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Survival with Breast Cancer: the Importance of Estrogen Receptor Quantity

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Abstract—*The survival of* 1184 *British Columbian women whose primary breast cancers were diagnosed and assayed for estrogen receptor (ER) between* 1975 *and* 1981 *was studied. Median follow-up was* 60 *months. ER concentrations yielded greater prognostic information than simple positive and negative categories. When ER data were divided into four strata:* ≤1, 2–9, 10–159 *and* ≥160 fmol/mg *cytosol protein, the association of higher ER with prolonged survival was highly significant* ($P < 0.0001$) *and independent of TNM stage, nodal status and menopausal status. ER* ≤ 1 *and ER* = 2–9 *groups were distinct with respect to overall disease-specific survival. Patient age did not predict survival when controlled for ER. Prolonged recurrence-free survival was associated with higher ER* ($P = 0.0001$) *for at least* 5 *years after diagnosis. This significant trend persisted after adjustments for nodal status, TNM stage, menopausal status and the type of systemic adjuvant therapy.*

INTRODUCTION

ESTROGEN RECEPTOR (ER) positivity is a good measure of tumor endocrine responsiveness and presence of ER is an advantage to survival after primary surgery for breast cancer. However, in several studies the prognostic value of ER was found to be greatest for duration of survival after the disease has recurred [1–3] and survival differences between ER positive (ER+) and ER negative (ER−) groups are reported to dissipate after prolonged follow-up [4–6]. Although the relationship of ER and overall disease-specific survival is not simply an additive function of that with recurrence-free survival (RFS) and post-recurrence survival (PRS), the correlations between ER and RFS, and ER and PRS, should be in the same direction if the biological influences signalled by the presence of ER are the same before and after disease recurrence.

We have shown [7] that greater prognostic information accrues from quantitative ER data. It is clinically relevant to ask whether lower primary tumor ER concentration significantly associates with early disease recurrence after primary surgery; in which case it may contribute to the precipitation of aggressive adjuvant treatments.

We studied the role of ER in a large and representative pool of breast cancer patients referred to a central agency with a well-defined treatment protocol and follow-up program. Relationships of breast cancer survival were examined with respect to several biologically plausible predictor variables.

MATERIALS AND METHODS

Patients

Women diagnosed to have primary breast carcinoma between 1975 and 1981 were referred to the Cancer Control Agency of British Columbia (CCABC). Patients were eligible for this study if they had an ER determination, known dates of diagnosis and no previous, concomitant or later malignancy regardless of site (including bilateral breast cancer) except nonmelanoma squamous cell and basal cell carcinomas of the skin. The distribution of these 1184 patients according to selected variables is shown in Table 1.

Postoperative clinical follow-up was complete on all but 21 patients. The type of primary treatment given was mainly dependent on the operability of the tumor (i.e. clinical stage of disease at presentation) and on the location of the primary tumor (i.e. inner or outer quadrant of the breast). Information on tumor ER contributed to the prescription of adjuvant endocrine treatment and the extent of axillary nodal involvement most influenced consideration of adjuvant chemotherapy. Patients who were surgically treated, with or without postoperative radiation, received complete physical examination 1 month later, every 3 months until the end of the 2nd year, every 6 months from the 3rd to the

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Table 1. Distribution of patients by characteristic (No. of patients in parentheses)

Age at diagnosis	<45 years (224); 45–54 years (291); 55–64 years (318); >64 years (351)
Menopausal status	premenopausal (341); postmenopausal (782); unknown (61)
ER concentration	range 0–998 fmol/mg cytosol protein; median 32; indeterminate (22); ER ≤ 1 (103); ER = 2–9 (278); ER = 10–159 (573); ER ≥ 160 (208)
ER status	positive ≥ 10 fmol/mg (771); negative <10 fmol/mg (391); indeterminate (22)
TNM clinical stage	I (322); II (589); III (158); IV (75); indeterminate (40)
Axillary node involvement	N0 (381); N1–3 (345); N4+ (251)
Primary treatment	surgery only (428); surgery + radiotherapy (598); biopsy only (62); biopsy + radiotherapy (84); unknown (12)
Adjuvant treatment	endocrine (63); chemotherapy (157)
First-line treatment	endocrine (149); chemotherapy (57); sequential: endocrine and chemotherapy (167); no systemic therapy (84)
Outcome	recurred (457); alive (677); dead of breast cancer (390); dead of other causes (96); lost to follow-up (21)

5th year, and once a year thereafter. Chest X-ray and mammography of the opposite breast were repeated annually. Patients who received adjuvant chemotherapy underwent detailed physical examination at the start of each course of chemotherapy. While patients were on an adjuvant regimen blood count and liver function tests were repeated at each visit; chest X-ray and carcinoembryonic antigen were assessed every 3 months. Mammography of the opposite breast and bone scans were performed annually or sooner if indicated. Results of follow-up by the primary care physician were reported on a standardized form. When recurrent disease was suspected or evident patients were referred back to the CCABC for evaluation and therapy planning. Histopathologic diagnosis of malignancy consistent with the primary tumor or evidence of metastatic disease on radiologic scans were used to confirm recurrent disease.

All patients were followed till death or last reported date of having been seen at the CCABC or by their private physicians. About half of these patients were described in a previous study [7]; this subgroup now has a maximum follow-up of 10 years. The minimum follow-up of the additional patients was 4 years. The combined group had a median follow-up of 60 months and a median survival of 111 months.

Staging and nodal status

Clinical TNM stage according to Union Internationale contre le Cancer (UICC) criteria was assigned to patients with complete information on size of lump with or without fixation to underlying pectoralis muscle or chest wall, palpability of axillary lymph nodes, and presence or absence of distant spread as verified by metastatic work-up. The number of axillary nodal metastases was taken from the original pathology report and categorized as N0, N1–3 and N4+.

Receptor analysis

Tumor biopsy or mastectomy specimens were frozen, transported and stored in liquid nitrogen, then trimmed to remove fatty, fibrotic and necrotic material. Tissue was pulverized with a Braun Mikro-dismembrator, homogenized in buffer and centrifuged at 39,000 ***g*** for 15 min to isolate cell cytosol which was incubated with [^{3}H]estradiol ± competitor. Unbound and loosely bound hormone was removed with dextran-coated charcoal and remaining bound [^{3}H]estradiol measured by liquid scintillation counting. Receptor concentration quantitated by Scatchard or Woolf plot was expressed as femtomoles of bound estradiol per mg of protein. Albumin concentrations of the tumor supernatants were measured by radial-immunodiffusion and used to correct for variable serum protein in the cytosol preparation, in accordance with the recommendation of the EORTC Breast Cancer Cooperative Group [8, 9]. All analyses were performed in the same laboratory, under the supervision of W.G., where the technique has remained essentially unchanged throughout the study period [10, 11].

Statistical analyses

Survival curves were estimated by the product limit method [12]. Differences in survival curves defined by covariates under study were examined with Mantel–Cox tests [13]. Program P:1L of BMDP Statistical Software [14] was used.

Overall survival was the time from date of diag-

nosis to date of breast cancer specific death taken from the death certificate or autopsy report. Recurrence was defined as the first confirmed disease relapse, which may have been locoregional (chest wall, ipsilateral regional nodes, ipsilateral breast of patients not having had a mastectomy) or distant dissemination (bone, visceral organs, brain). The date of last follow-up in lieu of date of death was used as the endpoint for those alive at the end of the study. Patients alive with evidence of disease, lost to follow-up (less than 2% of the total group), and dead from other causes were treated as censored data. Patients presenting with TNM IV and persistent disease were excluded from RFS analysis. ER was defined by the same concentration ranges as in the previous study [7], that is: ER $\leq$ 1, ER = 2–9, ER = 10–159 and ER $\geq$ 160. The number of patients per analysis differed according to the completeness of data on the individual variables.

A relative mortality ratio was derived from the Mantel–Haenszel test [15]; the number of observed deaths was compared with a conditionally expected number of deaths within each stratum. A relative recurrence ratio was similarly derived in RFS analysis in which disease recurrence was the end point. The Mantel extension [16] was used to apply a test for trend which was distributed approximately as a chi-square with one degree of freedom.

RESULTS

Overall disease-specific survival

Many laboratories use 10 fmol/mg cytosol protein as the usual cutoff to dichotomize receptor levels into ER+ and ER−. Our data are shown this way in Fig. 1. There was no convergence even at 7 years post-diagnosis, and the difference between the two groups is highly significant. However, there was a much greater distinction in survival with stratification by ER concentration (Fig. 2). The difference between the curves for ER $\leq$ 1 and ER = 2–9 was statistically significant ($P = 0.03$). The curves for ER = 2–9 and ER = 10–159 were also significantly different ($P < 0.0001$). A borderline significance was reached ($P = 0.07$) when the curves for ER = 10–159 and ER $\geq$ 160 were compared. This quantitative pattern was maintained with additional stratification by nodal status, menopausal status and TNM stage (Table 2).

The prognostic importance of quantitative ER was further demonstrated by two other methods. Firstly, a likelihood ratio test [17] comparing two Cox models [18]: one which contained ER categorized as four groups (ER $\leq$ 1, ER = 2–9, ER = 10–159, ER $\leq$ 160) and the other with ER categorized as two groups (ER+ and ER−). This yielded statistically significant results in favor of the improved prognostic value of the four groups ($\chi^2_2 = 8.1$, $P < 0.025$). Secondly, patients were divided into nine groups with approximately the same number in each group (Table 3). A highly significant chi-square test for trend of improved survival with increasing ER was found.

Since we had previously reported a concentration difference in ER among women of different ages [11] we examined the age effect on survival rates within the same four ER concentration strata (Table 4). None of the four age groups had better survival when their ER level was the same, albeit a borderline significance occurred when ER = 2–9. In contrast, when their age group was the same, patients with

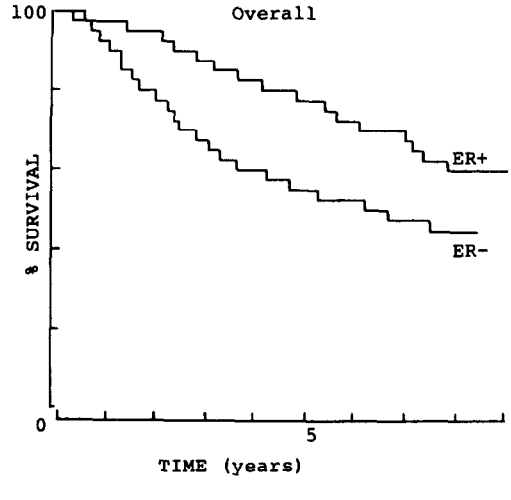

Fig. 1. Overall disease-specific survival of patients by ER status of their primary tumor. The number at risk at the beginning of each year, ER+ and ER− respectively, were: Year 1 (771, 391); *Year* 2 (737, 351); *Year* 3 (695, 290); *Year* 4 (630, 238); *Year* 5 (569, 201); *Year* 6 (434, 145); *Year* 7 (221, 62); *Year* 8 (89, 24); *Year* 9 (32, 11). *Survival curves discontinued when fewer than* 10 *patients under follow-up*; P < 0.0001.

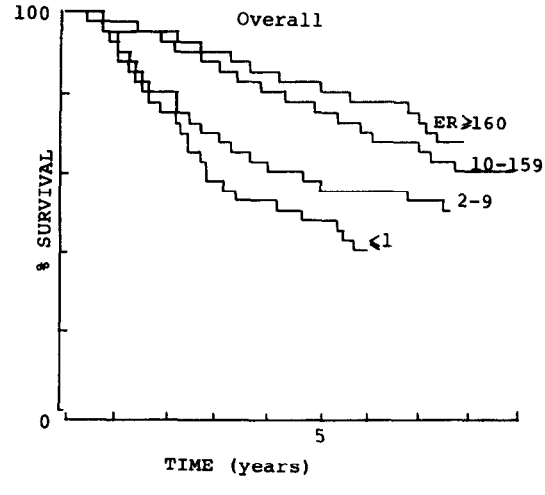

Fig. 2. Overall disease-specific survival of patients by ER concentration (fmol/mg *cytosol protein*) *in the primary tumor. The number at risk in each group were: ER* $\geq$ 160, 208; *ER* = 10–159, 573; *ER* = 2–9, 278; *ER* $\leq$ 1, 103. *Survival curves discontinued when fewer than* 10 *patients under follow-up*; P < 0.0001.

Table 2. Overall percentage survival at 5 years, by ER level, nodal status, menopausal status and clinical TNM stage (No. of patients remaining at risk at 5 years in parentheses)

	ER concentration (fmol/mg cytosol protein)				*P* value*
	≤1	2–9	10–159	≥160	
Nodal status					
N0	66 (15)	86 (51)	93 (118)	96 (48)	<0.0001
N1–3	40 (9)	59 (31)	83 (103)	83 (38)	<0.0001
N4+	39 (7)	40 (17)	59 (56)	68 (17)	0.0003
Menopausal status					
Pre-	44 (13)	63 (39)	78 (110)	100 (4)	<0.0001
Post-	48 (21)	53 (61)	76 (203)	84 (107)	<0.0001
TNM stage					
I	66 (13)	75 (32)	90 (114)	98 (44)	<0.0001
II	57 (19)	62 (65)	80 (176)	84 (66)	<0.0001
III	11 (1)	31 (6)	52 (29)	56 (11)	<0.0001
IV	0 (0)	0 (0)	33 (9)	44 (5)	

*Overall χ^2_3 of test for heterogeneity.

Table 3. Relative mortality ratio by ER concentration

ER concentration (fmol/mgprotein)	No. of patients	Observed/expected deaths*
≤ 1	103	2.16
2–3	134	1.57
4–9	132	1.48
10–20	130	1.15
21–39	126	0.83
40–69	136	0.66
70–122	135	0.64
123–229	135	0.77
≥230	131	0.53

*χ^2_1 of test for trend = 70.9, $P < 0.0001$.

higher ER levels had better overall survival. Patient age at diagnosis had no significant influence on overall survival (χ^2_1 for trend = 1.97; $P = 0.16$).

Recurrence-free survival

ER positivity (ER ≥ 10) associated with a significant prolongation of RFS, but convergence with the ER− group appears about 6 years post-diagnosis (Fig. 3). Stratification in the ER+ range yielded little more prognostic information (Fig. 4), and the difference between the ER ≤ 1 group and ER = 2–9 group was apparent only after 2 years from diagnosis. This difference was not statistically significant ($P = 0.12$).

Nodal status (number of positive nodes) and TNM stage are prognostic discriminators for risk of disease recurrence. The 5-year RFS rates for the three nodal categories were: N0 = 75%, N1–3 = 60%, N4+ = 32% ($P < 0.0001$), while those for TNM stage were: I = 73%, II = 56% and III = 30% ($P < 0.0001$).

There was a significant trend [19] of longer RFS with increasing ER, even after controlling for important covariates like nodal status, TNM stage and menopausal status (Table 5). However, it is notable that the recurrence free survival increment was greatest when the groups with ER ≤ 1, ER = 2–9 and ER = 10–159 were compared. The group with ER ≥ 160 had similar recurrence rates to that with ER = 10–159. To determine if the effect of ER on RFS is independent from treatment effects, relative recurrence ratios were calculated with adjustment for the type of systemic adjuvant therapy. A significant association was found in patients who had not received systemic adjuvant therapy and in those given adjuvant chemotherapy. However, there was no significant ER effect on RFS in patients given adjuvant endocrine therapy (Table 5).

DISCUSSION

Most published reports agree that patients with ER+ tumors have significantly longer survival from diagnosis than ER− patients [20–23]. We found overall disease-specific survival to be influenced favorably by higher ER concentration even when stratified by nodal status, TNM stage (I, II and III only), and menopausal status. Our findings contrast with a recent report by Aamdal *et al.* [5] who proposed that long-term prognosis is unaffected by ER status in the primary tumor. However, their relatively small number of patients were stratified by stage and menopausal status and substratified by ER status, which inevitably left few individuals at risk in the follow-up.

The group with ER ≤ 1 has a particularly poor prognosis. This distinction from the ER = 2–9 group would be concealed by the conventional classification of ER < 10 as ER−, or if an insensi-

Table 4. Percentage 5-year overall disease-specific survival rates by ER level and age at diagnosis (No. of patients in parentheses)

Age	ER concentration (fmol/mg cytosol protein)				χ^{2*}	*P* value
	≤ 1	2–9	10–159	≥ 160		
<45	47 (31)	63 (75)	71 (106)	100 (4)	8.17	0.04
45–54	37 (31)	65 (77)	78 (163)	88 (16)	38.9	<0.0001
55–65	63 (20)	43 (69)	76 (151)	83 (72)	31.2	<0.0001
≥65	45 (21)	50 (57)	76 (153)	78 (116)	28.3	<0.0001
χ^{2}†	5.3	7.9	1.9	3.5		
P value	0.18	0.05	0.42	0.33		

Overall χ^2_3 of test for heterogeneity: *ER controlled for age; †age controlled for ER.

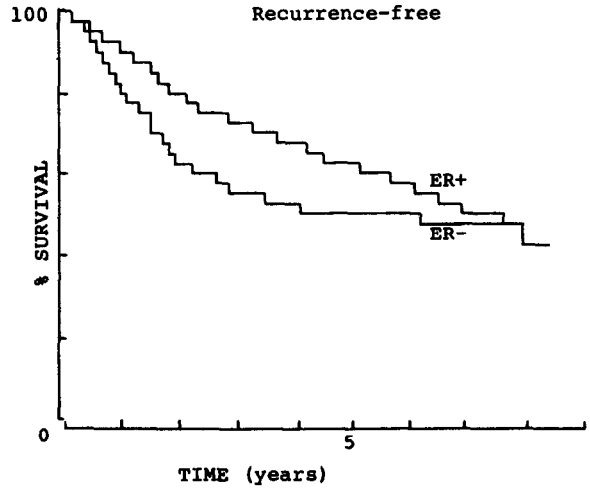

Fig. 3. Recurrence-free survival of patients by ER status of their primary tumor. The number at risk at the beginning of each year, ER+ and ER− respectively, were: Year 1 (710, 342); Year 2 (634, 268); Year 3 (549, 206); Year 4 (488, 180); Year 5 (434, 165); Year 6 (309, 117); Year 7 (142, 44); Year 8 (45, 18); Year 9 (16, 9). Survival curves discontinued when fewer than 10 patients under follow-up; P = 0.0001.

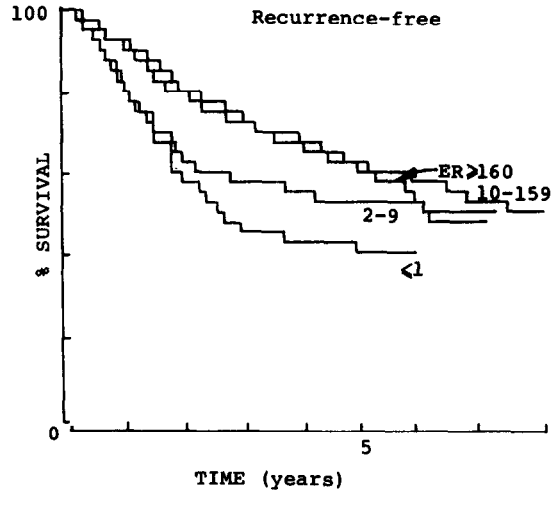

Fig. 4. Recurrence-free survival of patients by ER concentration (fmol/mg *cytosol protein) in the primary tumor. The number at risk in each group were: ER* ≥ 160, 208; *ER* = 10–159, 531; *ER* = 2–9, 246; *ER* ≤ 1, 88. *Survival curves discontinued when fewer than* 10 *patients under follow-up;* P = 0.0001.

tive assay was employed. The few studies of quantitative ER and overall survival overlooked this fine distinction in the ER− range; others have used categories such as: 0 vs. 5–30 vs. 30–60 [2]; <5 vs. 5–19 vs. ≥ 20 [23]; and <3 vs. 3–49 vs. ≥ 50 [24] fmol/mg. The choice of a cutoff value to define ER status is also very important. Forest *et al.* [25] had reported a significantly better prognosis for ER+ patients when ER positivity was defined as ≥ 0.1 fmol/mg wet weight, but a cutoff of 0.5 fmol/mg wet weight eliminated this difference between ER+ and ER− patients.

Most studies of RFS compared ER+ and ER− groups. Initial differences between ER+ and ER− RFS curves were not observed after follow-up times of 2 years [26], 3 years [27], 4 years [4], 5 years [28] or 7 years [20]. Our data by ER status (ER− and ER+) reveals a convergent pattern at about 6 years, although the difference between whole curves is highly significant.

When the data is analyzed by ER concentration a higher ER predicts longer RFS, especially when the groups ER = 2–9 and ER = 10–159 are compared. But having ER ≥ 160 does not prolong RFS compared to ER = 10–159, which cannot be readily explained on a biological basis. It is possible that this *a priori* cutoff point of ER ≥ 160 cannot adequately detect a more favorable survival that may associate with tumors very rich in ER (e.g. ER ≥ 400). Such a high level of ER was found in only about 3% of the patients studied and therefore was not appropriate for statistical testing. Nevertheless, we believe that the essence of analyzing survival with ER concentration is to detect the highly significant trend of better survival with higher ER. Whether pairwise differences between curves are statistically significant is relatively less important, since cutoff points for ER strata might be redefined in different data sets in order to obtain 'significant' statistical difference.

ER does not act exclusively through adjuvant therapy to prolong RFS. This is supported by better RFS with higher ER among patients who did not receive any adjuvant treatment. This significant

Table 5. Relative recurrence ratio by ER concentration, adjusted for stage, menopausal status and adjuvant systemic treatment

	ER concentration (fmol/mg cytosol protein)					
	≤1	2–9	10–159	≥160	χ^{2*}	*P* value
All patients	1.52	1.19	0.86	0.98	9.72	<0.005
Nodal status	1.70	1.15	0.82	1.08	8.12	<0.005
TNM stage	1.52	1.20	0.85	1.00	8.95	<0.005
Menopausal status	1.55	1.20	0.88	0.90	13.39	<0.005
Adjuvant therapy:						
Endocrine therapy	3.40	0.51	0.90	1.06	1.03	0.31
Chemotherapy	2.28	1.00	0.81	1.44	4.05	0.04
No adjuvant	1.24	1.29	0.86	0.97	4.75	0.03

*χ^2_1 of test for trend.

trend was also seen in patients who received adjuvant chemotherapy but was not evident in those who received adjuvant endocrine therapy. This suggests that the advantage of longer RFS might not be restricted to ER+ patients. Patients classified as ER− but whose tumor contained quantifiable amounts of ER could have derived sufficient benefit from this type of therapy to virtually eliminate RFS differences that otherwise exist when no adjuvant endocrine therapy was given. However, it is also possible that statistical significance was not reached as a result of the small number of patients in this subset.

ER+ patients recurred later and less frequently than ER− patients, at least over the 5 year post-surgery period during which the risk of recurrence is greatest [29]. Nevertheless, there was a tendency for the higher ER curves to converge with the lower. This is consistent with the hypothesis that ER influences the timing of a recurrence if it is to occur, rather than the likelihood of it occurring [30]. Unless primary surgical treatment is curative or it leaves a low tumor burden so that any residual disease is potentially curable by adjuvant therapy [31], the metastatic potential of all tumors exist but may be manifested at various times and dictated by tumor cell kinetics, which are generally correlated with ER status [32]. In view of this, it is not surprising that the curves converged when the observations were extended over time.

It is unlikely that the overall disease-specific survival curves will converge with long term follow-up. Since the relevant end point is disease-specific death, other causes of death are included as censored data in the analysis. After prolonged observation, e.g. past 15 years from diagnosis, the survival estimates of both ER+ and ER− groups would be similarly affected by greater censoring due to competing causes of death. The pattern of the curves would be expected to remain the same because disease-specific death would continue to be a function of ER.

Although ER is strongly correlated with patient age, there is no survival advantage in older patients. After controlling for ER level, the overall survival rates of the four age groups (<45, 45–54, 55–64, ≥65) did not differ. However, the overall survival of patients with higher ER was consistently better across the four age strata. Hence ER does not depend on age to express its influence on survival, and any effect of age on prognosis may be explained by variation in ER level. This may account for the prognoses of young women [33] and elderly women [34] being similar to that of other age groups. Our results disagree with a recent large study reported by Adami *et al.* which did not control for ER level but found the age group 45–49 to be most favored [35].

This study emphasizes the value of quantitative ER to breast cancer survival and verifies its prognostic importance independent of nodal status and TNM stage. The ER concentration ranges used in the present study served to demonstrate this generalized relationship of ER quantity and prognosis; they are not rigid cutoff points that define prognosis for a group of patients. The presence of tumor in axillary nodes is a very strong indication for some form of systemic adjuvant therapy, regardless of menopausal status [36]. However, axillary nodal status is not an absolute prognostic factor, since approx. 13% of node-negative patients have a recurrence within 5 years [37]. Measurement of the ER level may help to identify a subset of high risk patients with apparently uninvolved axillary nodes, or node-positive patients whose prognosis is not improved by usual systemic adjuvant therapy. More intensive adjuvant regimens may then be considered for these patients. Patient age did not add significant information about survival once the ER level was known. Variation in overall survival is thus better explained by ER level than the age at which breast cancer was diagnosed.

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