Is Tumor Dormancy Clinically Relevant?

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Abstract

Late progressions can be observed with all solid cancers. With the term dormancy a potential cause is offered for these observations. In this article we present a point of view from a cancer registry and analyze clinical data about metastasis (MET)-free survival, post-MET survival, and overall survival to quantify late progressions. If dormancy is a characteristic of the MET process then all types of MET, including local recurrences, regional MET in the lymph nodes, or distant MET in organs, must be considered. First, it can be deduced from clinical data that the initiation of secondary foci is a temporally sequential process, which can begin years, or days, before a R0-resection. Second, the growth time of these different MET can be estimated from the survival time and generally takes years. Third, remarkable growth differences of these secondary foci must be considered which already can be correlated, in part, with molecular subgroups. Within these subgroups, growth is quite homogeneous. These three factors of MET growth largely explain the variability of observed relapse-free survival times. In contrast, the term dormancy is vague. It is an appealing metaphor with strong analogies such as circulating tumor cells of hematological neoplasms or dormant tumor cells in transplanted organs. But late MET can be the result of a number of very different causes. Where a disseminated tumor cell

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lodges, in niches or in specific organs, how long a tumor cell circulates before settling and establishing a focus, or whether the tumor cell has differential growth or even cell quiescence phases, determined by a dynamic equilibrium of divisions and apoptosis, could all contribute to the differential occurrence of MET. MET detection may also be delayed by adjuvant treatment, and all causal variants can be functionally equivalent, delay MET diagnosis, and appear as a slow growing tumor. But time of initiation and the growth of tiny foci are inaccessible and impossible to measure in humans. Therefore, the term tumor dormancy conceals our ignorance of the multi-step MET process. Because it is such a cloudy and elusive term it cannot be clinically relevant. It is a hypothetical construct that fails to offer new research perspectives, additional prognostic factors or an opportunity for novel therapy.

Keywords
Tumor dormancy • Model • Breast cancer • Colorectal cancer • Metastasization • Long-term survial

Introduction

Tumor progression after an above-average, long, metastasis-free survival can be observed in all solid tumors. In many publications frequencies, characteristics, and survival of intact or fragmented tumor cells (TC) in blood, bone marrow, lymph nodes (LN) and organs are described. These facts are correlated with progressions and should show the relevance of dormant TC for late metastases (MET) (Meng et al. 2004; Naumov et al. 2002; Uhr and Pantel 2011; Weinberg 2008). The observation of a bimodal distribution of the MET-free survival time in breast cancer (BC) in one cohort study was already interpreted in 1990 as a result of a rest period of disseminated TC before growing up to a detectable MET (Demicheli et al. 2010). Since then, longer MET-free survival times for BC, e.g. beyond 5 years, are connected today with the term "TC dormancy" (Aguirre-Ghiso 2007).

In the following pages we describe, with the results of experimental and clinical studies, and with data from a cancer registry, the growth of secondary foci with MET-free, post-MET and overall survival. The Munich Cancer Registry (MCR) collects data about local, regional and distant relapses during the course of disease as important outcome criteria (Munich Cancer Registry). We present population-based data from patients who were registered from 1988 to 2009, did not have earlier or synchronous second malignancies and were followed-up during this period. It is important to note that the data about the courses of disease are not complete and therefore the percentage of primary MET of all cancer-related death is slightly overestimated. Additionally, MET is diagnosed during the course of disease if symptoms require clarification or a palliative chance exists. Therefore, any MET pattern is a selected perspective. Nevertheless, population-based data can add generally valuable aspects to the alternative view of heavily selected study cohorts.

Correlations of MET relapses with prognostic factors of the primary tumor (PT) reveal growth differences and an order of late progressions. Well known survival curves with adjuvant treatments describe further aspects of the MET process. Nonetheless, such a registry-based viewpoint does not contribute new results. Only additional facts can be considered and supplemental questions arise with our attempt to align known clinical outcomes with the hypothesis of dormant TC. But we have not been able to achieve this: therefore the current clinical relevance of the term tumor dormancy has to be questioned.

Basic Characteristics of the MET Process

Generally, MET is a secondary focus established by a disseminated TC of the PT. MET foci can arise locally, near the PT, regionally in the LN, or in distant organs. They are the result of a complex multistep process (Talmadge and Fidler 2010; Valastyan and Weinberg 2011). Three characteristics of the MET-process will be distinguished for the sake of reasoning (Hölzel et al. 2010); the temporally sequential initiation of MET, the

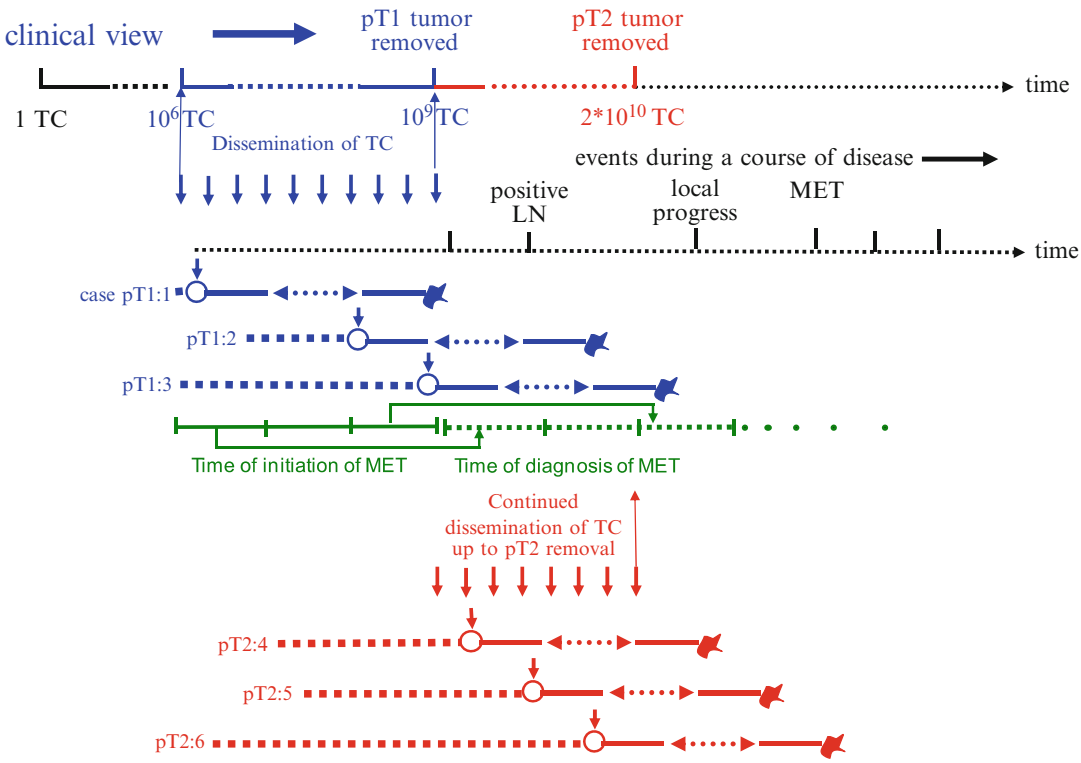

Fig. 2.1 Risk, initiation and detection of secondary foci in solid tumors. Local, regional and distant MET are initiated sequentially. Already tiny tumors – for breast cancer about 1 mm diameter – can initiate MET. The risk ends with the R0-resection of the primary tumor. The extremes are shown with case pT1:1, a primary advanced tumor and case pT1:3 with an initiation just before removal and a resulting long MET-free survival. If the tumor is removed only with a pT2 size (*red part of the figure*) the proportion of primary M1 rises and some cases (case pT1:2) may be diagnosed earlier due to symptoms of MET. Case pT1:3 shows a short MET free interval despite normal MET growth. Also with pT2 a long MET free interval can be observed (case pT2:6). The notation e.g. pT2:x for cases indicate an initiation of MET before pT2 and after pT1 ▪▪▪, ○, ◂···▸, 🐀

mean growth time of the different foci, and the subgroup-specific, homogeneous growth of all MET.

Temporally Sequential Initiation

To begin with, the initiation of TC dissemination that may become a detectable MET occurs in a temporally sequential process. MET foci could have been initiated by even small, 1 mm PT either years or days before a R0 resection. A very early MET initiation can be diagnosed as a primary M1, whereas the initiation that occurs shortly before R0-resecction may only be detectable years after the primary diagnosis. In colorectal cancer with a pT1 diagnosis, 1.4% MET and 8.1% pLN are observed. If the PT is first detected as a pT3 (Fig. 2.1 a delayed detection is shown in red) then in the course of further growth from pT1 to pT3, an additional 39.5% LN will have been infiltrated and primary M1 will be diagnosed in 17.0% of these pT3 patients. Most of these M1-MET foci were very likely initiated before pT1 was achieved. Together with the additional foci detectable at pT1, a total of 47.6% pLN and 18.4% M1 diagnoses are observed at pT3 (Table 2.1). Ten years after a pT1 or pT3 diagnosis, approximately 10.3 or 46.5% tumor associated deaths are observed, respectively. That means that after a M0 diagnosis, distant MET occurs in 8.9/26.2% for either pT1/pT3 tumors. In BC with an interval

Table 2.1 Terciles of the survival time from diagnosis of the primary tumor of metastasized and deceased patients with breast or colorectal cancer and the distributions of prognostic factors within the terciles

		Survival time of metastasized and deceased patients				
Subgroup	Characteristics (%)	1. Tercile	2. Tercile	3. Tercile	all	All patients (%)
Breast pT1	Time interval (ys or n)	<3.8	3.8–7.0	≥7.0 [12.3]	n = 1.255	n = 19.612
	M1	24.8	10.4	2.6	12.4	1.4
	0/≥4 pLK	39.3/34.9	44.1/30.6	57.8/17.2	47.3/27.3	76.1/5.7
	Grade 3–4	48.1	39.1	26.4	37.8	19.6
	HR negative	29.9	16.4	9.6	19.1	9.0
	age < 50 years	31.6	34.2	37.8	34.6	20.0
Breast pT2	Time interval (ys or n)	<2.9	2.9–5.8	≥5.8 [10.8]	n = 2.159	n = 11.088
	M1	33.0	15.1	5.8	17.7	4.3
	0/≥4 pLK	25.8/51.7	30.9/41.4	38.1/33.1	31.8/41.7	49.2/21.3
	Grade 3–4	69.4	56.7	42.2	56.1	39.4
	HR negative	34.7	19.4	8.4	21.1	13.6
	age < 50 years	22.6	27.6	34.7	28.4	18.0
Colon rectum pT2	Time interval (ys or n)	<2.2	2.2–4.7	≥4.7 [7.7]	n = 393	n = 4.265
	M1	76.3	29.2	11.4	38.9	4.7
	0/≥4 pLK	40.0/25.6	67.6/9.5	77.2/2.0	62.5/11.8	80.4/3.7
	Grade 3–4	32.3	13.7	19.5	21.8	14.6
	age (mean, ys)	66.9	64.1	62.2	64.3	69.7
Colon rectum pT3	Time interval (ys or n)	<1.2	1.2–2.8	≥2.8 [5.6]	n = 3808	n = 13.591
	M1	91.7	64.9	29.5	61.9	18.4
	0/≥4 pLK	18.6/54.8	27.6/43.5	54.1/21.4	33.7/39.7	52.4/19.4
	Grade 3–4	41.8	30.3	24.1	32.1	25.7
	age (mean, ys)	69.3	65.1	63.6	65.9	70.2

Data of all patients in the corresponding strata are presented in the last column. The value in brackets after the lower limit of the third tercile is the 90% percentile of the MET free survival time for all patients. Minor changes between the weighted terciles and the sum arise from missing data

of approximately 5–50 mm tumor diameter, there is a linear association between the tumor size and the occurrence of pLN ($y(\%) = 12 + 1.2 * d$, d = tumor diameter in millimeter). With every millimeter, regional and distant MET increases by approximately 1.2% (Engel et al. 2012).

Growth Time of Foci

Secondly, the time required for MET growth can be estimated from very different observational points of view. For BC MET, the time distribution of MET free survival is shown in Fig. 2.2a, b, whereby for 80% of pT1 patients, between approximately 1 and 8 years of growth time may occur before MET is detected. The double of the median MET free survial time is about 6 years and an estimator of the mean growth time. The variability is due to the temporally sequential initiation of MET approximately 6 years earlier, which would have occurred at the 10% limit approximately 5–6 years earlier, and at the 90% limit only days before PT diagnosis. However, there are longer times observed, apparently because the growth of the foci continuously slows. Figure 2.2c shows the survival post diagnosis and results from the MET-free survival time plus the survival following MET. The median survival following MET is about 2 years for receptor positive tumors (Fig. 2.2d). It is remarkable in Fig. 2.2b and c that with increasing survival, both survival times up to MET and after MET increase continuously and are not relevantly correlated. Such positively skewed distributions describe natural growth variations and

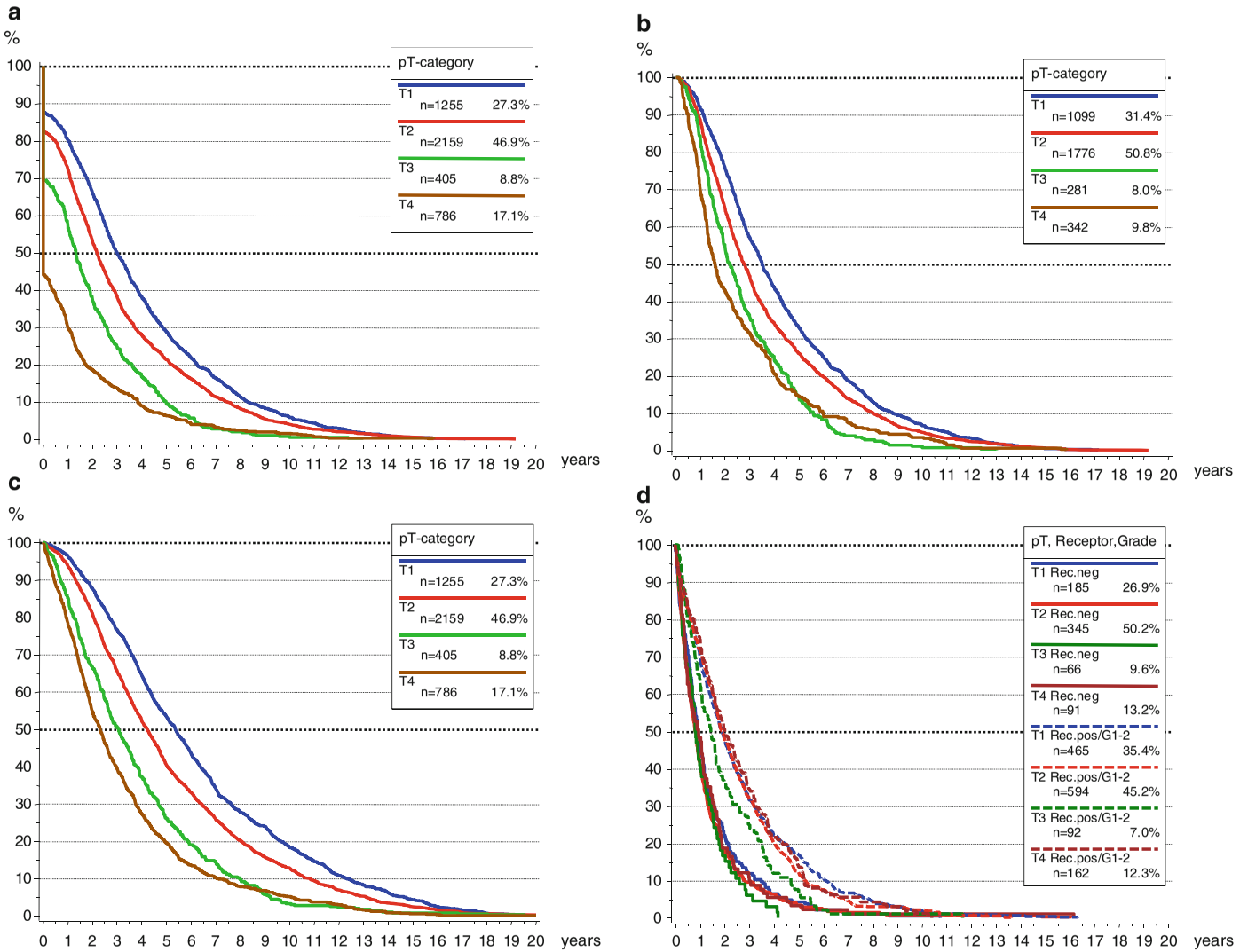

Fig. 2.2 Breast cancer: Distribution functions of the MET-free survival time with (**a**) and without (**b**) primary advanced diseases and of the survival time of all metastasized and deceased patients (**c**) and relapse related survival time after MET for receptor negative and positive tumors (**d**). All distributions are additionally stratified according to the pT-category. For convenient comparisons with survival curves all time distributions are presented as 1-empirical distribution function. In this article MET-free survival means the time from diagnosis to MET and events like death from any cause or second malignancies are not considered

therefore do not need an additional explanation by dormancy.

From the local recurrence (LR)-free survival time after breast conserving therapy with and without irradiation one can estimate about 5 years for the growth time of true LR from initiation to detection (Early Breast Cancer Trialists' Collaborative Group 2005; Hölzel et al. 2011). Indirectly, the growth of LN foci can be estimated from the distribution of ITC and micro MET in SLN which results in the same approximate 5 years as LR and MET (Engel et al. 2012). For colorectal cancer the estimation of growth time is approximately 4 years for the MET-free time, also in the subgroup of pT1-2 metastasized and deceased patients. The survival following MET for colorectal cancer in a population-based setting is about 13 months (data of the MCR not shown).

Homogeneous Growth Within Molecularly Distinct Subgroups

Thirdly, it is important to note that the growth of tumor-specific MET is very homogeneous. For example, the 10 year survival rates for colon cancer with pT1/pT3 diagnoses are at 89.7/53.5%, whereas for diagnoses with 0/3/6 pLN rates are at 75.0/39.4/19.7%. The corresponding numbers for BC are 89.0/48.7 for pT1/pT3 and 90.5/68.0/47.5% for each respective pLN status. For the survival following MET these classic prognostic factors have little additional influence (Fig. 2.2d). Therefore, MET is largely an autonomous process, independent of whether a rare MET from a pT1 tumor or a frequent MET from a pT3 tumor, already with multiple pLN, is observed. The similar growth time of all MET will become more apparent when, for example with BC, the molecular biologically defined subgroups of ER positive and negative tumors are compared. Figure 2.2d demonstrates how subgroup growth times may vary by a factor of almost 2, yet within each subgroup, a very homogeneous growth is observed.

Figure 2.1 shows 90% of the MET free survival times depicted in terciles (dotted green line). Homogeneous growth implies that this time interval can be transposed in the time before diagnosis of PT. That means normally late initiated MET will not appear as primary M1 and early initiated MET not after a long MET-free survival time. The arrows which connect the initiation and detection time of one MET illustrate the homogeneous growth. Therefore, for the most part, the variability of the MET-free survival time results from the sequential initiation with a comparable growth afterwards and not from an approximate 10- to 20-fold growth variation.

Homogeneous MET growth means, that for example in Fig. 2.2b, for all PT diagnosed at pT2, only a small portion of the 10% of MET diagnosed in the first year and of the 10% diagnosed after 8 years may have noticeably shorter or longer volume doubling times (VDT). Even M1 diagnoses or short MET-free intervals as shown in Fig. 2.1, case pT1:3, could have a delayed growth, particularly if the MET was initiated long before pT1 was reached, and then would be detected as a primary M1 at the time of pT2 discovery. Acceleration and retardation of growth cannot reliably be assessed from a short or long length of time after diagnosis of the PT.

An important consequence of these three aspects of MET growth is the sequential acquisition of the MET potency of a PT. More and more, this is being demonstrated with whole genome sequencing and the reconstruction of the evolution of the PT. In addition, the acquisition of MET-potency over time is a prerequisite for the prediction of outcomes with gene expression profiles from the PT (van't Veer et al. 2002). The time of dissemination of the first TC, of the first TC with MET-potency and of its first initiation of a MET are all unknown. The time difference of the last two events, and if not zero, the residence of the disseminated TC with MET potential, are the important questions.

Volume Doubling

Large foci and their changes over time can be well measured with modern imaging. Primary or secondary tumor foci with approximate 1 cm

diameters contain about 10^9 TC. Thirty VD are required to achieve such a size. Nonetheless, the heterogeneity of TC within the PT or a focus and their individual development, in particular during treatment, are not considered, not least because they may be comparable for PT and secondary foci. Therefore, time estimates and their reciprocal transformation from MET to PT, according to Fig. 2.1, seem to be plausible. With BC the VDT for all secondary foci are equivalent within 5–6 years. From these estimates the VDT of secondary foci of about 60 days and of the PT of about 140 days (obtained from screening Peer et al. 1993; Weedon-Fekjaer et al. 2008) result in a ratio of the PT to MET VDT of over two. This ratio may even be independent of varying VDT of the PT, that is, faster growing PT initiate even faster growing MET as seen in Figs. 2.2d and 2.4a. From the sequential initiation of MET and the long growth time follows, among others, that at least the first local, regional or distant MET that may be detectable at the PT diagnosis may be initiated independent of each other.

Relapse Related and Overall Survival

The presented MET process can be gleaned from survival data. The conclusions apply to all solid tumors. Nonetheless, BC is particularly suitable because of the large number of patients and the typically available mm size of the PT as well as the tumor spread in a homogeneous tissue, in contrast to e.g. colon cancer. Figure 2.2a demonstrates the MET-free time with attention towards primary advanced diseases. With increasing pT, the portion of patients with primary MET increases, even when the portion of M1-diagnoses in the MCR are slightly over estimated.

The distributions of MET-free time after a primary M0-diagnosis are comparable for different pT. This is easier to recognize in Fig. 2.2b, where primary MET have been excluded. No fundamentally different distributions result from overall survival after diagnosis of PT (Fig. 2.2c). Only the later occurring MET show an increasing MET-free survival and also concurrently increasing post-MET survival. The median overall survival is simply 2 years longer than the mean of the length of survival until MET. For the approximate 12/88% ER negative/postive diagnoses it can be seen that the mean survival after MET is 1/2 years, and nearly independent of classic prognostic factors such as pT (Fig. 2.2d). The PT reveals a comparable ratio for receptor neg/pos tumors e.g. at 90% with 1.5/4.3 years or at 70% with 5.0/13.6 years (Fig. 2.4a). A bimodal time distribution, that in extreme cases would produce a parallel to the time axis if there were non-overlapping distributions, is not observed in our registry data. It is possibly an artifact from heterogeneous selected groups according to the pT-category or receptor status (Demicheli et al. 2010).

Characteristics of Early and Late MET

Table 2.1 shows the survival time after a BC or colorectal cancer diagnosis of metastasized and deceased patients, grouped according to terciles of the survival times. The tercile limits are, of course, dependent on the follow-up time. For all surviving patients, the 50/90% percentiles of follow-up time are 6.1/15.1 years for BC and 5.2/14.4 for colorectal cancer.

The reduction of the upper tercile limit with increasing PT is notable. This is a lead time effect, because the biology of MET is not changing but rather the risk of initiating a MET. If the MET growth is homogenous, then the growth time of the PT accounts for the time difference of tercile limit, e.g. for BC from pT1 to pT2 of more than 1 year correspondent 3 VD (14–28 mm). The comparison of distributions of selected prognostic factors with all patients in one cohort shows the importance of each factor. The effect of differential growth can be seen in the portion of the primary advanced cancer (M1). Even in the third tercile there are patients who live longer with MET without there being any evidence of dormant TC or stagnating MET.

An unfavorable histologic grade for both cancers and receptor negative tumors for BC are also correlated with growth rate, therefore the proportion is decreasing in the third tercile (Table 2.1). The pLN are remarkable in that the high proportion

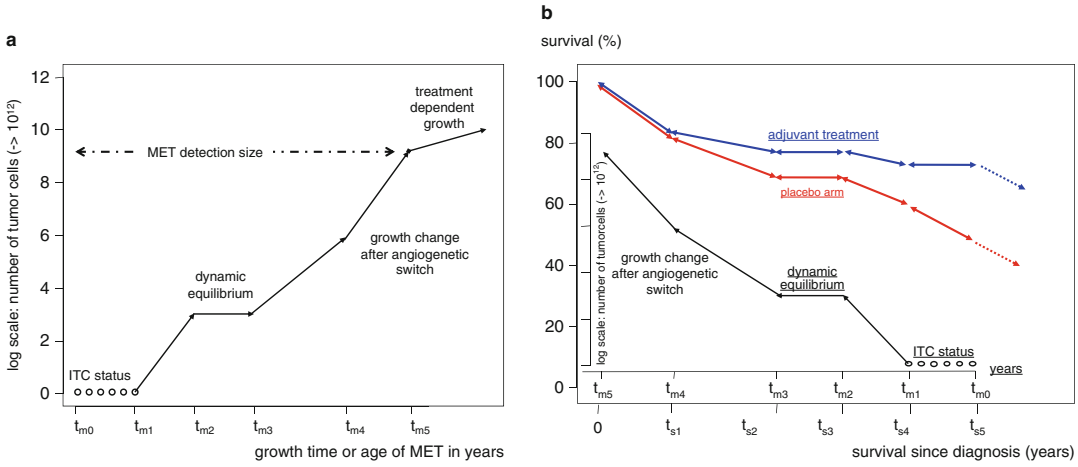

Fig. 2.3 (**a**) A growth trajectory for MET beginning with assumed dormant TC, a dynamic equilibrium and four phases with different VDT. The growth time tmx is also the age of the MET. (**b**) A fictive interaction of a placebo controlled adjuvant treatment with the different growth phases of a MET. An alternative interpretation of Fig. 2.3a is the distribution of prevalence of MET development stages. For the interaction, the trajectory from Fig. 2.3a is flipped horizontally and then shows the remaining time up to the detection of the MET in the placebo arm (*blue line*) and the interaction with the treatment (*red line*). If the treatment is longer than [t_{m1}–t_{m0}], each TC division would happen under treatment

of LN negative patients, particularly in colorectal cancer, demonstrate the MET risk without LN positivity. The increase in pLN with larger tumors is continuous and demonstrates that the number of pLN is an excellent chronometer for the duration of TC dissemination from the PT. The more pLN the more primary M1 can be observed and therefore the survival time is shorter. The differences in survival time in Fig. 2.2 are explained by a lead time effect and differences in biological VDT. The last aspect is also known as length time effect and results in a higher detection probability of prognostically favorable tumors with early detection. The trichotomy of the time intervals for MET initiation and detection supports the view of the three aspects of MET growth, namely the sequential initiation and long-lasting and homogeneous growth of secondary foci.

The superposition of the differential growth of biological or prognostic subgroups is transparent in Fig. 2.2d. The second aspect, the natural variability of VDT, is demonstrated particularly well in BC. From mammography screening (Weedon-Fekjaer et al. 2008) the 25/50/75% percentiles of VDT have been estimated at 65/143/308 days for 60–70 year old patients. This is a factor of 5 that with 30 VD makes a difference of 20 years for the growth of PT. These differing VDT of a PT are passed on to the disseminated TC and determine the growth of the MET. The example of receptor status shows this even when the reason for the growth acceleration of more than a factor of two has not yet been explained. That means that long MET free intervals in BC can be explained by natural differences in growth of the foci. There are no discontinuities in the survival curves and in distributions in Table 2.1, nor in the third tercile which could be most influenced by tumor dormancy phases.

Growth Trajectory

A growth trajectory is the path that a growing focus follows as a function of time. A fictive one is outlined in Fig. 2.3a. Due to the logarithmic y-axis for the number of TC of a MET, differential exponential growth phases are represented by straight lines with size dependent differential slopes (Fig. 2.3a: [t_{m1},t_{m2}] or [t_{m4},t_{m5}]). A possible turning point of growth velocity could happen at the angiogenetic switch (Naumov et al. 2006).

In this trajectory, growing MET reach the detection size with the age of t_{m5}. TC clusters in which cell division and apoptosis would compensate each other over a longer time constitute a dynamic equilibrium and result in a growth trajectory parallel to the x axis as any pause in growth $[t_{m2},t_{m3}]$. Isolated TC that reside in an organ in a dormant state for longer periods of time before the first division are depicted with a series of circles $[t_{m0},t_{m1}]$. This last status is functionally equivalent to disseminated TC with longer circulating times, or that reside in niches, or have a delayed extravasation and thereafter a rapid initiation of a MET in an organ.

Effects of Adjuvant Treatment

To understand possible interactions of different MET status and treatment, the growth trajectory is flipped horizontally in Fig. 2.3b. Thereby survival events are synchronized with the growth trajectory. All of these stages of MET development are represented in a patient cohort. The remaining growth time up to the time of MET detection is then tm5-tmx. How an adjuvant therapy works in dependence of the size and growth characteristics of a MET focus can be seen in the shape of the MET-free survival curve. Because of the homogeneity of MET growth, the respective time delay of a therapeutic effect is reflected in the growth phases. If the MET are too advanced, they are apparently irreversible, as many clinical studies support. Smaller foci, perhaps under 10^6 TC, that are not yet supplied by blood vessels (Naumov et al. 2006), maybe partly reversible, which results in opening survival curves ($[t_{m4},t_{m3}]$).

If, over a longer phase, foci are maintained in a dynamic equilibrium (Fehm et al. 2008; Udagawa 2008) $[t_{m3},t_{m2}]$, and were potentially all reversible with therapy, then the survival in the treatment group should have a phase that is parallel to the x axis. The interaction of an adjuvant therapy with dormant, solitary TC (Townson and Chambers 2006) could result in differing effects ($[t_{m1},t_{m0}]$). If adjuvant therapies take longer than the dormant phase, then all TC would begin with cell division and effective therapies would be recognized by a risk reduction. If the dormancy phase was longer than the therapy, then a change in the MET risk would be apparent (blue dotted line). Only therapies that continuously block the signal transduction of mitotic pathways would have survival curves that open like scissors if dormant TC initiated MET. Current adjuvant therapies show a less complex structure. In the beginning they run parallel, for a defined time the curves open in a scissor-like fashion, and thereafter they run parallel. If all TC have reached the location of focal initiation before the beginning of adjuvant therapy, then we see the outcome of treatment and there is no evidence of late, post R0 resection initiating TC.

Distant MET and Dormancy

If dormancy were a characteristic of the MET process the effect should occur in local, regional, and distant foci. Figure 2.2 shows that for distant MET, later occurring MET is less frequent with increasing PT size. Since on the other hand, MET are comparable for either large or small tumors, then the characteristics of being a late MET must have little to do with the size of the PT. An observation "the less favorable prognostic the PT, the shorter the dormancy" would require new characteristics of the initiated TC. Later MET that occur under 10 years are predominantly the result of a lead time effect since survival after MET is mostly independent of PT. Figure 2.1 illustrates that such misinterpretations can occur from the wrong association with the date of PT diagnosis. With the reference to the initiation of MET, a long-standing growth or dormancy could very likely be associated with a very short MET-free interval or even with primary M1 (Fig. 2.1 case pT2:4b). Figure 2.4 more likely suggests that the differential survival with ER+ and ER-tumors in BC can be explained by different VDT and not by differing lengths of dormancy phases dependent on receptor status. Late MET that occur after 10 years are characteristic for BC MET and need no explanation by tumor dormancy. A small portion of MET in BC may have particularly fast or

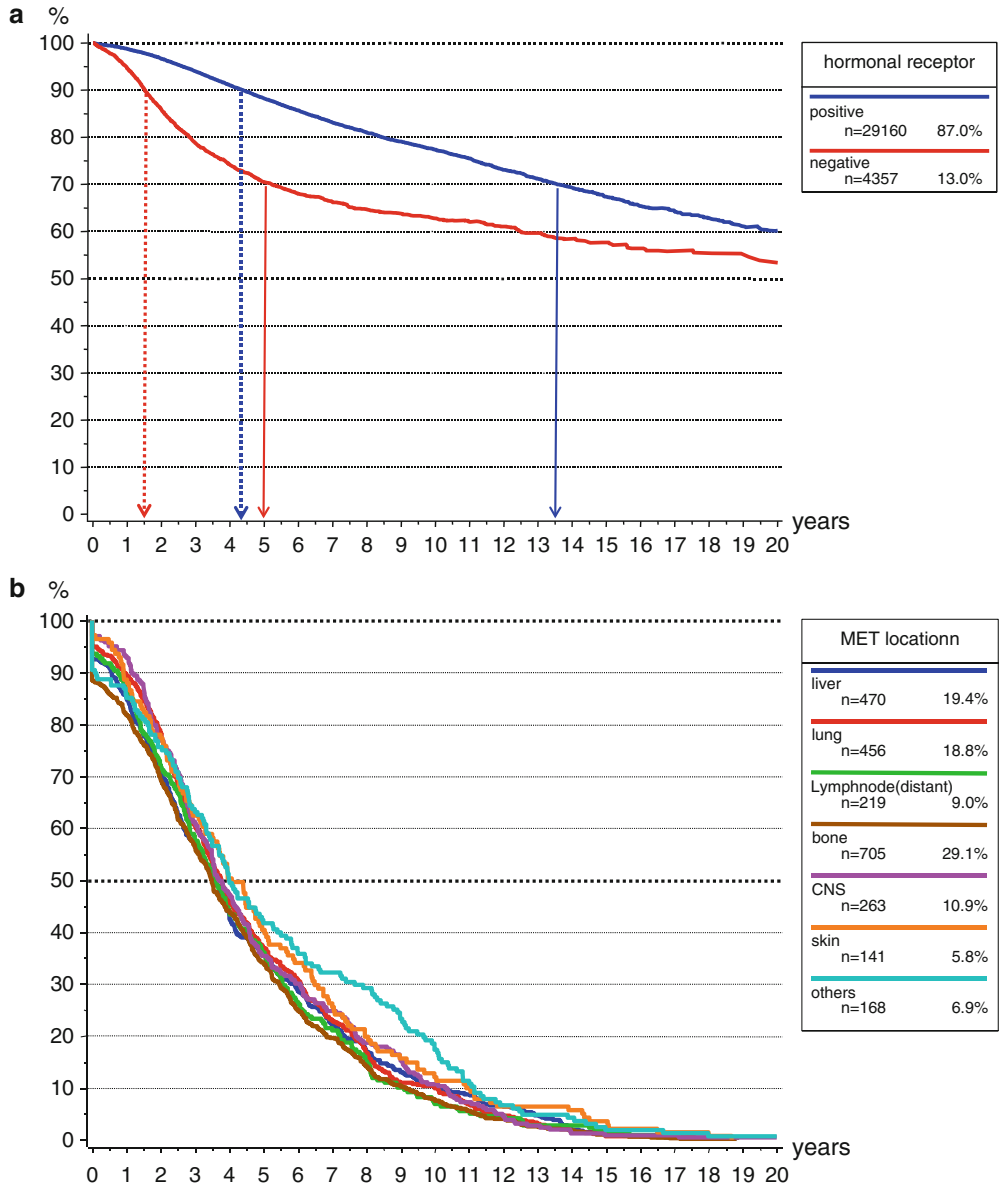

Fig. 2.4 (**a**) Tumor specific survival for breast cancer patients stratified according the receptor status without any indication of a discontinuity due to a dormant phase. (**b**) MET free survival time for different distant MET for breast cancer with a pT2 primary tumor. Primary advanced cases are also included, as indicated by the initial step

particularly slow growth. In this regard, different organs show different VDT with the same PT.

There are no facts that dormancy is involved if MET-free survival occurs after 5 years (Aguirre-Ghiso 2007; Brackstone et al. 2007). Additionally, it is important to assess the quality of data. For BC the risk of a second malignancy in 20 years is 40% (Kaplan Meier estimate from MCR data), among those 20% contra- or ipsilateral second breast cancer occurs, the latter after breast conserving treatment (Hill-Kayser et al. 2006). Such frequent second malignancies require critical assessment of the cause in respect to the cancer related death for every late MET.

Regional MET and Dormancy

How does it look with the infiltration of LN? Even in this case, pLN can occur long after the diagnosis of PT. If the delay were explained by dormant TC, then a high prevalence for ITC must be evident already with the meticulous dissection of the SLN. This is probably not the case. ITC, micro and macro foci in LN appear to be so distributed that the infiltration of the LN net through continuous dissemination and a growth without a dormancy phase seems plausible. However, ITC means that the whole range from ITC up to TC clusters of less than 0.2 mm can be detected in a SLN. A reseeding from TC in the LN would put into question the prognostic relevance of SL and the observable infiltration of the LN net from the effluent stream of the PT. There are no robust data for dormancy in LN.

Local MET and Dormancy

Even with LR there are no clinical data that would suggest dormancy. If one observes breast conserving therapy, the first point to make is the subdivision of residual tumors, true recurrences (TR, that have no contact with the PT), and de novo carcinomas. The growth rate of TR can be estimated from the time distribution of a metaanalysis of studies with and without radiation after breast conserving therapy, and results in approximately 5 years for 30 VD (Early Breast Cancer Trialists' Collaborative Group 2011). Even here, a sequential initiation and a homogeneous growth of over 5 years before R0-resection can be assumed. From this also follows the analogy to MET in distant organs and pLN, which can be detected simultaneously with the PT. These are the multifocal findings which are detected near the PT at diagnosis and are initiated from migrating TC. Late LR are most likely de novo cancer that occur in other quadrants and have other histologies. Late TR that occur near to the PT also exist. In comparison to the MET, it is possible that after 6–8 years only a few percentage are concordant with the variability of the VDT (Weedon-Fekjaer et al. 2008). Genomic tests of the PT and the local focus will hopefully soon clarify the type of synchronous or recurrent foci. For dormancy of local MET, no robust data are available either.

Implausible Implications for Dormant Tumor Cells

TC arrive very soon after hematogenous and lymphogenous dissemination in all organs (Fisher and Fisher 1966). The first steps of the MET process are very efficient. The inefficiency does not occur until TC growth after extravasation (Cameron et al. 2000; Luzzi et al. 1998). The challenging question is whether dormancy is a common characteristic of this step.

TC even from very small PT have MET potency. The linear relationship between size and MET confirms that the dissemination increases with the duration of the MET-risk. But the PT does not disseminate increasingly genetically potent cells. If gene signatures can predict the organ tropism, then these properties must be a very early property of the PT and not the product of an evolutionary development or even of maturation after dissemination. Since millions of TC can be disseminated by a PT, which passively reach all organs through lymph and blood vessels, survive there and show typical tumor-specific MET patterns, then a cascade like initiation from focus to focus can be excluded. This is shown in Fig. 2.4b with the distributions of the organ specific MET-free survival time for BC. The small differences between the distributions must be compared with the growth time from initiation of a MET up to the detectable size lasting for years. Therefore, MET foci arise independently from one another.

Also the assumption that the PT disseminates a TC, predetermined in its evolutionary development, and equipped with a specific gene signature for different organs, is not compatible with Fig. 2.4b. A predestined TC location cannot be confirmed by any MET-pattern in other solid tumors. Moreover, this would reduce the importance of the environment, which, as we know from embryology and wound repair, constrains

pluripotent cells to selective functions by changing gene-expression for organ or tissue formation.

A simple thought experiment reveals fundamental problems with dormancy. If dormancy were a characteristic of the MET process, then TC would exist in organs which were disseminated from the PT in different sizes. Because a different MET probability is associated with each tumor size, an intelligent mechanism of the TC and/or the environment must exist which knows among others the size at dissemination and the present duration of dormancy. This is because the PT size is correlated with MET frequency which has to be coordinated within the subset of all disseminated TC and even within a patient cohort. Ultimately, the disseminated TC would be equipped by the PT with a signature for a definite MET in the sense of a final destination and would reopen the discussion about entelechy for a teleological process from the Middle Ages. Furthermore, the remote control of TC by the PT up to the R0-resection with a signal protein also seems implausible but does not contradict colonisation by the PT. Such a thought experiment shows that MET is also, up to the initiation of a secondary focus, an autonomous mechanical process (Michaelson et al. 2005) with a probability of success which increases with the number of disseminated TC and therefore with time.

An evolutionary development of the PT with delayed dissemination of more aggressive or organ specific TC cannot be deduced from MET patterns. Also a change of the pattern during the course of disease cannot be observed. The determination of the prognosis, or even the location of the MET, from the PT would otherwise not be possible (Bos et al. 2009; van't Veer et al. 2002). That is to say, it is questionable whether successful TC did not have any dormancy phase a posteriori. Because TC lack a memory mechanism of their own history the number of long-lived, viable TC in all organs can only have a minor role. There are no convincing data about systematic initiation of MET after R0 resection, as there are no convincing data about a dormancy phase before initiation of a focus. However, this is not inconsistent with the existence of dormant TC.

Seed and Soil Observations

The lack of evidence of the importance of dormancy for MET does not conflict with observations from Paget (1889); that the distribution of secondary growth is not determined by the blood flow and random sampling. A tumor-specific organ tropism exists. A TC of liver adenocarcinoma remains unsuccessful initiating MET in the lung although it transits through the pulmonary capillaries, but it is very successful in all liver segments. In contrast to the liver, a primary lung adenocarcinoma shows a strong tropism for its homeland organ, which is evidenced by the frequent multifocal PT of the lung. The circulation path of the TC is identical in both cases. Because there is no correlation between organ tropism and blood flow, and TC are ubiquitous in all organs (Suzuki et al. 2006) tumor-specific driver genes must be diversified. The metastatic propensity of small cell lung cancer TC to the CNS or to adrenal gland points to the importance of the seed and the selection of the soil. The little overlap between genes identified as a signature for lung and bones fit with these observations (Landemaine et al. 2008). This correlation also explains the striking success of local or site-specific MET in the environment of the PT.

An adjuvant radiation of the CNS in patients with small cell lung cancer reduces CNS-MET and therefore TC must already be at that location at the time of diagnosis of the PT. The hypothesis that radiation destroys dormant TC instead of already growing foci, because their repair mechanisms are not activated, seems implausible. The analogy to the LAG Phase of bacterial growth, during which bacteria adapt themselves to growth conditions of a new environment, is fitting. Especially, CNS MET should have longer LAG phases or slow and differential growth of tiny foci. Perhaps a successful MET is correlated with the density of isolated TC in an organ if separately disseminated TC find each other and can then more easily activate nearby vessels together. Video microscopy suggests such an equilibrium of newly arriving TC and disappearing older ones (Kienast et al. 2010).

Last but not least, genome sequencing of a PT and different secondary foci confirms the temporal sequence of focus initiation (Campbell et al. 2010; Yachida et al. 2010). Additionally, the parallel evolution in primary sites must be considered as the result of very heterogeneous PT. It is noteworthy that the additional mutations shown by the phylogenetic reconstruction of the evolution of PT are not driver mutations for the respective organ. Also from this point of view, organ tropism should be established very early without noticeable delay between organs (Fig. 2.4b).

Conclusion

Millions of continuously disseminated TC and their ubiquitous detectability in animal models with different cell lines suggest the imprecise term of tumor dormancy for solid tumors. Historically, the metaphor may have been inspired by the knowledge of hematological cancers, hematopoietic stem cells, their treatment, and the development of recurrences. Also the transfer of TC with organ donations and the mobilization for MET initiation suggest the existence of TC in niches.

In reality, the term dormancy conceals our ignorance of the MET process of solid tumors, beginning with circulation up to the growth of isolated TC or clusters of local, regional and distant MET (Aguirre-Ghiso 2007). The detection of TC and their possible delayed division or apoptosis cannot explain or quantify our observations. It is only a surrogate for dissemination of a PT. For this reason, the adverse prognostic value of bone marrow TC detected at diagnosis of PT in early BC is not to be questioned. Nonetheless, the detection of dormant TC does not implicate them as MET precursors nor as causes of late recurrences. The dormancy concept opens no new line of vision, shows no promising research approach and is therefore not helpful (Klein 2011). It is even counterproductive that the term communicates timeliness and scientificness, so that in spite of our limited knowledge, a search for so-called dormant TC and their characterization is offered to patients as being useful.

Also the expectations of improving prognosis with dormant TC as a treatment target are not likely to be of clinical importance. The evidence of the heterogeneity of PT, the resulting lack of monoclonal TC, and the plasticity of each focus makes the therapeutic failure with currently available agents very likely, or chronifications of METs, unlikely. In addition, adjuvant therapies are likely to affect foci already growing in organs. Their improved interception with foci below the detectable size would be of clinical importance. In summary, it follows that the detection, properties, representativeness or interference of dormant TC in cell systems and animal models and the transferability to humans are certainly of great interest. But the significance of dormant TC for the scientific development and application of future therapies appears at present to be still very low. Thus far, tumor dormancy is a theoretical construct with marginal relevance for patients and with no contribution to the differentiation of thought and action and is therefore clinically meaningless.

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References

Aguirre-Ghiso JA (2007) Models, mechanisms and clinical evidence for cancer dormancy. Nat Rev Cancer 7(11):834–846. doi:10.1038/nrc2256, nrc2256 [pii]

Bos PD, Zhang XH, Nadal C, Shu W, Gomis RR, Nguyen DX, Min AJ, van de Vijver MJ, Gerald WL, Foekens JA et al (2009) Genes that mediate breast cancer metastasis to the brain. Nature 459(7249):1005–1009. doi:10.1038/nature08021, nature08021 [pii]

Brackstone M, Townson JL, Chambers AF (2007) Tumour dormancy in breast cancer: an update. Breast Cancer Res 9(3):208. doi:10.1186/bcr1677, bcr1677 [pii]

Cameron MD, Schmidt EE, Kerkvliet N, Nadkarni KV, Morris VL, Groom AC, Chambers AF, MacDonald IC (2000) Temporal progression of metastasis in lung: cell survival, dormancy, and location dependence of metastatic inefficiency. Cancer Res 60(9): 2541–2546

Campbell PJ, Yachida S, Mudie LJ, Stephens PJ, Pleasance ED, Stebbings LA, Morsberger LA, Latimer C, McLaren S, Lin M, McBride DJ, Varela I, Nik-Zainal SA, Leroy C, Jia M, Menzies A, Butler AP, Teague JW, Griffin CA, Burton J, Swerdlow H, Quail MA, Stratton MA, Iacobuzio-Donahue MR, Iacobuzio-Donahue C, Futreal PA (2010) The patterns and dynamics of genomic instability in metastatic pancreatic cancer. Nature 467(7319):1109–1113. doi:10.1038/nature09460, nature09460 [pii]

Demicheli R, Ardoino I, Boracchi P, Coradini D, Agresti R, Ferraris C, Gennao M, Hrusheky WJM, Biganzoli E (2010) Recurrence and mortality according to estrogen receptor status for breast cancer patients undergoing conservative surgery. Ipsilateral breast tumour recurrence dynamics provides clues for tumour biology within the residual breast. BMC Cancer 10:656. doi:10.1186/1471-2407-10-656, 1471-2407-10-656 [pii]

Early Breast Cancer Trialists' Collaborative Group (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366(9503):2087–2106

Early Breast Cancer Trialists' Collaborative Group (2011) Effect of radiotherapy after breast conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. Lancet 378:1707–1716. doi:10.1016/S0140-6736(11)61629-2, S0140-6736(11)61629-2 [pii]

Engel J, Emeny RT, Hölzel D (2012) Positive lymph nodes do not metastasize. Cancer Metastasis Rev 31:235–246. doi:10.1007/s10555-011-9343-7

Fehm T, Mueller V, Marches R, Klein G, Gueckel B, Neubauer H, Solomayer E, Becker S (2008) Tumor cell dormancy: implications for the biology and treatment of breast cancer. APMIS 116(7–8):742–753. doi:10.1111/j.1600-0463.2008.01047.x, APMapm_1047 [pii]

Fisher B, Fisher ER (1966) The interrelationship of hematogenous and lymphatic tumor cell dissemination. Surg Gynecol Obstet 122(4):791–798

Hill-Kayser CE, Harris EE, Hwang WT, Solin LJ (2006) Twenty-year incidence and patterns of contralateral breast cancer after breast conservation treatment with radiation. Int J Radiat Oncol Biol Phys 66(5):1313–1319

Hölzel D, Eckel R, Emeny RT, Engel J (2010) Distant metastases do not metastasize. Cancer Metastasis Rev 29:737–750. doi:10.1007/s10555-010-9260-1

Hölzel D, Emeny R, Engel J (2011) True local recurrences do not metastasize. Cancer Metastasis Rev 30:161–176. doi:10.1007/s10555-011-9275-2

Kienast Y, von Baumgarten L, Fuhrmann M, Klinkert WE, Goldbrunner R, Herms J et al (2010) Real-time imaging reveals the single steps of brain metastasis formation. Nat Med 16(1):116–122. doi:10.1038/nm.2072, nm.2072 [pii]

Klein CA (2011) Framework models of tumor dormancy from patient-derived observations. Curr Opin Genet Dev 21(1):42–49. doi:10.1016/j.gde.2010.10.011, S0959-437X(10)00189-9 [pii]

Landemaine T, Jackson A, Bellahcene A, Rucci N, Sin S, Abad BM, Sierra A, Boudinet A, Guinebretiere J, Ricevuto E, Nogues C, Briffod M, Bieche I, Cherel P, Garcia T, Castronovo V, Teti A, Lidereau R, Driouch K (2008) A six-gene signature predicting breast cancer lung metastasis. Cancer Res 68(15):6092–6099. doi:10.1158/0008-5472.CAN-08-0436, 68/15/6092 [pii]

Luzzi KJ, MacDonald IC, Schmidt EE, Kerkvliet N, Morris VL, Chambers AF, Chambers AF, Chambers AF, Groom AC (1998) Multistep nature of metastatic inefficiency: dormancy of solitary cells after successful extravasation and limited survival of early micrometastases. Am J Pathol 153(3):865–873

Meng S, Tripathy D, Frenkel EP, Shete S, Naftalis EZ, Huth JF, Beitsch PD, Leitch M, Hoover S, Euhus D, Haley B, Morrison L, Fleming TP, Herlyn D, Terstappen LW, Fehm T, Tucker TF, Lane N, Wang J, Uhr JW (2004) Circulating tumor cells in patients with breast cancer dormancy. Clin Cancer Res 10(24):8152–8162. doi:10.1158/1078-0432.CCR-04-1110, 10/24/8152 [pii]

Michaelson JS, Cheongsiatmoy JA, Dewey F, Silverstein MJ, Sgroi D, Smith B, Tanabe KK (2005) Spread of human cancer cells occurs with probabilities indicative of a nongenetic mechanism. Br J Cancer 93(11):1244–1249. doi:10.1038/sj.bjc.6602848

Munich Cancer Registry. http://www.tumorregister-muenchen.de/facts/specific_analysis.php (cited 2012 Dec 16)

Naumov GN, MacDonald IC, Weinmeister PM, Kerkvliet N, Nadkarni KV, Wilson SM, Morris VL, Groom AC, Chambers AF (2002) Persistence of solitary mammary carcinoma cells in a secondary site: a possible contributor to dormancy. Cancer Res 62(7):2162–2168

Naumov GN, Akslen LA, Folkman J (2006) Role of angiogenesis in human tumor dormancy: animal models of the angiogenic switch. Cell Cycle 5(16):1779–1787, doi: 3018 [pii]

Paget S (1889) The distribution of secondary growths in cancer of the breast. Lancet I:571–573

Peer PG, van Dijck JA, Hendriks JH, Holland R, Verbeek AL (1993) Age dependent growth rate of primary breast cancer. Cancer 71(11):3547–3551

Suzuki M, Mose ES, Montel V, Tarin D (2006) Dormant cancer cells retrieved from metastasis-free organs regain tumorigenic and metastatic potency. Am J Pathol 169(2):673–681, 169/2/673 [pii]

Talmadge JE, Fidler IJ (2010) AACR centennial series: the biology of cancer metastasis: historical perspective. Cancer Res 70(14):5649–5669. doi:10.1158/0008-5472.CAN-10-1040, 0008–5472.CAN-10-1040 [pii]

Townson JL, Chambers AF (2006) Dormancy of solitary metastatic cells. Cell Cycle 5(16):1744–1750, doi: 2864 [pii]

Udagawa T (2008) Tumor dormancy of primary and secondary cancers. APMIS 116(7–8):615–628. doi:10.1111/j.1600-0463.2008.01077.x, APMapm_1077 [pii]

Uhr JW, Pantel K (2011) Controversies in clinical cancer dormancy. Proc Natl Acad Sci U S A 108(30):12396–12400. doi:10.1073/pnas.1106613108, 1106613108 [pii]

Valastyan S, Weinberg RA (2011) Tumor metastasis: molecular insights and evolving paradigms. Cell 147(2):275–292. doi:10.1016/j.cell.2011.09.024, S0092-8674(11)01085-3 [pii]

van't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse HL, van der Kooy K, Marton MJ, Witteveen AT, Schreiber GJ, Kerkhoven RM, Roberts C, Linsley PS, Bernards R, Friend SH (2002) Gene expression profiling predicts clinical outcome of breast cancer. Nature 415(6871):530–536. doi:10.1038/415530a, 415530a [pii]

Weedon-Fekjaer H, Lindqvist BH, Vatten LJ, Aalen OO, Tretli S (2008) Breast cancer tumor growth estimated through mammography screening data. Breast Cancer Res 10(3):R41. doi:10.1186/bcr2092, bcr2092 [pii]

Weinberg RA (2008) The many faces of tumor dormancy. APMIS 116(7–8):548–551. doi:10.1111/j.1600-0463.2008.001168.x, APMapm_1168 [pii]

Yachida S, Jones S, Bozic I, Antal T, Leary R, Fu B, Kamiyama M, Hruban RH, Eshleman JR, Nowak MA, Velculescu VE, Kinzler KW, Vogelstein B, Iacobuzio-Donahue CA (2010) Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature 467(7319):1114–1117. doi:10.1038/nature09515, nature09515 [pii]