

Significance of Axillary Lymph Node Metastasis in Primary Breast Cancer

By Ismail Jatoi, Susan G. Hilsenbeck, Gary M. Clark, and C. Kent Osborne

Purpose: Axillary lymph node status is the single most important prognostic variable in the management of patients with primary breast cancer. Yet, it is not known whether metastasis to the axillary nodes is simply a time-dependent variable or also a marker for a more aggressive tumor phenotype. The purpose of this study was to determine whether nodal status at initial diagnosis predicts outcome after relapse and therefore also serves as a marker of breast cancer phenotype.

Patients and Methods: Survival experience after first relapse in 1,696 primary breast cancer cases was analyzed using Cox proportional hazards regression. The following explanatory variables and their first-order interactions were considered: number of axillary lymph nodes involved (zero v one to three v four or more), hormone receptor status (any estrogen receptor [ER] negativity v ER negativity/progesterone receptor positivity v other ER positivity), primary tumor size (< 2 cm v 2 to 5 cm v > 5 cm), site of relapse (locoregional v distant), disease-free interval (< 1.5 years v 1.5 to 3 years v > 3 years), adjuvant endocrine therapy (none v any), adjuvant chemotherapy (none v any), and menopausal status (pre-, peri-, or postmenopausal).

Results: Axillary lymph node status, site of relapse, and hormone receptor status were all highly significant as main effects in the model. After adjustment for other variables, disease-free interval alone was only modestly significant but interacted with nodal status. After disease-free interval, hormone receptor status, and site of relapse were accounted for, survival after relapse was poorer in node-positive cases, when compared with node-negative cases. The hazard ratios for patients with one to three and four or more involved nodes were 1.2 (95% confidence interval [CI], 0.8 to 1.9) and 2.5 (95% CI, 1.8 to 3.4), respectively.

Conclusion: Patients with four or more involved nodes at initial diagnosis have a significantly worse outcome after relapse than node-negative cases, regardless of the duration of the disease-free interval. We conclude that nodal metastasis is not only a marker of diagnosis at a later point in the natural history of breast cancer but also a marker of an aggressive phenotype.

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NODE-POSITIVE BREAST cancers have a worse prognosis than node-negative cases.¹ However, the significance of nodal metastasis is poorly understood. Late in the 19th century, Halsted² proposed that breast cancer spreads first to the axillary lymph nodes and then to distant sites. Thus, nodal metastasis was viewed as an indicator of tumor chronology. The better prognosis of node-negative tumors was attributed to timely resection, before distant metastasis via the axillary lymphatics had occurred.³

In more recent years, large randomized trials have shown that neither the extent of the mastectomy nor delay in the

treatment of the axilla has any influence on the prognosis of patients with operable breast cancer.⁴⁻⁶ In addition, long-term follow-up of node-negative patients reveals that 30% eventually die of metastatic breast cancer.⁷ Thus, the axilla does not seem to serve as a nidus for further spread of the cancer, as postulated by Halsted. Yet, nodal status is still considered an indicator of tumor chronology, and the better prognosis of node-negative patients is generally attributed to lead time bias.⁸ However, an alternative possibility may account for the difference in prognosis between node-negative and node-positive patients. Nodal status is perhaps also a marker of tumor biology, with node-positive tumors having a more aggressive phenotype.

In this study, we set out to better understand the significance of nodal metastasis through a multivariate analysis of the survival data from the San Antonio Tumor Bank (San Antonio, TX). To reduce the uncertainty associated with lead time bias, we correlated nodal status at initial diagnosis with outcome after relapse. If nodal status is, at least in part, a marker of tumor phenotype, then node-positive patients should have a shorter interval from first relapse to death than node-negative patients. Alternatively, if nodal status is simply a time-dependent variable, then it should not predict outcome after relapse.

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PATIENTS AND METHODS

Patient Population

The patients in this study were identified from a large database of patients who had hormone receptor assays or flow cytometry performed in our laboratory (University of Texas Health Science Center at San Antonio [UTHSCSA]). Eligible patients were initially diagnosed between 1970 and 1991 and presented with primary breast cancer treated with either radical or modified radical mastectomy, or lumpectomy and axillary node dissection with postoperative radiation therapy. These patients had no evidence of distant metastases at the time of diagnosis and were followed, as previously described,⁹ for relapse (defined as the first clinically recognized evidence of local or distant recurrence) and survival. Of 2,156 patients known to have relapsed locally, distantly, or both, we omitted 132 whose cancer recurred less than 6 months after the initial diagnosis and another 72 for whom we had no follow-up after relapse. Additional cases were omitted due to missing data (estrogen receptor [ER] results not available from the primary tumor, n = 178; menopausal status unknown, n = 61; and adjuvant therapy unknown, n = 17). The final data set, comprising 1,696 relapsed primary breast cancer cases, is summarized in Table 1.

Survival time is defined as time from relapse to last contact or death. As of June 1998, there have been 1,207 deaths, and median follow-up after relapse among living cases was 2.3 years. Survival of 35 cases still alive more than 10 years after relapse was truncated to 10 years for display in the survival curves.

Prognostic Variables

A number of potentially prognostic clinical and biologic variables were available. ER and progesterone receptor (PgR) status had been measured by ligand binding assay in our laboratory. Tumors with ≥ 3 fmol/mg protein of ER or ≥ 5 fmol/mg protein of PgR are considered hormone receptor-positive. Primary tumor size and number of positive axillary lymph nodes were abstracted from medical records. The disease-free interval (DFI), defined as the time from diagnosis to first relapse, was divided roughly at the tertiles to create DFI groups. About a third of relapses were locoregional (ie, chest wall, axillary, etc), while two thirds were distant (ie, liver, lung, bone, etc) or a combination of multiple sites.

Statistical Analysis

Univariate survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test.^{10,11} Multivariate analysis of survival was performed using Cox proportional hazards regression.¹² The purpose of the analysis was to examine the contribution of positive lymph nodes to survival after relapse, after accounting for the potential effects of other explanatory factors. Explanatory variables were treated as categorical variables and modeled using dummy variables, coded 0 or 1. The following main effects, and their first-order interactions, were considered: hormone receptor status (any ER- v ER+/PgR- v ER+/PgR+ or ER+/PgR unknown), number of positive axillary lymph nodes (zero v one to three v four or more), primary tumor size (< 2 cm v 2 to 5 cm v > 5 cm), DFI (< 1.5 years v 1.5 to 3 years v > 3 years), site of relapse (locoregional or any distant site), adjuvant endocrine therapy (none v any), adjuvant chemotherapy (none v any), menopausal status (premenopausal + perimenopausal v postmenopausal). The Cox model was pruned using hierarchical backward elimination, which requires removal of interaction terms before removal of associated main effects. Elimination stopped when all remaining terms eligible for removal from the model were significant at the alpha = 0.01 level. Initially, the data

Table 1. Patient Characteristics and Results of Univariate Analysis of Survival After First Relapse

Clinical Factors	No. of Patients	%	2-Year Survival Rate	P
All cases	1,696	100	.51	
Hormone receptor status				
ER-	455	26.8	.33	<<.00001
ER+	1,241	73.2	.57	
PgR-*	726	49.6	.39	<<.00001
PgR+	737	50.4	.62	
ER-	455	26.8	.33	<<.00001
ER+/PgR-	363	21.4	.47	
ER+/PgR+/?†	878	51.8	.61	
No. of axillary lymph nodes				
0	622	36.7	.61	<<.00001
1-3	400	23.6	.51	
4+	674	39.7	.40	
Tumor size, cm				
< 2	508	30.0	.59	.00001
2-5	765	45.1	.52	
> 5	423	24.9	.39	
Menopausal status				
Premenopausal	430	25.4	.53	.64
Perimenopausal	50	2.9	.40	
Postmenopausal	1,216	71.7	.50	
Adjuvant chemotherapy				
None	1,055	62.2	.57	<.00001
Any	641	37.8	.41	
Adjuvant endocrine therapy				
None	1,174	69.2	.52	.014
Any	522	30.2	.48	
DFI, years				
< 1.5	513	30.2	.39	<<.00001
1.5-3	567	33.4	.45	
> 3	616	36.4	.67	
Site of relapse				
Local only	532	31.4	.68	<<.00001
Any distant site	1,164	68.6	.43	
Year of diagnosis				
1970 to 1984	1,301	76.7	.52	.034
1985 to 1991	395	23.3	.47	

*A total of 233 cases did not have PgR data.

†The ER+, PgR+/? group included ER+ cases that were PgR+ (n = 704) or PgR unknown (n = 174).

set was split in half randomly, with one subset being used for model pruning. The final pruned model was then fit to the second subset. Because the results were virtually identical, we show the final pruned model refit to the entire data set. Proportional hazards assumptions were tested using graphical methods^{13,14} and were not violated. Model results were summarized by computing model estimates and approximate 95% confidence intervals (CIs) of 2-year survival after relapse for all possible combinations of the explanatory variables in the final model. Analyses were performed using SAS software version 6.12 (SAS, Inc, Cary, NC).

RESULTS

Univariate Analysis

The characteristics of the 1,696 cases included in this study are summarized in Table 1. At diagnosis, they were predominantly postmenopausal (71.7%) with ER+ tumors (73.2%). Tumor sizes tended to be greater than 2 cm (70%), and the majority of cases were lymph node–positive (63.3%). The median DFI was 2.2 years, and 68.6% of relapses included a distant site. A majority of patients were diagnosed before 1984 (76.7%) and did not receive adjuvant chemo- or endocrine therapy (62.2% and 69.2%, respectively).

Two-year survival after first relapse was 51% (95% CI, 48% to 63%). In univariate survival analysis, only menopausal status was not at least marginally associated with survival after first relapse (Table 1). Survival curves for number of axillary lymph nodes and type of relapse are shown in Figs 1 and 2. Hormone receptor status, number of axillary lymph nodes, tumor size, adjuvant chemotherapy, DFI, and site of relapse were all highly significant, with the worst outcome being associated with positive nodes, large tumor size, adjuvant chemotherapy, short DFI, and distant relapse. Adjuvant chemotherapy may be associated with poorer postrelapse outcome because patients with biologically aggressive disease were selected for treatment, or possibly because tumors that relapsed after therapy were more resistant to further therapy. Endocrine adjuvant therapy (or selection of patients as candidates for therapy) was only

modestly associated with a worse outcome. Similarly, patients diagnosed after 1984 ($n = 395$) did slightly worse after relapse ($P = .034$). This is likely due to the association between short DFI and poorer survival and to the association between chemotherapy and poorer survival. Patients with short DFIs are slightly overrepresented in the later cohort ($P = .014$ by χ^2 test for independence). Similarly, more patients in the later cohort were treated with adjuvant chemotherapy ($P = .001$ by χ^2 test for independence).

Multivariate Analysis

Cox regression was used to examine the independent prognostic value of each variable after adjusting for potential confounding effects of other variables. Variables comprising two groups, such as site of relapse, were represented by a single indicator variable taking on values of 0 or 1, whereas variables comprising three groups (eg, tumor size) were represented by two indicator variables, and therefore contribute two coefficients to the regression equation and two degrees of freedom. Interactions were represented by products of the corresponding main effects. The full range of possible interaction effects was therefore represented by combining main effect and interaction terms. The final pruned model (Table 2) was constructed by beginning with a full model containing terms for each prognostic variable and all of the corresponding two-factor interactions and progressively removing nonsignificant terms.

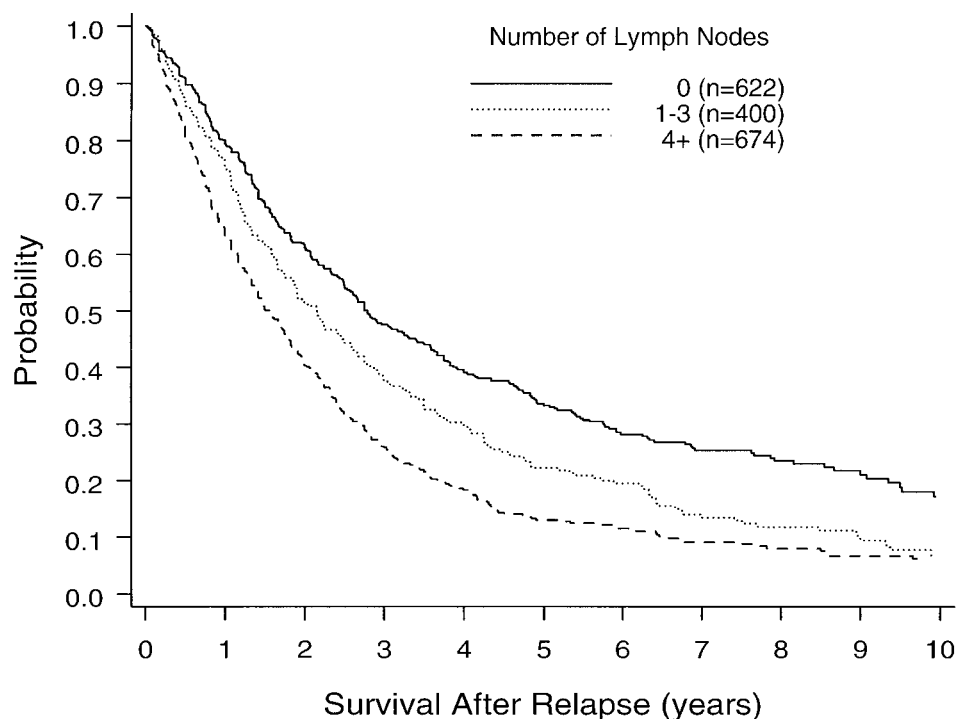
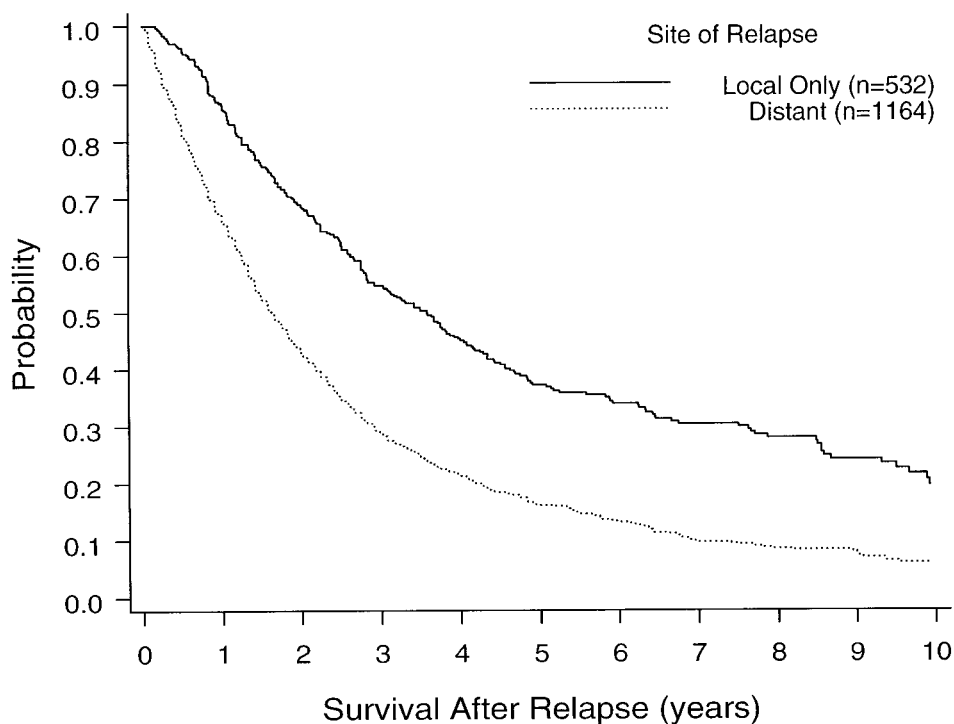


Fig 1. Survival after first relapse by number of positive axillary lymph nodes.

Fig 2. Survival after first relapse by site of relapse.



Site of relapse, number of axillary lymph nodes, and hormone receptor status were all highly significant as main effects in the model (Table 2). The risk of death after relapse was more than double in patients with a distant relapse compared with those with a local relapse (hazard ratio, 2.1) and similarly increased in patients who were diagnosed with four or more positive lymph nodes compared with those who were node-negative at diagnosis. Patients whose primary tumors were ER+/PgR+ had half the risk of those with ER- tumors. After adjustment for other variables, DFI alone was not significant as a main effect but interacted strongly with nodal status. A long DFI mitigates the otherwise deleterious effects of having four or more nodes.

There were no other significant interactions detected, and tumor size, menopausal status, adjuvant endocrine and chemotherapy, and all associated interactions were not

significant and were eliminated from the model. Although the level of significance for retention was set ahead of time at alpha = 0.01, no other terms achieved even the 0.05 level. Several representations of hormone receptor status were considered, including ER status alone, with nearly identical results to those above.

Cox model estimates of 2-year survival after relapse and 95% CIs are summarized in Table 3 and Fig 3. Regardless of other factors, survival probability was lower for hormone receptor-negative cases and for those with distant relapse. Overall, DFI had relatively little effect, but the effect of the nodes × DFI interaction is easily seen as a difference in the shapes of the curves across the panels. For short DFI, the prognosis for those with four or more nodes was markedly worse than for those with fewer nodes at diagnosis (Fig 3A). For patients with a long DFI (Fig 3C), there was less differential due to nodes, and the number of nodes involved was not important. Patients with an intermediate DFI exhibited an intermediate pattern.

After DFI, hormone receptor status, and site of relapse were accounted for, the predicted survival after first relapse of node-negative cases was always better than that of cases with four or more nodes at diagnosis, suggesting that lymph node involvement is, at least in part, a marker of biologic behavior that continues to exert an effect, even after relapse.

Table 2. Results of Cox Regression Analysis of Survival After First Relapse

Variable	df	P*
Site of relapse	1	<<.0001
No. of axillary lymph nodes	2	<<.0001
DFI	2	.14
No. of nodes × DFI	4	.00012
Hormone receptor status	1	<<.0001

*P value was associated with the loss in goodness of fit if this term was removed.

Table 3. Cox Model Estimates of Probability of 2-Year Survival After First Relapse and 95% CIs for All Possible Combinations of Model Terms

Site of Relapse	Hormone Receptor Status	No. of Nodes	2-Year Survival								
			DFI < 1.5 Years			DFI = 1.5 to 3 Years			DFI > 3 Years		
			Rate	95% CI*	No. of Patients	Rate	95% CI*	No. of Patients	Rate	95% CI*	No. of Patients
Local	ER-	0	.62	—†	24	.63	.55-.70	27	.68	.61-.75	20
		1-3	.54	.44-.63	13	.47	.37-.56	11	.62	.53-.69	5
		4+	.32	.24-.41	25	.41	.32-.50	17	.63	.55-.70	13
	ER+/PgR-	0	.71	.69-.73	11	.72	.65-.77	10	.76	.70-.81	12
		1-3	.64	.55-.72	9	.57	.48-.66	7	.70	.63-.77	12
		4+	.44	.35-.52	17	.53	.44-.60	14	.72	.65-.77	5
	ER+/PgR+/?	0	.78	.75-.80	19	.79	.72-.83	36	.82	.77-.86	65
		1-3	.72	.64-.79	14	.67	.58-.74	19	.77	.71-.83	29
		4+	.55	.46-.63	31	.63	.54-.70	34	.78	.72-.83	33
Any distant site	ER-	0	.37	.32-.42	34	.38	.28-.48	41	.45	.35-.55	24
		1-3	.28	.17-.39	26	.20	.12-.31	35	.36	.25-.47	16
		4+	.09	.05-.16	61	.16	.09-.24	44	.38	.28-.48	19
	ER+/PgR-	0	.49	.43-.54	29	.50	.40-.59	35	.56	.47-.65	38
		1-3	.39	.28-.51	12	.32	.21-.43	20	.48	.37-.58	25
		4+	.18	.10-.27	38	.26	.17-.36	36	.50	.40-.59	33
	ER+/PgR+/?	0	.59	.53-.65	38	.60	.50-.69	57	.66	.57-.74	102
		1-3	.51	.39-.62	34	.43	.32-.54	47	.59	.48-.68	66
		4+	.29	.19-.39	78	.38	.27-.48	77	.60	.51-.69	99

*Approximate 95% CIs estimated as $S_0(t = 2)^{x'b \pm 2 \cdot SE(x'b)}$, where $S_0(t)$ is the baseline survival function, x is the vector of values of predictors, b is the vector of regression coefficients, $x'b$ is the estimate of the linear predictor, and $SE(x'b)$ is the standard error of the linear predictor.

†For reference group, the linear predictor, $x'b$, was 0.0 and the standard error was 0.0.

DISCUSSION

Mueller¹⁵ analyzed the annual rates of death from the National Surgical Adjuvant Breast and Bowel Project 04 study and Connecticut Tumor Registry and found that they were consistently higher for node-positive patients than for node-negative patients. Therefore, he postulated that the two stages of breast cancer represented biologic variants of the same disease. However, his analysis did not account for the confounding effects of other prognostic factors on survival, and the possibility that nodal status was a surrogate for these other variables could not be excluded. Subsequently, Mitra and MacRae¹⁶ undertook a meta-analysis of published correlations between various prognostic factors in breast cancer and concluded that axillary lymph node status is simply a reflection of the chronologic age of the tumor. Yet, a meta-analysis has pitfalls, many of which were acknowledged by the authors. These include publication bias (journals tend to report only positive findings) and variability in laboratory analysis criteria (for instance, different laboratories adopt different criteria as to what constitutes ER positivity and ER negativity). In order to account for the shortcomings of the two previous studies, we undertook a multivariate analysis using a single, large database. All laboratory data were generated from the same institution, thereby accounting for the possible confounding effects of

other prognostic factors on survival and yet eliminating the deficiencies of the meta-analysis.

The clinical history of breast cancer is often marked by four milestones: inception, diagnosis, distant relapse, and death.⁸ The time of inception is not known, and therefore the interval between inception and diagnosis is not known and probably highly variable between patients. If the survival advantage of node-negative patients is due to lead time bias, then these patients may seem to do better only because their cancers are diagnosed earlier than in the node-positive group, resulting in a longer follow-up time to death. To reduce the uncertainty associated with lead time bias, we correlated nodal status at initial diagnosis with the interval between two known points in the clinical history of breast cancer: relapse and death. A long interval would suggest a biologically indolent tumor, while a shorter interval would indicate a more aggressive tumor phenotype. If nodal status is simply a marker of delay in diagnosis, then it should not correlate with outcome after relapse.

The importance of nodal status in predicting outcome after relapse is controversial. Some investigators have reported that nodal status has prognostic importance after relapse.¹⁷⁻¹⁹ However, others have found no correlation.²⁰⁻²⁴ There were relatively few patients in most of these studies, and the relationship between the number of involved nodes and prognosis after relapse was generally not examined (patients were categorized

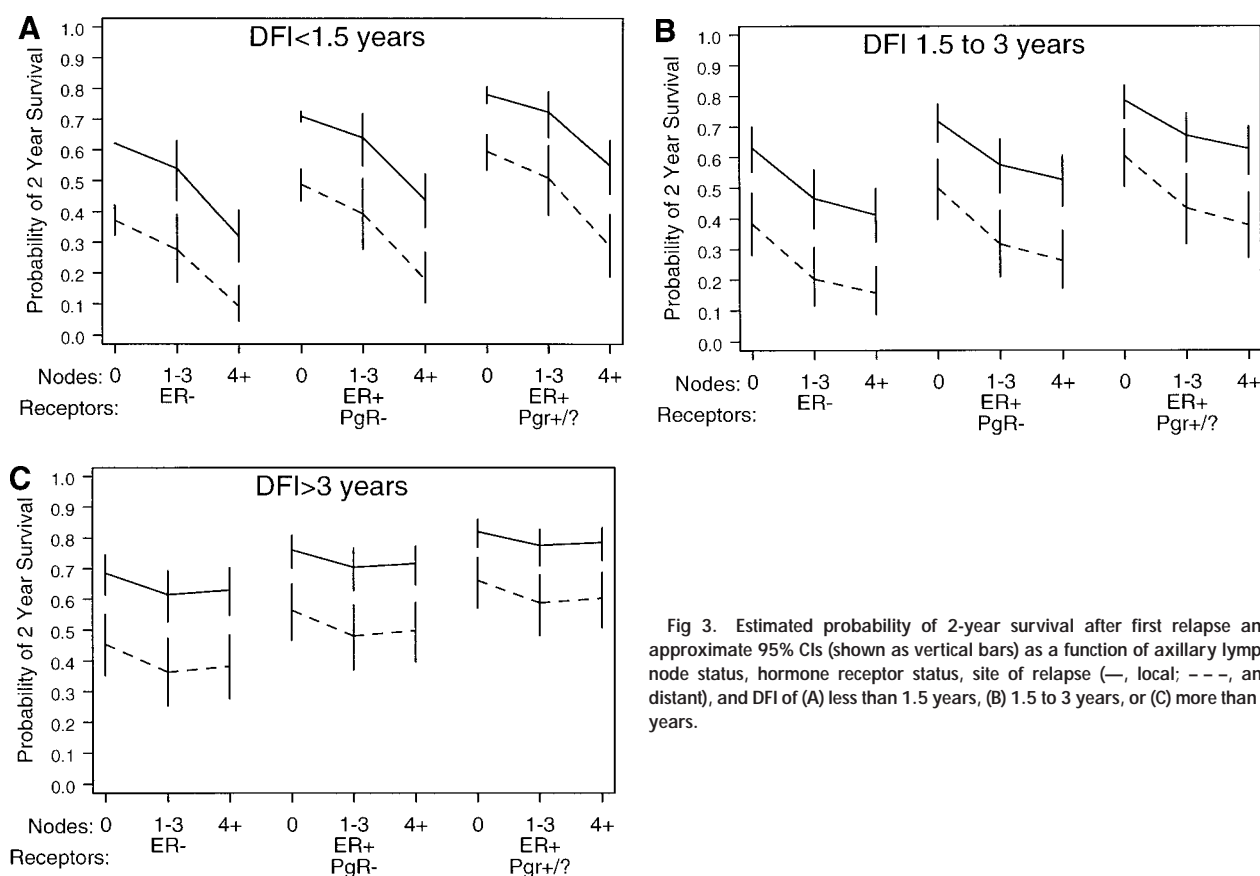


Fig 3. Estimated probability of 2-year survival after first relapse and approximate 95% CIs (shown as vertical bars) as a function of axillary lymph node status, hormone receptor status, site of relapse (—, local; ---, any distant), and DFI of (A) less than 1.5 years, (B) 1.5 to 3 years, or (C) more than 3 years.

simply as node-positive or node-negative). More recently, several authors have reviewed the literature on this subject and concluded that nodal status has no value in predicting outcome after relapse and is therefore simply an indicator of tumor chronology.^{8,25,26} Several years ago, a report from our institution suggested that nodal status does have prognostic importance after relapse.¹⁹ In the present study, we evaluate an expanded cohort of patients from that database and correlate the extent of nodal involvement with outcome after relapse.

Patients with large, hormone receptor-negative or node-positive tumors are often selected to receive adjuvant systemic therapy. Thus, it is not surprising that patients selected for adjuvant systemic therapy have a worse outcome after relapse in the univariate analysis but not the multivariate model, where the effect of these other confounding variables is taken into account. Similarly, the size of the primary tumor correlates with outcome after relapse in the univariate analysis but not the multivariate model. Therefore, one might speculate that tumor size is a surrogate for nodal status. In the multivariate model, only nodal status, site of relapse, and hormone receptor status are independent predictors of outcome after relapse. After these main effects and the interaction between number of nodes involved and

DFI are accounted for, nodal status remains a significant predictor of outcome after relapse. Indeed, when compared with node-negative patients, those with four or more involved nodes have a significantly worse outcome after relapse. However, for patients with only one to three involved nodes, the outcome is not significantly different from that of the node-negative patients. Thus, the number of involved nodes (rather than simply the absence or presence of nodal involvement) is a key determinant of prognosis after relapse.

The risk of axillary lymph node metastasis increases as tumor size increases, which suggests that nodal metastasis is indicative of tumor chronology.^{27,28} Yet, our study suggests that nodal status has prognostic importance after relapse, indicating that it is also a marker for tumor phenotype. These findings are not necessarily inconsistent. One might speculate that there is a continuum from slow-growing tumors with late axillary involvement to more aggressive tumors with early metastasis to the axilla.²⁹ A 1-cm, node-positive tumor might be chronologically early but biologically more aggressive when compared with a 2-cm, node-negative tumor. Thus, all breast cancers may eventually metastasize to the axillary nodes, with the propensity for early or late meta-

stasis having prognostic importance after relapse. Therefore, nodal status may indicate both tumor chronology and phenotype.

According to the theory of cancer screening, promulgated by Cole and Morrison,³⁰ the first round of any screening program (prevalent screen) should detect a greater fraction of indolent tumors, with a longer preclinical phase, while a greater percentage of aggressive tumors with a shorter preclinical phase should be detected in the screening rounds that follow (incident screens). In the Greater Manchester Breast Cancer Screening Unit, the prevalent screen detected a larger percentage of node-negative tumors, even though size of the average was greater than that of tumors detected at the incident screens.³¹ A similar trend was observed in the Edinburgh Breast Cancer Screening Trial.³² Taken together,

the theory of cancer screening and the results from the screening centers underscore the importance of nodal metastasis as a marker of tumor phenotype and support the findings of our study.

Since the time of Halsted, clinicians have generally regarded nodal metastasis as a time-dependent variable. This view is too simplistic, and the relevance of nodal metastasis to tumor phenotype merits additional investigation. Nodal metastasis may indicate a highly malignant tumor or serve as a marker of host response. Indeed, one might speculate that a weakened host response results in early metastasis to the axillary lymph nodes and a poorer prognosis. Further studies may clarify these issues and provide important insights into cancer growth and control.

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CORRESPONDENCE

Impact of American Society of Clinical Oncology Guidelines for Clinical Use of Colony-Stimulating Factors

To the Editor: Guidelines for the use of colony-stimulating factors (CSFs) were established by the American Society of Clinical Oncology (ASCO) to assist physicians with decision making.¹ However, there was limited evidence that they had any impact on clinical practice.

To assess the impact of the ASCO guidelines on CSF prescription in a Paris university hospital involved in cancer care, a "before-after" study was performed in 1996 (the period before implementation of the guidelines) and in 1997 (the period after, when guidelines were implemented for 6 months). In accordance with the previously published guidelines for medical practice,^{2,3} they were implemented throughout the hospital with a specific form summarizing the guidelines used at the time of the prescription. All inpatients who received CSF in the oncology, radiotherapy, and lung departments were enrolled onto the study. The main outcome measure was physician compliance, which was considered to be the number of CSF prescriptions that conformed to the guidelines. ASCO guidelines supported CSF use for primary prophylaxis with chemotherapeutic regimens with at least a 40% risk of febrile neutropenia, secondary prophylaxis when dose reduction was undesirable, and therapy administration on a case-by-case basis when febrile neutropenia with complicating factors occurred. Use of CSF for peripheral-blood progenitor cell (PBPC) transplantation and PBPC mobilization was unquestionable.⁴

Physicians' compliance with the guidelines increased significantly, from 39% to 62%, between the two periods ($P = .002$) (Table 1). The increase in the number of patients treated with PBPC transplantation, considered to be unquestionable,⁴ the significant increase in physicians' compliance in secondary prophylaxis ($P = .007$), and the decrease in the number of CSF prescriptions in therapy explained the improvement in physician compliance with the guidelines after their implementation.

However, as previously reported,⁵ primary prophylaxis represented the most common reason for CSF administration, even after implementation of the guidelines. Furthermore, we did not observe a significant change in the prescription of CSF in primary prophylaxis between the two periods. Actually, before and after implementation, 88% and 94% of physicians, respectively, did not comply with the guidelines because the chemotherapy regimens did not induce 40% febrile neutropenia, as recommended by the ASCO guidelines.

These results were confirmed in time as, in 1998, according to the same methodology, 94% of primary prophylaxis did not comply with the guidelines in our hospital. Furthermore, these results were in accordance with the preliminary results of a prospective study performed in 15 Paris university hospitals involved in cancer care in 1997. Implementation of guidelines might explain the 20% decrease in CSF

use between the two periods. However, as in any uncontrolled study, others factors may be involved in the change in medical practice. Even though no significant change was noted in hospital activity between the two periods, we cannot assert that the patients' conditions before guideline implementation were similar to those observed afterward. Moreover, treatment procedures did not change between the two periods. In addition, CSF caused no serious adverse effects, and the cost of CSF decreased.

Although physician compliance with the guidelines increased after their implementation in secondary prophylaxis and therapy, ASCO guidelines did not provide explicit guidance for the use of CSF in primary prophylaxis. Actually, the 40% incidence threshold in particular coincided with the results of cost analyses, showing that at the 40% incidence level, the estimated additional cost of CSF was equal to the estimated cost saving from avoiding hospitalization because of future neutropenia.⁶ In addition, although ASCO occasionally took into account risk factors for chemotherapy-induced infectious complications, criteria to precisely identify risk factors were still missing. To precisely identify risk factors, Blay et al⁷ proposed a predictive method to select patients who will experience febrile neutropenia.

Although other factors may be involved, implementation of guidelines seems to have an impact on medical practice, although a causal relationship could not be demonstrated. Our study shows that primary prophylaxis was the major clinical situation in which physicians could benefit from guidance about whether or not to use a CSF. A better definition of patients who should receive CSF in primary prophylaxis would enhance the impact of the ASCO guidelines on medical practice.

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Table 1. Physician Compliance

	Primary Prophylaxis		Secondary Prophylaxis		Therapy		PBPC Transplantation		PBPC Mobilization	
	%	No.	%	No.	%	No.	%	No.	%	No.
Before	39	41	32	33	10	11	10	11	9	9
Compliance	12		48		0		100		100	
After	40	33	17	14	0	0	28	23	15	12
Compliance	6		100				100		100	

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In Reply: The study by Debrix et al confirms the findings of two ASCO surveys of clinical oncologists that assessed the use of CSFs.^{1,2} In particular, use of CSFs in the setting of primary prophylaxis continues to be an area associated with overuse of these agents, while use of CSFs in the setting of secondary prophylaxis has decreased. Prior studies indicate that dissemination of guidelines in the form of written handouts to physicians, as done in the Debrix et al study, is unlikely to lead to meaningful changes in physician practice patterns, unless they are accompanied by discrete and targeted interventions.^{3,4} Local involvement in guideline development is especially important for improving adherence to recommended practices.⁵

Busy physicians, we suspect, rarely take the time to read forms such as those that summarize ASCO guidelines. Changes in CSF use, as described in this study, are more likely to reflect general temporal changes in physician practices rather than effects of publication and passive dissemination of written ASCO guidelines in the hospital setting. Other, more specific influences on CSF use might include increased experience with these agents, insurance denials, and widely publicized evidence.² Nonetheless, targeted educational efforts that address patterns of CSF use in the setting of primary prophylaxis continue to be needed. These efforts should be carried out in the context of a randomized clinical trial of guidelines versus no guidelines.

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Clinical Course of Stage IV Epithelial Ovarian Cancer

To the Editor: We were curious that Bonnefoi et al¹ should report a similar survival for patients with cytologically positive pleural effusions as compared to patients with visceral metastases, two groups of patients

who typically have very different prognoses. Their study prompted a retrospective review of patients presenting to the Massachusetts General Hospital with International Federation of Gynecology and Obstetrics stage IV ovarian cancer between 1980 and 1997. Patients were identified through the tumor registry and their charts were reviewed. After review, four patients were reclassified, and documentation of positive cytology could not be found for seven patients with large effusions that were clinically classified as stage IV. One hundred eight patients were identified, 52 with pleural disease and 56 with visceral metastases. Sixteen patients had liver metastases and 14 had lymphatic metastases with Sister Mary Joseph nodules or pathologically positive extra-abdominal lymph nodes. Other sites of metastases were the lung (seven patients), bone (four patients), spleen (three patients), CNS (three patients), and vulva-vagina (one patient), one patient had direct invasion of the abdominal wall, and one had a metastasis to the breast. Six patients had poorly defined metastases that apparently met the criteria for stage IV disease. Nineteen patients had multiple sites of metastases and 11 of those also had pleural effusions. Nine patients who presented with cytologically positive pleural effusions are still alive, and two of them are disease-free more than 5 years after diagnosis. In log-rank analysis, patients who had only cytologically positive pleural effusions had a statistically significantly better overall survival than patients with liver metastases ($P = .0001$), as illustrated in the Kaplan-Meier plot (Fig 1). There seemed to be a similar survival benefit for patients with lymphatic metastases. However, this did not reach statistical significance ($P = .0528$).

Despite proven improvements in surgery and chemotherapy, there has not been a dramatic effect on overall survival.² However, improvements in treatment have led to a considerable increase in the median duration of survival.³ Bonnefoi et al¹ report a similar prognosis for patients with pleural effusions and visceral metastases, and failing to find a prognostically significant influence for size of postoperative residual disease, therefore question the role of cytoreductive surgery for all patients with stage IV disease. In view of the apparently better survival in patients with malignant pleural effusions and the large number of patients with small, untapped, poorly sampled or clinically irrelevant effusions that are typically classified as stage III, this would seem to be a potentially deleterious stage-based "treatment migration." Interpretation of subset data is prone to error. Although our sample of patients is more recent and all received platinum-based treatment, both data sets are small. Patients with liver metastases clearly have a terrible prognosis, and the role of surgery should be questioned. However, denying standard treatment to patients with cytologically positive pleural effusions, and possibly nodal metastases, may adversely affect their outcome.

Other disease-related prognostic factors in advanced ovarian cancer may be better predictors of a poorer outcome than cytologically positive pleural effusions, such as initial volume of disease⁴ and the presence of ascites.⁵ Although the molecular phenotype may eventually be the most powerful predictor of outcome,⁶ the present technology may still be insufficient to predict prognosis.⁷

Patients who have stage IV epithelial ovarian cancer by virtue of cytologically positive pleural effusions or nodal metastases should not be denied the potential benefit of surgical cytoreduction.

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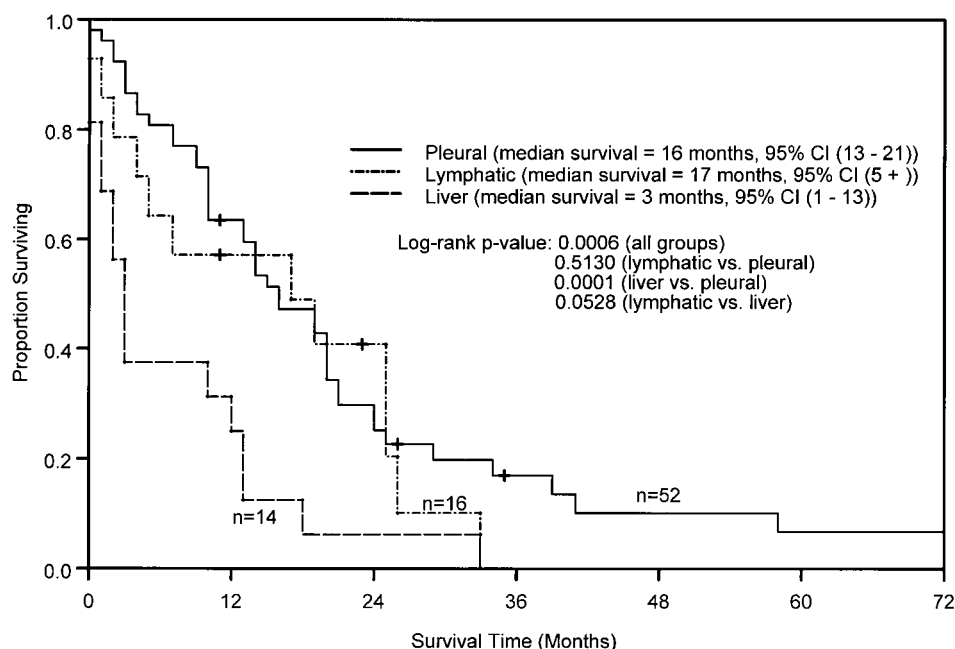


Fig 1. Stage IV ovarian cancer, 1980-1997.

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Current Status of Oral Anticancer Drugs in Japan

To the Editor: Recently, the *Journal of Clinical Oncology* published several articles outlining the promising future of oral anticancer drugs.¹⁻⁴ Although oral anticancer drugs are now receiving more attention than ever in the United States, probably because of health insurance constraints, the situation in Japan is different. Here, many oral anticancer drugs have been marketed for a number of years.⁵ Table 1 shows that 18 of 49 oral anticancer drugs are approved in both Japan

and the United States as of July 1999. Nineteen are approved in Japan but not in the United States, and 12 are approved in the United States but not in Japan. The United States was first to approve 16 of 18 mutually available drugs, approving them a median 54.9 months ahead of Japanese approval, whereas two drugs (tretinoin and toremifene) were first approved by the Japanese.

There are several characteristics of the approval status of Japanese oral anticancer drugs. The first thing to note is that drugs are sometimes licensed for tumors in many organs, partly because in Japan anticancer drugs are approved if they achieve objective tumor shrinkage, including a partial response, and because data from randomized, comparative phase III trials are not, in principle, essential for anticancer drug approval. The second point is that there is no discrepancy between the indication on the label and the indication covered by the insurer. This is because the Japanese health finance system is based upon fee-for-service reimbursement under a uniform national price schedule⁶ (the current National Health Insurance reimbursement tariff for oral anticancer drugs is shown in Table 1 and subscribers and their dependents have to pay a fee that is 20% to 30% of the drug's price (copayment) when obtaining prescriptions from hospitals or pharmacies). In contrast, in the United States, there are differences between the Food and Drug Administration (FDA)-approved indications and those covered by the insurer; for example, the Medicare coverage for anticancer chemotherapy is based not only on the FDA-approved indications (ie, the indications on the label) but also on those included in the *USP Drug Information*, *AHFS Drug Information*, or quality academic medical journals. The final point to note is that many fluoropyrimidine derivatives are approved for use. The second and third best-selling anticancer drugs in Japan, including those for infusion, are the oral fluoropyrimidine derivatives tegafur-uracil and doxifluridine. This unique situation may be largely due to the fact that fluorouracil-sensitive gastrointestinal tumors prevail in Japan, and stomach cancer had been the leading cause of cancer-related death for many years before 1993. Also, there is a long history of prescribing oral fluoropyrimidine derivatives in an adjuvant

The opinions expressed in this letter are solely those of the author and does not necessarily reflect the views of any government agency.

Table 1. Oral Anticancer Drugs Marketed in Japan

Date of First Approval		Drug Name	Current Japanese Indications for Oral Form Related to Oncology	Current Japanese Drug Price and Approved Usual Daily Dosage (as of July 1999)
Japan	United States			
12/26/56	09/11/53	Mercaptopurine	Acute leukemia, CML	10% 1 g (100 mg), \$0.90
05/30/57	06/04/43	Ethinylestradiol	Prostate, breast cancer (postmenopausal and androgen refractory)	1 tab (0.5 mg), \$0.43 (0.15-3 mg/d)
05/30/57	10/11/40	Methyltestosterone	Breast cancer (inoperable)	1 tab (25 mg), \$0.53 (20-50 mg/d)
10/07/57	06/25/54	Busulfan	CML	1% 1 g, (10 mg), \$1.31
01/26/60	—	Fosfestrol	Prostate cancer	1 tab (100 mg), \$0.83 (300-1,200 mg/d)
03/14/62	11/16/54	Cyclophosphamide	MM, malignant lymphoma, acute leukemia, breast, lung, neuroblastoma, retinoblastoma, ovarian cancer, etc	1 tab (50 mg), \$0.41
01/22/63	12/07/53	Methotrexate	Acute leukemia, CLL, CML, trophoblastic disease	1 tab (2.5 mg), \$0.44
10/15/64*	—†	Mitomycin	CLL, CML, gastric, liver, colorectal, lung, uterine cervix & corpus, breast, head & neck cancer	1 tab (1 mg), \$0.56 (2-6 mg/d)
(IV, 09/25/63)	—	Aceglatone	Bladder cancer (adjuvant)	1 tab (187.5 mg), \$0.23 (1,500 mg/d)
06/25/71	—	tegafur	Gastric, colorectal, breast cancer	1 cap (200 mg), \$1.95 (800 mg-1,200 mg/d)
04/20/73	—	Procarbazine	Malignant lymphoma	1 cap (50 mg), \$2.10 (50-100 mg/d)
04/20/73	07/22/69	Carboquone	Lung cancer, malignant lymphoma, CML	1 tab (0.5 mg), \$4.24 (1-1.5 mg/d)
09/06/74	—	Krestin (PSK)	Gastric (adjuvant),‡ colorectal (adjuvant),‡ small-cell lung‡ cancer	1 g, \$6.01 (3 g/d)
08/20/76	—	Mitobronitol	CML	1 cap (50 mg), \$0.78 (50-250 mg/d)
06/14/77	—	Mepitiostane	Breast cancer	1 cap (5 mg), \$1.04 (20 mg/d)
08/01/78	—	Improsulfan tosilate	CML	1 tab (10 mg), \$0.42 (20-90 mg/d)
08/01/78	—	Melphalan	Multiple myeloma	1 tab (2 mg), \$2.21
03/13/79	01/17/64	Flourouracil	Gastrointestinal (gastric, colorectal, etc), breast, uterine cervix cancer	1 tab (100 mg), \$4.50 (200-300 mg/d)
10/25/80	—†	Tamoxifen	Breast cancer	1 tab (20 mg), \$4.47
(IV, 07/24/67)	12/30/77	Carmofur	Gastric, colorectal, breast cancer	1 tab (100 mg), \$2.47 (12-18 mg/kg/d)
05/01/81	—	Estramustine	Prostate cancer	1 cap (156.7 mg), \$5.01 (4 caps/d)
06/04/81	12/24/81	Chlormadinone	Prostate cancer	1 tab (25 mg), \$1.28 (50 mg/d)
05/27/83	—	Tegafur-uracil	Head & neck, gastric, colorectal, liver, gall bladder, biliary duct, pancreas, lung, breast, prostate, uterine cervix cancer	1 cap (tegafur 100 mg), \$3.41 (3-6 caps/d)
05/27/83	—	Mitotane	Adrenal cancer	1 cap (500 mg) \$10.44 (1,500-3,000 mg/d)
09/21/83	07/08/70	Etoposide	Small-cell lung cancer, malignant lymphoma	1 cap (50 mg), \$18.90
03/31/87	12/30/86	Medroxyprogesterone	Breast, uterine corpus cancer	1 tab (200 mg), \$3.58 (400-1,200 mg/d)
03/31/87	(07/30/59)§	Ubenimex	Adult ANLL (maintenance)‡	1 cap (30 mg), \$17.08 (30 mg/d)
03/31/87	—	doxifluridine (5'-DFUR)	Gastric, colorectal, breast, uterine cervix, bladder cancer	1 cap (200 mg), \$3.60 (800-1,200 mg/d)
06/30/87	—	Hydroxycarbamide	CML	1 cap (500 mg), \$3.57 (500-2,000 mg/d)
07/03/92	12/07/67	Cytarabine ocfosfate	Adult ANLL, MDS	1 cap (100 mg), \$8.60 (100-200 mg/d for 2-3 wk)
10/02/92	—	Sobuzoxane	Malignant lymphoma, ATL	800 mg, \$44.67 (1,600 mg/d × 5 days, every 2-3 wk)
04/01/94	—	Flutamide	Prostate cancer	1 tab (125 mg), \$4.26 (375 mg/d)
10/05/94	06/27/89	Tretinoin	APML	1 cap (10 mg), \$7.85 (60-80 mg/d)
01/20/95	11/22/95	Toremifene	Breast cancer (postmenopausal)	1 tab (40 mg), \$5.33 (40 mg/d)
03/31/95	05/29/97	Fadrozole	Breast cancer (postmenopausal)	1 tab (1 mg), \$2.99 (2 mg/d)
06/30/95	—	Tegafur/CDHP/oxonic acid (S-1)	Gastric cancer	1 cap (tegafur 20 mg), \$6.66 (BSA ≥ 1.5 m ² ; 60 mg/d for 4 wk then 2 wk rest)
01/25/99	—	Bicalutamide	Prostate cancer	1 tab (80 mg), \$12.78 (80 mg/d)

NOTE. Among all FDA-approved oral anticancer drugs, alretamine, anastrozole, capecitabine (derivative of doxifluridine), chlorambucil, diethylstilbestrol (fosfestrol is diethylstilbestrol phosphate), letrozole, levamisole hydrochloride, lomustine, megestrol acetate, nilutamide, temozolomide, and thioguanine are not approved in Japan as of July 1999. The Japanese approval date is the first approval date for the oral form. The drugs with underlining are fluoropyrimidine derivatives. The Japanese drug price is that for each capsule or tablet and the price is the one for the branded drug in the National Health Insurance reimbursement tariff. Generics exist for fluoropyrimidine derivatives, krestin, tamoxifen, and estramustine. The prices are rounded up, based on \$1.00 = 120.

Abbreviations: ATL, adult T-cell leukemia/lymphoma; ANLL, acute nonlymphocytic leukemia; APML, acute promyelocytic leukemia; BSA, body surface area; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; PSK, protein polysaccharide obtained from *Coriolus versicolor* Quel; cap, capsule; tab, tablet.

*Despite its approval, the oral form of mitomycin has not been marketed since March 31, 1999, in Japan.

†There is no oral form of this drug in the United States.

‡The drug must be used with anticancer chemotherapy.

§The FDA indication for medroxyprogesterone does not include oncology.

setting, mainly by surgeons, without firm clinical evidence of any survival benefit. In addition, these agents are usually prescribed in order to relieve vague anxieties in both physicians and patients about cancer recurrence.

Because of these problems related to oral anticancer drugs in Japan, I was very interested to see the recent increase in the number of publications describing oral anticancer drugs in academically high-ranking medical journals, including this one, and I would like to point out several problems regarding the *Journal of Clinical Oncology's* recent articles.

First, I would like to make it clear to readers that *Gan To Kagaku Ryoho* is the same journal as the *Japanese Journal of Cancer and Chemotherapy* (Jpn J Cancer Chemother). These titles have been referred to separately in reference lists.³ This journal carries articles written in Japanese, with only concise abstracts in English.

Since the reviews^{2,3} cited many Japanese articles, I am afraid that selection bias might have occurred because the cited Japanese journals form only a small proportion of the many cancer-related journals published in Japan. Accordingly, it might be desirable for authors to include information on the sources and methods of selection used to choose the data reviewed. Considering the recent trend for preference of systematic reviews instead of narrative reviews, and the fact that the *Journal* publishes both systematic⁷ and narrative review articles, I would like to know the *Journal's* editorial policy for review articles.

Another point which was not discussed in detail in one review² was the difference in response criteria for gastric cancer between Japan and the United States/Europe. In Japan, there is a long history of tumor response evaluation in which the primary tumor site is regarded as measurable. In 1985, the Japanese Research Society of Gastric Cancer formally adopted evaluation criteria for the primary tumor site based on barium roentgenography and/or endoscopy findings. Almost all gastrointestinal oncologists have used these criteria for many years, even before 1985, when submitting their research articles to Japanese journals, whereas they have usually excluded data on the primary tumor site (or have been requested to do so by the journal reviewers) when submitting manuscripts to journals published in Western countries. Furthermore, Japanese clinical researchers have usually excluded nonassessable cases from the denominator when calculating the response rate. Therefore, readers should be aware of the need for caution when interpreting the data presented in the review² and any other articles from Japan.

The West Japan Study Group for Lung Cancer Surgery has recently reported the results of a randomized clinical trial comparing two courses of cisplatin + vindesine + mitomycin and 1 year of tegafur-uracil with no adjuvant treatment in 229 patients with completely resected stage I or II non-small-cell lung cancer.⁸ The 5-year survival rate for the surgery-only arm was reported to be 71.1% (stage I, 75.1%; stage II, 50.0%), not significantly different from that (76.8%) for the adjuvant chemotherapy arm.^{8,9} This prognosis for the surgery-only arm was far better than that for the same population in the group's previous study (stage I, 60.9%; stage II, 23.1%) reported in the *Journal*.^{4,10} I would like to know whether the authors found any difference in the prognostic factors of each surgery-only arm. Furthermore, their subgroup analysis, published in a Japanese journal in the same year as the *Journal's* publication, showed that a survival benefit was observed only in stage IIIA patients,¹⁰ although in their *Journal* article, the authors commented that tegafur-uracil therapy was useful for treatment of stage I and II, as well as IIIA, disease.⁴ In contrast, the subset analysis in their most

recent article showed that adjuvant chemotherapy improved the survival of pT1N0 patients.⁸ These facts cast doubt on their evidence supporting the benefit of adjuvant chemotherapy with oral fluoropyrimidine derivatives for non-small-cell lung cancer.

Finally, financial interest and its disclosure in scientific publications are now receiving more attention than ever,¹¹ and I understand that the *Journal* requires full disclosure. Although it is well known among Japanese clinical researchers that the West Japan Study Group for Lung Cancer Surgery is largely supported by a drug company, I wonder why the authors did not disclose this fact in their article.⁴ In addition, I also wonder whether the authors of a review failed to disclose a conflict of interest, since they used unpublished data on file from the company,² the credibility of which we, as readers, cannot evaluate. I understand that financial interest in itself does not imply any bias in the results of a paper and should not disqualify it from publication.¹¹ However, the aforementioned reluctance to disclose industry involvement by Japanese clinicians may be one of the reasons why clinical trials of new drug applications ("Chicken" in Japanese) and industry-sponsored clinical trials in the postmarketing setting have acquired such a bad academic and public reputation in Japan.

In conclusion, I hope that readers will take all these problems and facts into account when appraising articles describing Japanese oral anticancer drug clinical trials. Furthermore, it should be noted that the aforementioned problems related to Japanese clinical trials, especially for new drug applications, are rapidly being resolved due to the legal obligation of Good Clinical Practice and Good Post-Marketing Surveillance Practice, the establishment of the Pharmaceuticals and Medical Devices Evaluation Center and the Organization for Pharmaceutical Safety and Research as part of the ongoing reform of the Japanese new drug application review system,⁵ and because the notion of "evidence-based medicine" is becoming more widespread.

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ERRATUM

The August 1999 article by Jatoi et al, entitled “Significance of Axillary Lymph Node Metastasis in Primary Breast Cancer” (*J Clin Oncol* 17:2334-2340, 1999), contained a paragraph in which three sentences were illegible due to a technical problem with the printing process.

The third, fourth, and fifth sentences of the first paragraph of the Discussion section read:

“However, his analysis did not account for the confounding effects of other prognostic factors on survival, and the possibility that nodal status was a surrogate for these other variables could not be excluded. Subsequently, Mitra and MacRae¹⁶ undertook a meta-analysis of published correlations between various prognostic factors in breast cancer and concluded that axillary lymph node status is simply a reflection of the chronologic age of the tumor. Yet, a meta-analysis has pitfalls, many of which were acknowledged by the authors.”