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NON-THEMATIC REVIEW

Positive lymph nodes do not metastasize

Jutta Engel · Rebecca T. Emeny · Dieter Hölzel

Abstract Our understanding of the role of lymph nodes (LN) in the metastasization process (MET) is marginal. Positive LNs (pLN) are the most important prognostic factor and lymph node dissection (LND) is still standard practice in primary treatment. However, up to now, there is almost no evidence that elective LND has a survival benefit. Based on many clinical and experimental findings, we propose that tumor foci in regional LN are incapable of metastasization and can therefore not infiltrate further LN and organs. Available data demonstrate a very early infiltration of MET capable tumor cells from the primary tumor into regional LN, and thereafter an increased probability of subsequent LN infiltrations. Disparate growth rates of the first versus subsequent infiltrating tumors as well as the asymptotic growth and prognosis of large tumor foci in LN explain many clinical observations for solid tumors. The consequence of the hypothesis "pLN do not metastasize" would impact clinical treatment and research and contribute to understanding the mounting evidence against LND.

Keywords Breast cancer · Colorectal cancer · Positive lymph node · Tumor cell dissemination · Tumor growth

J. Engel · R. T. Emeny · D. Hölzel
Munich Cancer Registry (MCR) of the Munich Cancer Centre (MCC) at the Institute for Medical Informatics, Biometry and Epidemiology IBE, Ludwig-Maximilians-University, Clinic Großhadern,
Munich, Germany

D. Hölzel (✉)
Tumorregister München, Klinikum Grosshadern,
81377 Munich, Germany
e-mail: hoe@ibe.med.uni-muenchen.de

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Abbreviations

BC	Breast cancer
LN	Lymph node(s)
pLN	Positive lymph node(s)
LND	Lymph node dissection
SLN	Sentinel lymph node
MET	(distant) metastasization
PT	Primary tumor
TC(D)	Tumor cell (dissemination)
VD(T)	Volume doubling (time)
pN_{ITC}	Isolated TC in LN <0.2 mm
pN_{micro}	Micrometastasis in LN (0.2–2 mm)
pN	Pathological classification of regional lymph node

1 Randomized trials do not show a survival benefit of LND

Elective regional lymph node dissection (LND) has been a standard in tumor surgery for more than a century. Increasingly, however, many randomized trials are challenging this paradigm [1–9]. Not even a single randomized trial indicates a benefit of LND for survival for any solid tumor [10–14]. That is, the highest level of clinical evidence demonstrates no survival benefit. If this is true, then the lack of survival benefit from LND must also be logically deducible from the plethora of published data. The prognosis and growth rate of positive LN (pLN), the estimated time of first and subsequent LN infiltrations, and their very different probabilities will be discussed. The interpretation of and logical deduction from these data supports the basic LN hypothesis: "pLN do not metastasize".

2 PT-size-dependent LN status predicts mortality

The regional LN status of any cancer is dependent on the growth of the PT and therefore on the T-category of TNM classification [15]. Clinical breast cancer (BC) data is well suited to show this association since the tumor diameter is a continuous variable allowing for the correlation with regional or distant progressions. In addition, BC do not grow in varying morphological structures like, for example, colorectal and prostate cancer with volatile increases of pLN from pT2 to pT3. Figure 1 shows the decreasing relative survival, and the corresponding increasing tumor-related mortality, with increasing number of pLN in BC.

The dependence of LN status and 10-year BC-specific mortality (1-probability of relative 10-year survival) on PT diameter is demonstrated by data from over 40,000 BC patients from the Munich Cancer Registry (MCR, 1998–2000) [16]. In Fig. 2, patient data is organized by PT diameter; 10 cohorts of patients with PT diameters between 2.5 and 47.5 mm are depicted in 5-mm intervals. Regression lines derived from this data demonstrate that mortality as well as pN+ status are linearly correlated with tumor diameter, and both have identical slopes, as reported by others [13, 17]. With every millimeter increase in a BC diameter, both pN+ status and mortality increase by 1.2%. Cases with a PT >50 mm show large variance; therefore, the last data point on the curves is only grossly representative of the biologic properties of larger tumors. PT <5 mm are detected with mammography and show a higher mean number of pLN than pT1b, perhaps due to detection-related risk factors (Table 1). Therefore, the 10-year mortality is worse than pT1b. The dependency of LN status and mortality beyond this interval must be S-shaped, with few pLN occurring with very small PT and about 90% for very large PT. With the assumption of a Poisson process, the association between LN status and PT diameter can be calculated and generates comparable results for PT diameter between 7.5 and 47.5 [18].

3 Primary and secondary infiltration of the lymphatic network

Once a PT achieves the potential to infiltrate the LNs then a rapid spreading into the LN network occurs. Data from Table 1 provide a rough estimation based on the distribution of MCR patient data presented according to PT classification. Among 100 patients with a pT1c PT, 70.7% are pN0 and 29.3% are pN+, with a total of 117 pLN among them (Table 1, 4×29.3). In patients who are not diagnosed until 28.5 mm PT size then 48% remain pN0 and 52% will become pN+, with a total of 312 pLN (Table 1, 6×52). That is, in a cohort of 100 patients during the growth of the PT from 15 to 28.5 mm, 23 pN0 patients become infiltrated for the first time and about 195 new LN become positive for the 23 pN0 and 29 pN+ patients. Though the mean number of pLN increases from 4 for pT1c to 6 for pT2 and corresponds to a rate of 0.15 pLN per millimeter PT growth, the increase in the number of pLN for pN+ patients is more than 2-fold higher. This is almost a 20-fold increased probability compared to the first infiltration of a SLN. The infiltration process is shown in Fig. 3a with changes of LN involvement

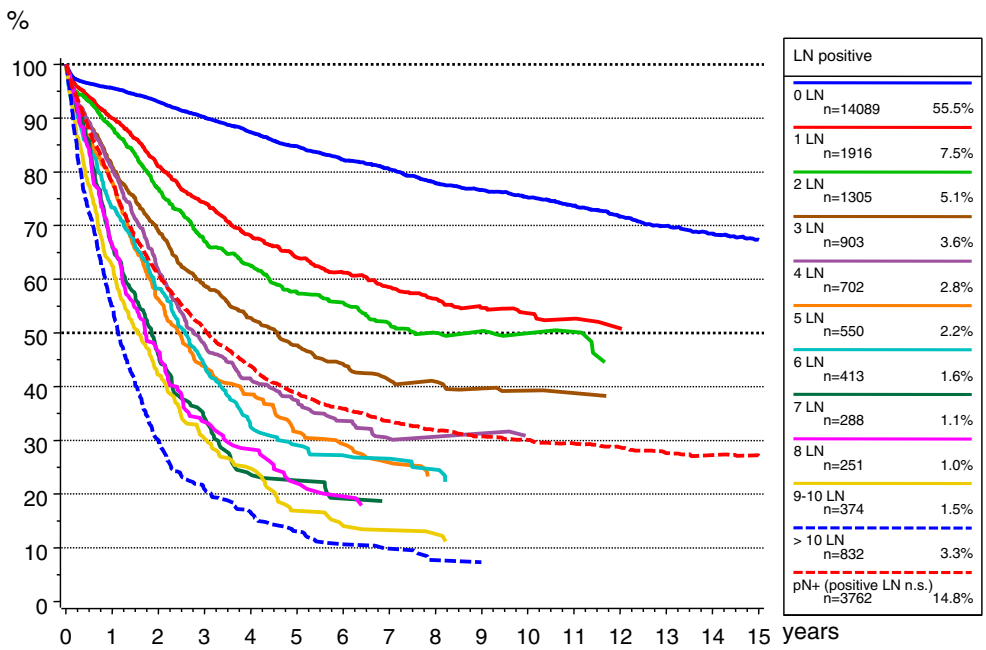

Fig. 1 Relative survival stratified by number of positive lymph nodes in breast cancer: (MCR data n=31,316)

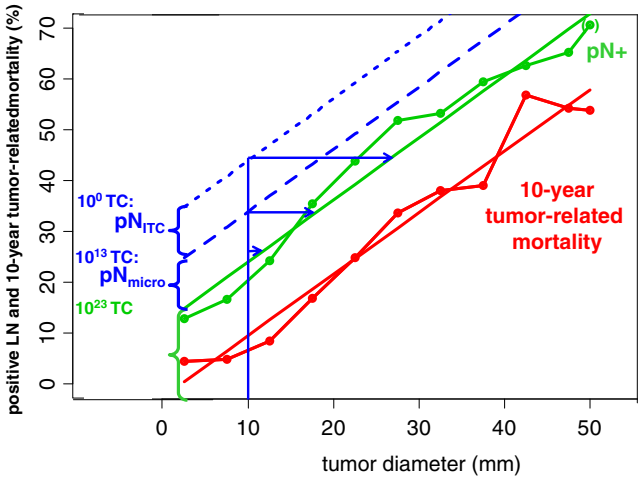

Fig. 2 Breast cancer: association between tumor diameter, 10-year tumor-related mortality (%), and a positive lymph node status (%) in ten cohorts of patients with pT diameter up to 50 mm in 5 mm intervals (MCR data n=40,698). The linear regression lines are for pN+: y_{pN+}= 11.9+1.22**d* (*green*) and tumor-related mortality: y_M=−2.44+1.21**d* (*red*) (*d*=diameter in millimeters). The *dashed* and *dotted* parallel *blue lines* describe the percentage of isolated tumor cells or cell clusters (pN_{ITC}) and micrometastases (pN_{micro}) that co-exist with any given size of PT, according to the magnitude reported in the literature. The number of TC and the size of macro- and microscopic LN foci are depicted to the *right* of the *y*-axis. The *arrows* show where unidentified micro foci co-existent with a PT of 10 mm will develop into an additional pLN as the PT increases in size

during the growth of a PT from pT1c to pT2. The prognoses of the different LN subgroups are specified with their respective contribution to mortality.

4 Growth time of involved lymph nodes versus PT

From these observations it may be deduced that LN are infiltrated sequentially. LN infiltration begins with isolated TC or with tiny TC clusters which, after successful colonization [19], grow up to 0.2 mm (pN_{ITC}), to a microscopic focus that reaches 2 mm (pN_{micro}), and further to a macroscopic focus with over 2 mm diameter (pN+). To reach these sizes with mean diameters of 0.1, 1, or 8 mm, approximately 10, 20, or 29 volume doublings (VD), respectively, are needed. Each focus has, in each case, a cellular mass of approximately 1,000, 1 million, or 0.5 milliard TCs, respectively. Figure 3b depicts the LN foci distribution in a pT1c cohort. A ranking according to number of LN and the size of microscopically involved SLN reflects the differing prognosis of the particular subgroup, with poorest being those with 10 and more pLN.

Meticulous histopathologic preparations of SLN provide crucial information regarding the distribution of ITC and microfoci in SLN [20, 21]. Approximately 10–20% of all patients show microscopic foci within SLN (pN_{micro}) [22–28]. Data about pN_{ITC} in SLN are more heterogeneous because such findings are necessarily dependent on the number and width interval of sections that are cut [29, 30]. In Fig. 2, the two dashed lines indicate about 10% pN_{micro} and a hypothetical 10% pN_{ITC} that contribute to the occurrence of pLN.

These clinical data indirectly allow estimations for the growth time. For patients with a PT of 10 mm diameter, about 24.1% are pN+ cases and an additional 10% are pN_{micro} positive (Fig. 2). If the PT grows further, new foci have to be continuously initiated in previously tumor free LN, and existing small foci will grow into macroscopic pN+. If the PT achieves 15, 20, or 30 mm, then the fraction of pN+ increases along the regression line, from 24.1% to 30.2%, 36.3%, and 48.5%, respectively. Therefore, even the dashed lines in Fig. 2 are parallel to the pN+ regression line because any positive SLN must have been initiated about 29 VD earlier and no change of VD time of LN foci or with tumor size has been observed. A varying frequency of prevalent submacroscopical foci would be an indication.

Table 1 Breast cancer: lymph node status, primary M1, and 10-year tumor-related mortality is dependent on pT category (MCR data n=40,698—1988–2008)

pT	pT %	Tumor Ø mm	M1 %	10-year tumor-related mortality %	mean pLN *n*	Percentile pLN (*n*)		pN0	1–3 pLN	4–10 pLN	>10 pLN	pN+ nos
						75%	90%	% →	%	%	%	← %
pT1a	3.3	4.5	1.5	6.1	3.9	4	11	89.1	9.1	0.4	1.4	0.0
pT1b	11.9	8.5	0.8	5.7	3.5	3	8	84.5	12.1	2.2	0.9	0.3
pT1c	38.2	15.1	1.8	14.6	4.0	4	10	70.7	21.4	5.3	2.2	0.4
pT2	36.2	28.5	4.2	33.5	6.0	8	15	48.0	29.0	14.4	7.7	0.9
pT3	4.7	64.6	12.4	53.6	9.7	14	22	26.3	23.1	25.5	23.3	1.9
pT4	5.6	52.9	26.4	70.1	10.2	15	21	16.6	25.0	27.4	24.6	6.4

10-year tumor-related mortality 1-probability of relative 10-year survival, *pLN* positive lymph node, *mean pLN* the mean number of positive lymph nodes if at least one positive LN exists, *nos* not otherwise specified

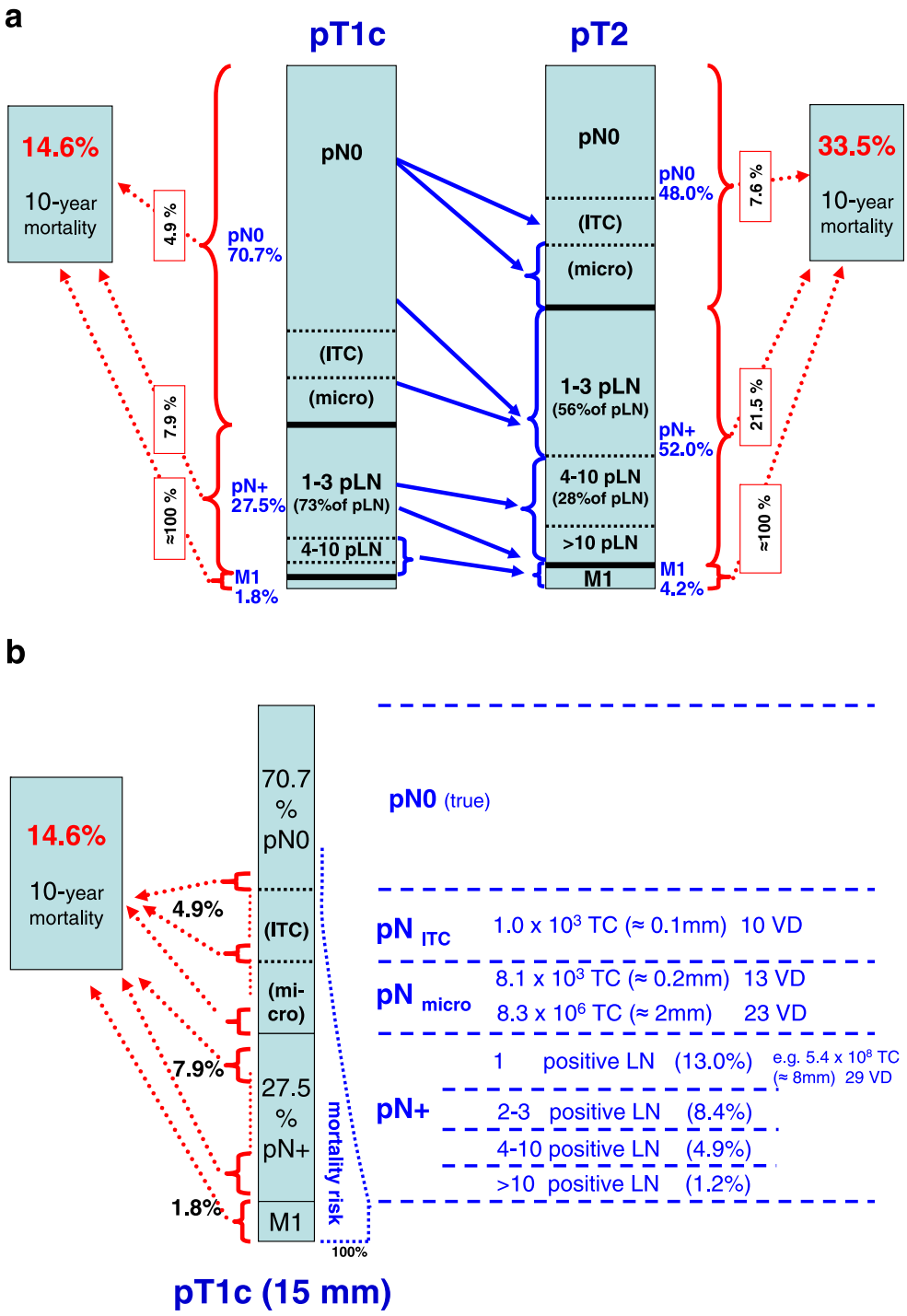

Fig. 3 Breast cancer: **a** contribution of pT1c and pT2 tumors to mortality, dependent on the lymph node status of the PT. The percentage for pN0, pN+, and M1 are derived from empirical data (Table 1) as well as the distribution of the number of positive LN. The distribution of ITC and micro are hypothetically estimated. The *dotted arrows* represent the different contribution to the tumor-related mortality for subgroups of pN+ and pN0 [with subgroups of isolated tumor cells, micro-MET and true pN0 (no LN involved)] with unknown specific contribution. Breast cancer TNM definitions: pN+ macroscopical foci, pN_{micro}: >0.2–2.0 mm, and pN_{ITC}: ≤0.2 mm; the latter stands for further infiltrated LN with ITC or micro-MET. *Blue arrows* depict the transition during the growth of the tumor from pT1c to pT2. **b** Ranking of LN status according to the number of positive LN and the size of the tumor foci for a pT1c primary breast cancer cohort. The decreasing risk of cancer-related mortality is indicated on the *right* of the *bar*

A logical consequence of continuous TCD is that pN_{micro} foci of 0.2–2 mm grow in parallel to a PT until they become macroscopic foci (pN+). About 10% of the pN_{micro} fraction of a 10 mm PT will grow to macroscopic pN+ by the time the PT reaches a diameter of about 18 mm (middle blue arrows in Fig. 2). A 2 mm focus will reach a macroscopic size of 8 mm after six VD, while a 0.2 mm focus needs 16 VD to achieve this size. A mean of 1 mm corresponds to 20 VD. If such a pN_{micro} focus reaches a mean diameter of 8 mm after another nine VD, then the PT would continue to grow from 10 to 18 mm. With the assumed 10% pN_{micro} fraction, one VD in the LN would occur in about 45 days, while the PT requires 407 days for this growth [31]. If the fraction of pN_{micro} would account for 20% of the diagnoses, then the corresponding size of the PT would be 26 mm after a 73-day VDT. That is, the higher the fraction, or prevalence, of pN_{micro}, the slower the growth of that tumor in the LN.

5 Early infiltration of LN before removal of the PT

If between 45 to 73 (mean 59) days are assumed for a VD in LN, and 29 VD are required before a pN+ status comes up, then the initiation of TC dissemination into the first LN must occur 3.6 to 5.8 (mean 4.7) years before the diagnosis of a 10 mm PT. This is consistent with 8.4 to 13.5 (mean 10.9) VD of the PT with a VDT of 157 days [31], and with an initiation of the first LN when the PT has a size of only 3×10^6 to 1×10^5 (mean 5×10^5) TC. Receptor negative BC and their MET show a 2-fold increased growth rate which is likely true for pLN as well [32]. If 59-day VDT is required for foci in pLN and about 13% of BC are receptor negative (with a 2-fold increased growth rate), then the VDT would be about 32 or 63 days for receptor negative or positive foci, respectively. Even if very early infiltration of LN is possible and TCD, once initiated, is a continuous process, then further LN infiltrations will occur up to the removal of the PT.

6 LN foci distribution

The temporally sequential LN infiltration, which starts very early from a PT of about 10^6 cells up to its removal, has several implications. In Fig. 4a, the foci distribution is drafted for a cohort of patients with PT of about 40 mm. The pLN of depicted cases are synchronized with the time of infiltration during the growth of the PT or equivalently, of the recent infiltration of a LN. Therefore, the digit represents the age of the pLN. The pLN with the highest digit is the oldest and generally the SLN. At this PT size of 40 mm, about 40% of the cohort still has a pN0 status. The mean of pLN of all pN+ cases is about seven pLN (Table 1). But it is necessary that there are cases with pN_{micro} and pN_{ITC} (one to three red dots) or others with 10 and more pLN. A further implication is obviously an asymptotic growth of pLN. If a pLN already had a macroscopic focus when the PT diameter was 10 mm, and diagnosis and removal of the PT would not occur until 40 mm, then an additional 2.6 years would have elapsed. With a VDT of 59 days, about 16 VD would be possible but the SLN generally keeps his size.

Figure 4b depicts several ordinary cases for different PT diameters. Just before the detection of the PT, the first (case 1) or further LN must be infiltrated from an ITC represented by red dots near the regression line. In addition, it is logical that the SLN is infiltrated at about the same time in most ordinary cases and further infiltrations into other LN continue to run in parallel, up to the removal of the PT. Furthermore, it can be estimated that in about 8–12 months the next LN will be infiltrated. With a VDT of 59 days about 4.7 years are needed for the tumor in an LN to grow up to a focus of 8 mm. That is, in three to four LN, smaller foci are already growing beneath macroscopical size (Fig. 4a–b).

Figure 5a describes the outlined process of LN infiltration assuming a Gompertz function. Two different views are possible for Fig. 5a: first, a stroboscopic view of a growing tumor focus in one LN; and second, an overlay of the growth trajectories of 15 sequentially infiltrated LN within one patient. Figure 5b questions the growth of LN foci with three different exponential growth phases. But the prevalence of the submacroscopical focus sizes in SLN does not support such a discontinuous growth pattern or a temporary dormancy phase.

7 pLN do not initiate regional MET

The anatomy of the lymphatic system and corresponding experiments show that LNs are not filters for TC [33–35]. Due to the function of LNs, it is clear that neither vasculatory nor lymphatic vessels can be considered as isolated, independent routes for TCD [36, 37]. The distinction of a hematogenous or lymphatic TCD seems to be quite artificial [36]. Furthermore, it is important to note that TC can traverse interstitial space of an extravascular position, invade the lymphatics again, invade nearby LN of the MET organ, or follow the course of other TC that have previously been disseminated via the lymphatics that drain the PT [38]. The rationale for LND, the filter function of LN and a delayed TC dissemination by a pLN, implies a temporary blockade of TCD from pLN, which excludes the possibility of a continuous flow through. The prognostic significance of circulating TC and their association with LN status also support the ubiquitous presence of TC from the PT as the cause of all secondary foci [39, 40].

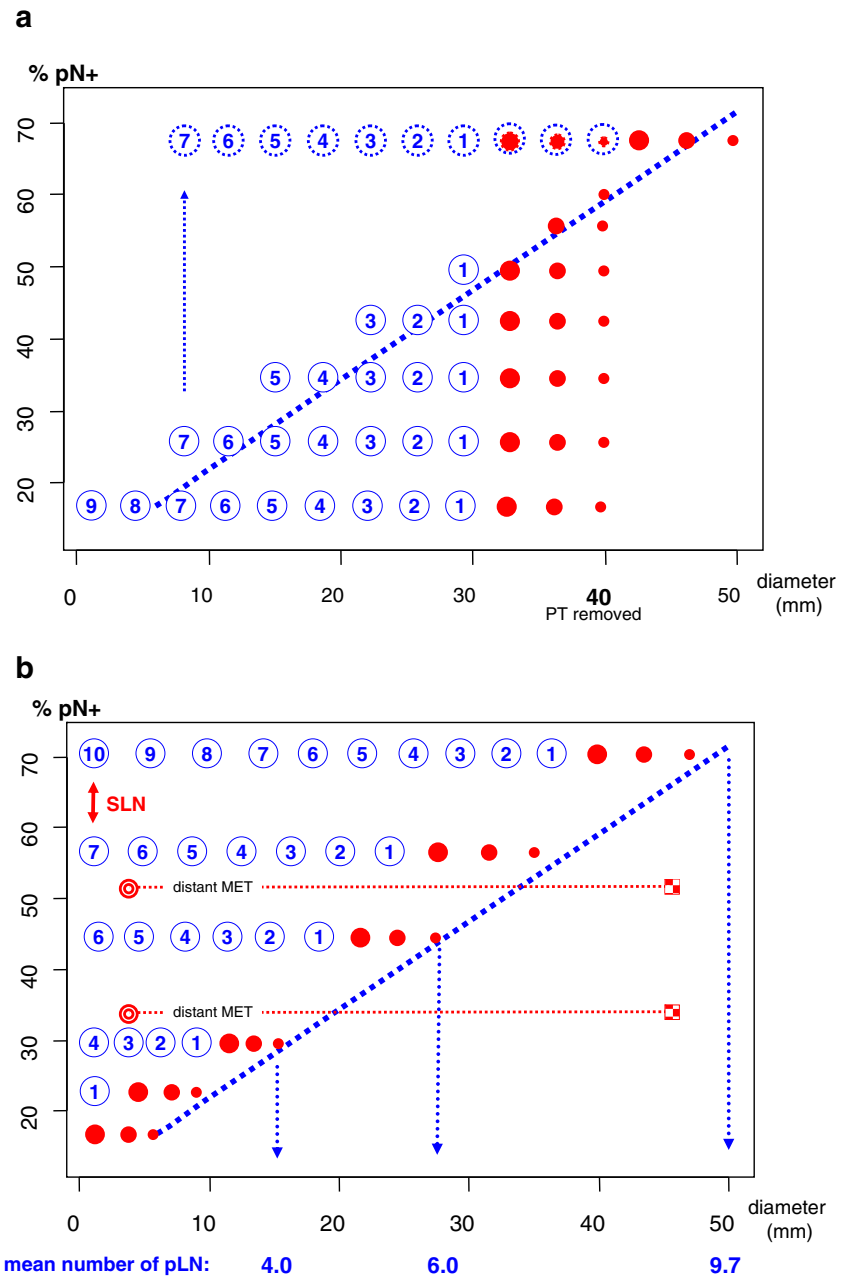

Fig. 4 **a** Infiltration of lymph nodes in cases with identical tumor size (40 mm) but different numbers of pLN. The figure shows fictive cases, all with PT removed at 40 mm, but with different numbers of involved LN. The seven cases are ranked according to the time since infiltration of the first LN. LN with microscopic foci must be infiltrated in all cases just before diagnosis (*red dots*), independent of the number of already macroscopically involved pLN. Again, the *number* inside the *blue circles* suggests the age of the pLN and shows the sequential infiltration of the lymphatic network with a growing primary tumor. Therefore, the highest digit in each row represents the longest growing positive LN, which is generally the involved sentinel LN. The LN row with *dotted circles* describes the continued development if a PT is not removed and the already involved LN grow further as others continue to infiltrate the lymphatics. **b** Increasing average number of positive LN is dependent on tumor diameter. The seven typical cases are synchronized to infiltration of the first (SL) lymph node. Due to a sequential infiltration, the last infiltration of a LN occurred shortly before the date of PT diagnosis. *Blue circles* represent macroscopic pLN; *red solid circles* stand for isolated tumor cells, tumor cell clusters, or micrometastases. Only 20% of pT1b BC tumors show pLN, some more already have microscopic foci. The *number* inside the *blue circles* indicates the ranking according to age and suggests the simultaneous infiltration of the first LN for typical cases. The mean number of pLN for pT1c, pT2, and pT3 cases is depicted below the *x*-axis. The *y*-axis shows the percentage of pN+ according to the linear regression line (Fig. 2). The lead time effect of the MET-free survival time through early detection of the PT is sketched for the two cases with 4 and 6 pLN and a simultaneous initiation of a MET

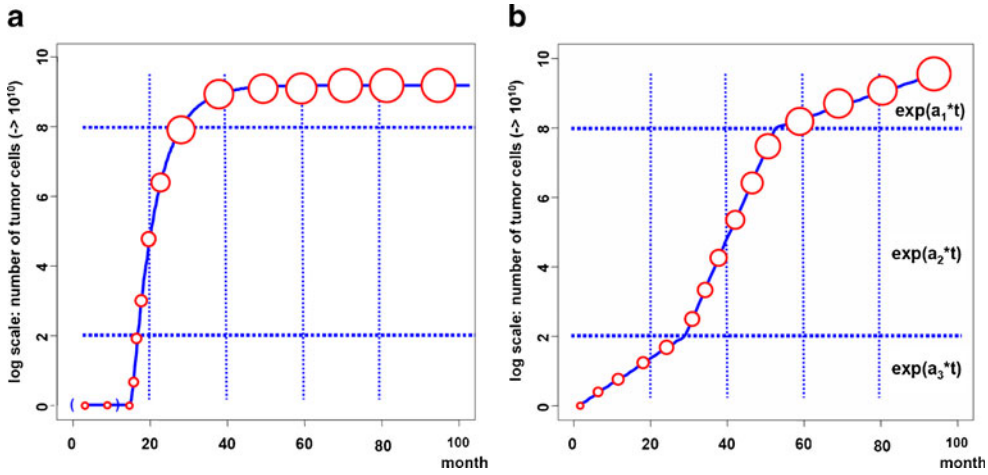

Fig. 5 Two growth alternatives for foci in lymph nodes. A Gompertz function (**a** c*exp$^{-\exp(-b*(x-m))}$) and three different step-by-step exponential growth functions (**b** exp$^{(a1*t)}$, exp$^{(a2*t)}$, exp$^{(a3*t)}$) are depicted. The first part of the *curve* in *brackets* shows a stable or dormant phase resulting in an initial phase of growth that runs parallel to the *x*-axis. Long dormant phases have not yet been observed with high percentages of prevalent pN_{micro}. Two perspectives can be applied to both graphs: first view: depicted is a stroboscopic view of a growing tumor focus in one LN starting from the first TC division with growth increases observed at 15 equidistant time intervals. Second view: overlay of the growth trajectories of 15 infiltrated LN, assuming equivalent growth curves of all involved LN in one patient. The *x*-axis show the age of the sequentially infiltrated LN, the *y*-axis the number of TC depicted also in the different sizes

The characteristics of a spatial, directed lymphatic network suggest the existence of at least one proximal LN, the SLN, as a needle eye, which drains the area surrounding a tumor. Of course, two and more LN can drain larger tumor infiltrated areas or different effluent vessels may exist near, for example, a BC tumor in medial quadrants [13, 34]. Bypass and flow through of TC to the next echelon of the network are possible because of this secure and optimized immune and drainage function. Also, the increase of MET frequency with increasing PT size but without LN infiltration supports the concept that TC can flow through the LN network without leaving a trace. An exclusively hematogenous TCD for the pN0 subgroup with MET is implausible.

From the linear and temporally sequential increase of the number of pLN, it can likely be concluded that a pLN does not infiltrate other negative LN. Although the SLN holds a special anatomic position, it is functionally equivalent to all other LN. Therefore, the SLN would not be the only bridgehead but rather each pLN could also be a source of TCD. Such a simultaneous increase of pLN with a growing PT would be exponential but is not observed. The effectivity of the LN infiltration is very remarkable if competent TCs reach the first LN because a positive SLN has a sensitivity of about 95%. This is also relevant for the infiltration of further, non-involved LN. Because flow through is possible, and infiltration of LN is stopped by R0 resection according to the randomized trials, infiltration must be caused by TC of the PT and not by TC in pLN. An alternative, a remote control of the homing of TC by the PT, is not a plausible explanation for the ending of further LN infiltration with a R0 resection.

The existence of many involved LN with differently sized tumor foci is another consequence of the temporally sequential infiltration of the LN network. This aspect of tumor growth is confirmed by results of a randomized SLN trial for melanoma [3]. Patients were assigned to immediate SLN biopsy or a delayed treatment only if nodal relapse occurred. In the first group, 1.4 pLN were removed; in the second, 3.3. The proposed LN hypothesis would suggest that at diagnosis, about three LN were already microscopically involved. Obviously, these already involved autonomous foci grow in LN, up to macroscopic size, without telecontrol by the PT. Also, in routine care, successive pLN can be detected along an infiltrated LN chain during the course of disease. Therefore, "LN recurrences" do not refute the LN hypothesis rather the term recurrence is appropriate and should be reconsidered because it is a delayed appearance.

Uncountable trials confirm for several different tumors that the number of detectable pLN increases with surgical radicalness [41]. But an expected benefit for survival has until now never been confirmed. Furthermore, the LND trials have demonstrated that neither a more conservative LND nor a complete waiving increases regional recurrences or mortality rates, despite unremoved pLN. Therefore, pLN are dead ends of TCD and do not further infiltrate other negative LN [42].

A cascade-like infiltration is also implausible due to the sequential initiation of LN foci. This would require that a disseminating pLN would acquire MET capability already as a tiny focus (Fig. 4a). Even the PT seems to need about 1 million TC before disseminating the first potent TC, which occurs perhaps only after a successful angiogenesis of the PT focus [43]. Moreover, genetic data are available, especially the sequences of genomes from different pLN which

show that the genetic evolution of the PT can be detected in different pLN [44–46]. This insight into tumor development confirms the temporally delayed initiation by different TC of the PT or the inability that even in pLN successful TC do not infiltrate other LN in a cascade-like fashion. Such evidence reflects the regional aspect of the LN hypothesis.

8 pLN do not initiate distant MET

The second part of the LN hypothesis addresses whether distant MET can be initiated by pLN. Again, many observations and logical deductions confirm the LN hypothesis. The noted randomized trials have provided the highest level of evidence that pLN do not metastasize. This argument is strong and timely. Furthermore, the LN hypothesis is generalizable for all solid tumors.

Figure 2 shows two linear and parallel regression lines for the 10-year BC specific mortality. The parallelism of the 10-year BC specific mortality with pN+ confirms the association only with the pN+ status and the beginning of an at least regionally successful TCD of the PT. The number of pLN is, for this reason, not only a marker for TC spread but an excellent chronometer for the TCD of the PT because the risk of distant MET increases with the duration of TCD. This is also supported by the resulting curves of the mortality differences of pN+ to pN0 from Fig. 1, which have an identical form, with a descent that increases with the number of pLN up to a constant survival rate relative to pN0 (curves not shown). A further continuous dissemination of TC from all pLN, which together can have a tumor mass greater than the PT, contradicts the clinical observation of a linear increase of mortality with PT size.

The ratio of pN+ and deceased patients according to the regression lines depicted in Fig. 2 is also remarkable. It amounts to 3.2 for 7.5 mm and to 1.3 for 47.5 mm BC tumor diameter. The decreasing ratio indicates a constantly delayed initiation of distant foci compared to regional LN foci. It is unknown whether different characteristics are necessary for regional and distant infiltration, or whether the easier, nearly passive access of TC to the LN is a sufficient explanation for the delay. The conformity of the survival curves in Fig. 1 is important. If each additional pLN during the growth of PT were to be a new source for MET, then a nonlinear increase of mortality in Fig. 2 or concave instead of convex survival curves in Fig. 1 would be necessary. However, the contrary is true; the more pLN, the more primary advanced BC will be observed. Therefore, MET within the subgroup of pN0 and pN+ have the same cause, the TC of the disseminating PT.

The remaining survival time for the subgroup with multiple pLN (e.g., ≥10) is comparable or even shorter than for primary M1, probably because the high number of pLN correlates with a longer TCD, followed by longer MET growth and with more and larger tumor foci in distant organs. The marginally decreasing median survival after primary MET with increasing pLN is in part a lead time effect due to the longer growth of the MET. The comparable shapes of survival curves after MET, with or without pLN, is a further argument for the lack of impact of pLN on survival. If the number of pLN were an additional cause of MET, it would result in an increased opening of the survival curves in Fig. 1.

The predictive power of the number and size of pLN foci is a further aspect of LN status that must be considered (Fig. 3b and Table 1). Patients without any detectable TC in SLN would represent a true pN0 status. The smaller the pN focus, the smaller the mortality risk. However, Fig. 3b suggests that even pN_{micro} and pN_{ITC} are risk factors, even if only the sentinel LN (SLN) is involved [8, 26, 47–51]. Therefore, a macroscopic pN0 cohort in Fig. 1 could be separated into the three prognostic subclasses, true pN0, pN_{ITC}, and pN_{micro}. Indeed, it has been shown that even only pN_{ITC} in a SLN is a risk factor, and patients benefit from adjuvant treatment [52, 53]. In these studies, the curves for disease-free survival for the pN_{ITC} subgroups with and without treatment or for the pN0 versus pN_{ITC} subgroups open like scissors after 2 years. Additionally, disease-free survival is shorter if SLN already harbors pN_{micro}. The obvious explanation is the longer TCD of the PT [54]. An initiation of distant MET by pN_{ITC} is hardly possible in such a short MET free interval because the growth time required for distant MET is quite longer, in BC about 7 years [55]. Again, this supports a delayed but parallel TCD by the PT into all possible locations [56]. Therefore, also pN_{ITC} and pN_{micro} support the chronometer function of involved LN and are not the cause of distant MET.

LND and irradiation of the regional LN network have the same goal, which is to optimize regional control and improve survival. Up to now, convincing data are missing for a survival benefit of irradiation. For BC, LND and irradiation yield comparable long-term results [57–59]. This is remarkable if level III and supraclavicular lymph nodes receive radiotherapy, in contrast to the locally limited surgical procedure, and therefore an advantage for irradiation should be expected. But both treatments are effectively equal concerning regional and distant control and therefore support the LN hypothesis.

Of special interest is also the location of BC, which influences TCD infiltration, and corresponding survival rates. The most frequent lateral BC are predominantly drained by axillary LN. In contrast, medial BC of comparable size have less axillary and more parasternal pLN. Normally, parasternal LN are not treated and as such, one would expect that unremoved pLN would influence survival, but this is not the case [60–62].

A self-contained argument in the sense of the philosophy of science is the obvious inability of the other secondary foci, true local recurrences and distant MET, to metastasize [55, 63]. Because pLN likewise cannot infiltrate the regional neighborhood, it is important to question why a pLN should be able to initiate a focus in a distant organ. There is evidence that the requisites on TC to achieve successful MET in one organ are not reversible in a new environment, and this suggests the uncomplex principle: only a PT can initiate MET.

The increasing knowledge about seed and soil conditions, and the LN-independent predictability of MET location and mortality by gene expression profiles of the PT, are further sound arguments for the LN hypothesis [64–67]. The genetic characterization delivers increasingly important prognostic and predictive information which overwhelm the informative capacity of LN status [64, 68–72].

It is well known that multifocal MET in one organ are not monoclonal. They are caused by different TC [73]. It is implausible to suggest that TC could make a detour across LNs, initiate a focus, and disseminate MET competent TC. Despite a logical conflict in the case of only one pLN and two non-monoclonal distant MET today, more and more hypotheses can be verified. The previously mentioned data generated by sequencing genomes from different areas of a PT and from different pLN, as well as from distant organs within one patient, already confirm the causal relationship. The data can even show the geographic origin, and the time of infiltration due to the genomic instability of the PT and its evolutionary development [45, 74–78]. The development of a phylogenetic tree for all foci would clarify the hypotheses about the PT as the only source of infiltrating TC.

9 Clinical considerations and the LN hypothesis

In the context of the LN hypothesis, multiple clinical aspects such as adjuvant and neoadjuvant radio- and chemotherapies, the impact on hospital outcome, or research strategies could be discussed. We will address only two aspects, namely LND and the existence of a SLN. The reluctance to accept the LN hypothesis is in part due to the age of the applied LND paradigm and in part to the association between the number of removed LN and survival. The latter is predominantly a stage migration effect [79, 80]. This effect is dependent on the anatomy of the LN network and is very small if a valid sentinel LN exists as in BC and in contrast to colon cancer. The staging function of LND is independent of the LN hypothesis and benefits from the chronometer function of the size and number of pLN. Also, the tiny risk of LN recurrences in the subgroup with positive SLN cannot generally be a justification to continue LND.

Even if some questions are answered by a true LN hypothesis, multiple others remain or arise. If tumor progression is a Poisson process with millions of TC disseminated from the PT resulting in only few initiated foci, then the existence of a valid SLN and the sequential infiltration of LN are remarkable [81, 82]. The infiltration of a LN must be very efficient. All sizes of foci are detectable in SLN and skipped pLN are few. Therefore, the number of competent TC within the stream of disseminated TC must be very few.

10 Conclusion

The LN hypothesis has long been known: already 30 years ago, L. Weiss summarized the hypothesis very strikingly: “The removal of LN will no more effectively control MET than removal of the speedometer from a car will reduce its speed (cited from [37])”. Nowadays additional arguments based on molecular research strengthen the LN hypothesis. The multiple statements about LN infiltration are based on observational data along with some basic assumptions, and are generalizable for all solid cancers. It is important, on the one hand, that the assumptions are falsifiable and can, in part, be rendered more precisely. On the other hand, many other observations around the LN hypothesis can be explained. Therefore, it is necessary to reconsider current treatment strategies in light of the evidence that pLN do not metastasize. Data from clinical cancer registries about the course of diseases for many different solid tumors allow for comparisons that can contribute to advancing knowledge.

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Conflicts of interest We declare that we have no conflicts of interest.

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