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Outcomes of special histotypes of breast cancer after adjuvant endocrine therapy with letrozole or tamoxifen in the monotherapy cohort of the BIG 1-98 trial

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Background: We investigated the outcomes of postmenopausal women with hormone receptor-positive, early breast cancer with special histotypes (mucinous, tubular, or cribriform) enrolled in the monotherapy cohort of the BIG 1-98 trial.

Patients and methods: The intention-to-treat BIG 1-98 monotherapy cohort (5 years of therapy with tamoxifen or letrozole) included 4922 women, of whom 4091 had central pathology review. Histotype groups were defined as: mucinous ($N = 100$), tubular/cribriform ($N = 83$), ductal ($N = 3257$), and other ($N = 651$). Of 183 women with either mucinous or tubular/cribriform tumors, 96 were randomly assigned to letrozole and 87 to tamoxifen. Outcomes assessed were disease-free survival (DFS), overall survival (OS), breast cancer-free interval (BCFI), and distant recurrence-free interval (DRFI). Median follow-up in the analytic cohort was 8.1 years.

Results: Women with tubular/cribriform breast cancer had the best outcomes for all end points compared with the other three histotypes, and had less breast cancer recurrence (97.5% 5-year BCFI) than those with mucinous (93.5%), ductal (88.9%), or other (89.9%) histotypes. Patients with mucinous or tubular/cribriform carcinoma had better DRFI (5-year rates 97.8% and 98.8%, respectively) than those with ductal (90.9%) or other (92.1%) carcinomas. Within the subgroup of women with special histotypes, we observed a nonsignificant increase in the hazard of breast cancer recurrence with letrozole [hazard (letrozole versus tamoxifen): 3.31, 95% confidence interval 0.94–11.7; $P = 0.06$].

Conclusions: Women with mucinous or tubular/cribriform breast cancer have better outcomes than those with other histotypes, although the observation is based on a limited number of events. In postmenopausal women with these histotypes, the magnitude of the letrozole advantage compared with tamoxifen may not be as large in patients with mucinous or tubular/cribriform disease.

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Key words: letrozole, tamoxifen, mucinous, tubular, cribriform, breast cancer

introduction

In recent years, appropriate adjuvant systemic therapies for operable breast cancer have been tailored to individual patients. Assessments of patient risk, co-morbidities, and patient preference are considered together with features that predict better response to therapy and better outcome [1–3].

However, less attention is paid to identifying special types of breast cancers with a distinct morphology that exhibits a different prognostic and predictive profile compared with more common histotypes, such as invasive ductal or lobular carcinomas, even

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with similar biological features and stages [4]. In particular, within luminal breast cancer, several special histotypes display an extremely good prognosis, often approaching or equaling that of the general population [5, 6]. Histotypes with good prognosis include: pure tubular carcinoma, a rare histology accounting for <2% of invasive breast cancer and with an excellent prognosis [7, 8]; cribriform carcinoma, which also has a very favorable prognosis irrespective of lymph node metastases [8, 9]; and pure mucinous breast carcinoma, representing 1%–4% of all breast cancers. If present in pure form, this histotype predicts a 10-year survival >90% [10, 11].

Limited results are available on the outcomes of these rare histotypes according to the adjuvant treatment received. Consequently, no information from retrospective analyses is available for tailoring adjuvant treatment of an individual patient with these special histotypes.

We investigated the outcomes of postmenopausal women with hormone receptor-positive (HR+), early invasive breast cancer with special tumor histotypes (mucinous, tubular, or cribriform) who were enrolled in the monotherapy cohort of the BIG 1-98 trial, and the relationship between outcomes and other biological or treatment characteristics.

patients and methods

The design and conduct of the BIG 1-98 trial have been described elsewhere [12, 13].

This analysis was based on the BIG 1-98 at 8.7 years median follow-up [14]. The analytic cohort for this analysis included women randomized to 5 years of tamoxifen or letrozole monotherapy whose tumors were centrally reviewed ($n = 4091$) (Figure 1). Histotypes considered in this analysis were mucinous ($n = 87$) or mucinous variant ($n = 13$), tubular ($n = 71$), or tubular variant ($n = 3$), and cribriform pure ($n = 4$) or mixed ($n = 5$) [15]. Mucinous and mucinous variants were combined into the 'mucinous' group, and tubular and cribriform types were combined into the 'tubular/cribriform' group (Figure 1). The histotypes studied included 183 patients with either mucinous or tubular/cribriform tumors, 4.4% of the analytic cohort. Ninety-six women were randomized to letrozole and 87 to tamoxifen. Comparator histologic groups were ductal and other histotypes: 406 with lobular histology, 234 with other classifications, and 11 with missing histology. Luminal A was defined as HR+, HER2-negative, and Ki-67 <14%; luminal B as HR+, HER2-negative, and Ki-67 ≥14% [16].

The tamoxifen group included 24 women (28%) who selectively crossed over to letrozole after the first interim efficacy results of the trial were released in 2005. Follow-up for these women was censored at the time of the selective crossover, reducing the median follow-up of the special histotype group ($n = 183$) to 8.1 years. No outcome events were lost as a result of the censoring.

All participants provided written informed consent. Ethics committees and relevant health authorities approved the protocol.

statistical analysis

All patients were analyzed according to randomized treatment. Comparisons of baseline disease, demographic, and prior treatment characteristics used Fisher's exact test for categorical variables and Wilcoxon rank-sum or Kruskal–Wallis tests for continuous characteristics. Four time-to-event outcomes are presented: disease-free survival (DFS), overall survival (OS), breast cancer-free interval (BCFI), and distant recurrence-free interval (DRFI).

DFS was defined as the time from randomization to the earliest invasive breast recurrence, new invasive breast cancer in the contralateral breast, any second (nonbreast) malignancy, or death from any cause. OS was defined as the time from randomization to death from any cause. BCFI was defined as the time from randomization to the earliest invasive breast recurrence or new invasive breast cancer in the contralateral breast. DRFI was defined as the time from randomization to the earliest distant metastases. For BCFI and DRFI, deaths without prior cancer events were censored. Comparisons of survival distributions were made using the log-rank test. Cox proportional hazards (PH) models, stratified by randomization option (two-arm/four-arm) and chemotherapy, were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Univariate Cox PH models included only treatment as a predictor.

Multivariable Cox PH models were fit to each outcome to assess important predictors. Candidate predictors in each model were: histology, tumor grade and size, subtype (luminal A or B, missing/other ER+), nodal status (N0/Nx, N+), and local therapy as the combination of radiotherapy (RT) and either mastectomy (MTX) or breast-conserving surgery (BCS) (BCS/RT, BCS/no RT, MTX/RT, MTX/no RT). Age divided at the sample median

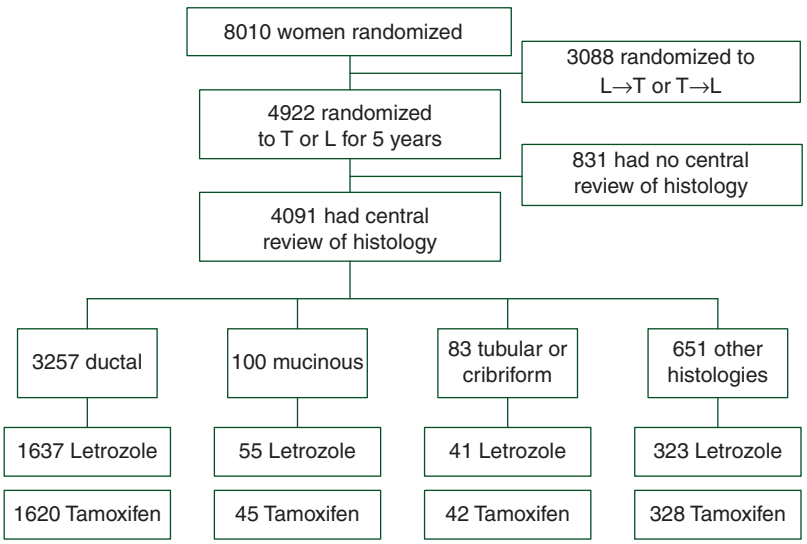

Figure 1. Patients from the BIG 1-98 trial included and excluded in this study according to treatment group and availability centrally reviewed histology. Other histologies were 651 (15.9%): 406 lobular/ 234 other/11 missing. L, letrozole; T, tamoxifen.

(≤64 years, >64 years) was included in models of DFS, BCFI, and DRFI. The OS model was stratified additionally by age. Two-way interactions between histology and treatment were included among model predictors to explore if the effect of treatment varied according to histology.

HRs and *P* values for the forest plot were estimated from the interaction of treatment and histology based on the univariate Cox PH model. *P* values for Cox PH models are from the Wald χ^2 test. Statistical significance is defined as $P < 0.05$; there are no corrections for multiple comparisons.

results

Baseline and prior treatment characteristics are shown according to histology in Table 1. Treatment assignment (letrozole or tamoxifen) was balanced between the histotypes.

outcome according to histology

Women with mucinous or tubular/cribriform tumors had characteristics of lower risk diseases compared with those with ductal or other histologies. Mucinous or tubular/cribriform tumors were more often characterized as luminal A, Ki-67 <14%, and no evidence of peritumoral vascular invasion. The tumors tended to be grade 1 with most measuring 2 cm or less. The majority of women with mucinous or tubular/cribriform histotypes were treated with RT with either breast-conserving surgery or mastectomy, and most had node-negative disease. Only 15 patients received chemotherapy as a part of their adjuvant or neoadjuvant treatment; therefore, the majority of women with mucinous or tubular/cribriform histologies ($n = 168$, 91.8%) received only tamoxifen or letrozole as adjuvant systemic therapy.

Patients with mucinous tumors had a higher proportion of luminal B disease (HER2-negative) (23%) compared with those with tubular/cribriform (4.8%); the proportion with luminal A disease with mucinous tumors was 64.0% compared with 81.9% with tubular/cribriform. Women with mucinous tumors were significantly older than women in the other histologies (median age: 69 versus 62).

Distributions and 5-year Kaplan–Meier estimates of outcomes for the four histology groups are summarized in Figure 2. Overall, women with tubular/cribriform tumors showed the best outcomes compared with those in the other three histologic groups. Women with mucinous carcinoma had comparable DFS and OS to women with ductal or other histotypes. Five-year recurrence rates were higher in patients with tubular/cribriform (97.5%) or mucinous (93.5%) disease than in patients with ductal (88.9%) or other histotypes 89.9%, $P = 0.03$). Women with mucinous or tubular/cribriform carcinoma had better DRFI (5-year DRFI: 97.8%, 98.8%, respectively) than those with ductal (90.9%) or other (92.1%) ($P = 0.002$) carcinomas.

outcome according to treatment (letrozole versus tamoxifen)

The median age at randomization was 65 and 64 years in the letrozole and tamoxifen arms, respectively. Women assigned to tamoxifen more often had N0/Nx disease (82% tamoxifen, 71% letrozole) or grade 1 tumors (76% tamoxifen, 66% letrozole). A lower percentage of patients in the tamoxifen group received neoadjuvant or adjuvant chemotherapy (3% tamoxifen, 11.5% letrozole); however, none of these differences were statistically significantly different.

The 5-year DFS estimates (±standard error of the estimate) were 83.2 ± 3.8% for patients in the letrozole group versus 94.9 ± 2.5% for those in the tamoxifen group (Figure 3A), whereas the 5-year OS estimates were 93.7 ± 2.5% versus 97.3 ± 1.9% (Figure 3B). Among patients receiving tamoxifen, the only distant recurrence occurred at ∼72 months of follow-up. As a result, 5-year estimates of DRFI were 100% in the tamoxifen group and 96.8 ± 1.8% in the letrozole group (Figure 3C). No recurrences were reported for the first year of follow-up in either treatment group.

When the effect of treatment upon outcomes was evaluated by univariate models, only BCFI showed a difference between letrozole and tamoxifen: the hazard of recurrence was 3.3 times higher among women receiving letrozole and was marginally significant [HR (letrozole versus tamoxifen) 3.31, 95% CI 0.94–11.7, $P = 0.06$]. This finding was upheld by the multivariable Cox PH model [HR (letrozole versus tamoxifen) 3.54, 95% CI 0.96–13.1, $P = 0.06$].

The sites of first recurrence were: local–regional and contralateral in 6.3% of patients in the letrozole group and 2.2% in the tamoxifen group; distant in 4.1% in the letrozole group and 1.1% in the tamoxifen group.

outcomes according to treatment and histotype

The relative effects of letrozole and tamoxifen were investigated according to the two histologic groups (mucinous versus tubular/cribriform). Looking at the four histotype-treatment combinations, patients with mucinous carcinoma treated with letrozole appeared to have the worst outcomes. In contrast, outcomes for patients with mucinous carcinoma treated with tamoxifen were similar to that of patients with tubular/cribriform, suggesting that, in these histotypes, the benefit of letrozole over tamoxifen is less clear than in ductal or other histologies (supplementary Figure S1, available at *Annals of Oncology* online). However, the HR (letrozole versus tamoxifen) did not reach statistical significance for any of the four outcomes considered (Table 2).

comparisons of treatment effects for histotype

The forest plot summarizes the effects of treatment overall and in each of four subgroups based on univariate models (Figure 4). Overall, letrozole has significantly greater efficacy than tamoxifen for all four end points. The superiority of letrozole is less clear in the rare histotypes. The HR estimates tend to favor tamoxifen for all four end points in the mucinous and tubular/cribriform groups, but the CIs are too wide to draw any conclusions favoring tamoxifen.

discussion

The present analysis provides an opportunity to study very rare histotypes that have been centrally evaluated and treated and followed uniformly within a large clinical trial. Others have reported the favorable prognosis of these histotypes, but there are no published reports about differential benefits of endocrine therapy.

Our report suggests that mucinous, tubular, and cribriform histotypes have a more favorable prognosis compared with

Table 1. Patient demographic, disease, and prior treatment characteristics by histology

Characteristic	Overall ($N = 4091$)		Histology								P value (4 histologies)	P-value (mucinous versus tubular/cribriform)
			Ductal ($N = 3257$)		Mucinous ($N = 100$)		Tubular or cribriform ($N = 83$)		Other histology ($N = 651$)			
Age at enrollment (years) Median (range)	62 (38–86)		62 (38–86)		69 (49–84)		62 (45–81)		62 (39–84)		<0.0001	<0.0001
	N	%	*N*	%	*N*	%	*N*	%	*N*	%		
Subtype											<0.0001	0.003
Luminal A	1885	46.1	1422	43.7	64	64.0	68	81.9	331	50.8		
Luminal B (HER2-negative)	1571	38.4	1374	42.2	23	23.0	4	4.8	170	26.1		
Unknown	537	13.1	391	12.0	11	11.0	9	10.8	126	19.4		
Other ER+	98	2.4	70	2.1	2	2.0	2	2.4	24	3.7		
ER present/absent											<0.0001	0.99
Absent	63	1.5	54	1.7	–	–	–	–	9	1.4		
Present	3554	86.9	2866	88.0	89	89.0	74	89.2	525	80.6		
Unknown	474	11.6	337	10.3	11	11.0	9	10.8	117	18.0		
PgR present/absent											<0.0001	0.35
Absent	433	10.6	341	10.5	4	4.0	8	9.6	80	12.3		
Present	3186	77.9	2584	79.3	83	83.0	65	78.3	454	69.7		
Unknown	472	11.5	332	10.2	13	13.0	10	12.0	117	18.0		
HER2 status											<0.0001	0.99
Negative	3410	83.4	2731	83.9	88	88.0	74	89.2	517	79.4		
Positive	257	6.3	234	7.2	1	1.0	–	–	22	3.4		
Unknown	424	10.4	292	9.0	11	11.0	9	10.8	112	17.2		
Ki-67 ≥14											<0.0001	0.001
No	1979	48.4	1500	46.1	64	64.0	69	83.1	346	53.1		
Yes	1560	38.1	1369	42.0	23	23.0	4	4.8	164	25.2		
Unknown	552	13.5	388	11.9	13	13.0	10	12.0	141	21.7		
Nodal status											<0.0001	0.40
N0/Nx	2371	58.0	1847	56.7	79	79.0	60	72.3	385	59.1		
1–3 positive	1211	29.6	1003	30.8	15	15.0	19	22.9	174	26.7		
4+ positive	506	12.4	405	12.4	6	6.0	4	4.8	91	14.0		
Unknown	3	0.1	2	0.1	–	–	–	–	1	0.2		
Peritumoral vascular invasion											<0.0001	0.50
No	3653	89.3	2877	88.3	97	97.0	83	100.0	596	91.6		
Yes	389	9.5	358	11.0	2	2.0	–	–	29	4.5		
Unknown	49	1.2	22	0.7	1	1.0	–	–	26	4.0		
BRE grade											<0.0001	<0.0001
1	803	19.6	631	19.4	48	48.0	81	97.6	43	6.6		
2	2279	55.7	1750	53.7	48	48.0	1	1.2	480	73.7		
3	904	22.1	854	26.2	4	4.0	–	–	46	7.1		
Unknown	105	2.6	22	0.7	–	–	1	1.2	82	12.6		
Tumor size											<0.0001	<0.0001
≤2 cm	2527	61.8	2063	63.3	50	50.0	72	86.7	342	52.5		
2–5 cm	1376	33.6	1088	33.4	43	43.0	8	9.6	237	36.4		
>5 cm	158	3.9	90	2.8	7	7.0	2	2.4	59	9.1		
Unknown	30	0.7	16	0.5	–	–	1	1.2	13	2.0		
Adjuvant/neoadjuvant chemo											<0.0001	0.99
No	3170	77.5	2519	77.3	92	92.0	77	92.8	482	74.0		
Yes	921	22.5	738	22.7	8	8.0	6	7.2	169	26.0		
Local therapy											<0.0001	0.0007
BCS/RT	2075	50.7	1706	52.4	41	41.0	58	69.9	270	41.5		
BCS/no RT	134	3.3	104	3.2	5	5.0	5	6.0	20	3.1		
Mastectomy/RT	761	18.6	577	17.7	14	14.0	6	7.2	164	25.2		
Mastectomy/no RT	1115	27.3	867	26.6	39	39.0	14	16.9	195	30.0		
Unknown	6	0.1	3	0.1	1	1.0	–	–	2	0.3		

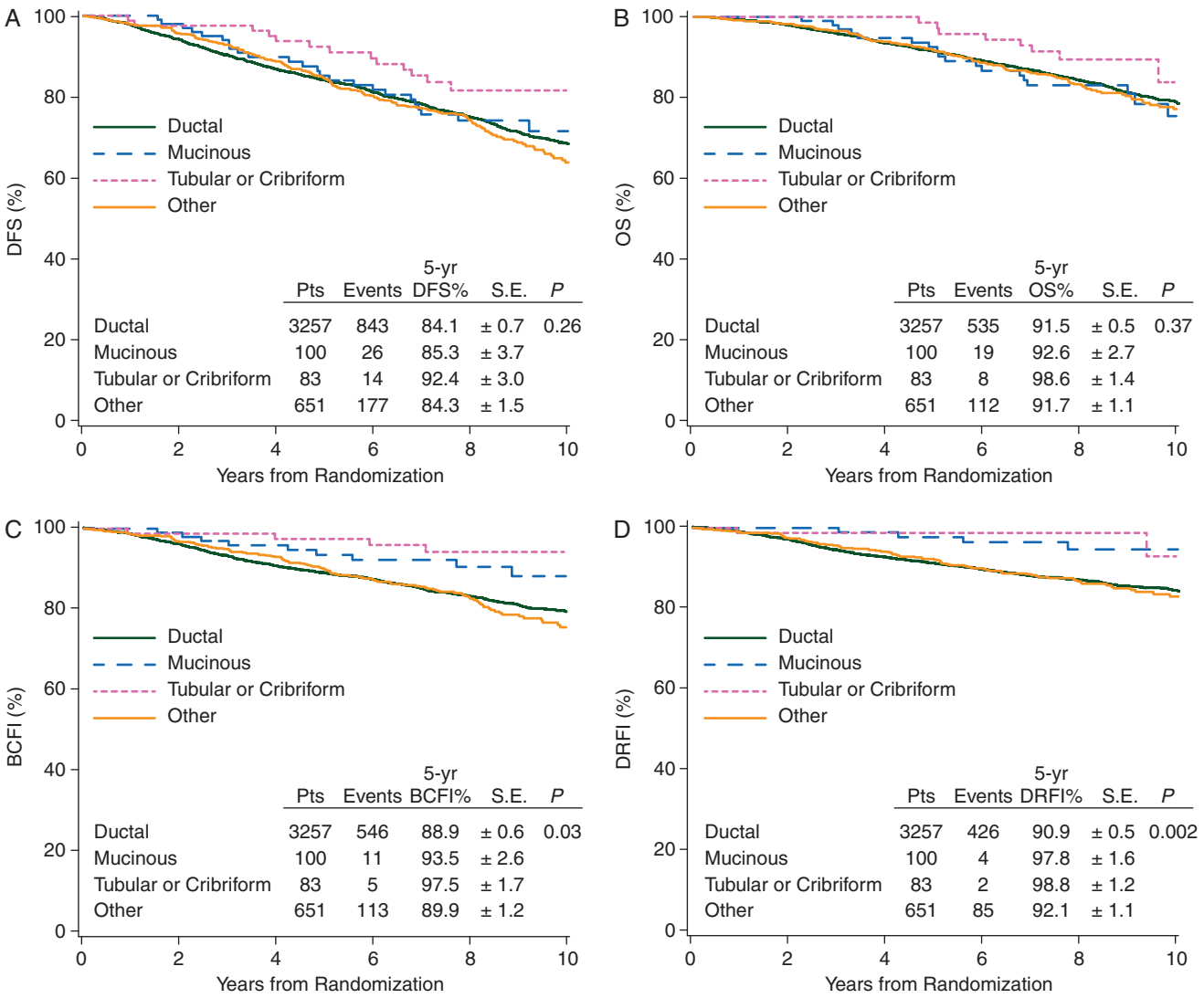

Figure 2. Kaplan–Meier estimates of disease-free survival (DFS, A), overall survival (OS, B), breast cancer-free interval (BCFI, C), and distant recurrence-free interval (DRFI, D) according to histotype for the 4091 patients in the analytic cohort.

other histotypes. Similar favorable outcomes have been reported in the literature. In a series of 111 patients with tubular breast cancer, the locoregional recurrence rate was low (<1%) and no patient developed distant metastases [17]. Likewise, in a series of 102 patients, none of the patients with tubular carcinoma developed distant metastasis or died from breast cancer [18]. The survival of patients with tubular carcinoma is similar to the general population, and there is no evidence that adjuvant therapy influences survival, even if sentinel node biopsy is positive [19]. Tubular carcinoma also has a favorable long-term prognosis, even if axillary nodes were involved; thus, nodal status may not be an indicator of poor outcome [20].

Our results also suggest that tamoxifen may be a treatment choice for women with these histotypes. The overall benefit of letrozole over tamoxifen observed in ductal or other histologies was not as strong in the special histotypes, although based on a limited number of events. Patients with mucinous carcinoma treated with letrozole had the worst outcome among the groups studied. In contrast, outcomes for patients with mucinous disease who were treated with tamoxifen were similar to those with tubular/cribriform breast cancer. Side-effect profile and patient preference should guide the choice of adjuvant endocrine treatment of women with these histologies.

It should be noted that patients in our study with special histotypes had lower risk characteristics (72% had luminal A). Mucinous, tubular, and cribriform histotypes are found among luminal A cancers more than in other histotypes [16, 21]. In our series, patients with tubular and cribriform histotypes were more frequently classified as luminal A, while patients with mucinous breast cancer had a greater proportion with luminal B (HER2-negative). The lower risk disease in our study sample contributed to small numbers of outcome events, especially for BCFI or DRFI, which could influence the power of our multivariable models to find factors associated with outcome.

Adjuvant therapy with aromatase inhibitors provides, on average, superior outcomes to tamoxifen for postmenopausal women with endocrine-responsive early breast cancer; however, data from BIG 1-98 suggest that, in low-proliferating tumors,

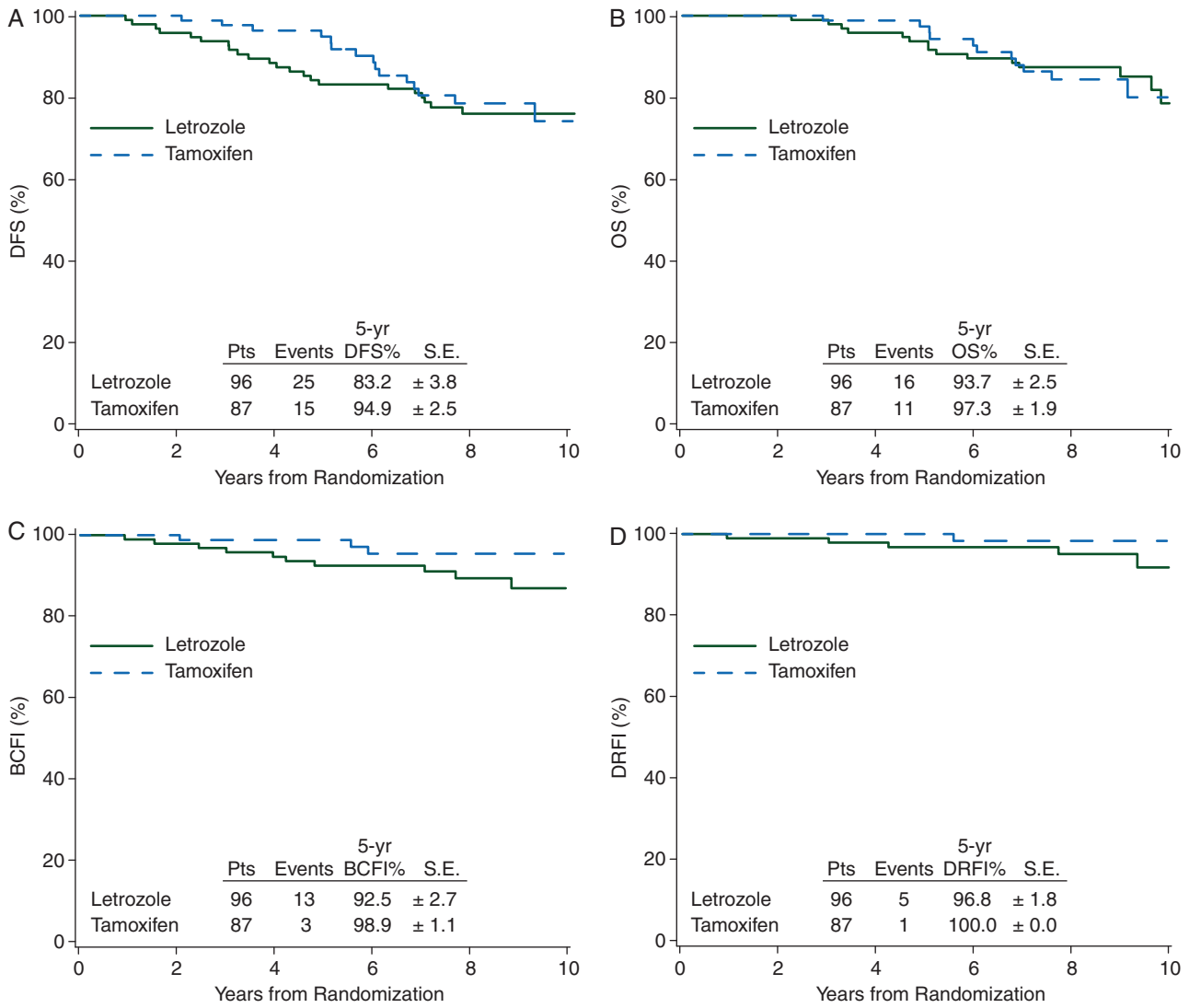

Figure 3. Kaplan–Meier estimates of disease-free survival (DFS, A), overall survival (OS, B), breast cancer-free interval (BCFI, C), and distant recurrence-free interval (DRFI, D) according to randomly assigned treatment group for the cohort of 183 patients with mucinous, tubular, or cribriform histotypes.

Table 2. Univariate and multivariable Cox models results for patients with special histotypes

DFS	Hazard ratio	Univariate Cox PH model		Multivariable Cox PH model	
	(Let versus Tam)	Mucinous	Tub/crib	Mucinous	Tub/crib
	(95% CI)	1.49 (0.7–3.3)	1.06 (0.4–3.1)	1.52 (0.7–3.5)	1.05 (0.3–3.1)
	Interaction *P* value (treatment by histology)	0.62		0.59	
OS	Hazard ratio	Univariate Cox PH model		Multivariable Cox PH model	
	(Let versus Tam)	Mucinous	Tub/crib	Mucinous	Tub/crib
	(95% CI)	1.28 (0.5–3.3)	0.67 (0.2–2.7)	1.04 (0.4–2.8)	0.64 (0.1–3.0)
	Interaction *P* value (treatment by histology)	0.45		0.60	
BCFI	Hazard ratio	Univariate Cox PH model		Multivariable Cox PH model	
	(Let versus Tam)	Mucinous	Tub/crib	Mucinous	Tub/crib
	(95% CI)	3.39 (0.7–15.8)	3.11 (0.4–28.0)	4.47 (0.9–22.4)	2.43 (0.2–24.0)
	Interaction *P* value (treatment by histology)	0.95		0.67	
DRFI	Hazard ratio	Univariate Cox PH model		Multivariable Cox PH model	
	(Let versus Tam)	Mucinous	Tub/crib	Mucinous	Tub/crib
	(95% CI)	2.01 (0.2–19.5)	Not defined[a]	9.7 (0.3–300)	Not defined[a]
	Interaction *P* value (treatment by histology)	0.99		0.99	

[a]There were no DRFI events in the tamoxifen arm.

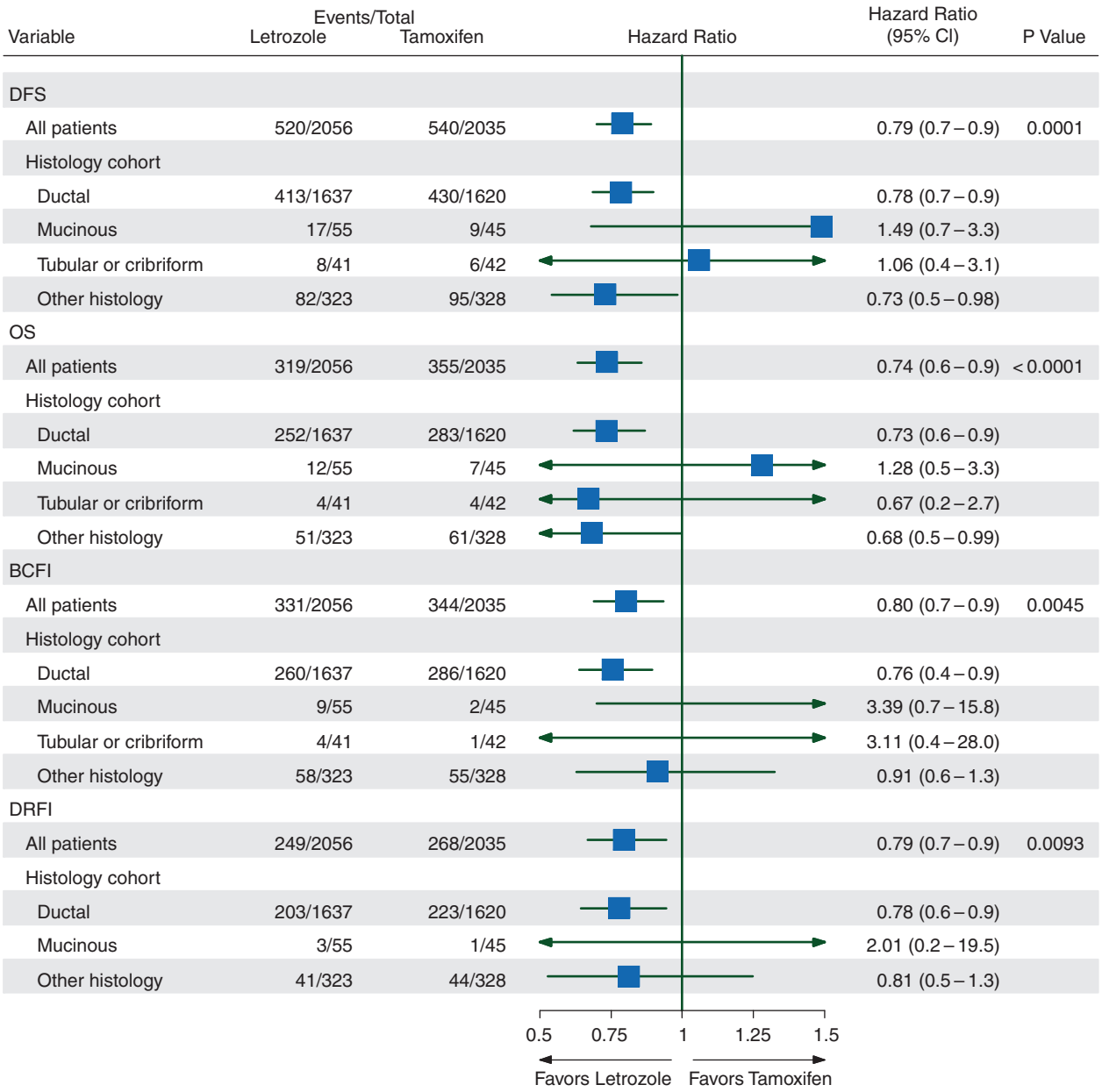

Figure 4. Proportional hazards model results of disease-free survival (DFS), overall survival (OS), breast cancer-free interval (BCFI), and distant recurrence-free interval (DRFI) in histology subgroups. Hazard ratios and *P* values were estimated from the interaction of treatment and histology based on the univariate Cox PH model. There were no events in the tamoxifen arm for tubular or cribriform DRFI, so this comparison is not included in the forest plot.

the magnitude of letrozole benefit versus tamoxifen might not be as large as in more highly proliferative tumors [22, 23], thus suggesting a similar treatment benefit in luminal A tumors. In general, in the current analysis, patients with rare histologies and luminal B (HER2-negative) disease had a threefold increase in the hazard of death compared with luminal A disease.

One possible explanation of the better outcome of these histotypes may be found in their genomic expression. Cribriform and tubular carcinomas usually display similar immunophenotypes and are characterized by similar types and patterns of genetic aberrations, commonly found in most low-grade luminal-type breast carcinomas [10, 24, 25]. However, significant differences were detected and validated by quantitative reverse transcriptase PCR, which may in part explain the reported, more favorable outcome of cribriform/tubular [8]. Some authors also suggest that tubular and cribriform carcinomas have similar clinical presentation, natural history, and are probably associated with the same family of precursor and preinvasive lesions [5, 26], thus indicating a common etiological background or the involvement of common genetic pathways during carcinogenesis [25].

In conclusion, patients with rare histologies treated with 5 years of letrozole or tamoxifen in the BIG1-98 trial had better outcomes than other histologies. The magnitude of the letrozole advantage compared with tamoxifen seen in the overall population was not

observed in patients with mucinous or tubular/cribriform disease. For these rare histologies, our data suggest that tamoxifen could be a reasonable treatment option.

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disclosure

The authors have declared no conflicts of interest.

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