ORIGINAL ARTICLE

SATB2 Is Superior to CDX2 in Distinguishing Signet Ring Cell Carcinoma of the Upper Gastrointestinal Tract and Lower Gastrointestinal Tract

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背景—印戒细胞癌

- 定义：为腺癌的一种亚型，肿瘤主要（50%以上）或全部由印戒细胞构成。

- 印戒细胞特征：细胞中心有一光镜下透明的球状胞浆黏液滴和一个偏心的细胞核。

- 最常见于消化道，罕见于泌尿、肺、乳腺等部位。

- 是一种恶性程度很高的低分化腺癌，分化差、不易早期诊断，患者就诊时往往以脏器转移和腹水形成为首发症状，诊断具有挑战性。

背景—CDX-2

- CDX-2（Caudal- related homeobox transcription factor 2），同源盒结构基因，高度保守基因，原肠发育时的一个重要转录因子。

- 正常表达：十二指肠到直肠（中肠、后肠）。

- 病变表达：肠道上皮性肿瘤和神经内分泌肿瘤，发生于肺、胰胆、卵巢、膀胱且具有黏液上皮和/或肠上皮分化特征的肿瘤，肠上皮化生。

SATB2在结直肠肿瘤中的表达

1.SATB2 showed a high sensitivity (93%) and specificity (77%) to determine a cancer of colorectal origin and in combination with CK7 and CK20, the specificity increased to 100%。

2.SATB2 was positive in 93.8% of appendiceal tumours and in only one ovarian tumour; SATB2 was 97.5% specific for appendiceal origin.

Am J Clin Pathol. 2014; 141:630–638.

Histopathology. 2016;68:977–987.

背景—SATB2

- SATB2（Special AT-rich sequence-binding protein 2 ）：DNA结合蛋白，参与染色体重塑和转录调节。

- 突变：唇裂、大脑发育异常。

- 正常表达：结直肠和阑尾上皮，骨母细胞，大脑皮质和海马的神经元，非生发中心的淋巴细胞，睾丸和附睾的导管上皮。

- 病变表达：结直肠癌、骨肉瘤、肠型鼻腔 / 鼻窦腺癌及阑尾黏液性肿瘤中。而在前列腺癌、乳腺癌及卵巢癌中几乎不表达, 或仅有个别病例表达。

目的

最近研究报道33%原发于膀胱的印戒细胞癌SATB2呈阳性表达，2例肺印戒细胞癌卵巢转移SATB2表达缺失，而本研究首次使用大样本评估SATB2在上、下消化道印戒细胞癌的表达情况，包括远端食管/食管胃交界部，并探讨其应用价值。

材料与方法

- 病例来源

  收集匹兹堡大学的外科病理库中159例诊断为印戒细胞癌的病例（胃、远端食管/食管胃交界、阑尾和结直肠）及13例转移性乳腺癌。
- 免疫组化染色：SATB2、CDX2，均定义为核染色的阳性，
- 同时对染色强度及比例进行半定量评分

染色强度评估：不存在：0

在×10或更大物镜下可见核弱染色：1+

在×2或×4物镜下可见核强染色：2 +

染色比例评估：用目测法检测肿瘤细胞的核染色百分比。

计算每例SATB 2和CDX 2的改良H评分（即肿瘤细胞的强度数×核染色的肿瘤细胞百分比）。

结果

共159例印戒细胞癌（下消化道82例，上消化道77例），比较SATB2 CDX2阳性率、染色强度、H值。

TABLE 1. SATB2 and CDX2 Immunohistochemistry Results Stratified by Site of Origin of Signet Ring Cell Carcinoma

	Lower GI				Upper GI				
	All Lower GI Cases	Appendix	Colon	*P*	All Upper GI Cases	Stomach	Distal Esophagus/ Esophagogastric Junction	*P*	*P**
Total	82	33	49	NA	77	54	23	NA	NA
SATB2									
SATB2$^+$ (n [%])	70 (85)	27 (82)	43 (88)	0.5	15 (19)	7 (13)	8 (35)	0.06	< 0.01
SATB2 intensity									
Weak (1+) (n [%])	18 (26)	6 (22)	12 (28)	0.7	13 (87)	7 (100)	6 (75)	0.03	< 0.01
Strong (2+) (n [%])	52 (74)	21 (78)	31 (72)		2 (13)	0	2 (25)		
H-score (mean [range])	103 (0-200)	102 (0-200)	103 (0-200)	1.0	3 (0-100)	1 (0-20)	7 (0-100)	0.02	< 0.01
CDX2									
CDX2$^+$ (n [%])	74 (90)	30 (91)	44 (91)	1.0	39 (51)	23 (43)	16 (70)	0.05	< 0.01
CDX2 intensity									
Weak (1+) (n [%])	10 (14)	3 (10)	7 (16)	0.9	13 (33)	11 (48)	2 (13)	0.01	0.03
Strong (2+) (n [%])	64 (86)	27 (90)	37 (84)		26 (67)	12 (52)	14 (87)		
H-score (mean [range])	124 (0-200)	143 (0-200)	111 (0-200)	0.04	39 (0-200)	29 (0-200)	63 (0-200)	0.01	< 0.01
SATB2$^+$ and CDX2$^+$ (n [%])	65 (79)	26 (79)	39 (80)	0.7	11 (14)	4 (7)	7 (30)	0.04	< 0.01
SATB2$^+$ and CDX2$^-$ (n [%])	5 (6)	1 (3)	4 (8)		4 (5)	3 (6)	1 (4)		
SATB2$^-$ and CDX2$^+$ (n [%])	9 (11)	1 (3)	5 (10)		28 (36)	19 (35)	9 (39)		
SATB2$^-$ and CDX2$^-$ (n [%])	3 (4)	2 (6)	1 (2)		34 (44)	28 (52)	6 (26)		

**P*-value calculated from comparing signet ring cell carcinomas of lower GI tract origin with those of upper GI tract origin.
NA indicates not available.

SATB 2的表达在下消化道印戒细胞癌明显高于上消化道印戒细胞癌，此外，SATB 2在下消化道印戒细胞癌的表达常显示强着色（74%），而上消化道印戒细胞癌即使SATB2表达也常显示弱阳性。SATB2 CDX2的表达在阑尾及结直肠印戒细胞癌中无差异，远端食管/食管-胃交界部印戒细胞癌高于胃印戒细胞癌，来源于远端食管/食管-胃交界部印戒细胞癌可见SATB 2强表达

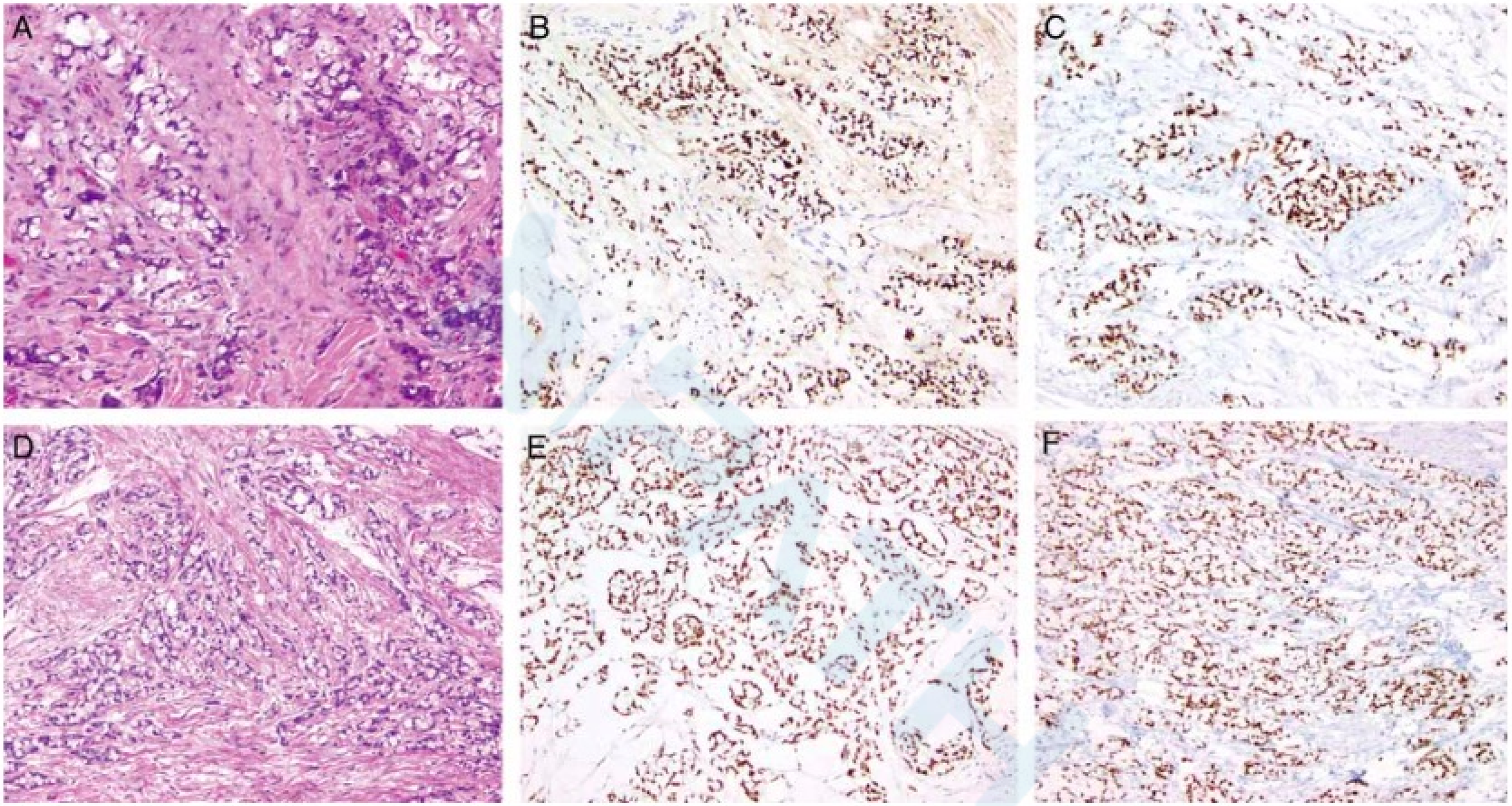

FIGURE 1. Dual SATB2 and CDX2-positive expression is a relatively specific marker for signet ring cell carcinoma of lower GI tract origin. This appendiceal signet ring cell carcinoma with peritoneal metastasis (A, hematoxylin and eosin) demonstrated strong expression of SATB2 (B) and CDX2 (C). This colorectal signet ring cell carcinoma with peritoneal metastasis (D, hematoxylin and eosin) demonstrated strong expression of SATB2 (E) and CDX2 (F).

腹膜转移的阑尾及结直肠印戒细胞癌中SATB2　CDX2的表达

TABLE 2. SATB2 and CDX2 Immunohistochemistry Results Stratified by Primary and Metastatic Signet Ring Cell Carcinoma

	Lower GI			Upper GI							
	Metastasis of Lower GI Primary	Primary	*P*	Metastasis of Upper GI Primary	Primary	*P*	Metastatic Breast Carcinoma	*P**	*P*†	*P*‡	*P*§
Total	50	32	NA	16	61	NA	13	NA	NA	NA	NA
SATB2											
SATB2$^+$ (n [%])	44 (88)	26 (81)	0.5	3 (19)	12 (20)	1.0	2 (15)	<0.01	<0.01	<0.01	1.0
SATB2 intensity											
Weak (1+) (n [%])	7 (16)	11 (42)	0.02	3 (100)	10 (83)	1.0	2 (100)	<0.01	<0.01	<0.01	1.0
Strong (2+) (n [%])	37 (84)	15 (58)		0	2 (17)		0				
H-score (mean [range])	118 (0–200)	79 (0–200)	0.1	3 (0–20)	3 (0–100)	0.9	0 (0–2)	<0.01	<0.01	<0.01	0.7
CDX2											
CDX2$^+$ (n [%])	47 (94)	27 (84)	0.3	6 (38)	33 (54)	0.3	0	<0.01	<0.01	<0.01	<0.01
CDX2 intensity											
Weak (1+) (n [%])	5 (11)	5 (19)	0.5	4 (67)	9 (27)	0.2	0	<0.01	0.01	<0.01	<0.01
Strong (2+) (n [%])	42 (89)	22 (81)		2 (33)	24 (73)		0				
H-score (mean [range])	137 (0–200)	104 (0–200)	0.04	5 (0–30)	48 (0–200)	0.05	0 (0–0)	<0.01	<0.01	<0.01	0.03
SATB2$^+$ and CDX2$^+$ (n [%])	43 (86)	22 (69)	0.1	1 (6)	10 (16)	0.3	0	<0.01	<0.01	<0.01	0.1
SATB2$^+$ and CDX2$^-$ (n [%])	1 (2)	4 (13)		2 (13)	2 (3)		2 (15)				
SATB2$^-$ and CDX2$^+$ (n [%])	4 (8)	5 (16)		5 (31)	23 (38)		0				
SATB2$^-$ and CDX2$^-$ (n [%])	2 (4)	1 (3)		8 (50)	26 (43)		11 (85)				

原发病例=93，转移病例=66，转移性乳腺癌=13

**P*-value calculated from comparing metastatic signet ring cell carcinomas of lower GI tract origin with metastatic carcinomas of upper GI origin.
†*P*-value calculated from comparing primary signet ring cell carcinomas of lower GI tract origin with primary carcinomas of upper GI origin.
‡*P*-value calculated from comparing metastatic signet ring cell carcinomas of lower GI tract origin with breast cancer metastases.
§*P*-value calculated from comparing metastatic signet ring cell carcinomas of upper GI tract origin with breast cancer metastases.
NA indicates not available.

SATB 2 、CDX2在来源于上、下消化道的原发及转移性印戒细胞癌中的表达比例及强度无统计学差异。
SATB 2表达在来源于下消化道的原发及转移性印戒细胞癌中明显高于上消化道的原发及转移性印戒细胞癌。
转移性乳腺癌可显示SATB2的弱表达。

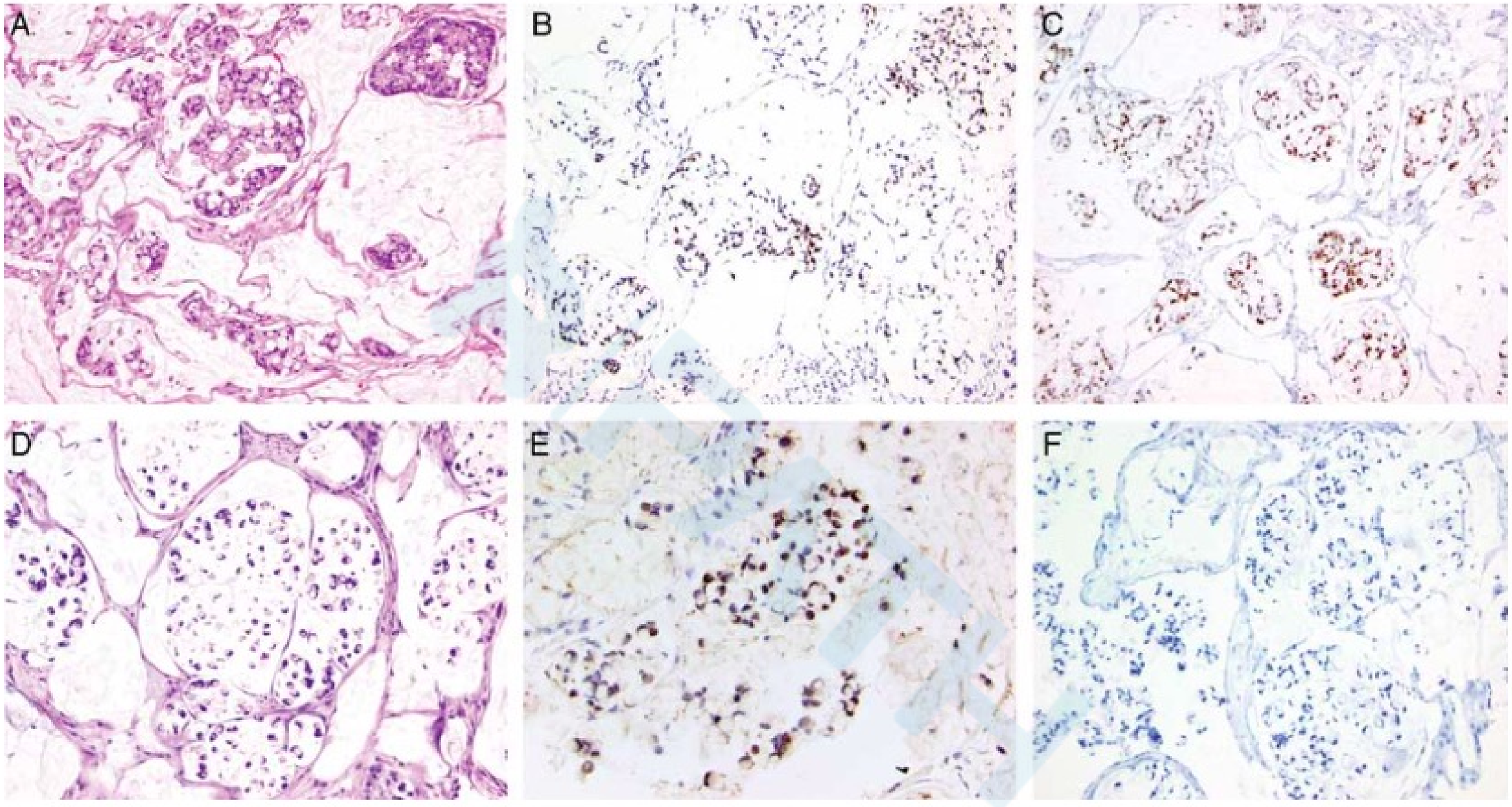

FIGURE 2. SATB2 expression can be identified in some signet ring cell carcinomas of the upper GI tract. This primary esophageal/esophagogastric adenocarcinoma (A, hematoxylin and eosin) demonstrated SATB2 expression in ~50% of tumor cells (B) and diffuse CDX2 expression (C). This gastric signet ring cell carcinoma with peritoneal metastasis (D, hematoxylin and eosin) demonstrated focal and weak SATB2 expression in 10% of tumor cells (E) and negative expression of CDX2 (F) expression.

SATB 2在某些上消化道印戒细胞癌中表达

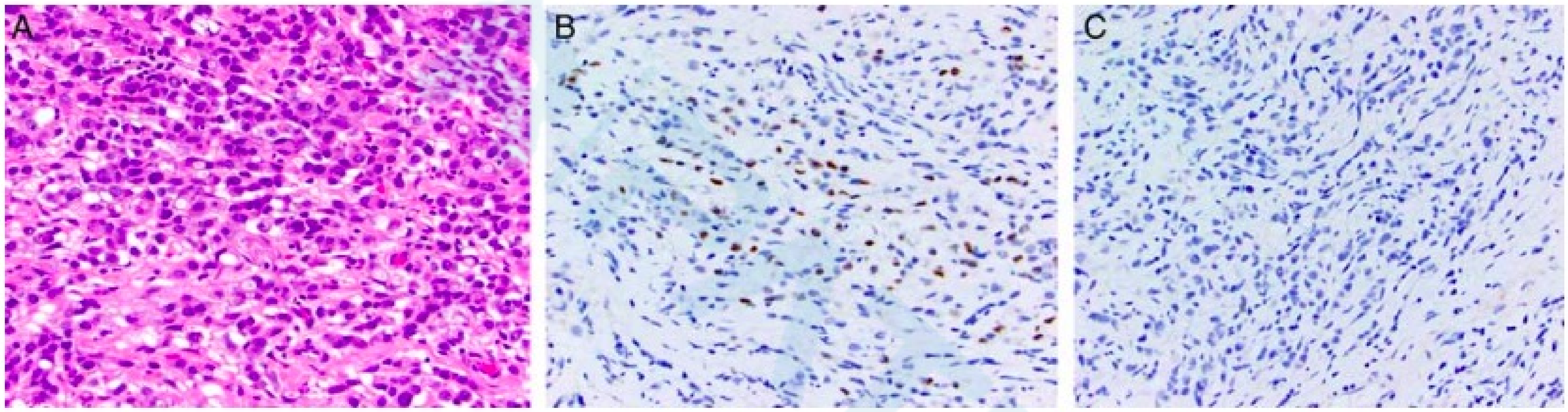

FIGURE 3. SATB2 expression can be identified in rare metastatic breast carcinomas. This breast carcinoma with signet ring cell features metastatic to the colon (A) demonstrated focal and weak SATB2 expression in <5% of tumor cells (B) and negative expression of CDX2 (C).

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H-score (mean [range])	103 (0-200)	102 (0-200)	103 (0-200)	1.0	3 (0-100)	1 (0-20)	7 (0-100)	0.02	< 0.01
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SATB2$^+$ and CDX2$^-$ (n [%])	5 (6)	1 (3)	4 (8)		4 (5)	3 (6)	1 (4)		
SATB2$^-$ and CDX2$^+$ (n [%])	9 (11)	1 (3)	5 (10)		28 (36)	19 (35)	9 (39)		
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**P*-value calculated from comparing signet ring cell carcinomas of lower GI tract origin with those of upper GI tract origin.
NA indicates not available.

下消化道印戒细胞癌SATB 2+/CDX 2+表达率为79%，而上消化道印戒细胞癌为14%；上消化道印戒细胞癌常显示SATB 2-/CDX 2-或仅有CDX 2的表达

TABLE 2. SATB2 and CDX2 Immunohistochemistry Results Stratified by Primary and Metastatic Signet Ring Cell Carcinoma

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SATB2											
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SATB2 intensity											
Weak (1+) (n [%])	7 (16)	11 (42)	0.02	3 (100)	10 (83)	1.0	2 (100)	< 0.01	< 0.01	< 0.01	1.0
Strong (2+) (n [%])	37 (84)	15 (58)		0	2 (17)		0				
H-score (mean [range])	118 (0–200)	79 (0–200)	0.1	3 (0–20)	3 (0–100)	0.9	0 (0–2)	< 0.01	< 0.01	< 0.01	0.7
CDX2											
CDX2$^+$ (n [%])	47 (94)	27 (84)	0.3	6 (38)	33 (54)	0.3	0	< 0.01	< 0.01	< 0.01	< 0.01
CDX2 intensity											
Weak (1+) (n [%])	5 (11)	5 (19)	0.5	4 (67)	9 (27)	0.2	0	< 0.01	0.01	< 0.01	< 0.01
Strong (2+) (n [%])	42 (89)	22 (81)		2 (33)	24 (73)		0				
H-score (mean [range])	137 (0–200)	104 (0–200)	0.04	5 (0–30)	48 (0–200)	0.05	0 (0–0)	< 0.01	< 0.01	< 0.01	0.03
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SATB2$^+$ and CDX2$^-$ (n [%])	1 (2)	4 (13)		2 (13)	2 (3)		2 (15)				
SATB2$^-$ and CDX2$^+$ (n [%])	4 (8)	5 (16)		5 (31)	23 (38)		0				
SATB2$^-$ and CDX2$^-$ (n [%])	2 (4)	1 (3)		8 (50)	26 (43)		11 (85)				

**P*-value calculated from comparing metastatic signet ring cell carcinomas of lower GI tract origin with metastatic carcinomas of upper GI origin.
†*P*-value calculated from comparing primary signet ring cell carcinomas of lower GI tract origin with primary carcinomas of upper GI origin.
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§*P*-value calculated from comparing metastatic signet ring cell carcinomas of upper GI tract origin with breast cancer metastases.
NA indicates not available.

来源于下消化道的转移性印戒细胞癌常显示SATB2$^+$/CDX2$^+$ ，而来源于上消化道的转移性印戒细胞癌常显示SATB 2−/CDX 2−或SATB 2−/CDX 2+，转移性乳腺癌SATB 2+/CDX 2−（2/13，15%）。

TABLE 3. Diagnostic Test Characteristics of SATB2 and CDX2 Immunohistochemistry for Lower GI Tract Origin

	Distinguishing Lower GI Tract From Upper GI Tract Origin (%, [95% CI])		Distinguishing Lower GI Tract from Either Upper GI Tract or Breast Origin (%, [95% CI])		Distinguishing Lower GI Tract from Breast Origin (%, [95% CI])	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
$SATB2^+$	85 (76-92)	81 (70-89)	85 (76-92)	81 (71-89)	85 (76-92)	84 (55-98)
$CDX2^+$	90 (82-95)	49 (38-61)	90 (82-96)	57 (46-67)	90 (82-96)	100 (75-100)
$SATB2^+$ and $CDX2^+$	79 (69-87)	86 (76-93)	79 (69-87)	88 (79-94)	79 (69-87)	100 (75-100)
$SATB2^+$ and/or $CDX2^+$	96 (90-99)	44 (33-56)	96 (90-99)	50 (39-61)	96 (90-99)	84 (55-98)

CI indicates confidence interval.

然而CDX 2单独用于鉴别下消化道印戒细胞癌与来源于乳腺的转移癌的特异性为100%，而SATB 2+或SATB 2+/CDX 2+的特异性都为84%，但差异无统计学意义，可能是由于本研究中转移性乳腺病例相对较少所导致。

讨论

- 现有的标记物在区分肿瘤是否来源上、下消化道时有较大的限制性，该研究首次使用大样本评估SATB2否有助于鉴别上、下消化道印戒细胞癌。

- 该研究结果证实SATB 2表达率在下消化道印戒细胞癌中明显高于上消化道印戒细胞癌，包括阑尾印戒细胞癌。

- 首次研究SATB2在远端食管/食管胃交界的印戒细胞癌中的表达情况，结果证实胃印戒细胞癌（13%）、远端食管/食管胃交界的印戒细胞癌（35%）及具有印戒细胞特征的转移性乳腺癌中（15%）有一部分呈SATB 2阳性表达，但表达常较弱且局灶，其中2例远端食管/食管胃交界的印戒细胞癌为强表达。

- 与CDX 2相比，SATB 2+和SATB 2、CDX 2双阳性表达对鉴别下消化道来源的印戒细胞癌都有很高的特异性，但也可见于上消化道来源的印戒细胞癌。

- 与以往研究结果一致，SATB 2与CDX 2用于鉴别下消化道来源的原发和转移性印戒细胞癌中都具有较高敏感性。

- 之前的研究结果表明原发或转移性乳腺癌可显示SATB2 0-20%阳性率，但CDX2表达都为阴性，本研究结果同样也显示SATB2在鉴别下消化道印戒细胞癌与转移性乳腺癌时的特异性低于CDX2。

结论

- SATB2对来源于下消化道的原发和转移性印戒细胞癌具有相对特异性，进一步证实了其应用价值。
- SATB 2在远端食管/食管胃交界部印戒细胞癌以及具有印戒细胞特征的乳腺癌中均有阳性表达。
- 判断下消化道印戒细胞癌，SATB2+及SATB2+ / CDX 2+较单纯CDX2+具有更高的特异性。

谢 谢