抄読会 令和 3 年 4 月 5 日

Clinico-pathologic predictors of patterns of residual disease following neoadjuvant chemotherapy for breast cancer

Ricardo G Pastorello, Alison Laws, Samantha Grossmith, Claire King, Monica McGrath, Elizabeth A Mittendorf, Tari A King, Stuart J Schnitt

Mod pathol. 2020 Nov 20. doi: 10.1038/s41379-020-00714-5.

要旨：
術前化学療法(NAC)を受け pCR を得られなかった乳癌患者において、乳房内の残存病変のパターンは様々であるが、残存病変のパターンを予測する治療前の臨床病理学的特徴は確立されていない。筆者らは、2004 年～2014 年にかけて NAC 後に根治手術を施行した乳癌患者のうち、残存病変を評価できた 389 症例について検討した。287 例(73.8%)が scattered pattern であり、102 例(26.2%)が circumscribed pattern であった。
単変量解析において腫瘍のサブタイプと残存病変のパターンは有意に関連が認められた。特に、ホルモンレセプター(HR)陽性症例の 86.1%は scattered patten であったが、HR 陰性症例では 47.2%であった($p < 0.001$)(Table 1)。
多変量解析では、腫瘍のサブタイプに加えて組織学的悪性度と腫瘍サイズも関連していた。組織学的悪性度が低い、また腫瘍サイズが大きいほど、scattered pattern と関連していた(Table 2)。
さらに、残存した浸潤癌細胞や間質 TIL の治療関連の組織学的変化も、腫瘍のサブタイプと有意に関連していた(Table 3)。
腫瘍床の特徴においても腫瘍のサブタイプにより有意に異なっていた(Table 4)。

Take Home Message：
NAC により pCR が得られなかった乳癌患者においては、腫瘍サイズ、組織学的グレード、腫瘍のサブタイプが残存病変のパターンと有意かつ独立して関連していた。残存癌のパターンとその予測因子が、さらなる追加の局所治療の指針となるか、あるいはその後の遠隔再発、局所再発、同側乳房再発等のリスク予測となり得るかはさらに検討する必要がある。

査読者　橋元 麻生

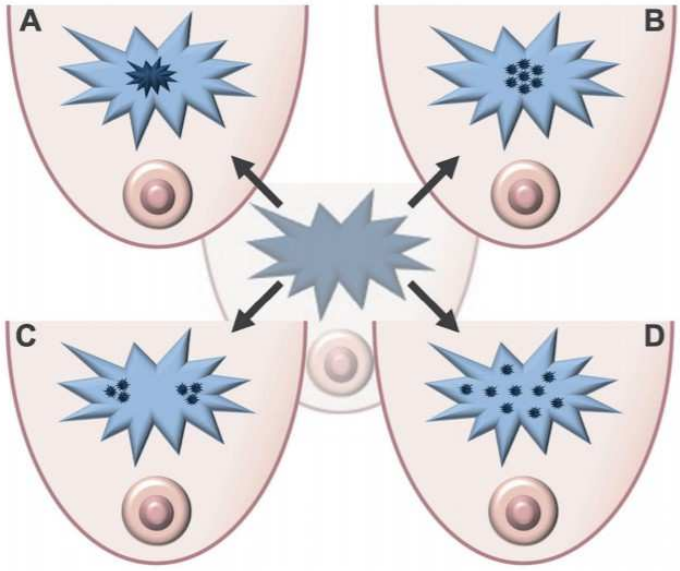

Fig. 1 Schematic representation of patterns of residual disease following neoadjuvant chemotherapy. **a** Solitary, confined focus of residual tumor with little or no intervening treatment-related fibrosis. **b** Tumor cell nests are separated by small areas of treatment-related fibrosis but are confined to a circumscribed area. **c** Scattered, clustered foci of residual tumor, with large intervening areas of treatment-related fibrosis. **d** Diffusely scattered tumor cells, singly and in small clusters, with prominent associated treatment-related fibrosis.

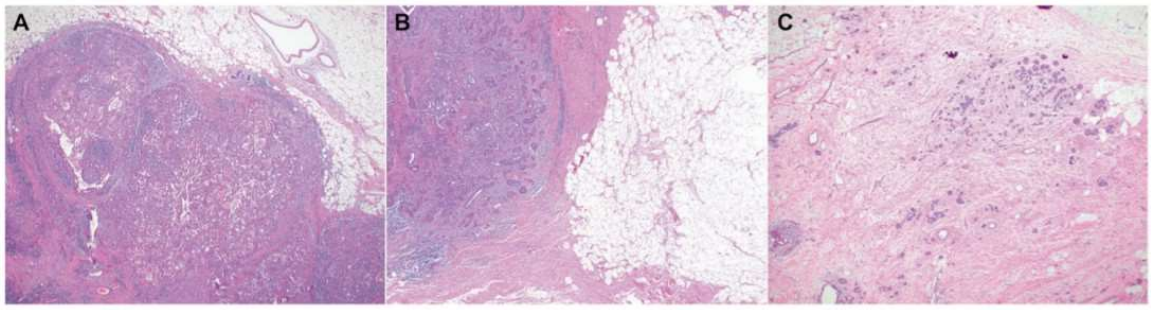

Fig. 2 Histologic images of patterns of residual tumor. a In this case there is a single, circumscribed focus of residual invasive carcinoma with a patchy associated lymphoid infiltrate. This pattern of residual tumor corresponds to that depicted in Fig. 1a. **b** In this case the residual tumor is composed of nests of tumor cells, separated by treatment-related fibrosis, but the tumor cell nests are present in a confined, circumscribed area. This pattern of residual tumor corresponds to that depicted in Fig. 1b. **c** In this case there are widely scattered residual tumor cells, in small clusters and as single cells, broadly distributed across a fibrotic tumor bed. This pattern corresponds to that depicted Fig. 1d.

Table 1 Pattern of residual disease related to clinico-pathologic features at initial presentation among 389 patients with evaluable residual disease in the breast.

	Circumscribed ($n = 102$)	Scattered ($n = 287$)	p value
Age (mean, years)	48	49	0.05
Tumor size (mean, cm)	31.3	37.1	**0.001**
Clinical node status			**0.04**
Positive ($n = 236$)	53 (22.5%)	183 (77.5%)	
Negative ($n = 153$)	49 (32.0%)	104 (68.0%)	
Chemotherapy			0.988
Anthracycline and/or taxane-based ($n = 366$)	96 (26.2%)	270 (73.8%)	
Other ($n = 23$)	6 (26.1%)	17 (73.9%)	
Focality			**0.02**
Unifocal ($n = 246$)	69 (28.0%)	177 (72.0%)	
Multifocal ($n = 94$)	28 (29.8%)	66 (70.2%)	
Multicentric ($n = 49$)	5 (10.2%)	44 (89.8%)	
Histologic grade[a]			**<0.001**
1 or 2 ($n = 152$)	14 (9.2%)	138 (90.8%)	
3 ($n = 235$)	88 (37.4%)	147 (62.6%)	
Hormone receptor status			**<0.001**
Positive ($n = 266$)	37 (13.9%)	229 (86.1%)	
Negative ($n = 123$)	65 (52.8%)	58 (47.2%)	
Tumor subtype			**<0.001**
HR+/HER2− ($n = 189$)	20 (10.6%)	169 (89.4%)	
HER2+ ($n = 107$)	31 (29.0%)	76 (71.0%)	
Triple-negative ($n = 93$)	51 (54.8%)	42 (45.2%)	

HR hormone receptor.

[a] Two patients did not have grade information for the pre-treatment biopsy.

Table 2 Multivariate analysis relating clinico-pathologic features to likelihood of scattered pattern of residual tumor.

	OR	95% CI	p value
Tumor size (per mm)	1.022	1.005–1.040	**0.013**
Nodal status			
Negative	1 (ref)		
Positive	1.135	0.655–1.967	0.651
Focality			
Unifocal	1 (ref)		
Multifocal	2.742	0.984–7.644	0.05
Multicentric	0.975	0.527–1.804	0.94
Histologic grade			
3	1 (ref)		
1 or 2	2.894	1.468–5.704	**0.002**
Tumor subtype			
Triple-negative	1 (ref)		
HR−/HER2+	1.344	0.563–3.211	0.505
HR+/HER2+	3.275	1.589–6.750	**0.001**
HR+/HER2−	6.673	3.374–13.197	**<0.001**

OR odds ratio, *CI* confidence interval, *HR* hormone receptor.

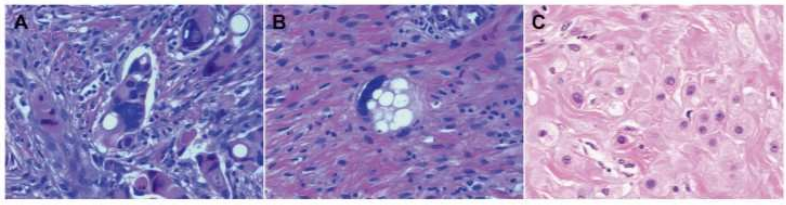

Fig. 3 Treatment effects in invasive carcinoma cells. (**a**) Marked cytologic atypia, (**b**) Prominent cytoplasmic vacuolization (**b**), (**c**) Tumor cells with an appearance similar to foamy histiocytes.

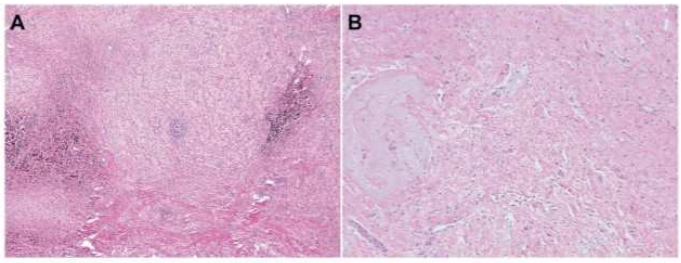

Fig. 4 Tumor bed features related to tumor subtype. (**a**) Foamy histiocytes and stromal hemosiderin deposition were more common in the tumor bed of triple negative breast cancers, (**b**) Stromal elastosis was more commonly seen in the tumor bed of HR+/HER2− cancers.

Table 3 Treatment effects in invasive tumor cells and stromal TILs among 468 cases with residual invasive disease in the breast related to tumor subtypes.

	HR+/HER2− ($n = 216$)	HER2+ ($n = 127$)	TNBC ($n = 125$)	p value
Moderate/marked nuclear atypia	97 (44.9%)	55 (43.3%)	92 (73.6%)	**<0.001**
Cytoplasmic vacuolization/foaminess	110 (50.9%)	72 (56.7%)	100 (80.0%)	**<0.001**
Tumor cells resembling histocytes	33 (15.3%)	21 (16.5%)	35 (28.0%)	**0.01**
High stromal TILs[ab]	34 (15.9%)	33 (27.3%)	67 (54.5%)	**<0.001**

HR hormone receptor, *TNBC* triple negative breast cancer, *TILs* tumor infiltrating lymphocytes.

[a]High TILs defined as greater than average percentage of TILs in cases with residual invasive disease in the breast (cutoff 16.8%).

[b]Ten patients with residual carcinoma only in lymphovascular spaces did not have stromal TILs assessed and were excluded.

Table 4 Tumor bed changes related to breast tumor subtype.

	HR+/HER2− ($n = 242$)	HER2+ ($n = 216$)	TNBC ($n = 207$)	p value
Fibrosis/scarring	241 (99.6%)	209 (96.8%)	206 (99.5%)	**0.014**
Foamy macrophages	39 (16.1%)	60 (27.8%)	67 (32.4%)	**<0.001**
Hemosiderin laden-macrophages	110 (45.5%)	110 (50.9%)	136 (65.7%)	**<0.001**
Hemosiderin deposition	132 (54.5%)	106 (49.1%)	146 (70.5%)	**<0.001**
Stromal elastosis	94 (38.8%)	67 (31.0%)	51 (24.6%)	**0.005**
Myxoid change	46 (19.0%)	29 (13.4%)	17 (8.2%)	**0.004**
Stromal mucin	20 (8.3%)	11 (5.1%)	1 (0.5%)	**0.001**

HR hormone receptor, *TNBC* triple negative breast cancer.