PERGAMON

European Journal of Cancer 39 (2003) 1794–1806

European Journal of Cancer

www.ejconline.com

The process of metastasisation for breast cancer

J. Engel[a,*], R. Eckel[a], J. Kerr[a], M. Schmidt[a], G. Fürstenberger[c], R. Richter[c], H. Sauer[b], H.-J. Senn[c], D. Hölzel[a]

[a]*Tumorregister am Tumorzentrum München, Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie (IBE), Klinikum der Ludwig-Maximilians-Universität, Großhadern, D-München, Germany*

[b]*Medizinische Klinik III, Klinikum der Ludwig-Maximilians-Universität, Großhadern, D-München, Germany*

[c]*Zentrum für Tumordiagnostik und Prävention (ZeTuP), Ch-St. Gallen, Switzerland*

Received 6 November 2002; received in revised form 3 February 2003; accepted 8 February 2003

Abstract

To investigate the process of metastasis, primary clinical data and disease events such as metastases, local recurrence and survival (median follow-up 9.4 years) from the Munich Cancer Registry from 1978 to 1996 were analysed. Since metastases, even from small tumours, may be initiated before the diagnosis of the primary tumour, the growth of the primary tumour and metastasisation may be two autonomous processes. In our data, survival following metastases was almost unrelated to primary tumour size. However, the number of M1 cases and the time to metastasisation depended on the tumour diameter at diagnosis. The time from initiation of metastases to its diagnosis was estimated as 5.8 years. The growth of metastases was almost homogeneous. However, the growth time following metastasisation—depending on the metastases-free time, receptor status and histological grade—only varied by approximately a factor of 2. Local recurrence, above all, was an indicator of metastases. Furthermore, local recurrence may also have the potential to metastasise. Excess mortality due to local recurrence was estimated up to 9.3 years after diagnosis. Our hypothesised metastases model illustrates the importance of early detection, the concept of breast-conserving therapy and additional metastases from local recurrence. It highlights the benefits of optimal local therapy of the primary tumour and the limitations of systemic therapy. It also questions the use of axilla dissection and lymph node irradiation. Its generalisation to solid tumours may help to clarify many of the current controversial debates.
© 2003 Elsevier Ltd. All rights reserved.

Keywords: Breast cancer; Metastasis; Local recurrence; Epidemiology; Tumour registry

1. Introduction

With improvements in long-term survival rates through loco-regional radiotherapy following mastectomy [1,2], metastases have become an area of concern [3] and the following questions have been raised. Are loco-regional recurrence and metastasisation independent events or can loco-regional recurrence cause secondary metastases [4–10]? When does metastasis start [11,12]? As a result of such questions, both Halsted's [13] and Fisher's [14] paradigms are being debated. For example, does metastasis spread continually from the primary tumour or is it already an established systemic disease at diagnosis [15–17]? To address these questions, we have analysed the metastasisation process qualitatively and quantitatively using data from the Munich Cancer Registry. The implications for clinical research and population-based healthcare delivery will be discussed.

The aim of this paper was to demonstrate the importance of tumour size in the disease course. While the frequency of metastases increases as the tumour grows, metastatic growth itself, viewed from several angles, appears to be homogeneous and not dependent on the pT stage. Finally, while local recurrence may be an indicator of primary metastasisation, it may also play a role in secondary metastasisation.

2. Patients and methods

2.1. Data collection

The empirical data for the following analyses and discussion was provided by the Munich Cancer Registry

* Corresponding author. Tel.: +49-89-7095-4489; fax: +49-89-7095-4753.

E-mail address: engel@ibe.med.uni-muenchen.de (J. Engel).

0959-8049/03/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0959-8049(03)00422-2

(MCR). Breast cancer data extends back to the end of the 1970s, where data collection started in two medical faculties in three hospitals. In the beginning, only 20% of patients in the Munich region were accounted for but, today, the data are almost population-based. The MCR now routinely records all cancer patients that are treated in Munich and surrounding areas (part of southern Bavaria). At the time of this study, the population size was approximately 2.3 million; currently it stands at 3.7 million. All pathology reports for solid tumours from all the pathology laboratories in the Munich area are sent, almost on a weekly basis, to the MCR. From these reports, the total number of breast cancer patients in the region is systematically known and the main prognostic factors, such as pTNM stage, tumour grade, histology, lymph node harvest and resection margins are ascertained. Lymph node metastases refer to the ipsilateral axilla (without supraclavicular fossa) and the ipsilateral lymph nodes of the *mammaria interna*, but the latter is not normally operated upon (according to the fifth edition of the TNM classification, which was valid until 2001 and applies to the cohort analysed). Histological grade was based on the criteria of Bloom and Richardson, with the modifications of Elston and Ellis [18].

In parallel, clinicians completed standardised forms concerning patients' domicile, tumour diagnosis, primary therapy, follow-up and palliative care. Doctors' letters and radiotherapy reports were also available. Progression and life-status were monitored throughout the follow-up, the latter maintained systematically through death certificates and the inhabitants registration office. All MCR data are registered according to the official documentation guidelines for cancer registries. Thus, at present, follow-up, in terms of life status, is available in approximately 95% of the catchment area.

It is not possible to achieve complete data in a tumour registry over such a long period of time. For example, receptor status was not assessed until the mid-1980s, likewise the number of investigated and positive lymph nodes or tumour diameter were not always recorded. Complete prognostic and progression data were also not feasible from the routine documentation of such a patient sample, thus missing data are not presented. While incompleteness of this data must be taken into consideration, it should not affect the critical reasoning presented here.

2.2. Patient sample

New breast cancer patients (invasive tumours only), without a synchronous or metachronous second non-breast malignancy, were included in the analysis. Sarcoma cases were excluded. For the correlation between tumour diameter and lymph node status, primary data from 1988 to 2001 were evaluated. All other analyses (survival analyses, time analyses of disease progression) pertained to patients from 1978 to 1996. 1996 was chosen as the cut-off date in order to ensure at least 5 years of follow-up (to 2001) and to avoid bias towards cases with early progression.

2.3. Outcome measure

Three outcomes were assessed in these analyses: metastasisation (MET)—distant metastasis usually determined by image processing—, local recurrence (LR)—LR can be both a second invasive or ductal carcinoma *in situ* (DCIS) event, independent of the primary method of operation—and lymph node recurrence (LNR).

2.4. Statistical analyses

The MCR data is managed in an Oracle database. Statistical analyses were conducted in SAS (version 6.1). Overall survival following diagnosis and progression was assessed by the Kaplan–Meier method and compared by the log rank chi-square statistic. The expected survival of age-matched women was calculated according to the observation time of each woman and the life-tables of the German 'normal population'. Relative survival was computed by the ratio of the observed survival rate to the expected survival rate [19]. Frequencies were compared using chi-square tests and means by U-tests. Due to the large sample size, most results were significant and are thus not presented here. Instead, we wish to focus on the pattern of these results and their logical implications.

Two basic principles were employed in the analyses. First, all analyses were stratified by pT category, irrespective of primary MET or lymph node status, as tumour size describes the growth process better than International Union Against Cancer (UICC) stage or lymph node status. Even if the latter is appropriate for individual prognoses. Second, M1 cases—with a MET-free time of zero—were included in all of the time analyses. Even though the data for the entire period under observation are not population-based, by stratifying these analyses by pT category and including M1 cases, systematic bias should have been avoided.

3. Results

A total of 12 423 patients, recruited by the MCR between 1978 and 1996, contributed to this description of the disease process. Survivors were followed-up for a median of 9.4 years. Table 1 describes the distribution of the most important prognostic factors by pT category. In the median observation period of 9.4 years,

3078 metastases (of which 596 (4.8%) were M1), 1320 (10.6%) LRs and 442 (3.6%) LNRs were recorded. A total of 4550 (36.6%) patients died during this time. The relationship between prognostic factors and pT category can be clearly seen in Table 1. Fig. 1 outlines overall survival by pT category, and thus by tumour size. The strong association between tumour size and lymph node status, the most important prognostic factor, is demonstrated in Fig. 2. A linear correlation between these two parameters is evident. Fig. 3—overall survival following MET—shows homogenous metastatic growth, almost independent of pT category.

In Fig. 4, mean MET-free time (including M1 cases with a MET-free time of zero) and progression time following MET (from Table 1) are displayed for each pT category. Death was chosen as the reference point for all of the pT categories. There was no correlation between the pT category and survival following MET, but a lead time effect can be seen. This lead time reduces the time to MET with increasing pT category. MET frequency (and thus tumour-related mortality) was, above all, dependent on the tumour size. So while the tumour size increases, i.e. during the lead time, the frequency of MET increases. The proportion of T2 that eventually kill the patient (47.7%, i.e. 100–15 years relative survival) minus the proportion of fatal T1 (22.4%) gives an estimate of the additional metastasisation that may occur between T1 and T2 (47.7–22.4 = 25.3).

In Fig. 5, the cumulated MET-free time and survival time curves are displayed for the 2405 patients with MET who died. The cumulative distribution curve for the hypothesised initiation of MET was calculated from the time to MET curve.

Fig. 6 shows the overall survival following MET by histological grade. The differences between the survival curves were just significant. The survival curves following MET, stratified by MET-free time, portrayed in Fig. 7, indicate only a slight relationship between these factors. The lack of a correlation between the MET-free time and survival following MET can also been seen in the scatter diagram in Fig. 8. The correlation analysis for each pT category accounted for less than 1% of the explained variance.

In contrast with survival after MET, Fig. 9 indicates that survival following LR (without considering

Table 1
Patient and tumour characteristics by pT category

Characteristics		pT1	pT2	pT3	pT4
pT					
n = 12 423		5772	4897	671	1092
Proportion	(%)	46.4	39.4	5.4	8.8
Age (mean) (years)	(years)	57.0	58.1	55.9	65.3
Lymph node (LN)-positive	(%)	30.3	55.1	76.5	73.6
Histological grade (G)					
G1	(%)	11.8	3.2	1.8	1.4
G2	(%)	62.5	52.8	41.7	47.5
G3	(%)	25.7	44.0	56.6	51.1
Oestrogen receptor-negative	(%)	29.4	30.3	36.2	26.9
Metastasisation primary (M1)	(%)	1.1	4.2	9.7	21.1
Follow-up (number of person years)	(years)	45 490	33 602	3714	4846
Follow-up (mean time of patients alive)	(years)	9.4	9.4	10	9
Local recurrence (LR)	(%)	9.1	11.3	16.8	11.7
Cumulative LR-rate after 10 years (Kaplan–Meier)	(%)	11.3	15.3	25.5	19.2
Local lymph node recurrence (LNR)	(%)	2.6	4.3	4.9	4.7
Metastasisation[a] (MET)	(%)	14.7	28.9	43.4	47.8
MET/LR	(%)	1.6	2.6	2.6	4.1
Deceased	(%)	24.5	41.6	56.8	65.9
Relative survival after 15 years	(%)	77.6	52.3	31.4	24.1
Time from diagnosis to LR (mean)	(months)	47.9	40.9	32.5	25.4
Time from diagnosis to LR (median)	(months)	39.0	29.4	21.5	15.2
Time from diagnosis to MET (mean)	(months)	43.7	36.7	27.2	17.1
Time from diagnosis to MET (median)	(months)	35.3	26.2	19.9	3.7
Time from MET to death (mean)	(months)	25.0	24.9	24.1	22.3
For patients with MET only:					
Time from diagnosis to MET (mean)	(months)	38.3	32.6	24.0	13.9
For patients with MET and LR only:					
Time from diagnosis to MET (mean)	(months)	55.9	44.5	30.0	24.9

The expected survival of age-matched women was calculated according to the observation time of each woman and the life-tables of the German 'normal population'.

[a] M1 inclusive.

synchronous or subsequently diagnosed metastases) was dependent on the pT category. This emphasises that the growth process for local recurrence was not dependent on metastasisation. For each pT category, survival following LR was worse than that following the primary diagnosis. Thus, the role of pT-dependent LR as an indicator for MET, originating from the primary tumour, is also apparent. In addition, Fig. 10 illustrates the possibility that a secondary MET may develop from LR.

4. Discussion

4.1. pT category, positive lymph nodes and survival

Growth is essential for the development of tumours. Tumour size is therefore the most important factor in describing tumour biology. This is emphasised by the observed 1% increase in mortality with every millimetre increase in tumour diameter. The pT category system itself recognises the prognostic importance of tumour

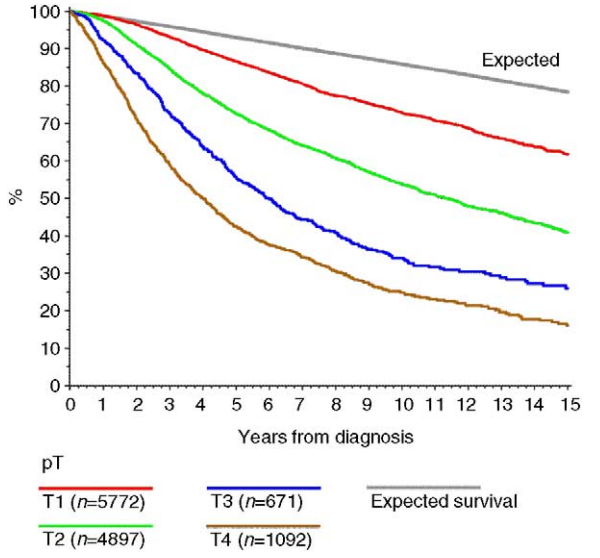

Fig. 1. Overall survival following diagnosis by pT category. Overall survival by pT category following diagnosis and expected survival of a gender and age comparable cohort in the normal population were compared. After 5 years, one would expect breast cancer survival to parallel the expected survival. In contrast, there was a continuous excess mortality, especially in the pT1 and 2 groups.

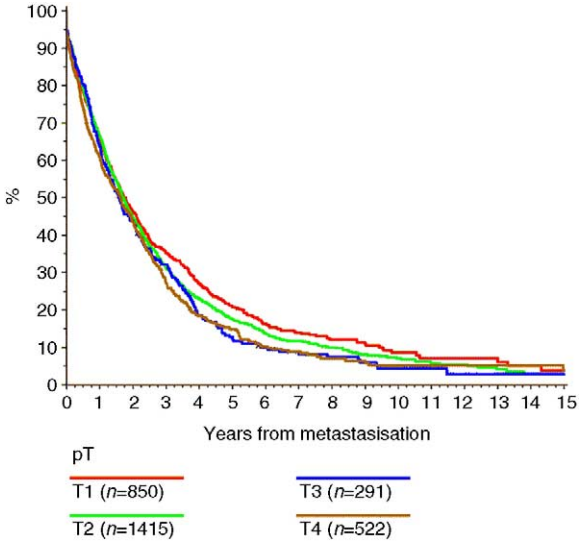

Fig. 3. Overall survival following metastasisation by pT category. Overall survival after metastasisation was compared by pT category. The difference between the survival curves was only just significant. After metastasisation occurred, survival appeared to be independent of pT category, indicating an almost homogeneous growth of metastases.

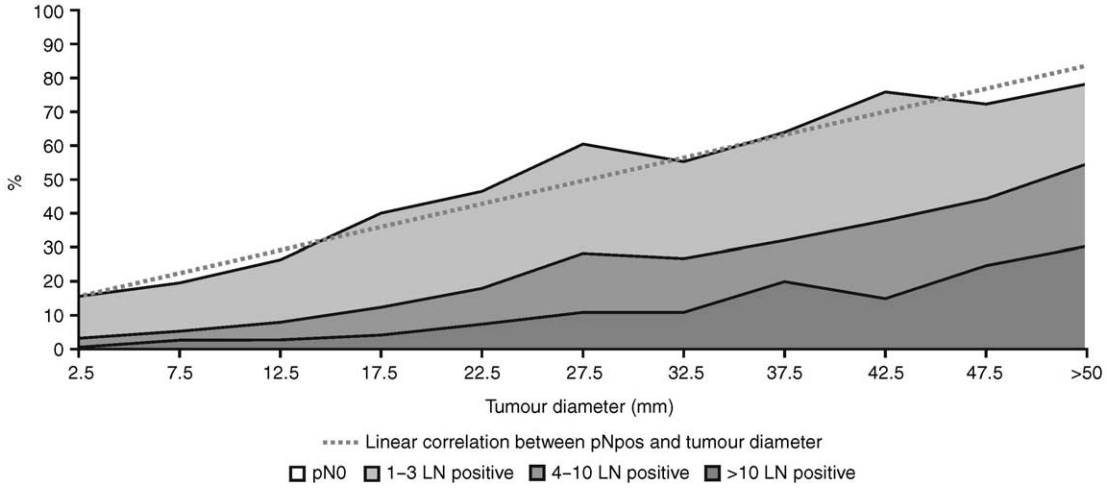

Fig. 2. Proportion of positive lymph nodes by tumour diameter. Tumour diameter, in 5-mm intervals up to over 50 mm, is specified on the *x*-axis. The first interval on the *x*-axis is for all invasive tumours of 5 mm or less, the second of 10 mm or less, but more than 5 mm, and so on. For each interval, the proportion of negative lymph nodes, 1–3, 4–10, and over 10 positive lymph nodes (LN), are outlined. The analysis was based on 5000 patients with pT1–pT3 tumours. The dotted line demonstrates the linear correlation between tumour diameter and the number of positive lymph nodes.

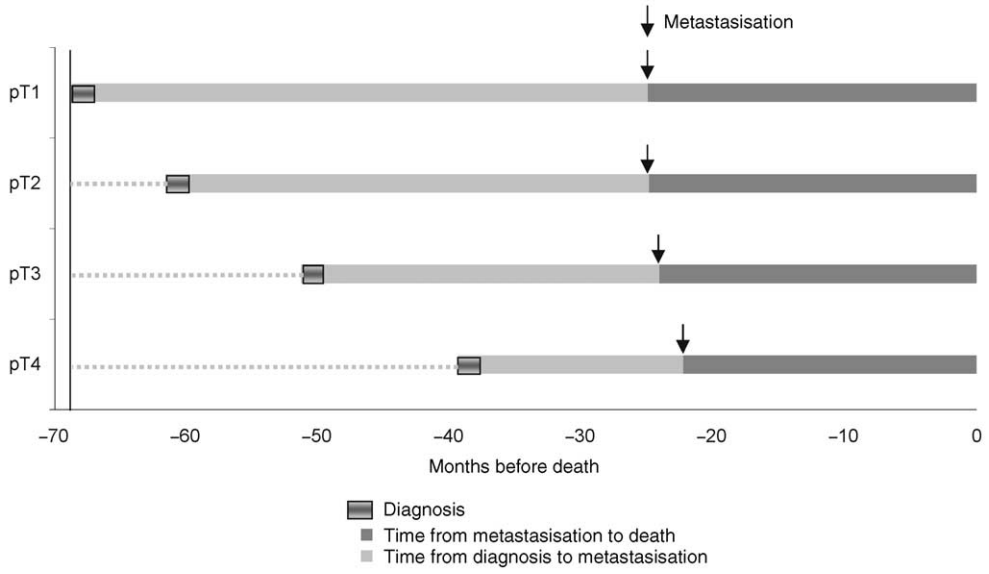

Fig. 4. Mean metastases-free survival time and mean progression time by pT category, synchronised to time of death. As the pT category increased, time to metastasisation and, therefore, the overall survival time decreased. With death as the fixed reference point, time from metastasisation to death was similar across all pT categories. The difference in survival time can be explained, therefore, by a lead time effect. This indicates delayed detection, not a tumour growth characteristic.

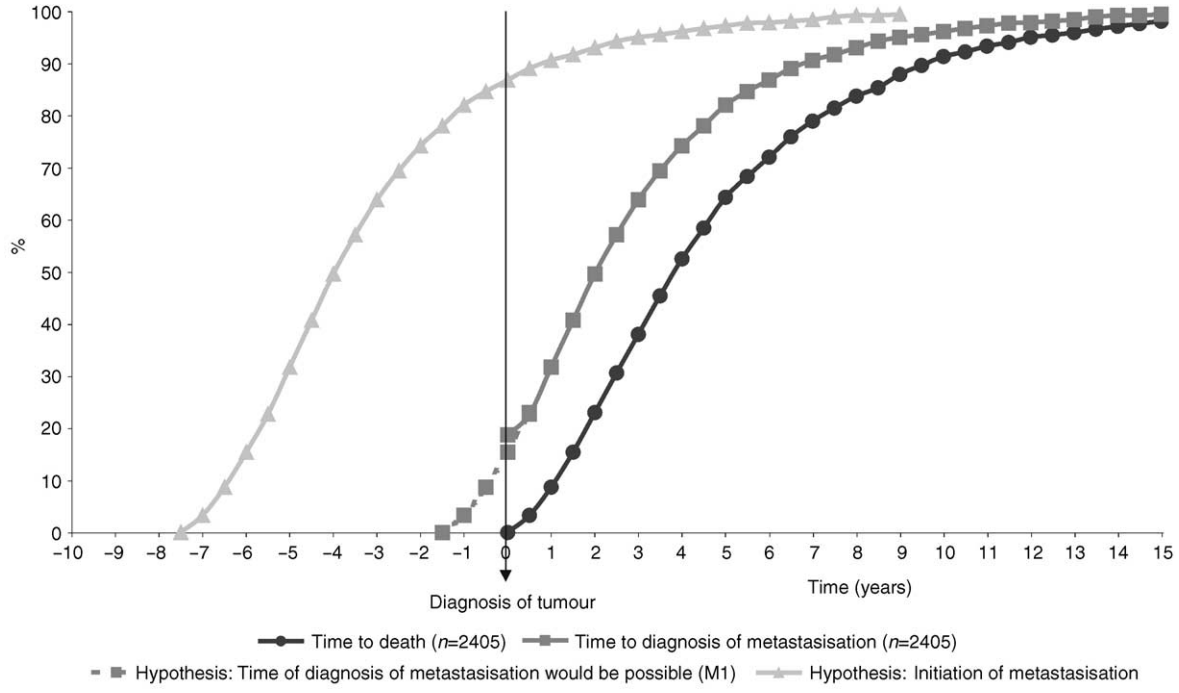

Fig. 5. Cumulative distribution of the metastases-free survival time, the overall survival time and the hypothetical initiation of metastases. Out of 4550 deceased patients, metastases were recorded for 2405. The two curves, time to diagnosis of metastasisation and time to death, were calculated from these patients with metastasisation. The beginning of the time to diagnosis of metastasisation curve indicates the percentage (18.8) of M1 cases of all deceased patients with metastasisation (compared with 4.8% in the total sample). To hypothesise when metastases could have been detected, the shape of the time to death curve was replicated and shifted to the base of the time to diagnosis of metastasisation curve. As metastases growth seemed to be homogeneous, a curve of similar shape would be expected to represent the initiation of metastasisation. The magnitude of the potential shift should be estimated, however, from the time to metastasisation of pT1 tumours, where time to metastasisation is most accurately assessed without a lead time effect (see Fig. 4). The median time to metastasisation for pT1 tumours was 2.9 years (Table 1, 35.3 months). The maximum time to metastasisation must, therefore, be 2-fold the median, i.e. 5.8 years. Thus, to hypothesise the possible time of initiation of metastasisation, the time to diagnosis of the metastasisation curve has been shifted 5.8 years, assuming that metastasisation growth is homogeneous for all of the pT categories. The small percentage of metastasisation that would still occur after the diagnosis of the primary tumour (and its removal) may be attributed to metastasisation induced by local recurrence.

size (see Table 1 and Fig. 1). As the tumour size increased, so the probability of finding positive lymph nodes increased (Fig. 2). Another study group also found this linear correlation up to 5 cm [20]. However, the number of positive lymph nodes is the strongest prognostic factor for individual prognoses, as it indicates that disease spread has already occurred.

4.2. The role of the pT category on survival time before and after MET

The frequency of MET and mean survival time (of metastasised patients) following diagnosis was dependent on the pT stage (Table 1). Breast cancer-specific mortality is almost always a result of MET. Thus, survival time can be split into two steps, MET-free time and progression time after MET until death. Table 1 shows a crucial reduction in the tumour-free time as the pT stage increases. Thus, MET is expected to occur earlier in patients with larger tumours. However, the argument that this shorter tumour-free time and the greater number of M1 cases is evidence of tumour aggressivity is flawed. The time when a breast cancer tumour is detected, whether by mammography, palpation, self-examination or due to symptoms, is coincidental. While tumour size and the detection method are important [20], the time of the detection itself is practically unrelated to tumour biology, as is often reported in the literature [21]. Fig. 3 provides empirical proof of this. pT category, and with it the number of M1 cases, did not influence survival time following MET, in contrast to the results of some studies [11,22]. Mean survival time following MET ranged between 22 and 25 months (Table 1). Progression time after MET was thus very homogeneous. It follows, then, that the MET growth process continued after initiation, independent of the size and growth of the primary tumour.

If the disease process after MET is homogeneous, then it seems logical that the disease process before the diagnosis of MET is also homogeneous. Thus, the number of M1 cases or the length of the tumour-free period are not the result of different biological behaviours. Fig. 4 outlines this relationship. Survival time was presented separately for each pT category and has been synchronised so that death was the fixed time point at zero. Time was then run backwards from this point. Thus, it can be seen that the point of diagnosis for

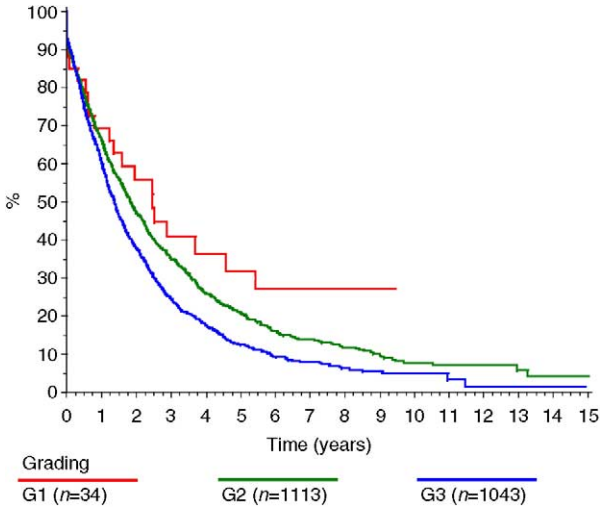

Fig. 6. Overall survival following metastasisation by histological grade. Overall survival after metastasisation was compared by tumour grade (G1, G2, G3). G, grade.

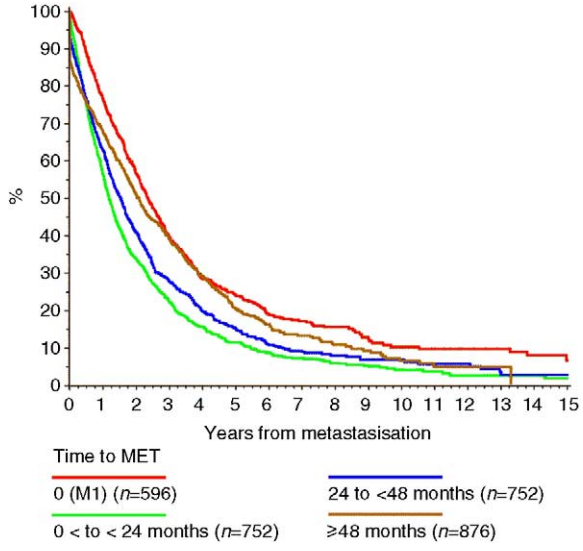

Fig. 7. Overall survival following metastasisation by time to metastasisation. Overall survival after metastasisation appeared only slightly related to the time from diagnosis to metastasisation. The unexpected greater survival of M1 cases could be due to the early detection of metastasisation through better perioperative diagnostics.

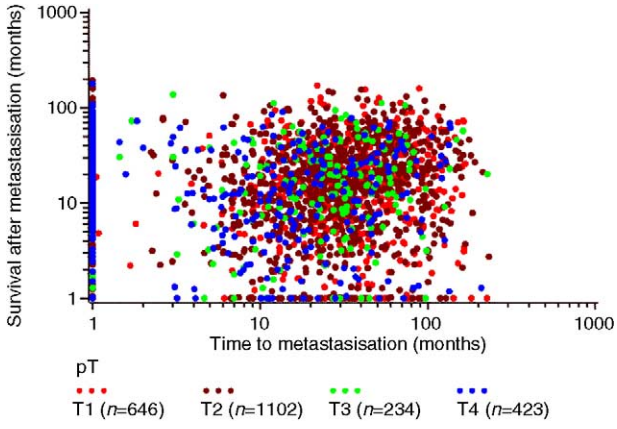

Fig. 8. Scatter diagram for the metastases-free survival time and the survival time after metastasisation. The correlation between time to metastasisation and survival time after metastasisation is shown in the scatter diagram with logarithmic scales. Less than 1% of the variance was explained by the correlation analysis. The M1 cases, with zero time to metastasisation, can be seen beside the *y*-axis. The variability in the survival time for the M1 cases was comparable to that observed for cases at 10 or 100 months to metastasisation.

pT2–4, relative to pT1, simply occurred later in the process of tumour growth. It is also evident that the MET process progressed independently. Thus, there were more M1 cases and a shorter tumour-free interval, the longer the primary tumour had time to grow. The actual time of diagnosis is almost a random event in relation to the process of tumour growth and the independent MET process. Only the frequency of the MET process (that was already underway) and not its velocity was related to tumour diameter. The earlier the tumour is detected, the less chance that MET has already been initiated. The difference in MET-free survival time between the pT categories indicates a lead time effect, as has been identified elsewhere [23].

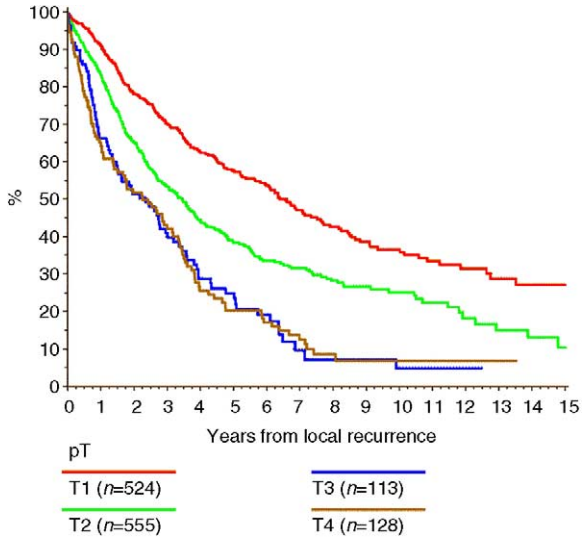

Fig. 9. Overall survival following local recurrence by pT category. Compared with Fig. 1 (survival after diagnosis), survival after local recurrence was worse for all pT categories. This emphasises the role of local recurrence as an indicator for metastasisation. In contrast to survival after metastasisation (seen in Fig. 3), survival following local recurrence appears to be related to the pT category of the primary tumour, especially for the pT1 and pT2 groups. This indicates that the growth process of local recurrence was also not dependent on metastasisation.

4.3. Tumour growth and the frequency of MET

The difference in the number of M1 cases, that are clinically manifest at diagnosis, from 1.1% for pT1 to 21.1% for pT4 (Table 1) is evidence of the frequency and duration of the active MET process. Three points will be discussed concerning the time to MET. Firstly, the data show that over a 15-year period, a mean of 22.4% of MET occurred in pT1 patients (15-year relative survival 77.6%, therefore 22.4% breast cancer-specific mortality, i.e. from MET). If the tumour were not removed at pT1 (mean diameter 14mm) then the rate of MET could increase a further 25.3% in the time that the tumour grows into a pT2 tumour (mean diameter 28 mm) (Table 1). In other words, almost half of the MET estimated at pT2 (47.7%) may have already started before the tumour was of a pT1 size, long before the point of diagnosis of a pT2 tumour.

Second, there is some evidence regarding the time it takes for a pT1 tumour to grow into a pT2 tumour. Since growth requires time, this point can be seen in the average age difference between the pT1 and pT2 patients. In a population-based study with over 3300 patients, recruited over a 2-year period, the average age of pT1 patients was 59.8 years and 61.8 years for pT2 patients [24]. Table 1 shows an average age difference of only 1.1 years between the pT1 and pT2 categories for all MCR patients over a 20-year period. Thus, it takes approximately one to 2 years for a tumour to double in diameter (from 14 to 28 mm) or for the tumour volume to increase 8-fold. An 8-fold increase is equivalent to doubling the tumour volume three times. Thus, for the tumour volume to double, it would take between 120 and 245 days (1–2 years divided by three). In previous studies, the time for a tumour to double in volume was

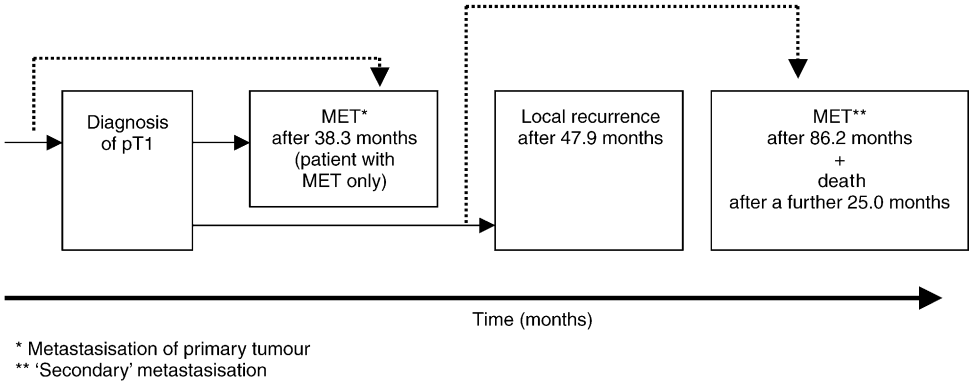

Fig. 10. 'Secondary' metastasisation. Besides metastasisation of the primary tumour, secondary metastasisation also exists. Secondary metastasisation may be initiated by local recurrence. The mean time from diagnosis to local recurrence for pT1 tumours was 47.9 months (Table 1). If one assumes the same growth duration from local recurrence to secondary metastasisation, as from diagnosis of the primary tumour to primary metastasisation (38.3 months), secondary metastasisation for pT1 tumours would be expected after 86.2 months, with death predicted approximately 25 months later. This later mortality may help to explain the excess mortality (seen in Fig. 1) up to 9 years after diagnosis.

80–188 days (depending on the patient's age), or 157 days for the 50–70-year-old age group [25,26]. Likewise, these results show a variation in the possible growth time by a factor of 2.

The third point is related to breast cancer screening [27]. The sojourn-time concept applies to the preclinical phase, when the tumour is detectable by mammography, but before it is clinically evident. When the time between the two examinations is 3 years, between 54 and 82% of the expected breast cancer cases appear as so-called 'interval cancers' in the third year, before the next appointment [28]. In a 2-year period, there is a realistic chance of detecting 50% of all invasive tumours under 15 mm diameter, a recognised quality indicator for mammography [29]. From these well known facts and our data, it can be concluded, qualitatively and quantitatively, that the MET process starts several years before the diagnosis of a primary tumour.

4.4. Estimating the initiation of the MET process

The time from initiation to the diagnosis of MET can be estimated [30]. If the MET process runs homogeneously over time, then the disease process, from the initiation to the diagnosis of MET and on to death, is less related to the biological variability in the tumour and has more to do with a chronological chain of events. Thus, if MET is detected shortly after tumour diagnosis, even for small tumours, then it must have been initiated long before the diagnosis. MET that is found a long time after diagnosis must have been initiated shortly before diagnosis. Based on this assumption, the cumulative distribution of the MET-free time and survival time, for patients who had MET and died, provides evidence for the initiation of MET (Fig. 5). The distribution of the empirical data shows evidence for MET around 2 years before death (Table 1). The start of the MET-free time distribution curve indicates a jump between the number of M1 cases found at diagnosis and all other MET. The dotted line was equivalent to the distribution of the time to death curve and provides evidence for a postponement of M1 detection, up to 1.5 years.

If MET growth were homogeneous, the initiation of MET could be described by shifting the distribution of the MET-free time into the preclinical phase. The magnitude of the potential shift should be estimated from the time to metastasisation of pT1 tumours, where time to metastasisation is most accurately assessed without a lead time effect. Median time to MET in pT1 tumours was 2.9 years (35.3 months, Table 1). The minimum time to MET was zero for the few M1 cases, the maximum time double the median, i.e. 5.8 years. Hypothetically then, the empirically calculated cumulative distribution curve for MET-free time can be moved 5.8 years before the diagnosis of the first metastases. Hence, the earliest MET could have occurred 7.3 years (5.8 plus 1.5 years) before diagnosis and could have been diagnosed then as a very early M1 case. MET initiated just before diagnosis would therefore be detected 5.8 years after diagnosis of the primary tumour. Thus, in total, the duration from initiation of MET to death would be 7.8 years (5.8 plus 2 years). Tumour diameter at diagnosis was related to the frequency of observed MET and can be the observed retrospectively with the distribution curve as a M1 case or prospectively as differing tumour-free intervals. After diagnosis of the primary tumour, the s-shape of the hypothetical curve indicates a slower approach of the distribution curve to 100%. In particular, this asymmetry could point towards evidence for secondary MET caused by LR which occurs after the point of diagnosis.

4.5. Prognostic factors and proliferation speed

The important prognostic factor, pT category, was correlated with an increasing MET rate and, in contrast, only to a very small extent with the speed of growth. What relationship is there between other prognostic factors and growth? In our data, the survival time after MET for G3 cases was a median of 5 months shorter than for G2 cases (Fig. 6). Differences are also reported between pN+ and pN0 or ER+ and ER− [21,31,32]. Thus, varying speeds of growth exist, which have already been shown to be a factor of 2 for the tumour volume doubling time, for example [25,26].

This factor of 2 was also evident in the relationship between the MET-free time and the survival time. Fig. 7 shows the survival curve following MET varying by different tumour-free times. Between 0–24 months and 48 months and over, the median survival time varied from 1.2 to 2.1 years, again only a factor of 2. The survival curve for M1, however, was similar to MET after a 48-month tumour-free interval, confirming that M1 cases were not a sub-group with particularly bad prognoses. The unexpected greater survival of M1 cases could be due to the early detection of MET through better perioperative diagnostics, although most M1 detections are delayed.

How can this variability be interpreted? From the homogeneity of the MET process, it seems obvious to postulate, for all tumour sizes, a variability in growth by a factor of 2. This can also be found in other analyses of tumour growth [25]. Evidence of the plausibility of this reasoning can be found in the scattergram of tumour-free time and progression time (Fig. 8). This does not show a relationship such that the shorter the tumour-free time, the shorter the survival time after MET. Less than 1% of the variance (R^2) was explained by the slight increase in survival time in the longer clinically metastases-free time periods. In addition, survival times for M1 cases showed a similar level of variability in this scattergram.

Our hypothesis of an early MET initiation questions the morphological and genetic correlation between the primary tumour and MET, because the primary tumour at the time of dissemination would have been much smaller and probably had prognostically favourable characteristics.

Would a wide range of growth velocity contradict our hypothesis of an early initiation? An initiation of MET up to 5.8 years before diagnosis seems plausible. Five years would correspond to 10 duplications of tumour volume. If the tumour at diagnosis has approximately 10^9 cells (1 cm), then the earliest dissemination could be possible at approximately 10^6 cells. If large differences in the growth velocity of the metastases exist, then positive lymph nodes and MET with an unknown primary tumour should be more frequent, because the size of the primary tumour would be below a detectable size with approximately 10^7 cells.

Another question concerns MET in different organs. Due to the long 'incubation time' of MET and the short time interval between the detection of MET (at different locations), a cascade-like MET process (one MET location initiating the other) seems unlikely. This short time interval between the detection of MET could explain the limited progress that has been made in the treatment of advanced breast cancers.

4.6. Local recurrence and the relationship between the pT category and time before and after local recurrence

To discuss the long-term effect of adjuvant local radiotherapy, which reduces the frequency of LR, four different causes of LR should be highlighted. First, positive margins are a known cause of recurrence, hence recurrence that results from this serves as an indicator of the quality of the surgical treatment [33,34]. The second type of recurrence appears following breast-conserving therapy of a multifocal tumour. A third established cause of recurrence are subsequent ispilateral second tumours [35,36] which, compared with the primary tumour, occur much later and may sometimes have a different histology and quadrant location [35,37–41]. A fourth group, for which the causes remain unknown, should also be mentioned, when there are negative margins (R0), no risk factors for multifocality and when the recurrence occurs soon after or near the primary tumour. This 'genuine' recurrence—perhaps from tumour cells in the extracellular matrix—is evident in the first studies of breast conservation therapy, where a recurrence rate of 40% in patients without radiotherapy was reported [42,43]. Normally all four types of recurrence are documented as local recurrence.

The frequency of LR increased as the pT stage increased (Table 1) [44]. Compared with survival after diagnosis (Fig. 1), survival after LR was worse for all pT categories. This emphasises the role of LR as an indicator for metastasisation. In contrast to survival after MET (Fig. 3), survival following LR appears to be related to the pT category of the primary tumour, especially the pT1 and pT2 groups (Fig. 9) [45,46]. This also emphasises that the LR growth process is not dependent on metastasisation [17,41,47–49]. Mean time to LR also appeared to be dependent on pT (Table 1). However, is the decrease in recurrence-free time as the tumour diameter increases a biological phenomenon? In contrast to MET, the disease process for all genuine recurrences with R0 can be synchronised to the point of diagnosis, thus all LR in contrast to MET must have tumour removal as the starting point. If primary tumour growth and MET growth are unrelated, the (removed) primary tumour should also have no influence on the time period of recurrent growth. This suggests that the dependence of LR-free time on pT may merely be an artefact of follow-up. Due to the poor prognosis of pT3-4 cases and the associated shorter MET-free time, and thus shorter survival, many patients with advanced disease do not live long enough to present LR, compared with pT1 patients [45]. In prognostically unfavourable groups, there is, therefore, less late LR. The increasing MET/LR ratio demonstrates this (Table 1).

It is important to note that, in addition to genuine recurrences, as time goes by the chance of a newly developed secondary ipsilateral tumour increases. The risk of recurrence, thus, even after 5 years, does not fall, as it does for MET cases.

As multivariate analyses from other studies [4,7,9] and the MCR data confirm, LR is, above all, an indicator of a poor prognosis; indicating a higher risk of MET. Insufficient local control—despite R0 resection—is thus linked to a higher rate of MET, and dependent on the pT category.

4.7. 'Secondary' metastasisation through local recurrence

Does the indicator function of LR mean that LR can not initiate MET [9,10,17,50,51]? The interpretation of the MET process data form the basis on which to unravel this question of secondary MET through LR. If some of the tumour remains after operation, or a 'secondary' ipsilateral tumour develops, it has the potential to metastasise again like a primary local tumour. Its prognosis would, again, depend on the size of the LR [7].

Evidence of 'secondary' MET can be derived from the following arguments concerning the disease process. There are three sub-groups, either LR only which is not an indicator of MET, MET only or MET and LR. These three types of progression demonstrate very different properties from the primary tumour. The crucial question is when does MET with LR and when does MET without LR occur? LR stemming from larger

tumours is more frequent and has thus a higher risk of MET. Hence, the development of MET in the course of MET and LR would be expected somewhat earlier in large tumours.

For primary pT1 cases, the time to MET for patients with both MET and LR was significantly longer, 55.9 months, than the time to MET of MET only cases, 38.3 months (Table 1). One can hypothesise that this average value of 55.9 months consists of two groups, MET started by the primary tumour (38.3 months) and MET initiated by LR (86.2 months (38.3 + 47.9 months)) (Fig. 10). For the sub-group of patients with MET and LR, 37% of the MET derived from LR and 63% from the primary tumour. It is also assumed that LR-induced MET develops similarly to primary-induced MET. With, on average, 47.9 months before LR, 38.3 months before MET and 25 months before death, excess mortality would still be expected after 111.2 months, or 9.3 years after diagnosis of the primary tumour. That LR, especially after breast-conserving therapy, can also occur with a comparable risk after 5 or 10 years [7], suggests that over and above the 5.3 years (38.3 + 25 months) after LR, there is a delayed excess mortality from 'secondary' MET. Thus, a successful permanent reduction of LR increases the survival benefit for 10 or more years after diagnosis.

Another way to describe the relevance of this finding is to estimate the number of cases needed to show a difference in survival of 2.4% in 10 years. With a survival rate of 80%, more than 3000 patients per group (with and without LR) would be required. This is the reason why studies to prove such results are so difficult. The risk of secondary metastasis is small and therefore it is only possible to estimate it with a large sample size. This small effect on survival can be seen in Peto's paper, where almost 20 000 women (19 582) were included [52]. In Fisher's paper [53] for example 'only' 2163 women were randomised in three treatment groups. A total of 51 locoregional events occurred versus 111 versus 87. This sample size is too small to show an additional risk by local recurrence for secondary metastasisation.

4.8. Implications for practice and research

The data we have presented describe a model of metastasisation. Such a model is more valuable, the more it explains and raises new questions. Our MET model, based on empirical data, further confirms the well known equal value of the two primary treatments for breast cancer [53,54]. Breast-conserving therapy and mastectomy have virtually the same influence on survival, if the tumour is removed and further MET development prevented. In addition, outcome-improvements cannot be expected by establishing breast centres.

Our MET model also provides a plausible interpretation of the well known studies of irradiation at the site of the primary tumour after mastectomy to prevent further LR and with it the risk of MET. Recurrence after mastectomy has the same risk as that after breast-conserving therapy. With up to 20 years of follow-up, these studies show an increasing survival benefit from local irradiation. Optimal local therapy is thus crucial [46]. With very high LR rates of approximately 30%, a 6–7% survival benefit may be attributed to the reduction in LR [52]. Speculation about a systemic effect of local irradiation, therefore, seems redundant [2,43,55,56]. However, it is not clear, because the studies involve irradiation to both the chest wall and lymph nodes, whether the chest wall is sufficient or whether the whole area must be treated [57]. The use of adjuvant radiotherapy for LN recurrence does not fit our MET model [58–60]. LN recurrence develops from cells that have already spread and are systemically established. Furthermore, it should be noted that positive lymph nodes may be left despite axilla dissection. Some studies show up to 30% positive lymph nodes in level III (including skip metastases) [61,62]. Even after axillary lymph node dissection for levels I and II, where 10–20 lymph nodes have been removed, positive lymph nodes remain in levels I and II. Lymph nodes of the *mammaria interna* also remain. If axillary radiation (level III inclusive) is comparable with operative axillary dissection (level III exclusive) the effectiveness of both procedures must be questioned. The 25-year follow-up study of the National Surgical Adjuvant Breast Project (NSABP) shows equal survival between axillary dissection and abandonment of axillary dissection [63]. Logically then, it would seem justifiable to cease LN irradiation and LN dissection, which remained when the radicality of the operation was revised [64]. It would also greatly improve patients' quality of life [65,66]. The sentinel concept is a first step in this direction, but not a change of the paradigm.

The differences in the first studies in the 1980s on lymph node dissection, with or without radiotherapy, can also be clarified. All control arms without irradiation showed LR rates increasing to 40% and increased MET [42]. The increased mortality in the group that was not irradiated was a small effect that could not be substantiated with such a small sample size, when the number of cardiac deaths from the radiation techniques at that time were high and the observation time (under 10 years) limited [43,67].

The studies of adjuvant therapy with tamoxifen provide further examples to support our model [68–70]. Since tamoxifen reduces the rate of LR—the survival curve of the control group indicates a higher LR risk—the increasing excess mortality can be explained. Radiotherapy and systemic therapies both reduce LR, and are so similarly effective compared with the control group that it has already been suggested that radiotherapy could replace hormonal therapy [71]. Although systemic therapy and radiotherapy operate in different ways, they both reduce the incidence of MET [17,72].

The MET model also acknowledges the equal value of expensive machine and symptom-oriented aftercare [73]. Since the MET process may already have begun before diagnosis, it cannot be prevented by local and adjuvant primary therapy. The use of tumour markers, therefore, makes little sense. Regular mammography screening in the recovery period to detect LR early is more important since the potential for MET increases with the size of the LR [7,74].

The implications for screening are also obvious. Our calculations indicate that screening every 3 years may be insufficient. However, as shown empirically, mortality can effectively be lowered with at least a 2-year interval. If an early detection programme discovers, on average, 15-mm tumours, then mortality would be around 5% higher than if early detection could spot 10-mm tumours.

Shifting the timing of the primary operation is also related to tumour growth [75,76]. A 10-mm tumour can double in volume in 4 months (120 days) making a 12.6-mm diameter tumour. In this time, further MET may be initiated in 2.6% of those concerned (1%/mm). Such an effect would only be evident with a large patient sample. In a 20-mm tumour, a 4-month delay in treatment could result in a 5% increase in mortality. Immediate operation of large tumours can save lives. Waiting for LR as an indicator to start systemic therapy may cause additional deaths [77].

Some limitations can be found in the proposed simple MET model. The MET model does not provide any explanation for the different adjuvant therapy outcomes, evident in the survival curves, which show worse survival in the control groups, practically from the start of the studies [2,78–80]. Such a level of effectiveness would mean that both already initiated individual tumour cells, which lead to MET after a long tumour-free interval, and MET approximated at the diagnostic threshold, would respond to therapy. Such partial effectiveness would then also be apparent in M1 cases as well as testicular tumours treated with cisplatin. However, the MET model also highlights the limited effectiveness of systemic therapies, which are not as successful at treating definite MET as cisplatin for testicular tumours. If a therapeutic window for tumour cells were proposed [81,82], in which effective treatment is possible, then the survival curves would only move apart slowly after a longer identical period. This early divergence would also be associated with a large variance in tumour growth, which the empirical data for breast cancer do not indicate.

5. Concluding remarks

First of all, it should be noted that our MET model can also be applied to other solid tumours. Secondly, the value of a large patient sample, with clinical data and long follow-up that can be achieved in a tumour registry, has been demonstrated. Thirdly, it is clearly important to consider the evidence and its implications, from studies as well as empirical findings, and to work out the pros and cons of possible models. It is clear that breast cancer may already be a systemic illness, at the point of diagnosis, for most of the female patients who develop MET today. Only for the sub-group whose primary local disease later develops into LR, can the MET be caused by LR only. Thus, LR appears to be both an indicator and a cause of MET. Our MET model indicates a process that is difficult to influence with treatment, it justifies optimal local therapy, but shows the limitations of systemic therapy. It also supports the cessation of axilla dissection and irradiation. Finally, the MET model underlines, in contrast to the Cochrane review [83], the possibility of avoiding deaths by moving the diagnosis forward and by establishing systematic early detection with tumour diameter as the target criterion.

Acknowledgements

We thank all the hospitals and departments that participated in the documentation of the data. The authors thank also all colleagues of the MCR for the co-operation, processing of the data and the reliable infrastructure. The Munich Cancer Registry (MCR) is part of the Munich Comprehensive Cancer Center (MCCC), an institution of the Ludwig Maximilians Universität and Technische Universität. Additionally, funding is given by the Deutsche Krebshilfe, the Wilhelm Sander-Stiftung, the Bavarian Ministry of Health and the Federal Ministry of Health.

References

1. Overgaard M, Hansen PS, Overgaard J, *et al*. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997, **337**, 949–955.
2. Ragaz J, Jackson SM, Le N, *et al*. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997, **337**, 956–962.
3. Hellman S. Stopping metastases at their source. *N Engl J Med* 1997, **337**, 996–997.
4. Arriagada R, Rutqvist LE, Mattsson A, Kramar A, Rotstein S. Adequate locoregional treatment for early breast cancer may prevent secondary dissemination. *J Clin Oncol* 1995, **13**, 2869–2878.
5. Bartelink H, Horiot J-C, Poortmans P, *et al*. Group ftEOfRaToCRaBC. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *New Engl J Med* 2001, **345**, 1378.
6. Evans RA. Radiotherapy and chemotherapy in high-risk breast cancer. *N Engl J Med* 1998, **338**, 331 [discussion 331–332].

7. Fortin A, Larochelle M, Laverdiere J, Lavertu S, Tremblay D. Local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy. *J Clin Oncol* 1999, **17**, 101–109.
8. Gelman R, Harris JR. Editorial comment on "the link between local recurrence and distant metastasis in human breast cancer" by Serge Koscielny and Maurice Tubiana. *Int J Radiat Oncol Biol Phys* 1999, **43**, 7–9.
9. Kemperman H, Borger J, Hart A, Peterse H, Bartelink H, van Dongen J. Prognostic factors for survival after breast conserving therapy for stage I and II breast cancer. The role of local recurrence. *Eur J Cancer* 1995, **31A**, 690–698.
10. Veronesi U, Marubini E, Del Vecchio M, *et al*. Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. *J Natl Cancer Inst* 1995, **87**, 19–27.
11. Demicheli R, Retsky MW, Swartzendruber DE, Bonadonna G. Proposal for a new model of breast cancer metastatic development. *Ann Oncol* 1997, **8**, 1075–1080.
12. Karrison TG, Ferguson DJ, Meier P. Dormancy of mammary carcinoma after mastectomy. *J Natl Cancer Inst* 1999, **91**, 80–85.
13. Halsted W. The results of operations for the cure of the cancer of the breast performed at the Johns Hopkins Hospital from June 1889 to January 1894. *Arch Surg* 1894, **20**, 497.
14. Fisher B. The surgical dilemma in the primary therapy of invasive breast cancer: a critical appraisal. *Curr Probl Surg* 1970, **33**, 1.
15. Hellman S, Harris JR. The appropriate breast cancer paradigm. *Cancer Res* 1987, **47**, 339–342.
16. Jatoi I. Breast cancer: a systemic or local disease? *Am J Clin Oncol* 1997, **20**, 536–539.
17. Koscielny S, Tubiana M. The link between local recurrence and distant metastases in human breast cancer. *Int J Radiat Oncol Biol Phys* 1999, **43**, 11–24.
18. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 1991, **19**, 403–410.
19. Hakulinen T. Cancer survival corrected for heterogeneity in patient withdrawal. *Biometrics* 1982, **38**, 933–942.
20. Michaelson JS, Silverstein M, Wyatt J, *et al*. Predicting the survival of patients with breast carcinoma using tumor size. *Cancer* 2002, **95**, 713–723.
21. Kamby C, Sengelov L. Survival and pattern of failure following locoregional recurrence of breast cancer. *Clin Oncol R Coll Radiol* 1999, **11**, 156–163.
22. Leivonen MK, Kalima TV. Prognostic factors associated with survival after breast cancer recurrence. *Acta Oncol* 1991, **30**, 583–586.
23. Shapiro S, Goldberg JD, Hutchison GB. Lead time in breast cancer detection and implications for periodicity of screening. *Am J Epidemiol* 1974, **100**, 357–366.
24. Engel J, Baumert J, Sauer H, Hölzel D. Qualitätssicherung in der Onkologie am Beispiel des Mammakarzinoms der Feldstudie München. *Onkologe* 2001, **7**, 307–320.
25. Peer PG, van Dijck JA, Hendriks JH, Holland R, Verbeek AL. Age-dependent growth rate of primary breast cancer. *Cancer* 1993, **71**, 3547–3551.
26. Hart D, Shochat E, Agur Z. The growth law of primary breast cancer as inferred from mammography screening trials data. *Br J Cancer* 1998, **78**, 382–387.
27. Tabar L, Vitak B, Tony HH, Yen MF, Duffy SW, Smith RA. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer* 2001, **91**, 1724–1731.
28. Woodman CB, Threlfall AG, Boggis CRM, Prior P. Is the three year breast screening interval too long? Occurrence of interval cancers in NHS breast screening programme's north western region. *Br Med J* 1995, **310**, 224–226.
29. Perry N, Broeders M, deWolf C, Törnberg S. *European Guidelines for Quality Assurance in Mammography Screening*, 3rd edn. Brussels, European Commission, 2001.
30. Hölzel D, Engel J, Schmidt M, Sauer H. Modell zur primären Metastasierung beim Mammakarzinom und dessen klinische Bedeutung. *Strahlenther Onkol* 2001, **177**, 10–24.
31. Blanco G, Holli K, Heikkinen M, Kallioniemi OP, Taskinen P. Prognostic factors in recurrent breast cancer: relationships to site of recurrence, disease-free interval, female sex steroid receptors, ploidy and histological malignancy grading. *Br J Cancer* 1990, **62**, 142–146.
32. Vogel CL, Azevedo S, Hilsenbeck S, East DR, Ayub J. Survival after first recurrence of breast cancer. The Miami experience. *Cancer* 1992, **70**, 129–135.
33. Salvadori B. Local recurrences after breast-conserving treatment: an open problem. *Semin Surg Oncol* 1996, **12**, 46–52.
34. Schnitt SJ, Abner A, Gelman R, *et al*. The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast-conserving surgery and radiation therapy. *Cancer* 1994, **74**, 1746–1751.
35. Kurtz JM, Amalric R, Brandone H, *et al*. Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course, and prognosis. *Cancer* 1989, **63**, 1912–1917.
36. Recht A, Hayes DF, Eberlein TJ, Sadowsky L. Local-reginal recurrence after mastectomy or breast conserving therapy. *Dis Breast*, 1996, 649–667.
37. Bartelink H, Borger JH, van Dongen JA, Peterse JL. The impact of tumor size and histology on local control after breast-conserving therapy. *Radiother Oncol* 1988, **11**, 297–303.
38. Reid SE, Murthy MS, Kaufman M, Scanlon EF. Endocrine and paracrine hormones in the promotion, progression and recurrence of breast cancer. *Br J Surg* 1996, **83**, 1037–1046.
39. Touboul E, Buffat L, Belkacemi Y, *et al*. Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer. *Int J Radiat Oncol Biol Phys* 1999, **43**, 25–38.
40. Voogd AC, Peterse JL, Crommelin MA, *et al*. Histological determinants for different types of local recurrence after breast-conserving therapy of invasive breast cancer. Dutch Study Group on local Recurrence after Breast Conservation (BORST). *Eur J Cancer* 1999, **35**, 1828–1837.
41. Willner J, Kiricuta IC, Kölbl O. Locoregional recurrence of breast cancer following mastectomy: always a fatal event? Results of univariate and multivariate analysis. *Int J Radiat Oncol Biol Phys* 1997, **37**, 853–863.
42. Macmillan RD, Purushotham AD, George WD, *et al*. Local recurrence after breast-conserving surgery for breast cancer. *Br J Surg* 1996, **83**, 149–155.
43. Pierce LJ, Lichter AS. Defining the role of post-mastectomy radiotherapy: the new evidence. *Oncology (Huntingt)* 1996, **10**, 991–1002 [discussion 1006–1007, 1011].
44. Voogd A, Nielsen M, Peterse J, Bilchert-Toft M, *et al*. Group DBCC, Cancer BCCGotEOfRaTo. Differences in risk factors for local recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol* 2001, **19**, 1688–1697.
45. Fowble B, Solin LJ, Schultz DJ, Rubenstein J, Goodman RL. Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment. *Int J Radiat Oncol Biol Phys* 1990, **19**, 833–842.
46. Levitt SH. The importance of locoregional control in the treatment of breast cancer and its impact on survival. *Cancer* 1994, **74**, 1840–1846.
47. Haffty BG, Fischer D, Beinfield M, McKhann C. Prognosis following local recurrence in the conservatively treated breast cancer patient. *Int J Radiat Oncol Biol Phys* 1991, **21**, 293–298.

48. Halverson KJ, Perez CA, Kuske RR, Garcia DM, Simpson JR, Fineberg B. Survival following locoregional recurrence of breast cancer: univariate and multivariate analysis. *Int J Radiat Oncol Biol Phys* 1992, **23**, 285–291.
49. Recht A, Schnitt SJ, Connolly JL, *et al*. Prognosis following local or regional recurrence after conservative surgery and radiotherapy for early stage breast carcinoma. *Int J Radiat Oncol Biol Phys* 1989, **16**, 3–9.
50. Cowen D, Jacquemier J, Houvenaeghel G, *et al*. Local and distant recurrence after conservative management of "very low-risk" breast cancer are dependent events: a 10-year follow-up. *Int J Radiat Oncol Biol Phys* 1998, **41**, 801–807.
51. Cuzick J, Stewart H, Rutqvist L, *et al*. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol* 1994, **12**, 447–453.
52. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000, **355**, 1757–1770.
53. Fisher B, Anderson S, Bryant J, *et al*. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002, **347**, 1233–1241.
54. Veronesi U, Cascinelli N, Mariani L, *et al*. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002, **347**, 1227–1232.
55. Overgaard M, Jensen MB, Overgaard J, *et al*. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999, **353**, 1641–1648.
56. Wolberg WH, Robins HI. Radiotherapy and chemotherapy in high-risk breast cancer. *N Engl J Med* 1998, **338**, 329–330 [discussion 331–332].
57. Mokbel K, Reed MJ. Benefits of post-mastectomy radiotherapy. *Lancet* 1998, **351**, 219.
58. Fisher BJ, Perera FE, Cooke AL, *et al*. Long-term follow-up of axillary node-positive breast cancer patients receiving adjuvant systemic therapy alone: patterns of recurrence. *Int J Radiat Oncol Biol Phys* 1997, **38**, 541–550.
59. Vicini FA, Horwitz EM, Lacerna MD, *et al*. The role of regional nodal irradiation in the management of patients with early-stage breast cancer treated with breast-conserving therapy. *Int J Radiat Oncol Biol Phys* 1997, **39**, 1069–1076.
60. Yarnold J. Benefits of post-mastectomy radiotherapy. *Lancet* 1997, **350**, 1415–1416.
61. Danforth Jr. DN, Findlay PA, McDonald HD, *et al*. Complete axillary lymph node dissection for stage I-II carcinoma of the breast. *J Clin Oncol* 1986, **4**, 655–662.
62. Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with breast carcinoma. *Cancer* 1992, **69**, 2496–2501.
63. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med* 2002, **347**, 567–575.
64. Keshtgar MR, Baum M. Axillary Dissection over the years: where to from here? *World J Surg* 2001, **25**, 761–766.
65. Veronesi U, Paganelli G, Galimberti V, *et al*. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet* 1997, **349**, 1864–1867.
66. Veronesi U, Galimberti V, Zurrida S, *et al*. Sentinel lymph node biopsy as an indicator for axillary dissection in early breast cancer. *Eur J Cancer* 2001, **37**, 454–458.
67. Clark RM, Whelan T, Levine M, *et al*. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. *J Natl Cancer Inst* 1996, **88**, 1659–1664.
68. Dalberg K, Johansson H, Johansson U, Rutqvist LE. A randomized trial of long term adjuvant tamoxifen plus postoperative radiation therapy versus radiation therapy alone for patients with early stage breast carcinoma treated with breast-conserving surgery. Stockholm Breast Cancer Study Group. *Cancer* 1998, **82**, 2204–2211.
69. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998, **351**, 1451–1467.
70. Fisher B, Costantino J, Redmond C, *et al*. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med* 1989, **320**, 479–484.
71. Kurtz JM. Tamoxifen and breast conservation: do we still need radiotherapy? *Cancer* 1998, **82**, 2090–2092.
72. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Senn HJ. Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. Seventh International Conference on Adjuvant Therapy of Primary Breast Cancer. *J Clin Oncol* 2001, **19**, 3817–3827.
73. DelTurco MR, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V. Intensive diagnostic follow-up after treatment of primary breast cancer. *JAMA* 1994, **271**, 1593–1597.
74. Stotter AT, McNeese MD, Ames FC, Oswald MJ, Ellerbroek NA. Predicting the rate and extent of locoregional failure after breast conservation therapy for early breast cancer. *Cancer* 1989, **64**, 2217–2225.
75. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. *Lancet* 1999, **353**, 1119–1126.
76. Sainsbury R, Johnston C, Haward B. Effect on survival of delays in referral of patients with breast-cancer symptoms: a retrospective analysis. *Lancet* 1999, **353**, 1132–1135.
77. Fisher B, Anderson S, Fisher ER, *et al*. Significance of ipsilateral breast tumour recurrence after lumpectomy. *Lancet* 1991, **338**, 327–331.
78. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 1992, **339**, 71–85.
79. Riethmuller G, Holz E, Schlimok G, *et al*. Monoclonal antibody therapy for resected Dukes' C colorectal cancer: seven-year outcome of a multicenter randomized trial. *J Clin Oncol* 1998, **16**, 1788–1794.
80. Rutqvist LE, Cedermark B, Glas U, *et al*. Radiotherapy, chemotherapy, and tamoxifen as adjuncts to surgery in early breast cancer: a summary of three randomized trials. *Int J Radiat Oncol Biol Phys* 1989, **16**, 629–639.
81. Diel IJ, Kaufmann M, Costa SD, *et al*. Micrometastatic breast cancer cells in bone marrow at primary surgery: prognostic value in comparison with nodal status. *J Natl Cancer Inst* 1996, **88**, 1652–1658.
82. Pantel K, von Knebel Doeberitz M, Izbicki JR, Riethmuller G. Disseminated tumor cells: diagnosis, prognostic relevance, phenotyping and therapeutic strategies. *Chirurgia* 1997, **68**, 1241–1250.
83. Olsen O, Gøtzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001, **358**, 1340–1342.