

Mortality/Morbidity Abstract 180M-1

PROGNOSTIC FACTORS IN LOCALIZED BREAST CANCER

RICHARD B. SINGER, MD
Consultant to ALIMDA

References

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2. Tandon AK, Clark GM, Chambers GC et al. "Cathepsin D and Prognosis in Breast Cancer." *New Eng J Med* 1990;322:297-302.
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4. EA Lew and J Gajewski, editors. Abstract 509, "Cancer of the Breast" in *Medical Risks: Mortality by Age and Time Elapsed*. New York: Praeger, 1990: 5-69 to 5-74.
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Objectives of This Abstract

To summarize survival results of three recent series of women with node-negative breast cancer, to estimate annualized mortality and recurrence rates, and to compare mortality with similar but older results in the extensive 1976 fifth report from the National Cancer Institute, the first under the SEER program (Surveillance, Epidemiology, and End Results).

Subjects Studied

1, 2. These two series of patients were drawn from a breast cancer registry managed by the University of Texas Health Sciences Center at San Antonio, Texas.

In the database were approximately 1000 women with primary breast cancer treated 1974-1985, prior steroid-receptor assay of a frozen tumor specimen sent to the Center laboratory at the time of diagnosis or mastectomy, with at least 100 mg remaining, negative axillary lymph nodes (at least 5 examined), documented tumor size, and age of patient at diagnosis. About half of the patients were in south Texas, but there was a nationwide distribution of the other patients, clinical data and the frozen specimen having been supplied by collaborating physicians. In series 1, 395 verified specimens were subjected to DNA flow cytometry to determine ploidy of tumor cells and the fraction in the S (synthesis) phase, in an effort to improve prognosis and the desirability of adjuvant therapy despite the negative lymph nodes. However, an interpretable result was obtained in only 345 of the 395 patients. Mean age is not given, but 94 of the patients were classified as age 50 or

under, and 251 as over age 51, a distribution similar to that derived from the six age groups in the 24,277 patients in the SEER program (see Table 1A). In series 2 the same 1974-1985 database was used to select 199 women with node-negative breast cancer and 198 with node-positive breast cancer. The residual frozen specimens were assayed for Cathepsin D by the Western Blot method and densitometry. Cathepsin D is an estrogen-induced lysosomal protease, with properties described in the reference. It was chosen as a potential prognostic indicator because of its growth-promoting activity and proteolytic activity (reference 2). A similar age distribution was reported for the node-negative cases (62 women under age 50, and 137 age 50 up), and for the node-positive cases (69 women under age 50 and 129 age 50 up). The 199 node-negative patients were also compared with 2,096 additional node-negative patients in the database, patients who did not have a Cathepsin D assay. No age data were reported for these "control" patients.

3. In the health care region of southern Sweden between September, 1982, and January, 1986, there were 410 cases of node-negative breast cancer diagnosed, with tumor specimen available in the tumor bank of the University Hospital, Lund. It was necessary to exclude 43 cases for various reasons, such as carcinoma in situ, absence of any tumor cells after examination of the specimen by a pathologist, breast cancer in a male patient, etc. Treatment details, tumor size, number of nodes examined, and other data were recorded for each of the 367 patients in the follow-up series. Laboratory assays on the tumor included estrogen-receptor and progesterone-receptor content (346 and 325 patients, respectively), DNA flow cytometry for ploidy (305 patients), and fraction of cells in the S phase (286 patients). This series represented about 25% of all patients treated for node-negative breast cancer in the southern region in this time period, out of a total population of approximately 1.5 million. Median age was 62 years, with a range from 21 to 96 years.

4. End Results Report No. 5 of the National Cancer Institute was the source of the results on 24,277 women with localized breast cancer in Abstract 509, cited in reference 4. Additional details about this study may be found in Abstract 501 of the monograph cited. Supplementary annual life tables supplied by Dr. Myers to the editors have been used in Table 1B of this abstract (results by duration in Abstract 509 and other cancer abstracts have been condensed to intervals 0-2, 2-5, 5-10, 10-15, and 15-20 years, to conserve space). Table 1A gives the age distribution and derivation of the mean age for this very large series. Even though the term "node-negative" is not used, it is implicit in the categorization as localized cancer, because ax-

illary dissection and examination of the lymph nodes have been the virtually uniform practice, even when radical mastectomy was not the surgical procedure used.

Follow-up

In series 1 and 2, follow-up data on recurrence, death, survival, and treatment were collected annually by mail from collaborating physicians of patients resident outside southern Texas. Teams of trained data collectors visited clinics or the offices of physicians to obtain the needed follow-up data from these records on a semiannual or quarterly basis. Because these were historical prospective studies, all patients entered were followed from date of entry to the cutoff date. Median follow-up of cutoff date survivors was 59 months in series 1, and in series 2, 59 months for patients with node-positive cancer and 62 months for patients with node-negative cancer.

In series 3 patients were re-examined annually, and a complete evaluation of the medical records was carried out in the latter half of 1988. Death certificates were also reviewed. The median length of follow-up was 48 months, with a range of 24 to 70 months. At the end of follow-up, 275 patients survived without any evidence of cancer recurrence, 15 survived with distant recurrence, and 16 with only localized recurrence. There were 32 deaths due to or with advanced cancer, and 28 deaths due to other causes, with no evidence of recurrence.

In series 4, follow-up was performed at least annually in accordance with the methods used by the two state and two large hospital registries. Entrants from 1950 to 1973 were followed to 1975.

Expected Rates

In Table 1B the SEER data by duration for women with breast cancer, all ages combined, show a 5-year expected survival rate of .874, and a mean annual mortality rate, q' , of 26 per 1000 (for both aggregate and geometric means). The mid-point of the observation period is about 1960. The first adjustment used has been a 20% decrease to allow for the secular change over about 20 years from the early 1960s to the early 1980s, the observation period for the three recent series. This produces a mean annual rate of 21 per 1000 for breast cancer patients with a mean age of 60. Age distribution is assumed to be similar in all series. The adjusted mean annual mortality rate has been estimated at 21 per 1000 in series 1 (mean age 60), again 21 in series 2 (mean age 59), and 22 per 1000 in series 3 (median age 62). The SEER data demonstrate a wide difference between the tabular rate corresponding to the mean age and the actual mean q' , the latter being much higher. This phenomenon, present in all patient groups with a wide range, including older patients, was the reason for using the older SEER results as a basis for q' , despite the need for adjustment for the secular decrease in q' at the older ages in the past two decades. The 1981 mortality rates for Swedish women (1982 UN Demographic Yearbook) are lower than for white U.S. females (1979-81 Tables) at ages 55-69, but higher at ages 70-84. The net difference for all ages combined appears to be small, and no adjustment has been made for difference in national death rate.

With respect to morbidity, the minimum survival rates free of

recurrence have been used in the three recent series as the basis for comparison with rates in the other categorized groups. The mean annual rate of the morbid event, recurrence, is the complement of the geometric mean of the 5-year survival rate without recurrence.

Results

Tables 1A and 1B provide basic SEER data on age distribution and mortality up to 5 years in women observed 1955-1970. The peak excess mortality by duration is not in the first year, but rather at duration 2-4 years, with a mortality ratio between 240% and 235%, and an EDR of 38-39 extra deaths per 1000 per year. The pattern of excess mortality by age shows the usual decrease in mortality ratio with advancing age, from 4700% in the youngest age group to only 134% in women age 75 and up. EDR, on the other hand, is remarkably stable, about 31 per 1000, from age 35 up, with the highest EDR of 50 per 1000 observed in young women age 25-34. The average mortality ratio is 225%, and the average EDR is 33 per 1000. The more recent 5-year experience of women with node-negative or localized breast cancer reflects a smaller overall excess mortality: in Series 2 the EDR was 18 per 1000 per year for the 194 tested patients and 16 per 1000 in the 2096 similar patients in the database who were not tested (see Table 1C). All of the remaining results in Table 1C are for patients categorized by one or more of the various laboratory tests employed in the three series. In Series 1, the lowest mortality ratio, only 110%, was found in the 97 patients with normal diploid cell division in the tumor, and a low fraction of cells in the S phase. However, in the small group of 15 patients with diploidy but a high fraction of cells in the S phase, mortality was significantly higher ($P = 0.01$). Aneuploid patients had a mortality ratio close to 140% and EDR of 7-9 per 1000, regardless of a low or high progesterone-receptor (PR) level. In Series 2, patients from the same cancer database at the University of Texas Center at San Antonio showed no excess mortality with a low Cathepsin D level, and a mortality ratio of 350% and EDR of 53 per 1000 with a high level of Cathepsin D, a marked and highly significant difference ($P = 0.0001$). There was no significant difference by Cathepsin D level in the node-positive patients. Other prognostic markers were tested in both univariate and multivariate analysis; details of these results may be found in the article (reference 2). Finally, in Series 3, the Swedish study, three indicators, tumor size, S phase fraction, and progesterone-receptor level, were combined into a series of risk factors. A relatively small excess mortality was found in the 155 patients in the low or intermediate risk groups: mortality ratio of 164% or less and EDR of 14 per 1000 or less. By way of contrast, the 93 patients (38% of the total classified) who had a high risk score of 2.0-3.0 showed a very high excess mortality, with a mortality ratio of 680% and an EDR of 128 per 1000 per year. Again, details of results by individual risk factors are to be found in the original article (reference 3). It is apparent that several of the laboratory tests used in these studies did serve as effective prognostic discriminators. Very low or no excess mortality was found in some groups of these localized breast cancer patients, and higher than average, sometimes very high mortality was found in other groups.

Table 1D presents results for annualized recurrence rates. All of the articles describing these follow-up studies provide recurrence-free survival curves as well as the survival curves reflecting total mortality. The derived mean annual recurrence rates used as "expected" were the lowest rates in each series: 18 per 1000 per year for the patients with diploidy and low S fraction in Series 1; a rate of 51 per 1000 in the control patients in Series 2; and a rate of 19 per 1000 in the low-risk group in Series 3. These rates are shown on the first line of data for each series. The morbid event (recurrence) rates are designated by the symbol *r* for the observed rate and *r'* for the expected rate. Excess recurrence rates in Series 1 were 38 per 1000 per year for the aneuploid group, and 71 per 1000 for the small group with high S fraction and diploidy; the corresponding morbidity ratios were 310% and 495%, respectively. In Series 2 there was little excess recurrence in the low cathepsin D group, but a high rate, 83 per 1000 with a morbidity ratio of 265% in Series 2. The control recurrence rate was considerably higher than in the other two series. Excess recurrence was at the rate of 16 per 1000 in the intermediate risk group of Series 3 (with a morbidity ratio of 184%), and a much larger 75 per 1000 in the high-risk group (morbidity ratio of 495%). The prognostic indicators used in these series were successful in differentiating cancer recurrence rates, as well as patient survival and mortality.

Comment

These test procedures are relatively new and by no means widely used at the present time, to the best of my knowledge. However, as is the case with all new laboratory procedures, the medical director has a responsibility to be acquainted with its interpretation, and the implications of the result when this

crosses up in a report on an insurance applicant. The evidence from these studies suggests two conclusions. The first is an apparent secular decrease in overall mortality in localized or node-negative female breast cancer cases as compared with earlier decades. Does the mortality pattern by duration suggest the possibility that the waiting period for applicants with localized breast cancer might be reduced in comparison with the waiting period for applicants with other types of localized cancer? Should the flat extra be higher for patients under age 35 at the time of diagnosis and operation? The second conclusion is that some of these newer tests do provide prognostic information with regard to both recurrence and mortality, and this raises the question of possible medical director modification of the standard rating for localized breast cancer to take account of the differences in mortality in the first five years. The authors of the Series 3 article state that the survival for their cases with a risk score under 2.0 were very close to the survival curves for the age-matched Swedish population. I do not confirm this from the comparative mortality methods that I have used, although the calculated excess mortality is not very large. I do not believe this can be explained by lower Swedish than U.S. white female mortality rates (see section on Expected Rates). However, it should also be noted that no excess mortality was found in the patients with a low cathepsin D level, in Series 2. It is my opinion that we do not yet have sufficient evidence to offer standard insurance to a select few of the applicants with node-negative breast cancer! However, some reduction in the customary rating might be in order on the basis of this type of favorable evidence, if it is balanced by a higher rating, in the event that the test result is unfavorable.

Table 1A

Age Distribution and Mean Age, Localized Breast Cancer, National Cancer Institute, SEER Program, 1950-75 Results

Age Group	No. of Patients	Decimal Fraction	Mean Age	Age Increment
years	<i>l</i>	<i>f</i>	<i>x</i>	(<i>f</i>)(<i>x</i>)
25-34	573	.024	(30)	0.71
35-44	3,369	.139	(40)	5.55
45-54	5,699	.235	(50)	11.74
55-64	5,363	.221	(60)	13.25
65-74	5,150	.212	(70)	14.85
75 up	4,123	.170	(80)	13.59
Total	24,277*	1.000	59.7	59.69
25-44	3,942	.163	(38.4)	6.26
45-49	(2,750)	.113	(47)	5.32
<50	6,692	.276	est. 42.0	11.58
50-54	2,949	.121	(52)	6.32
55 up	14,636	.603	(69.1)	41.69
50 up	17,585	.724	est. 66.3	48.01

* Life table "all patients" gives total of 24317.

Table 1B
5-Year Experience 1950-1975, Women with Localized Breast Cancer,
SEER Program of the National Cancer Institute

Group	Exposure Pt.-Yrs.	No. of Deaths		Mortal. Ratio	Mean Ann. Mort. Rate/1000			5-Yr. Obs.	Surv. Exp.
		Obs.	Exp.*		Observed	Expected*	Excess		
	E	d	d'	100d/d'	q	q'	(q-q')	P	P'
Total Patients, All Ages Combined, by Duration									
Duration									
0-1 yr.	24,006	1,159	601	193%	48	25	23	.952	.975
1-2	21,916	1,233	553	230	56	25	31	.898	.950
2-3	19,425	1,250	510	245	64	26	38	.840	.925
3-4	16,966	1,116	465	240	66	27	39	.785	.900
4-5	14,762	921	417	220	62	28	34	.736	.874
0-5	92,075	5,679	2,530	225	59	26	33	.736	.874
Patients (Table 1A) by Age, Durations 0-5 Years Combined									
Age (Yrs.)									
25-34	2,398	122	2.60	4,700%	51	1.1	50	.765	.994
35-44	14,512	495	37.2	1,330	34	2.6	31	.838	.987
45-54	24,072	810	122.4	660	34	5.0	29	.835	.973
55-64	21,886	964	277	350	44	13	31	.792	.937
65-74	20,394	1,356	673	200	66	33	33	.703	.843
75 up	14,109	1,923	1,438	134	102	71	31	.480	.574

* Basis of expected deaths: contemporaneous U.S. Life Table rates.

Table 1C
Overall 5-Year Experience, 3 Series of Women with Node-Negative
Breast Cancer, Grouped by Various Prognostic Indicators

Prognostic Indicator*	No. of Patients	Survival Rate		Mean Ann. Mort. Rate/1000			Mortality Ratio
		5-Yr.	Annual	Observed	Expected†	Excess	
	<i>l</i>	P	p	q	q'	(q-q')	100q/q'
Series 1, 345 Patients, Estimated Mean Age 60 Yrs.							
Aneuploid+Neg.PR	132	.859	.970	30	21	9	143%
Aneuploid+Pos.PR	101	.865	.972	28	21	7	133
Diploid + Low S	92	.891	.977	23	21	2	110
Diploid + High S	15	.777	.951	49	21	28	235
Series 2, 199 Patients, Estimated Mean Age 59 Yrs.							
Low Cathepsin D	135	.901	.979	21	21	0	100%
High Cathepsin D	64	.682	.926	74	21	53	350
All Tested Pts.	199	.82	.961	39	21	18	186
Pts. Not Tested	2,096	.83	.963	37	21	16	176
Series 3, 367 Patients, Sweden, Median Age 62 Yrs.							
Low Risk Score 0	59	.826	.964	36	22	14	164%
Score 0.5-1.5	96	.891	.971	29	22	7	132
High Risk, 2.0-3	93	.619	.850	150	22	128	680

* Series 1: ploidy status from DNA flow cytometry, also fraction of synthesis (S) phase; assay of progesterone-receptor (PR) as a fraction of cytosolic protein. Series 2: cathepsin D by Western Blot assay. Series 3: Risk Score from combination of scores for tumor size, PR assay and S-phase fraction.

† Basis of expected mortality: 80% (secular trend adjustment) of q' of 26 per 1000 per year, SEER mean rate in Table 1B, adjusted for difference from SEER mean age 60 years.

Table 1D

Annualized Recurrence Rates, 3 series of Women with Node-Negative Breast Cancer, Grouped by Various Prognostic Indicators

Prognostic Indicator*	Number of Pts.	Survival Rate		Mean Ann. Morbidity Rate/1000			Morbidity Ratio
		5-Yr.	Annual	Observed	Expected†	Excess	
	<i>l</i>	<i>P</i>	<i>p</i>	<i>r</i>	<i>r'</i>	(<i>r-r'</i>)	100 <i>r/r'</i>
Series 1, 345 Patients, Texas Registry							
Diploid+Low S	97	.913	.982	(18)	18	(0)	(100%)
Aneuploid	233	.748	.944	56	18	38	310
Diploid+High S	15	.570**	.911	89	18	71	495
Series 2, 199 Patients, Texas Registry							
Pts. Not Tested	2,096	.77	.949	(51)	51	(0)	(100%)
Low Cathepsin D	135	.757	.946	54	51	3	106
High Cathepsin D	15	.487	.866	134	51	83	265
Series 3, 367 Patients, Swedish Registry							
Low Risk Score 0	59	.907	.981	(19)	19	(0)	(100%)
Score 0.5-1.5	96	.835	.965	35	19	16	184
High Risk, 2.0-3	93	.609	.906	94	19	75	495

* See first footnote, Table 1C.

† Control group with minimum recurrence rate.

** Recurrence-free survival rate at 6 years, instead of 5 years, all other rates.