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The 21-gene recurrence score in special histologic subtypes of breast cancer with favorable prognosis

Gulisa Turashvili¹, Edi Brogi¹, Monica Morrow², Clifford Hudis³, Maura Dickler³, Larry Norton³, and Hannah Y. Wen¹

¹Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

²Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY 10065, USA

³Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

Abstract

Background/purpose—The 21-gene recurrence score (RS) assay predicts the likelihood of distant recurrence and chemotherapy benefit in early-stage, estrogen receptor (ER)-positive, HER2-negative breast cancer. Data on the RS of special histologic subtypes of invasive breast carcinoma with favorable prognosis are limited.

Methods—We reviewed our institutional database to identify patients with special histologic subtypes of breast cancer associated with favorable prognosis and available RS results. Our cohort consists of fifty-seven women: thirty-three patients with pure mucinous carcinoma (MC), ten with tubular carcinoma (TC), nine with encapsulated papillary carcinoma (EPC), and five with solid papillary carcinoma (SPC).

Results—Most (44/57, 77.2%) carcinomas had low RS (≤ 17), and none had high RS (≥ 31). All EPCs had low RS, but other subtypes had RS 18–30. Higher RS was associated with lower progesterone receptor (PR) expression by immunohistochemistry and lower PR mRNA scores ($P = 0.007$). No morphologic feature (tumor grade, biopsy site changes, cellular stroma, inflammatory cells) was associated with RS ≤ 18. At a median follow-up of 40 months, the distant recurrence-free survival was 100%. One patient with SPC developed locoregional recurrence at 22 months.

Conclusions—As the largest series to date, our study raises the question of whether the RS assay is necessary for breast cancers with favorable histology. Reflex testing of node-negative, ER +/HER2– breast cancers may be deferred for these special histologic subtypes, emphasizing the

Correspondence to: Hannah Y. Wen.

Compliance with ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Institution Review Board. For this type (retrospective) of study, formal consent is not required.

Ethical standards The experiments (data analyses) comply with the current laws of the country in which they were performed (United States of America).

need for multidisciplinary discussions between breast pathologists and other members of the breast cancer team.

Keywords

Breast cancer; Favorable histology; Mucinous carcinoma; Tubular carcinoma; Solid papillary carcinoma; Encapsulated papillary carcinoma; 21-gene recurrence score assay

Introduction

Breast cancer is a heterogeneous disease with variable morphologic features, molecular profiles, and prognosis [1–4]. The most common (40–75%) histologic type of invasive breast cancer is invasive breast carcinoma of no special type (NST), also known as invasive ductal carcinoma (IDC) NST. IDC NST is defined by the 2012 World Health Organization (WHO) classification as “the heterogeneous group of tumors that fail to exhibit sufficient characteristics to achieve classification as a specific histological type.” There are 21 special subtypes of invasive breast cancer. Invasive lobular carcinoma (ILC) is the most common (5–15%), and has a better or similar outcome within 10 years of diagnosis compared to IDC [5, 6]. The other special subtypes are rare and vary significantly in their prognosis and response to adjuvant treatment [7–10]. Tubular, mucinous and papillary carcinomas are known to have an extremely favorable outcome with significantly higher recurrence-free survival rates compared to IDC and ILC [11, 12]. Therefore, recommendations for adjuvant systemic therapy may differ in this group compared to patients with IDC NST [13].

The 21-gene recurrence score (RS) multigene assay (Oncotype Dx™, Genomic Health, Redwood City, CA) evaluates the expression of 16 cancer-related genes and 5 reference genes based on quantitative reverse transcription polymerase chain reaction [14]. The assay yields a numeric variable on a scale of 0–100 that quantifies the risk of distant recurrence at 10 years after diagnosis and predicts the benefit of chemotherapy in patients with lymph node-negative, estrogen receptor (ER)-positive, HER2-negative breast cancer treated with five years of tamoxifen [15–20]. In the past decade, the RS assay has been integrated into standard clinical practice and has greatly impacted treatment decision making by medical oncologists. The benefit of chemotherapy in patients with breast carcinoma of low RS (< 17) is estimated to be too small to outweigh the risks of side effects [21]. In contrast, patients with carcinoma of high RS (≥ 31) are at a higher risk of distant recurrence and thus benefit from chemotherapy [20, 22–30]. Studies have reported associations between the RS and standard pathologic and biomarker variables [31–37], including the tumor histologic type [38–40]. However, to date the data on the RS of special histologic subtypes of breast carcinoma with favorable prognosis remain very limited.

In this study, we describe fifty-seven women with breast carcinoma of favorable histology and available RS data treated at our center between 2006 and 2015.

Materials and methods

At our center, all lymph node-negative and selected node-positive ER+/HER2– breast cancers measuring ≤ 0.5 cm in patients medically suitable for chemotherapy are sent for

evaluation by the 21-gene RS assay. For each case, we carefully select the best tumor block suitable for analysis, avoiding areas of biopsy site changes and/or marked inflammatory infiltrate [14], as feasible.

Through a search of our institutional database, we identified patients with special histologic subtypes of breast cancer with favorable prognosis (mucinous, papillary, and tubular carcinomas) who were treated at our center between September 2006 and January 2015 and had the RS results of their tumors available. Two pathologists reviewed the hematoxylin-eosin-stained slides and confirmed the diagnosis of all cases. Only carcinomas of pure morphology (>90% of tumor mass) were included. Cases of mixed IDC NST (>1.5 mm) and papillary carcinoma were excluded to ensure that RS results were not affected by the presence of a significant IDC component. We recorded clinicopathologic characteristics, including patient age at breast cancer diagnosis, tumor size, grade, ER and progesterone receptor (PR) expression level by immunohistochemistry (IHC), lymph node status, local and systemic treatment, and clinical outcome. We also reviewed the original RS assay reports and recorded the RS results, including ER and PR mRNA scores. The Institution Review Board approved the study.

Statistical analysis was performed using SPSS 24.0. Clinicopathologic covariate and RS associations were assessed using contingency tables, and significance of associations was determined using Pearson's χ^2 test (categorical variables) or Pearson's correlation (continuous variables). Medians for continuous variables were also compared using independent samples median test. A significance level of $P < 0.05$ was used for all the comparisons.

Results

Patients with breast carcinoma of special subtype

We identified fifty-seven women with breast carcinoma of special subtype, including thirty-three women with pure mucinous carcinoma (MC), ten with tubular carcinoma (TC), nine with encapsulated papillary carcinoma (EPC), and five with solid papillary carcinoma (SPC). The median patient age was 54 years (range 36–84). Twenty-one patients (36.8%) were <50 years of age, and four patients (7%) were <40 years old. Twenty-eight patients (49.1%), including eleven women with MC, seven with TC, seven with EPC and three with SPC, had a family history of breast cancer. Two women with TC and two with MC (7%) had a family history of ovarian cancer. Only one patient with EPC had known BRCA1 and BRCA2 mutations. An additional patient had a personal history of contralateral IDC NST seven years prior to the diagnosis of MC.

The median tumor size was 1.2 cm (range 0.5–3.5). Three patients (5.3%) had multifocal tumors with similar morphology. Most carcinomas (40/57, 70.2%) were of grade 2, and none was of grade 3. Most tumors (55/57, 96.5%) were ER+/PR+, and only two tumors (3.5%) were ER+/PR-. The median percentages of ER+ and PR+ cells by IHC were 98 (range 20–100) and 90 (range 0–100), respectively. All index tumors were completely resected with negative final surgical resection margins. Most patients (56/57, 98.2%) underwent a sentinel

lymph node biopsy. Four patients (7%) had lymph node micro- or macrometastases ranging from >0.2 to 14 mm in size.

A total of forty-two patients (73.7%) had breast conserving surgery (BCS), and thirty-six (63.2%) patients received radiation therapy post BCS. The remaining fifteen patients (26.3%) had a total mastectomy. Systemic therapy included adjuvant endocrine therapy alone in fifty-five patients (96.5%) and endocrine therapy plus chemotherapy in seven patients (12%). At a median follow-up of 40 months, the distant recurrence-free survival was 100%. Only one patient (1.8%) developed locoregional recurrence at 22 months.

Recurrence Score (RS) of special subtypes of breast carcinoma

The median RS of the carcinomas in our study was 11 (range 0–28). Most tumors (44/57, 77.2%) had a low RS (≤ 17). Only one carcinoma had RS >25, and none had a high RS (≥ 31) (Table 1). The median ER mRNA score was 10 (range 7.1–12.5), and median PR mRNA score was 8.1 (range 4–10). Statistical analysis showed that higher RS values were associated with lower ER and PR mRNA scores ($P < 0.0001$) and lower percentage of PR+ cells by IHC ($P = 0.007$). In addition, PR mRNA scores correlated with the percentage of PR+ cells by IHC ($P < 0.0001$), whereas ER mRNA scores showed no association with the percentage of ER+ cells by IHC ($P = 0.932$). The distributions of ER and PR mRNA scores, and the percentage of ER+ and PR+ cells by IHC are illustrated in Fig. 1a, b. Analysis of binarized (low and intermediate) RS data revealed no association with any of the clinicopathologic variables. RS ≥ 18 was not associated with any specific morphologic features such as tumor grade, biopsy site changes, cellular stroma, or inflammatory cells.

Mucinous carcinoma (MC)

The thirty-three patients with MC had a median age of 52 years (range 36–77). Twelve patients (36.4%) were < 50 years of age, and three patients (9.1%) were < 40 years old. The median tumor size was 1.2 cm (range 0.5–3.5). Most MCs were of grade 2 (28/33, 84.8%). Two patients (6.1%) had multifocal disease. Three patients (9.1%) with MC spanning 0.5 cm, 1.4 cm, and 2.1 cm, respectively, had lymph node micrometastases. All three carcinomas had a low RS (Fig. 2a, c). One patient had isolated tumor cells (ITCs) in one sentinel lymph node. The median percentages of ER+ and PR+ cells by IHC were 97 (range 20–100) and 90 (range 0–99), respectively. Most MCs (26/33, 78.8%) had a low RS, and only 21.2% (7/33) had an intermediate RS (Fig. 2b). The median RS of MC was 13 (range 3–28). The median ER and PR mRNA scores were 9.8 (range 7.9–12.5) and 7.9 (range 5–9.4), respectively.

A total of twenty-six patients (78.8%) with MC underwent BCS, and twenty-two patients (66.7%) had BCS with radiation therapy. Seven patients (21.2%) received a total mastectomy. All patients were treated with endocrine therapy. Six patients (18.2%) received chemotherapy, including three patients with MC of intermediate RS, and three patients with MC of low RS. At a median follow-up of 41 months, none of the patients with MC developed locoregional or distant recurrence (Table 2).

Tubular carcinoma (TC)

The median age of ten patients with TC was 46 years (range 37–69). Seven patients (70%) were <50 years of age, and only one patient (10%) was <40 years old. The median tumor size was 0.8 cm (range 0.5–1.8). One patient (10%) had a multifocal TC. All TCs were of grade 1 and ER+/PR+/HER2-. The median percentages of ER+ and PR+ cells by IHC were 95 (range 90–100) and 90 (range 5–100), respectively. None had lymph node involvement. Six tumors (60%) had a low RS and 40% (4/10) had an intermediate RS (Fig. 3a, b). The median RS was 14 (range 9–23). The median ER and PR mRNA scores were 8.4 (range 7.1–9.8) and 8.1 (range 6.2–9.4), respectively.

Seven patients (70%) with TC underwent BCS followed by radiation therapy, and three patients (30%) had a total mastectomy. All patients were treated with endocrine therapy. One patient also received chemotherapy for her TC of an intermediate RS. Another patient developed contralateral breast cancer, while on endocrine therapy, within a year of diagnosis of TC with an intermediate RS. The new contralateral cancer was a mixed ductal and lobular carcinoma with a high RS. Chemotherapy was then added to her endocrine therapy. At a median follow-up of 49 months, none of the patients developed locoregional or distant recurrence (Table 3).

Solid papillary carcinoma (SPC)

The median age of five patients with SPC was 65 years (range 45–75). One woman (20%) was <50 years of age. The median tumor size was 1.3 cm (range 0.7–1.5). All cases were of grade 2, unifocal, and lymph node negative. Two carcinomas (40%) had associated minute foci of conventional invasive carcinoma spanning <1 mm (Fig. 4c) and 1.5 mm, respectively. The median percentages of ER+ and PR+ cells by IHC were 98 (range 90–99) and 70 (range 5–90), respectively. The median RS was 7 (range 3–25). Three SPCs (60%) had a low RS, and 2 (40%) had an intermediate RS (Fig. 4a, b). The median ER and PR mRNA scores were 11.2 (range 10.5–12.3) and 7.4 (range 4–10), respectively.

Two patients (40%) with SPC underwent BCS followed by radiation therapy, and three patients (60%) had a total mastectomy. All patients received endocrine therapy, and none received chemotherapy (Table 4). At a median follow-up of 32 months, none of the patients with SPC developed distant recurrence.

One patient, age 75 years at initial diagnosis of SPC, developed locoregional recurrence in the ipsilateral breast at 22 months of follow-up. The index SPC spanned 1.3 cm and was associated with ductal carcinoma in situ (DCIS) but not with conventional stromal invasion (Fig. 4b). The index SPC was diffusely positive for ER (nuclear staining with strong intensity in 98% of tumor cells), with low PR expression (nuclear staining with strong intensity in 5% of tumor cells). It yielded a RS of 25, with an ER mRNA score of 12.3 and a negative PR mRNA score of 4. The patient was treated with BCS followed by radiation therapy and brief endocrine therapy (she did not complete her treatment course due to poor tolerance). The morphology and immunophenotype of the recurrent SPC was similar to the index SPC. The patient underwent a total mastectomy at the time of LRR and received no additional systemic therapy. She remains disease free at 67 months of follow-up.

Encapsulated papillary carcinoma (EPC)

The median age of nine patients with EPC was 64 years (range 47–84). Only one patient (11.1%) was <50 years of age. The median tumor size was 1.5 cm (range 0.6–2.4). Minimal (1.5 mm) stromal invasion was associated with EPC in one case (Fig. 5c). Most tumors (7/9, 77.8%) were of grade 2 and unifocal. The median percentages of ER+ and PR+ cells by IHC were 99 (range 90–100) and 95 (range 80–100), respectively. One patient had a lymph node macrometastasis spanning 14 mm (Fig. 5d). Two patients had ITCs in one sentinel lymph node. All nine EPCs had a low RS with a median RS of 3 (range 0–11) (Fig. 5a, b). The median ER and PR mRNA scores were 11 (range 10.3–12.5) and 8.9 (range 7.2–10), respectively.

Seven patients (77.8%) with EPC underwent BCS followed by radiation therapy in five patients (55.6%), and two patients (22.2%) had a total mastectomy. Seven patients (77.8%) received endocrine therapy, and none received chemotherapy (Table 4). At a median follow-up of 35 months, none of the patients developed locoregional or distant recurrence.

Discussion

In the past decade, there has been a substantial effort in identifying novel predictive and prognostic biomarkers of breast cancer, and selecting patients who can potentially benefit from adjuvant systemic therapy. Currently, the 21-gene RS assay is the test that most closely satisfies the aforementioned goals [41]. It estimates the likelihood of distant recurrence (prognostic value) and the benefit of adjuvant chemotherapy (predictive value) in patients with lymph node-negative, ER+/HER2– breast cancer treated with endocrine therapy [15–20, 22–30, 42, 43]. The predictive value of this assay has been partially validated in a subset of cases from retrospective and prospective randomized clinical trials, including NSABP B20 (National Surgical Adjuvant Breast and Bowel Project B20) and SWOG 8814 (Southwest Oncology Group 8814) [15, 16, 18]. Some prospective trials such as TailorX [Trial Assigning Individualized Options for treatment (Rx)] are still ongoing [21, 44]. Preliminary data from this trial suggest that 98.7% of patients with RS 0–10 and treated with hormonal therapy alone are free of locoregional or distant recurrence at five years of follow-up [21]. A number of studies have described the association of the RS with morphologic features and biomarker expression [31–40]. To the best of our knowledge, only one study reported the RS results of special histologic subtypes known to have a favorable prognosis, but the data pertain to only five cases (four MCs and one TC) [39].

Breast cancer is a heterogeneous disease with multiple histologic subtypes. The accurate subclassification of breast carcinoma is a critical step for optimal patient management, due to differences in the metastatic potential, prognosis, and response to adjuvant treatment of different forms of breast cancer [6–10]. Some special histologic subtypes of breast cancer, including tubular, mucinous and papillary, tend to have an excellent prognosis [5], but occasionally they develop locoregional or distant recurrence. So far, the utility of information on the RS of the special subtypes of breast carcinoma remains very limited and has not been addressed in large studies. Most of the carcinomas with favorable prognosis in our cohort (44/57, 77.2%) had a low RS (17), and none had a high RS (31). Interestingly, thirteen carcinomas (22.8%) had an intermediate RS, and only one yielded RS >25. Some

investigators have suggested that the presence of stromal and inflammatory cells, especially if mitotically active, can significantly influence the results of the 21-gene recurrence score assay, as the latter evaluates genes involved in cell proliferation [45, 46]. This may account for intermediate or high RS results in some low-grade breast cancers [47]. None of the morphologic features we examined in our series, including tumor grade, biopsy site changes, cellular stroma, or inflammatory cells, were associated with RS [18]. We found that higher RS was associated with lower PR expression by IHC and lower PR mRNA scores ($P = 0.007$), in agreement with the literature [32, 33, 36–38]. This finding suggests that low PR expression by IHC may be used to guide the use of the 21-gene RS assay for the favorable subtypes of breast carcinoma, but larger series are needed. Although the median follow-up of 40 months may be somewhat limited for these special subtypes of breast cancer, the distant recurrence-free survival was 100% in our study, as expected [5].

By definition, pure MC has a >90% mucinous component [5]. MC has low rates of local recurrence and distant metastases, and the 10-year overall survival is 80–100% [10, 48]. At a median follow-up of 41 months, none of our thirty-three patients with MC developed locoregional or distant recurrence. Most MCs (78.8%) in our study had a low RS with a mean RS of 13 ± 6 . Although three of thirty-three (9.1%) patients with MC had lymph node micrometastases, the RS was low at 11 in all three tumors. The only other study reporting the RS of MC found that three of four MCs had an intermediate RS [39]. Recently, MC with a micropapillary growth pattern in >50% of the tumor has been described as a clinically more aggressive variant of MC with increased rates of lymphatic invasion and regional lymph node metastasis [49]. None of the MCs in our series exhibited micropapillary morphology.

TC is composed of haphazardly arranged angulated glands with open lumina comprising >90% of the tumor. The glands are lined by a single layer of neoplastic ductal cells in a background of cellular and desmoplastic or elastotic stroma [5]. Patients with pure TC have a very favorable prognosis with long disease-free survival and breast cancer-specific survival close to normal life expectancy [11, 50]. This may be due to the upregulation of “ER signaling pathway” in pure TC compared to grade 1 IDC NST [50]. None of the patients with TC in our series had lymph node metastasis, or developed locoregional and distant recurrence. Most of our cases of TC (60%) had a low RS. The stroma associated with TC was desmoplastic in all cases, with no discernible difference in the stromal cellularity between the TCs with low RS versus TC with intermediate RS. Notably, the ER mRNA levels in our cases of TC appeared to be lower than in the other carcinomas of special subtype despite the high percentage of ER+ cells detected by IHC. We hypothesize that the cellular stroma admixed with the neoplastic glands may account for the relatively lower levels of ER mRNA levels and subsequent increase in RS values, possibly contributing to the relative increase in the RS in all TCs.

EPC and SPC represent rare (<2%) subtypes of papillary carcinoma with controversial definitions and management recommendations. Most authors currently believe that these tumors are invasive carcinomas with an expansile growth pattern [51]. Both carcinomas usually lack myoepithelial cells throughout and at the periphery of the lesion. However, a well-defined basement membrane layer may be present [52]. Due to the favorable prognosis

in most patients [53, 54], the current consensus of the WHO Working Group is that, in the absence of a conventional invasive carcinoma, EPC and SPC should be staged and managed as DCIS [5]. There is no widely accepted definition of invasion in these tumors [53], and identification of small foci of invasion remains problematic.

EPC is composed of delicate fibrovascular cores covered by monomorphic neoplastic epithelial cells with low to intermediate nuclear grade and surrounded by a thick fibrous capsule [5]. In the absence of associated DCIS, EPC has a very favorable prognosis with complete surgical excision alone [55]. Rare cases of EPC metastases to axillary lymph nodes have been reported [53, 54, 56]. In fact, one patient in our cohort had a lymph node macrometastasis at initial diagnosis of EPC without evidence of other breast carcinoma. Nonetheless, none of our patients with EPC developed locoregional or distant recurrence. All our EPCs had a low RS with a mean RS of 4 ± 4 .

SPC is composed of closely apposed expansile, solid, and papillary nests with delicate or inconspicuous fibrovascular cores. SPC is often associated with extracellular mucin and may have neuroendocrine features [5]. In the absence of an associated invasive carcinoma, the prognosis of SPC is excellent. Rare lymph node metastases or locoregional recurrence may occur in patients with associated invasive growth [57–61]. In our cohort, 60% of cases with SPC had a low RS with a mean RS of 12 ± 10 . One patient with SPC and a RS of 25 developed LRR in the ipsilateral breast within two years of the initial diagnosis of SPC.

In conclusion, this is the largest series reporting the 21-gene RS assay results in special histologic subtypes of breast cancer with favorable prognosis. Most tumors had a low RS and none had a high RS. Although the prognostic value of low RS results in these rare morphologic subtypes of breast cancer appears to be similar to that in IDC NST, the significance of an intermediate RS remains uncertain and could be evaluated in larger series. Our study raises the question of whether the RS assay is necessary for breast cancers with favorable histology. Reflex testing of node-negative, ER+/HER2– breast cancers may be deferred for these subtypes, emphasizing the need for multidisciplinary discussions between breast pathologists and other members of the breast cancer team.

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Fig. 2. Examples of MC. **a** MC with a RS of 3, the lowest RS for this subtype; **b** MC with a RS of 28, the highest RS for this subtype; **c** MC with a RS of 8, and lymph node micrometastasis (not shown). Magnification $\times 200$. *IHC* immunohistochemistry, *PR* progesterone receptor, *RS* recurrence score

Fig. 3. Examples of TC. **a** TC with a RS of 9, the lowest RS for this subtype; **b** TC with a RS of 23, the highest RS for this subtype. Magnification $\times 200$. *RS* recurrence score, *TC* tubular carcinoma

Fig. 4. Examples of SPC. **a** SPC with a RS of 3, the lowest RS for this subtype; **b** SPC with a RS of 25, the highest RS for this subtype; **c** SPC with microinvasion and a RS of 7. Magnification $\times 200$. *IHC* immunohistochemistry, *PR* progesterone receptor, *RS* recurrence score, *SPC* solid papillary carcinoma

Fig. 5.

Examples of EPC. **a** EPC with a RS of 0, the lowest RS for this subtype; **b** EPC with a RS of 11, the highest RS for this subtype; **c** EPC with 1.5 mm stromal invasion and a RS of 3; **d** Metastatic EPC to the lymph node (primary EPC with a RS of 2). Magnification $\times 200$. *RS* recurrence score, *EPC* encapsulated papillary carcinoma

Table 1

Summary of selected clinicopathologic variables of special histologic subtypes of breast cancer with favorable prognosis

	MC (<i>n</i> = 33)	TC (<i>n</i> = 10)	SPC (<i>n</i> = 5)	EPC (<i>n</i> = 9)	All (<i>n</i> = 57)
RS: median, range	13, 3–28	14, 9–23	7, 3–25	3, 0–11	11, 0–28
Age: median, range (years)	52, 36–77	46, 37–69	65, 45–75	64, 47–84	54, 36–84
Tumor size: median, range (cm)	1.2, 0.5–3.5	0.8, 0.5–1.8	1.3, 0.7–1.5	1.5, 0.6–2.4	1.2, 0.5–3.5
Lymph node positive: <i>n</i> (%)	3 (9.1%)	0	0	1 (11.1%)	4 (7%)
ER mRNA score: median, range	9.8, 7.9–12.5	8.4, 7.1–9.8	11.2, 10.5–12.3	11, 10.3–12.5	10, 7.1–12.5
PR mRNA score: median, range	7.9, 5–9.4	8.1, 6.2–9.4	7.4, 4–10	8.9, 7.2–10	8.1, 4–10
ER% by IHC: median, range	97, 20–100	95, 90–100	98, 90–99	99, 90–100	98, 20–100
PR% by IHC: median, range	90, 0–99	90, 5–100	70, 5–90	95, 80–100	90, 0–100

EPC encapsulated papillary carcinoma, *ER* estrogen receptor, *IHC* immunohistochemistry, *MC* mucinous carcinoma, *PR* progesterone receptor, *RS* recurrence score, *SD* standard deviation, *SPC* solid papillary carcinoma, *TC* tubular carcinoma

Table 2

Clinicopathologic variables in thirty-three MCs

	Low RS (<i>n</i> = 26)	Intermediate RS (<i>n</i> = 7)	All (<i>n</i> = 33)
RS: mean (SD), median (range)	11 (4), 11 (3–17)	22 (3), 22 (18–28)	13 (6), 13 (3–28)
Age: mean (SD), median (range), year	56 (11), 59 (36–77)	52 (11), 52 (39–69)	55 (11), 52 (36–77)
Grade			
1	3	2	5 (15.2%)
2	23	5	28 (84.8%)
Tumor size: mean (SD), median (range), cm	1.4 (0.6), 1.3 (0.5–3.5)	1.1 (0.4), 1.2 (0.5–1.6)	1.4 (0.6), 1.2 (0.5–3.5)
Multifocality	2	0	2 (6.1%)
Lymph node positive	3	0	3 (9.1%)
Surgery			
BCS	20	6	26 (78.8%)
TM	6	1	7 (21.2%)
Radiation therapy	18	4	22 (66.7%)
Endocrine therapy	26	7	33 (100%)
Chemotherapy	3 ^a	3	6 (18.2%)
ER mRNA score: mean (SD), median (range)	10.2 (0.8), 9.8 (9.3–12.5)	9.5 (0.9), 9.4 (7.9–10.4)	10.1 (0.9), 9.8 (7.9–12.5)
PR mRNA score: mean (SD), median (range)	8 (0.9), 8.2 (6.3–9.4)	6.4 (0.8), 6.6 (5–7.5)	7.7 (1.1), 7.9 (5–9.4)
ER% by IHC: mean (SD), median (range)	91 (18), 95 (20–100)	92 (12), 99 (70–100)	91 (17), 97 (20–100)
PR% by IHC: mean (SD), median (range)	78 (27), 90 (0–99)	65 (43), 85 (0–99)	75 (31), 90 (0–99)

BCS breast conserving surgery, *ER* estrogen receptor, *IHC* immunohistochemistry, *MC* mucinous carcinoma, *PR* progesterone receptor, *RS* recurrence score, *SD* standard deviation, *TM* total mastectomy

^aThree patients with low RS received chemotherapy for large (3.5 cm) tumor, positive lymph node status, and a RS of 17, respectively

Table 3

Clinicopathologic variables in ten TCs (all cases are grade I, node negative)

	Low RS (<i>n</i> = 6)	Intermediate RS (<i>n</i> = 4)	All (<i>n</i> = 10)
RS: mean (SD), median (range)	12 (2), 13 (9–14)	21 (2), 20 (19–23)	15 (5), 14 (9–23)
Age: mean (SD), median (range), year	48 (4), 47 (44–54)	49 (14), 45 (37–69)	49 (9), 46 (37–69)
Tumor size: mean (SD), median (range), cm	0.9 (0.5), 0.8 (0.6–1.8)	1 (0.4), 1 (0.5–1.4)	0.9 (0.4), 0.8 (0.5–1.8)
Multifocality	1	0	1 (10%)
Surgery			
BCS	3	4	7 (70%)
TM	3	0	3 (30%)
Radiation therapy	3	4	7 (70%)
Endocrine therapy	6	4	10 (100%)
Chemotherapy	0	1	1 (10%)
ER mRNA score: mean (SD), median (range)	8.7 (0.7), 8.7 (7.9–9.8)	8.3 (1.1), 8.1 (7.1–9.8)	8.5 (0.9), 8.4 (7.1–9.8)
PR mRNA score: mean (SD), median (range)	8.1 (1), 8 (6.6–9.4)	7.7 (1), 8.1 (6.2–8.3)	7.9 (1), 8.1 (6.2–9.4)
ER% by IHC: mean (SD), median (range)	96 (3), 95 (90–99)	96 (5), 98 (90–100)	96 (4), 95 (90–100)
PR% by IHC: mean (SD), median (range)	59 (42), 70 (5–99)	76 (38), 93 (20–100)	66 (39), 90 (5–100)

BCS breast conserving surgery, *ER* estrogen receptor, *IHC* immunohistochemistry, *PR* progesterone receptor, *RS* recurrence score, *SD* standard deviation, *TC* tubular carcinoma, *TM* total mastectomy

Table 4

Clinicopathologic variables in five SPCs and nine EPCs

	SPC			EPC
	Low RS (<i>n</i> = 3)	Intermediate RS (<i>n</i> = 2)	All (<i>n</i> = 5)	Low RS (<i>n</i> = 9)
RS: mean (SD), median (range)	5 (2), 5 (3–7)	22 (4), 22 (19–25)	12 (10), 7 (3–25)	4 (4), 3 (0–11)
Age: mean (SD), median (range), year	56 (10), 59 (45–65)	70 (7), 70 (65–75)	62 (11), 65 (45–75)	63 (11), 64 (47–84)
Patients <50 years of age	1	0	1 (20%)	1 (11.1%)
Grade				
1	0	0	0	2 (22.2%)
2	3	2	5 (100%)	7 (77.8%)
Tumor size: mean (SD), median (range), cm	1.1 (0.4), 1.3 (0.7–1.4)	1.4 (1), 1.4 (1.3–1.5)	1.2 (0.3), 1.3 (0.7–1.5)	1.4 (0.6), 1.5 (0.6–2.4)
Multifocality	0	0	0	0
Lymph node positive	0	0	0	1 (11.1%)
Surgery				
BCS	1	1	2 (40%)	7 (77.8%)
TM	2	1	3 (60%)	2 (22.2%)
Radiation therapy	1	1	2 (40%)	5 (55.6%)
Endocrine therapy	3	2	5 (100%) ^a	7 (77.8%)
Chemotherapy	0	0	0	0
Locoregional recurrence	0	1	1 ^a	0
ER mRNA score: mean (SD), median (range)	11.1 (0.8), 10.9 (10.5–12)	11.8 (0.8), 11.8 (11.2–12.3)	11.4 (0.8), 11.2 (10.5–12.3)	11.1 (0.6), 11 (10.3–12.5)
PR mRNA score: mean (SD), median (range)	8.8 (1.3), 8.9 (7.4–10)	4.9 (1.3), 4.9 (4–5.8)	7.2 (2.4), 7.4 (4–10)	9 (1), 8.9 (7.2–10)
ER% by IHC: mean (SD), median (range)	96 (5), 98 (90–99)	99 (1), 99 (98–99)	97 (4), 98 (90–99)	98 (3), 99 (90–100)
PR% by IHC: mean (SD), median (range)	83 (12), 90 (70–90)	35 (42), 35 (5–65)	64 (35), 70 (5–90)	94 (7), 95 (80–100)

BCS breast conserving surgery, *EPC* encapsulated papillary carcinoma, *ER* estrogen receptor, *IHC* immunohistochemistry, *PR* progesterone receptor, *RS* recurrence score, *SD* standard deviation, *SPC* solid papillary carcinoma, *TM* total mastectomy

^aOne patient did not complete endocrine therapy due to poor tolerance. She developed locoregional recurrence at 22 months