitosis (/10 HPF)													
< 30	72 (47.7)	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference
≥ 30	79 (52.3)	1.41	0.89-2.26	0.147	1.29	0.77-2.15	0.333	1.71	1.16-2.53	0.007*	1.72	1.12-2.63	0.013*
Lymphatic invasion													
Absent	57 (37.7)	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference
Present	94 (62.3)	1.40	0.85-2.30	0.184	0.92	0.53-1.61	0.772	1.49	0.99-2.26	0.057**	0.82	0.51-1.31	0.403
Vascular invasion													
Absent	41 (27.2)	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference
Present	110 (72.8)	2.76	1.41-5.38	0.003*	1.84	0.83-4.08	0.136	2.56	1.54-4.27	< 0.001*	1.79	0.97-3.31	0.064**
Perineural invasion													
Absent	77 (51.0)	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference
Present	74 (49.0)	1.33	0.83-2.11	0.232	0.81	0.48-1.36	0.420	1.80	1.22-2.65	0.003*	1.02	0.66-1.58	0.924
Noncomedo necrosis													
Absent	87 (57.6)	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference
Present	64 (42.4)	1.71	1.07-2.72	0.024*	1.01	0.59-1.72	0.974	1.63	1.11-2.39	0.013*	1.05	0.68-1.60	0.835
Histologic origin													
De novo	57 (37.7)	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference
Ex pleomorphic adenoma	89 (58.9)	0.95	0.59-1.52	0.826	1.23	0.74-2.04	0.420	0.80	0.54-1.19	0.275	0.96	0.63-1.45	0.842
Dominant growth pattern													
Intraductal	34 (22.5)	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference
Invasive	117 (77.5)	3.74	1.71-8.17	0.001*	1.86	0.79-4.39	0.154	3.08	1.72-5.53	< 0.001*	1.67	0.87-3.21	0.124
Tumor budding													
Low	112 (74.2)	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference
High	39 (25.8)	1.60	0.98-2.63	0.062**	2.07	1.18-3.62	0.011*	1.96	1.30-2.96	0.001*	2.68	1.69-4.25	< 0.001*
Poorly differentiated clusters													
Low	77 (51.0)	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference
High	74 (49.0)	2.90	1.75-4.81	< 0.001*	3.10	1.75-5.49	< 0.001*	2.32	1.56-3.44	< 0.001*	2.34	1.51-3.62	< 0.001*
Tumor-stroma ratio													
Low-stromal component	122 (80.8)	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference
High-stromal component	28 (18.5)	0.96	0.53-1.76	0.898	0.96	0.51-1.78	0.891	1.28	0.81-2.04	0.290	1.31	0.81-2.12	0.264

Adjusted by age, sex, primary tumor site, TNM classification, first-line treatment, and histologic origin. As for histologic origin, adjustment was performed for age, sex, primary tumor site, TNM classification, and first-line treatment.

*$P < 0.05$, statistically significant difference.

**$P = 0.05$ to < 0.1, marginally significant difference.

Supplementary TABLE 1. Univariate and Multivariate Analysis of Factors Associated with Clinical Outcomes (N=151)

			Overall survival						*Progression-free survival*					
			Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
Histopathological parameter	N	%	HR	95% CI	*P*-values	HR	95% CI	*P*-values	HR	95% CI	*P*-values	HR	95% CI	*P*-values
Nuclear size and pleomorphism														
Score 1	0	0.0	1.00	-	reference	1.00	-	reference	1.00	-	reference	1.00	-	reference
Score 2	6	4.0	NE	-	-	NE	-	-	NE	-	-	NE	-	-
Score 3	145	96.0	NE	-	-	NE	-	-	NE	-	-	NE	-	-
Mitosis														
Score 1 (up to 8)	7	4.6	1.00	-	reference	1.00	-	reference	1.00	-	reference	1.00	-	reference
Score 2 (9 to 17)	16	10.6	NE	-	-	NE	-	-	NE	-	-	NE	-	-
Score 3 (18 or more)	128	84.8	NE	-	-	NE	-	-	NE	-	-	NE	-	-
Lymphatic invasion (D2-40 stain)														
Absent	109	72.2	1.00	-	reference	1.00	-	reference	1.00	-	reference	1.00	-	reference
Present	36	23.8	1.75	1.03-2.99	0.04*	1.25	0.71-2.23	0.441	1.58	1.03-2.43	0.038*	0.95	0.57-1.57	0.840
Vascular invasion (EVG stain)														
Absent	65	43.0	1.00	-	reference	1.00	-	reference	1.00	-	reference	1.00	-	reference
Present	77	51.0	1.44	0.88-2.36	0.146	0.94	0.55-1.59	0.815	1.83	1.20-2.77	0.005*	1.22	0.79-1.88	0.378
Tubule formation														
Score 1	34	22.5	1.00	-	reference	1.00	-	reference	1.00	-	reference	1.00	-	reference
Score 2	79	52.3	0.91	0.53-1.56	0.739	0.90	0.50-1.60	0.711	0.89	0.56-1.40	0.607	0.85	0.53-1.37	0.509
Score 3	38	25.2	0.41	0.20-0.84	0.015*	0.70	0.31-1.57	0.381	0.37	0.20-0.69	0.002*	0.67	0.34-1.32	0.248
Nottingham grade														
Grade 1	1	0.7	1.00	-	reference	1.00	-	reference	1.00	NE	reference	1.00	-	reference
Grade 2	47	31.1	NE	-	-	NE	-	-	NE	-	-	NE	-	-
Grade 3	103	68.2	NE	-	-	NE	-	-	NE	-	-	NE	-	-

Abbreviations: CI, confidence interval; EVG, elastica van Gieson; HR, hazard ratio

Adjusted by age, sex, primary tumor site, TNM classification, first-line treatment, and histologic origin.

* Statistically significant difference ($P<0.05$).

**Marginally significant difference ($P=0.05$ to <0.1).

RESULTS

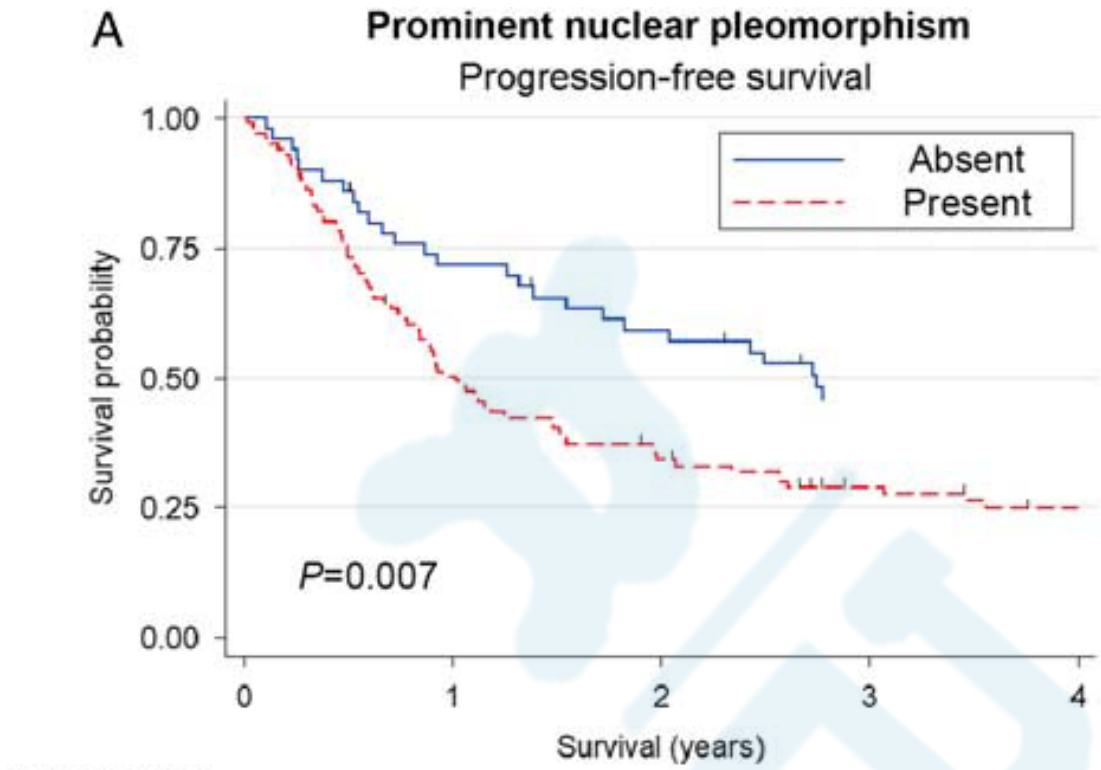
- **Univariate analysis**
  - **Negative prognostic indicators for the OS and PFS**
    - Prominent nuclear pleomorphism (P=0.004 and 0.007)
    - Lymphatic invasion with D2-40 stain (P=0.04 and 0.038)
    - Vascular invasion assessed by H&E stain (P=0.003 and <0.001)
    - Noncomedo necrosis (P=0.024 and 0.013)
    - Dominant invasive growth (P=0.001 and <0.001)
    - High PDC (P<0.001 and <0.001)

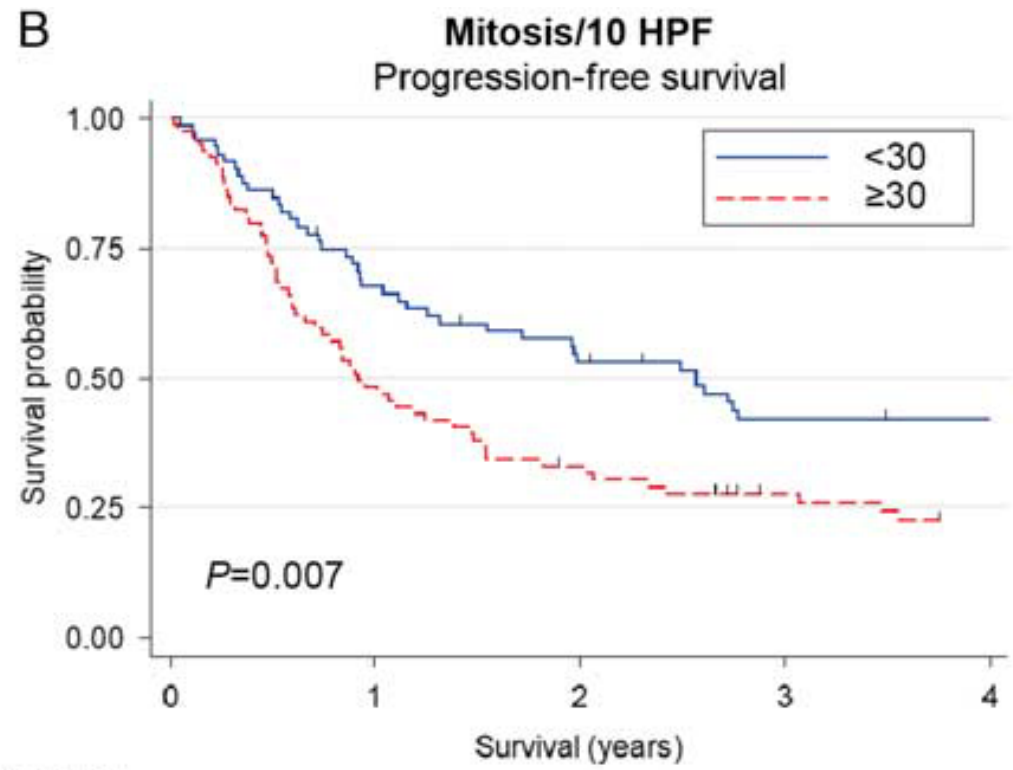
RESULTS

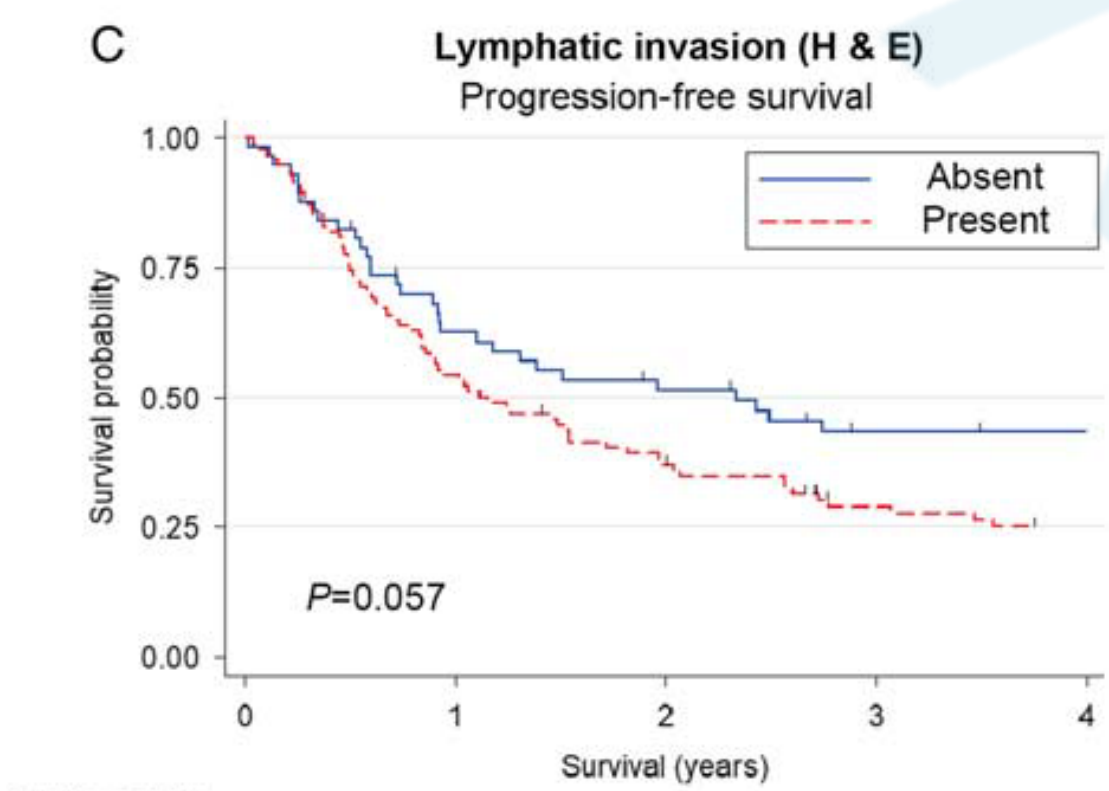
- **Univariate analysis**
  - **Poor PFS**
    - ⩾30 mitoses/ 10 HPF (P=0.007)
    - Vascular invasion with EVG stain (P=0.005)
    - Perineural invasion (P=0.003)
    - High tumor budding (P=0.001)
  - **Better OS and PFS**
    - The loss of tubule formation(P=0.015 and 0.002)

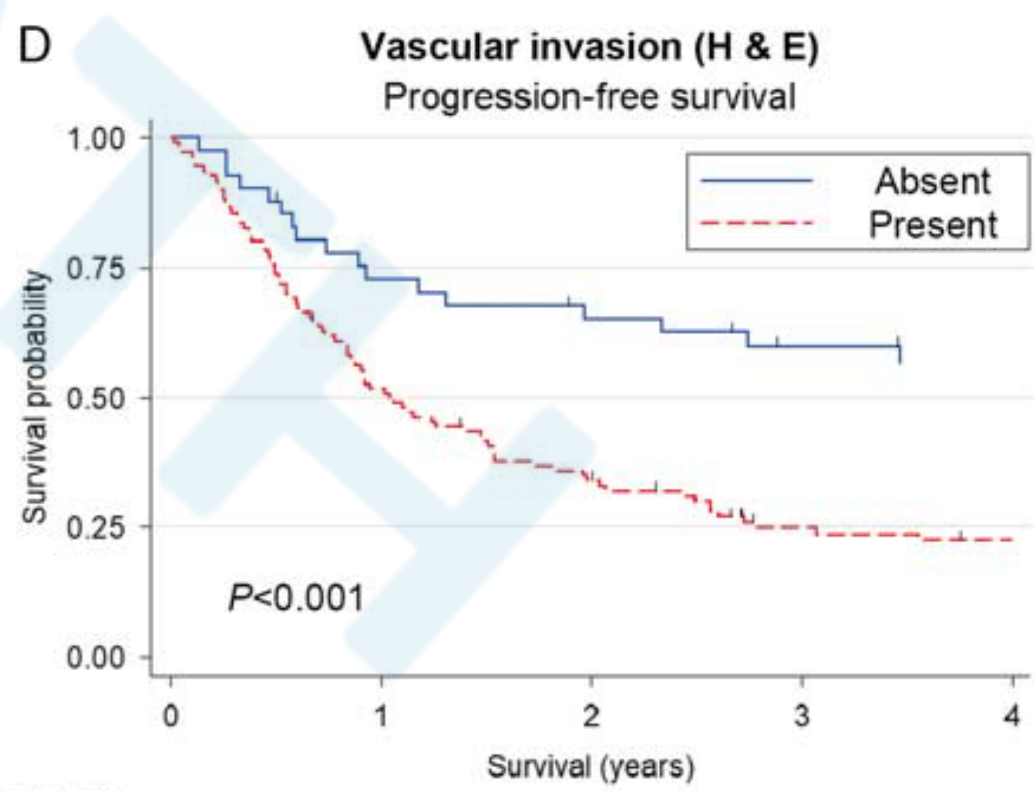
RESULTS

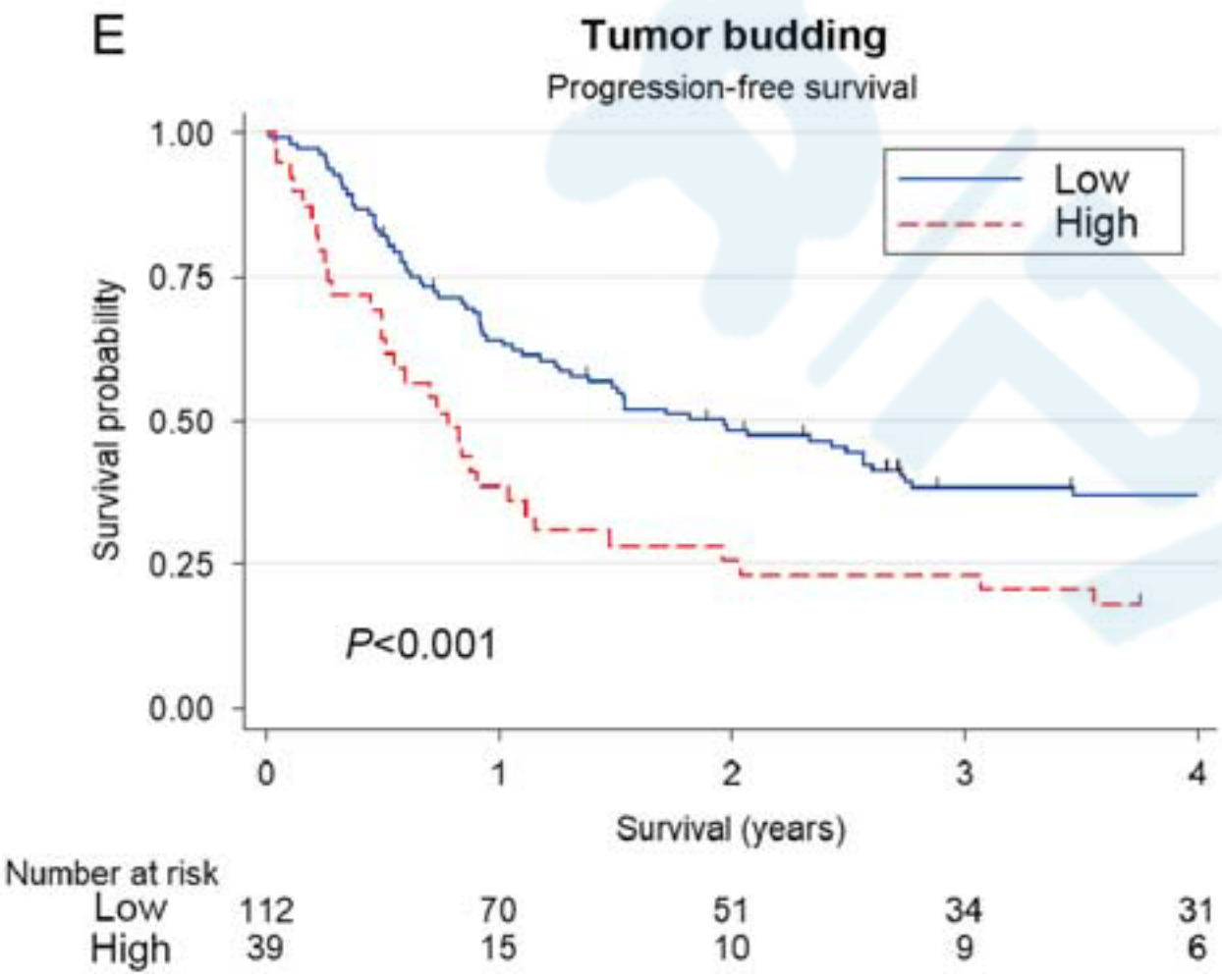
- **Multivariate analysis**
  - **Worse OS and PFS**
    - Prominent nuclear pleomorphism (P = 0.013 and 0.019)
    - High tumor budding (P =0.011 and <0.001)
    - High PDC (P < 0.001 and <0.001)
  - **Inferior prognosis for the PFS**
    - ⩾ 30 mitoses/10 HPF (P =0.013)
    - Vascular invasion


A
Prominent nuclear pleomorphism
Progression-free survival
Absent
Present
P=0.007
Survival probability
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
Survival (years)
Number at risk
Absent 50 35 28 20 20
Present 101 50 33 23 17


B
Mitosis/10 HPF
Progression-free survival
<30
≥30
P=0.007
Survival probability
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
Survival (years)
Number at risk
<30 72 47 36 27 25
≥30 79 38 25 16 12


C
Lymphatic invasion (H & E)
Progression-free survival
Absent
Present
P=0.057
Survival probability
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
Survival (years)
Number at risk
Absent 57 34 27 20 18
Present 94 51 34 23 19


D
Vascular invasion (H & E)
Progression-free survival
Absent
Present
P<0.001
Survival probability
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
Survival (years)
Number at risk
Absent 41 29 25 21 19
Present 110 56 36 22 18



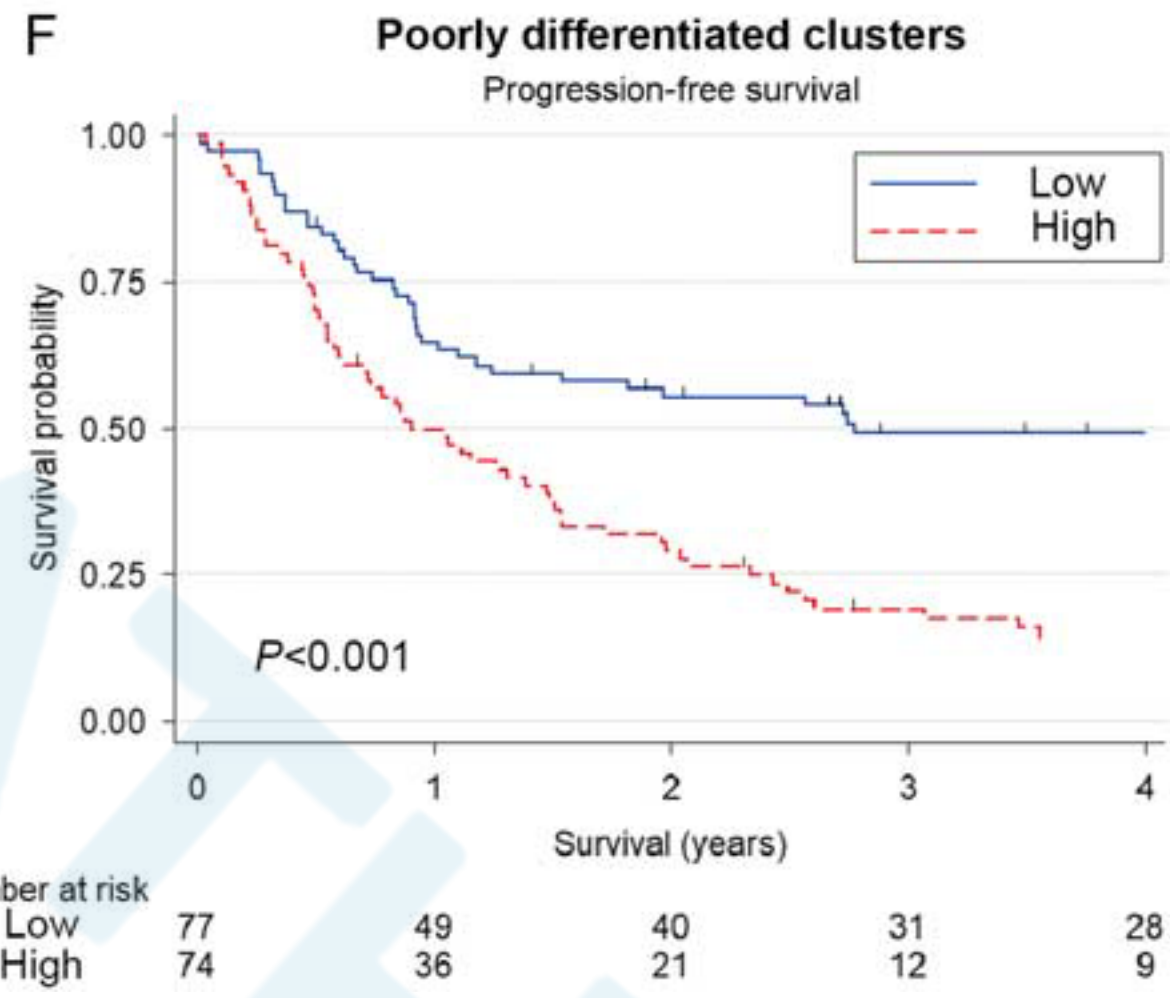


FIGURE 3. Kaplan-Meier survival curves of PFS of patients with SDC stratified by the following histologic parameters. A, Prominent nuclear pleomorphism. B, Mitosis/10 HPF. C, Lymphatic invasion. D, Vascular invasion. E, Tumor budding. F, PDCs.

RESULTS

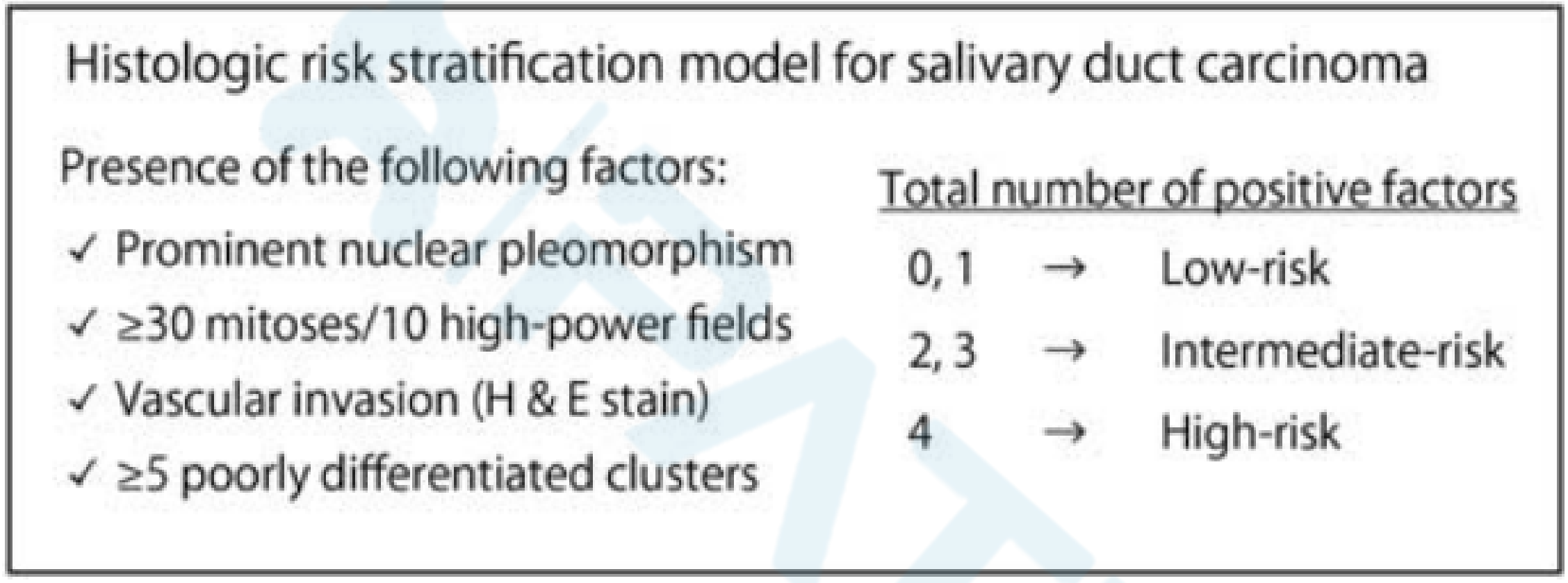


FIGURE 4. A schematic illustration of the proposed histologic risk stratification model.

TABLE 3. Univariate and Multivariate Analyses of Histologic Risk Stratification Model and Clinical Outcomes (N = 151)

		OS						PFS					
		Univariate Analysis			Multivariate Analysis			Univariate Analysis			Multivariate Analysis		
	n (%)	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Histologic risk group													
Low risk (score 0, 1)	35 (23.2)	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference	1.00	—	Reference
Intermediate risk (score 2, 3)	81 (53.6)	2.75	1.28-5.90	0.009*	2.13	0.92-4.92	0.077**	2.61	1.45-4.68	0.001*	2.28	1.19-4.35	0.012*
High risk (score 4)	35 (23.2)	5.01	2.25-11.15	< 0.001*	4.99	2.06-12.08	< 0.001*	4.44	2.36-8.37	< 0.001*	4.50	2.21-9.16	< 0.001*
P_{trend}			< 0.001			< 0.001			< 0.001			< 0.001	

Adjusted by age, sex, primary tumor site, TNM classification, first-line treatment, and histologic origin.

Histologic risk group was determined by 4 histologic features (prominent nuclear pleomorphism, mitosis ≥ 30/10 HPF, vascular invasion, and high PDCs). The total number of positive factors among these 4 were assigned low risk to high risk as follows: low risk, 0 to 1 point; intermediate risk, 2 to 3 points; high risk, 4 points.

*$P < 0.05$, statistically significant difference.

**$P = 0.05$ to <0.1, marginally significant difference.

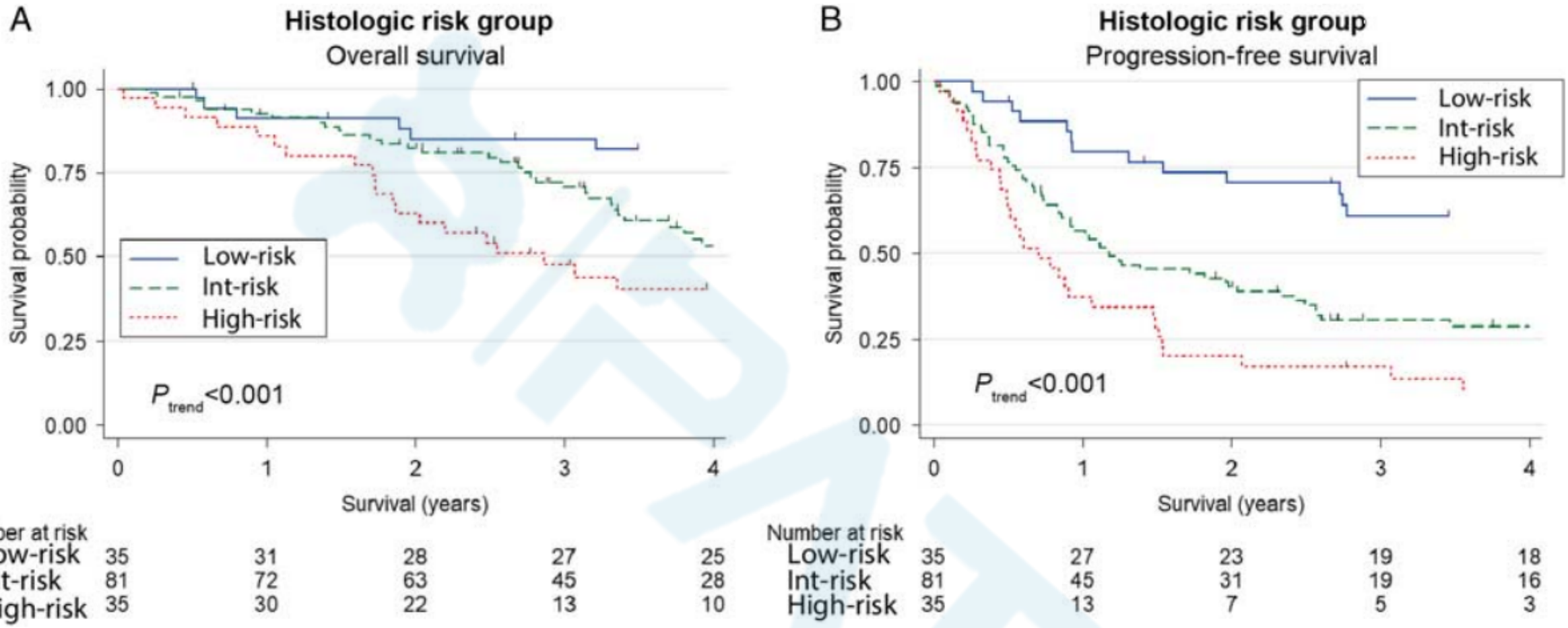


FIGURE 5. Kaplan-Meier survival curves for OS (A) and PFS (B) of patients with SDC stratified by the histologic risk stratification model. Int-risk indicates intermediate risk.

Our histologic risk stratification model could effectively predict patient survival and may be a useful aid to guide clinical decision-making in relation to the management of patients with SDC

DISCUSSION

- **Lymphatic, vascular, and perineural invasion**
  - Vascular invasion should be separately evaluated from lymphatic invasion
    - Vascular invasion showed a stronger association with the PFS than lymphatic invasion
    - This association was also observed in the multivariate analysis
- **EVG staining and D2-40 immunohistochemical staining**
  - Do not predict a poor patient prognosis more precisely than H&E staining
  - Additional stains might not necessarily be required to detect lymphatic or vascular invasion[36]

DISCUSSION

- **Tumor budding and PDC**
  - Not been evaluated previously for SDC
  - High tumor budding and PDC were strongly related to a poor OS and PFS in univariate and multivariate analyses
    - PDC was more prevalent than tumor budding
    - High PDC was associated with a higher HR and lower P-value than high tumor budding
    - PDC as an item for determining the histologic risk group

DISCUSSION

- **Histologic origin**
  - In our cohort, 89 SDC cases (58.9%) arose from preexisting pleomorphic adenoma, whereas others were de novo
  - In line with previous studies, the prognosis of SDC was not influenced by the histologic origin in either a univariate or multivariate analysis

DISCUSSION

- **Tubule formation**
  - Associated with a better prognosis in a univariate analysis but not in a multivariate analysis
  - Not included in the proposed histologic risk stratification model

DISCUSSION

- **Predominant intraductal component has been considered to have a better prognosis than invasive SDCs?**
  - These cases showed a better prognosis than SDC with a dominant invasive growth in univariate analysis, this difference disappeared in multivariate analysis

DISCUSSION

- **Tumor-stroma ratio**
  - Many previous studies of the tumor-stroma ratio concluded that high-stromal content was associated with a poor prognosis in other organs
  - In our analysis, no significant association was noticed

DISCUSSION

- 4 histologic features deemed capable of predicting a poor OS or PFS
  - Prominent nuclear pleomorphism, ⩾30 mitoses/10 HPF, vascular invasion, and high PDC,classified 3 different risk groups
- Useful and practical system and which requires no special ancillary testing
  - Assigned based on the findings of a microscopic evaluation with H&E staining alone
  - The combination of these 4 histologic features might minimize the intra-observer variation

DISCUSSION

- The present study was associated with several limitations
  - Some of the evaluated features could be subjective
    - Prominent nuclear pleomorphism
  - The histologic features on H&E sections and the molecular biomarker profiling classification
    - Androgen receptor, HER2, and Ki-67 expression status

CONCLUSION

- Prominent nuclear pleomorphism, ⩾ 30 mitoses/10 HPF, vascular invasion, ⩾ 5 tumor budding, and ⩾ 5 PDCs were strong prognostic predictors of a poor OS or PFS
- The histologic risk stratification model based on these factors is a concise and practical method for predicting patient prognosis and providing appropriate therapeutic options

THANK YOU