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Letter

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

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Demicheli and Retsky rightly emphasise that models cannot be proven to be true, but can be questioned or even rejected if they are incompatible with empirical findings [1]. A model can be better than another if it is simpler, can be empirically tested and is able to explain more facts. Models are the theoretical beginnings of innovations and help us to ask the right questions. Models are developed as antitheses of existing theses and to improve existing models. The basis of model development is observation. In medicine, observation can be biased if only clinical trial data are assessed and no epidemiological data are available. Exclusion of M1 patients, small patient numbers or stratification by stage instead of tumour diameter—the most important factor in describing tumour biology—thwarts model development in medicine.

In this piece we want to respond to Demicheli and Retsky's comments [1] and in doing so clarify some points. First of all we apologise that editing during the review process resulted in a false citation of Demicheli and colleagues [2]. We claimed wrongly that this paper affirmed that survival following clinical evidence of metastasis was dependent on tumour size.

Three aspects of our data are convincing because they are reproducible with any data-set. First, there is a linear correlation between tumour diameter, positive lymph node status and mortality. This seems astonishing since compared with fractal volume ($>r^3$) or fractal surface ($>r^2$), tumour diameter is less representative of the tumour size. A linear correlation is plausible, if metastasisation (MET) from one tumour cell is an infrequent event based on millions of migrating cells [3]. In addition, this MET-risk is only linear in a relatively small section around a primary tumour with approximately 10^9 cells (not in the range from one cell to a one kilogram tumour with 10^{12} cells). Moreover, a sigmoid growth process is necessary, described by a logistic function. The second reproducible point is that disease-free survival time becomes shorter with increasing tumour diameter. Third, there is evidence that after MET occurs, survival is independent of the primary tumour diameter. Other primary tumour prognostic factors such as grading, receptor status, positive lymph nodes or time to metastases show only slight survival variability (after MET). That is why we claimed that metastasis growth, after diagnosis of the first metastasis, was homogenous and independent of the primary tumour diameter.

The first comment from Demicheli and Retsky, that M1 patients' survival was better than that of patients with a 24-month tumour-free interval and similar to patients with a 48-month tumour-free interval, is not evidence against the homogeneity hypothesis. Intensive staging diagnostics may result in a "forward shift" of metastases, thus M1 patients appear to survive longer. Because breast cancer is not curable after the MET-stage, this "forward shift" merely leads to a prolongation of the progression time after MET detection, and is known as a lead-time effect.

Our conclusion that, if the disease process after MET were homogeneous, then it seems logical that the disease process before the diagnosis of MET would also be homogeneous, was interpreted by Demicheli and Retsky as an antithesis of their dormancy hypothesis. Homogeneous metastases growth, indicated by survival after MET that is independent of the primary tumour diameter, means that an infrequent MET from a 5 mm tumour would be identical in its growth process and mean time structure to a frequent MET from a 50 mm

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tumour. This homogeneity says nothing about the process of MET itself, migration, or sojourn in different compartments and so on. Dormancy could also play a role within the median growth time of approximately 6 years.

If tumour growth is homogeneous in this sense, then why are there different tumour-free intervals for each pT-category? This inconsistency suggests that the time of diagnosis of the primary tumour is not the appropriate reference point for the initiation of MET. Our data show that, over a 15-year period, a mean of 22.4% of MET occurred in pT1 patients. If the tumour was not removed at pT1 (mean diameter 14 mm) then the rate of MET could increase a further 25.3% in the time (approximately 1.5 years) that the tumour grows into a pT2 tumour (mean 28 mm). Thus, it takes approximately 1–2 years for a tumour to double in diameter or for the tumour volume to increase 8-fold. In other words, almost half of the MET diagnosed during a disease course of a pT2-tumour may have already started before the tumour was pT1-sized, and long (1.5 years or more) before the point of diagnosis of a pT2 tumour. Overall, the time from initiation of metastases to its diagnosis was estimated as approximately 6 years. Because of this early initiation of metastases it is incorrect to describe the MET-course by characteristics of the primary tumour. 6 years is equivalent to doubling the tumour volume 12 times and this leads to the hypothesis that the first metastasis, initiation could start from an undetectable tumour with 10^6 cells.

The third comment concerning an implausible metastases growth rate seems inappropriate because we did not make any statement about doubling of metastasis volume, only about doubling of (primary-) tumour volume. Initiation includes migration, sojourn in different compartments, angiogenesis, etc. It is not possible to derive from empirical data why skeleton metastases occur earlier than metastases in the central nervous system (CNS). However, our time estimation does not support the cascade theory. It is more probable therefore that metastases in lymph nodes, the skeleton, or the CNS arise from primary tumour cells which have different special attributes for the particular environment of the metastasis localisation [4], this means that tumour cells, which are able to grow in a lymph node, should be unable to produce metastases in other organs. Trials from Fischer [5] and Veronesi [6] support this hypothesis, because they did not find any survival benefit from removing positive lymph nodes. However, our data show that local recurrences may have the potential to metastasise (like a primary tumour).

Our MET-model is very simple. Tumour cells, which have a MET-potential, migrate very early during the growth process of a tumour, when the tumour has approximately 10^6 cells. Some of these migrating cells begin independent growth processes in lymph nodes and distant MET-localisations. The fourth comment from Demicheli and Retsky questioned this independent growth referring to "models about the enhancing effect of surgery on metastasis growth". How then can the concept of "cancer with an unknown primary" (CUP) be explained? Our model provides an explanation. If distant tumours (metastases) grow faster than the primary tumour (and independent of it), this may result in so-called CUPs. Our data show that when the tumour size increases, the frequency, and therefore the probability of MET, increases. Out of all metastases, 18% were discovered at the time of primary therapy. This percentage depends on the pT stage. However, with removal of the primary tumour the risk of additional MET is removed.

The concern that our model does not consider the benefits of adjuvant systemic therapy is misplaced. Patients with metastases cannot be cured. If initiation of metastases takes place years before the detection of the primary tumour then most so-called systemic adjuvant therapies are actually ineffective first-line palliative therapies. Moreover, if there is a MET-risk at the time of primary tumour removal then there is only a small time-frame for MET-prevention.

These simple, but consistent, findings should be integrated into other models, including the dormancy hypothesis. A hypothesis should apply to CUPs, M1 patients and MET patients with tumour-free intervals shorter than 7–8 years. These are more than 90% of MET-patients and for these 90%, a dormancy model does not help to explain the course of the disease.

There is also no evidence from our data for a "bimodal pattern of risk of distant recurrence" [7], especially in prognostically-favourable pT1 cases, where it may be possible. Most patients with pT3/4 tumours have died before such a pattern is visible. Our data show an excess mortality for patients with local recurrence (LR). Further, secondary metastases (induced by LR) can be expected 7–8 years at the earliest after diagnosis of the primary tumour. These secondary metastases (due to LR) can explain the differences in even 20 year survival curves after adjuvant radiotherapy, where there is better local control [8]. It is necessary to explain such observations and correlations with a model or to integrate them into an existing model to strengthen, weaken or even reject it. Generalisation to other solid tumours and consideration of the clinical consequences shows why models are important. Consistent, repeatable findings are a challenge for any model.

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