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European Journal of Cancer 40 (2004) 619–620

European Journal of Cancer

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Letter

Comment on "The process of metastasisation for breast cancer" by J. Engel, R. Eckel, J. Kerr *et al.*☆

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Received 30 September 2003; accepted 30 September 2003

In a recently published paper [1], analysing an impressive amount of data from breast cancer patients, Engel and colleagues propose a model for the process of metastasisation. Beyond a minor note about an erroneous statement attributed to us (in the quoted paper [2] we did not affirm that the survival following clinical evidence of metastasis depends on the primary tumour size), we wish to outline some critical remarks about the proposed model, bearing in mind that a given model cannot be proven to be true, while it can be questioned (or even rejected) if it is unable to explain (or incompatible with) findings from clinical or laboratory investigations.

Engel and co-workers themselves have already noted weak points when the model is requested to fit to a few findings. M1 patient survival is similar to that of patients with 48-month tumour-free intervals, in spite of their assumed older metastases; morphological and genetic correlation between primary tumour and metastases remains poorly explained; outcome patterns of adjuvant therapies are not given 'any explanation'. However, other much more important points should be considered, that question just the model framework.

The main assumption underlying the model is explicitly stated: as the metastasis growth process following its diagnosis is homogeneous (resulting in similar residual survival for all pT categories) "it seems logical that the disease process before diagnosis of metastasisation is also homogeneous". Implicit in this statement is the assumption that all tumour deposits display continuous growth from seeding. However, continuous growth was proven to be incompatible with clinical data for local recurrences [3] and unable to explain the bimodal pattern of the risk of recurrence [4,5] and death [6,7] for patients with resectable breast cancer.

Even a careful analysis of Engel's own data uncovers the inadequacy of this assumption. Indeed, according to their estimate, a given metastasis would have initiated its growth 5.8 years before it was clinically evident. Therefore, assuming continuous exponential growth, their estimate results in a diameter doubling time of 7 months (even significantly more assuming other more realistic retarded growth models such as the Gompertzian growth model), an implausible value that is too high to be compatible with clinical data. As an example, a 2-cm metastatic lesion in the chest (75th percentile for the maximum diameter of local recurrences [3]) or in the lung (median value for most solid tumours [8]) would have been more than 1 cm 6 months before and more than 0.5 cm 1 year before. It is difficult to accept that such recurrences were systematically missed during the follow-up, even for patients not included in clinical trials, for whom less frequent follow-up controls are planned. Moreover, according to data from Table 1, as pT4 patients showed a median time from diagnosis to evidence of metastasis of 3.7 months, it should be concluded that half of them were considered metastasis-free at the diagnosis of the primary tumour in spite of the presence of lesions with diameters only less than 30% smaller than those actually observed at the diagnosis of metastasis.

A further important point should be considered. The proposed model assumes that the primary tumour and metastases have independent development and that surgical removal of the former does not interfere with growth of the latter. However, this assumption does not agree with several well established experimental studies using laboratory animal models [9–11] on the enhancing effect of surgery on metastasis growth. Moreover, the surgery-driven acceleration of metastasis development can provide a satisfactory explanation to some otherwise unanswered clinical findings, such as the different

☆ *Eur. J. Cancer* 39 (2003) 1794–1806. doi of article referred to: doi:10.1016/S0959-8049(03)00422-2.

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doi:10.1016/j.ejca.2003.09.038

survival patterns between breast cancer patients undergoing surgery and patients never given treatment [12], the bimodal pattern of the recurrence risk [4,5], and the paradoxical early mortality excess in the invited group for younger women recruited for mammographic screening studies [13].

In our opinion, a model assuming tumour dormancy and the effect of surgical primary tumour removal [2] could reasonably explain the data reported in Engel and colleagues paper, without contradicting others. According to this model [14], the unperturbed growth of the primary tumour results in a growing risk of a M1 status, while its surgical removal triggers the growth of still dormant micro-metastases, resulting in the pT-associated frequency of the following clinical metastases. Most of these micro-metastases display a near homogeneous growth rate, explaining the lack of association between survival patterns following distant recurrences and both pT and metastasis-free time [2].

It would be very interesting to evaluate, using the rough data from Engel's study, the ability of this model to explain findings, in particular the recurrence dynamics. Indeed, the timing of recurrence (either local-regional or distant) has a complex, non normal distribution (means and medians are quite different) and using mean values (the average patient) may be misleading. This model could turn out to be strengthened, weakened or even rejected. After all, it is a model too.

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