apy usually heralds a meaningful tumour response, even in the absence of complete normalisation of the marker level. Still unanswered is the question of how long suramin has to be continued, once disease stabilisation or response has been obtained, and what would be the optimal target plasma concentration for maintenance treatment in these circumstances. Efforts should be undertaken at defining the subgroup of prostate cancer patients who are most likely to respond to suramin, based either on pretreatment characteristics or biochemical changes which occur early after the initiation of therapy.

A number of phase II trials exploring suramin in other tumour types are ongoing. These include renal cell carcinoma, adrenal cortical carcinoma, non-small cell lung cancer, melanoma, ovarian carcinoma and malignant glioma. Salmon reported a 15% response rate in ovarian carcinoma patients. The activity of suramin in malignant melanoma, however, appears to be modest. Several *in vitro* studies have indicated synergism between suramin and other biological response modifiers or cytotoxic drugs [14, 15]. Future developments will include the combination of suramin with these agents.


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# Axillary Lymph Node Metastasis in Breast Cancer: Prognostic Indicator or Lead-time Bias?

## INTRODUCTION

AXILLARY LYMPH NODE metastasis is the strongest predictor of disease-free and overall survival in breast cancer and is the single most important prognostic factor used in the clinical management of the disease [1]. The prognostic influence of axillary lymph node metastasis is mediated through two mechanisms: the relative risk of relapse and death (hazard rate) [1–3] and the relative length of time to relapse and death (delay) [4–6]. These two prognostic end-points have a strictly arithmetic relationship with the number of involved lymph nodes; the hazard rate increases and the disease-free period decreases with progressively increasing involvement of the axilla [1–6].

An important issue relating to the natural history of breast cancer has so far not been settled. This is whether the relatively poor prognosis of patients with breast cancer that has spread to the axillary lymph nodes is due to an increased biological aggressiveness and/or metastatic potential of the tumour or a greater chronological age at diagnosis, or a combination of these possibilities. To address this issue, a meta-analysis of all published reports on correlations between various prognostic factors in breast cancer has recently been performed [7]. The conclusion from this meta-analysis, together with other evidence [4–6, 8–15], strongly suggest that axillary lymph node metastasis (and tumour size) has little to do with the biological behaviour of breast cancer but is a reflection of the relative chronological distance between inception and diagnosis of breast cancer. Viewed from this standpoint, the prognostic influence of axillary lymph node metastasis, both in terms of hazard rate and delay, can be explained entirely on the basis of a lead-time effect.

Corespondence to I. Mittra.
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## BIOLOGY OR CHRONOLOGY?

*Post-relapse survival*

While it is agreed that the presence (and extent) of axillary node metastasis is the best predictor of disease-free and overall survival in breast cancer, one aspect of the prognostic influence

of axillary node involvement has been largely overlooked. This is the observation made by many investigators that once breast cancer recurs after ostensibly curative local therapy, axillary lymph node status (or tumour size or stage) ceases to have any prognostic significance and that post-relapse survival is the same for node-positive and node-negative patients [4–6, 8–15]. This appears to be particularly true for patients who develop distant metastasis rather than for those who recur exclusively at loco-regional sites [4, 6]. On the other hand, at least five biological prognostic factors, namely, oestrogen receptor (ER) status [4, 8–11, 13–16], progesterone receptor (PgR) status [16, 17], tumour labelling index (TLI) [18], S-phase fraction (SpF) [19] and the degree of differentiation of the tumour [11] have been shown to continue to be predictive even after relapse with receptor-positive patients or those with low TLI or SpF or a favourable tumour grade surviving longer after relapse than their respective counterparts.

*Overview of correlations between prognostic factors*

Recently the results of a meta-analysis of all published reports that have investigated the interrelationships between various prognostic factors in breast cancer have been reported [7]. In this analysis, a distinction was made between anatomical prognostic factors—namely, axillary lymph node status and tumour size—and eight different biological prognostic factors. The latter included tumour grade, ER and PgR status, TLI, DNA ploidy, SpF, epidermal growth factor receptor expression and c-*erb*B-2 gene amplification (or overexpression). Given its inherent limitations [7], the meta-analysis revealed that a broad correlation existed between the eight biological prognostic factors themselves, suggesting that these factors reflect, directly or indirectly, some common properties of breast cancer, such as growth rate and/or metastatic potential. On the other hand, little inter-relationship was found between axillary lymph node status (and tumour size) on the one hand and the biological prognostic factors on the other. This suggested that node-positive (or large size) tumours are biologically no different from those that are node negative (or small in size), and that they both have the same chance of being ER positive or negative, being diploid or aneuploid, having high or low SpF, having single or multiple copies of the oncogene c-*erb*B-2 and so on. Tumours that are either biologically aggressive or indolent can, therefore, be expected to be distributed equally between the two groups.

## LEAD-TIME BIAS

On the basis of the above information the natural history of breast cancer of a group of node-negative and a group of node-positive patients, all of whom relapsed and eventually died, is depicted in Fig. 1 (b and c, respectively). Since clinical symptoms and signs of relapse (such as backache or X-ray evidence of lung metastasis) can be expected to appear at the same stage of tumour dissemination in both node-positive and node-negative patients, the time-point of relapse has been shown to be the same for both groups. If we now apply the knowledge that the biological properties of tumours in the two groups of patients are not dissimilar, it is not difficult to understand why survival after relapse of node-negative and node-positive patients have been found to be identical [4–6, 8–15]. Then when we trace the natural history of the disease backwards from the point of relapse to the point of tumour inception (again taking account of the information that the biological properties and, therefore, the growth rates and metastatic potential of tumours in the two groups are similar), we arrive at respective starting points of their natural histories that we find are identical. A re-examination of Fig. 1 now reveals that the longer delay between mastectomy and relapse or death for node-negative patients relative to those that are node positive is not real but an illusion created by a lead-time bias resulting from earlier detection. Since the relationship between the size of a tumour and the risk of axillary lymph node metastasis is strictly linear [3], this bias can be visualised as shifting progressively in a step-wise manner, between scenarios (b) and (c) (Fig. 1), with the involvement of each successive axillary lymph node. An examination of Fig. 1 also reveals that the probability of a tumour being detected and treated prior to the occurence of first metastasis, leading to a cure (Fig. 1a), is likely to be higher for node-negative than for node-positive patients. The prognostic influence of axillary lymph node metastasis, in terms of both risk of and time to recurrence and death can, therefore, be explained entirely on the basis of a lead-time effect.

The model presented above makes the assumptions that some breast cancers are potentially curable if treated prior to the appearance of systemic metastasis (Fig. 1a). This assumption is in variance with the concept that breast cancer is a systemic disease from inception and, therefore, in principle, incurable [20]. However, the current results of screening for breast cancer, especially those from randomised trials [21], suggest that this nihilistic view may not necessarily be corect. Moreover, although long-term follow-up studies of breast cancer patients have recorded a persistent excess attrition from breast cancer than from other causes, these studies have not ruled out the possibility that there does exist a group of patients whose breast cancer is actually cured [22].

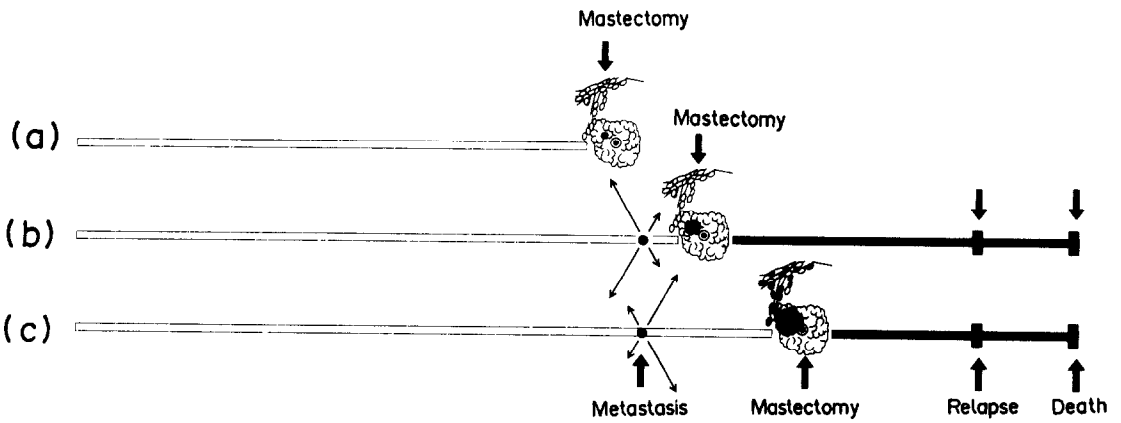


Fig. 1.

## CONCLUSION

Breast cancer has four milestones in its natural history. These are (1) the point of inception of the tumour, (2) the point of dissemination of first metastasis, (3) the point of relapse, and (4) the point of death. The model presented here underscores fallacy of the tradition of using the point of tumour *detection* as the primary reference point in describing the natural history of breast cancer. The point of detection of breast cancer is an accidential event which is chronologically variable. The presence and extent of axillary lymph node metastasis is a reflection of this chronological variability, and tells us little about the biological behaviour of breast cancer. What the model proposed here does is to use the point of *relapse* as the key reference point. The merit in doing this lies in the fact that, although (apparently) chronologically variable, the point of relapse is biologically fixed, in the sense that clinical signs and symptoms of relapse can be expected to arise at a fixed stage (or extent) of tumour dissemination within the body, irrespective of the biological nature (aggressive or indolent) of the tumour. An assessment of post-relapse survival, therefore, provides the key to a clearer understanding of the true biological nature of breast cancer. By using the point of relapse as the biologically fixed reference point, and by making a clear distinction between time-dependent and biological prognostic factors, axillary lymph node metastasis can be seen merely as a confounding factor, of no biological consequence, in our understanding of the natural history of breast cancer.

Indraneel Mittra
Departments of Surgery and Laboratory Medicine
Tata Memorial Hospital
Bombay - 400012
India

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