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Short communication

Tumor dormancy at bedside: A late awakening

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ABSTRACT

Breast cancer recurrence may occur at variable times following primary tumor removal. The corresponding event dynamics displays a structured multipeak pattern, which can be explained by the occurrence of microscopic phases of metastasis quiescence (tumor dormancy) followed by wake up, growth and timed clinical appearance. This model provides a meaningful justification of the early recurrence pattern and even explains the effectiveness of adjuvant systemic therapies. Yet, late recurrences, which were less investigated, are fairly little known and a few researchers supported their steady state appearance. We report here the analysis of the late clinical course from patients who were disease-free at 5 years of follow-up, which again displays a structured pattern, supporting the view that tumor dormancy can explain the late recurrence risk as well. Tailored treatments are needed to address late clinical recurrences.

1. Introduction

Surgery is usually able to remove many apparently local cancers. However, a number of resected patients suffer successive disease recurrence and eventually decease for metastases, which were subclinical at the time of primary tumor removal. In breast cancer, the knowledge of the subclinical phase following primary tumor removal is of paramount importance to identify treatments improving the unsatisfactory results of surgery alone [1]. About 20 years ago, the belief that metastasis development during the subclinical phase is explainable by a continuous tumor growth was established to be incompatible with the clinical behavior of local recurrences after mastectomy [2]. This discovery raised the "tumor dormancy" concept as a useful approach for understanding the disease course, a role that was reinforced by the finding that the recurrence dynamics in patients undergoing mastectomy alone, without any adjuvant treatment, far from being steady, displays peaks during the follow-up [3]. These findings, in addition to computerized simulations, suggested a new paradigm of breast cancer metastatic development [4,5], involving the notions of tumor homeostasis, tumor quiescence in specific metastatic microscopic phases and surgery-related acceleration of the metastatic process. According to this biology, after tumor cell shedding from the primary, the development of metastases includes sequential passage through a few dormancy phases. This orderly process is controlled by the primary tumor, which can exert restraints on transitions between dormancy phases, thus retarding or inhibiting metastasis development. Surgical removal of primary tumor is a disrupting factor of such a homeostatic steady state, with sudden synchronization and acceleration of the metastatic process, at least for a number of patients. Support and improvement of the model were achieved by the analysis of recurrence dynamics by menopausal status [6] and in patients receiving adjuvant chemotherapy [7]. Likewise, multipeak recurrence dynamics was discovered for other neoplasms as well (e.g. non-small cell lung cancer [8], and ocular melanoma [9]), suggesting that the model may have wide validity.

The proposed model reasonably explained peak behavior during the first four years after primary tumor removal [10]. Yet, the recurrence dynamics pattern also displays a few quite modest structures at later times, which should be explored when addressing treatments aimed at reducing late recurrences. Indeed, the occurrence of temporary increases of the recurrence hazard (i.e. some structured recurrence dynamics pattern) suggests the occurrence of specific time-related phases of metastasis

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development that could be addressed by tailored treatments (as occurs for adjuvant systemic therapy), while a steady state risk advocates a different therapeutic approach.

The detection of recurrence risk structures requires focused ad hoc examination of clinical data, since usual analyses may be unable to reveal such patterns. For instance, a long-lasting recurrence risk "at a steady rate throughout the study period from 5 to 20 years" has been recently reported in estrogen receptor positive breast cancer patients, who were disease-free after 5 years of adjuvant endocrine treatment [11]. The statement is compatible with the reporting modality, which aimed at estimating cumulative incidence risks and annual rates of distant recurrence over 5-years period by a meta-analysis. While averaging over such long time periods allows more stable estimates across the different case series involved in the meta-analysis, yet, it is also expected to introduce major bias, preventing the identification of relevant time patterns. Therefore, in homogeneous case series, a continuous analysis on time according to a finer discretization is crucial for detecting hazard rate structures (according to the bias-variance trade-off principle of non-parametric estimation). In our experience, analyzing events in a 3-month time lag allowed detecting the fine structure of premenopausal recurrence risk during the first three years of follow-up [6] that was elusive in the previous 6-month analysis and that is undetectable in a 12-month analysis.

Tumor dormancy can explain the late recurrence risk, as even suggested by others [12], hypothesizing that this phenomenon is underlying the long disease-free time. To this purpose, we analyzed data from patients who were disease-free at 5 years of follow-up in randomized clinical trials on the effectiveness of adjuvant chemotherapy in axillary node-positive patients.

1.1. Patients and methods

We analyzed randomized clinical trials that were approved by the ethics committee. The first was carried out at the Istituto Nazionale dei Tumori of Milan comparing different drug regimens (Cyclophosphamide, Methotrexate, and Fluorouracil ± Doxorubicin) [13,14] while the three-arm Belgian multicenter clinical trial compared two doses of Epirubicin plus cyclophosphamide with the classical Cyclophosphamide, Methotrexate, and Fluorouracil regimen [15].

The distant recurrence dynamics during years 5–15 was estimated in 582 node positive at risk of recurrence, Estrogen receptor positive patients selected according to the following inclusion criteria: less than 75 years of age, tumor diameter $\leq$2.0 cm, less than 10 axillary positive nodes and chemotherapy as unique adjuvant treatment. This choice was dictated by the following reasons: i) analyzed patients should not have received adjuvant hormone treatment in addition to chemotherapy; ii) patient characteristics needed to be similar to those reported in the important meta-analysis [11]; iii) the number of patients and events should allow reliable estimates of the hazard rate for distant metastases. Main patient characteristics are reported in Table 1.

Distant recurrence dynamics was investigated by estimating the cause-specific hazard rates, i.e. the rate of manifestation of distant recurrence as first event at a certain follow-up time. Local-regional recurrences and second primary tumors, including contralateral breast cancers, as well as deaths without recurrence were considered as competing events and the corresponding follow-up times were censored at the time of their occurrence. A formal classification of the distant recurrence site (mainly viscera and bone) was performed in about half relapsing patients, while others were classified as recurring in multiple sites. A discretization of the time axis in 6-month units was applied, a kernel-like estimator was adopted, and smoothed curves were graphically represented.

Table 1
Main characteristics of the analyzed T1, ER-positive patients.

Total number	582
Median age (range)	47y (25y – 71y)
Pre-menopause	76%
Post-menopause	24%
1–3 node positive	77%
4–9 node positive	23%
Distant metastases (years 5–15)	92

2. Results

Distant recurrence patterns were estimated for two subsets of T1 patients, (450 with 1–3 positive nodes and 132 with 4–9 positive nodes). Hazard rate curves for the two levels of nodal involvement are reported in Fig. 1.

Despite the relatively small sample size, the hazard rate structure is quite evident, displaying an increase peaking at year 10–11 and an additional decrease until year 15.

3. Discussion

The structured recurrence risk that is observed after 5 years of follow-up is in line with previous findings regarding the early years successive to primary tumor removal, when peaks with definite timing are observable [10]. Moreover, the fact that a powerful determinant of the risk of late recurrence is the number of lymph nodes containing cancerous cells, which was originally used to grade aggressiveness of the primary cancer, parallels what we already observed in the study of early recurrences [10].

It is here important to recall the multidimensional nature of dormancy and the need of investigating on reasons triggering the interruption of dormancy. Yet, it should be recognized that the most noticeable event correlating with microscopic metastasis awakening is primary tumor surgical removal [10,16,17]. Tumor homeostasis disruption at primary tumor removal, which was recently experimentally observed in animal models [18], underlies the synchronizing phenomenon of sudden interruption of

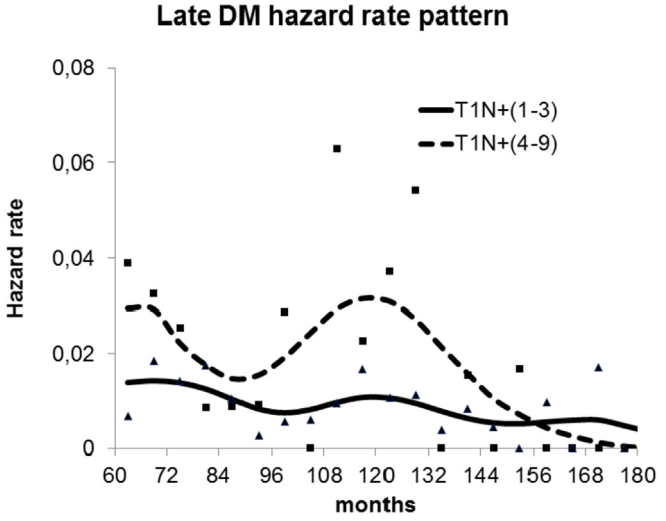

Fig. 1. Hazard rate patterns for distant recurrence in 450 patients with 1–3 positive nodes (continuous line) and 132 patients with 4–9 positive nodes (dashed line) who were given adjuvant chemotherapy and were disease-free at 5 years of follow-up. Single point hazard estimates are reported as well. The hazard rate displays a structured pattern with an increase peaking at year 10–11 and an additional decrease until year 15.

dormancy states resulting in clinical appearance of metastases. It implies that what we see at a certain time of follow-up (e.g. at the tenth year) may have roots in what happened many years earlier, e.g. at the first line treatment. This reasoning was able to well explain the recurrence pattern during the early years, e.g. changes in the recurrence peaks for patients who received adjuvant chemotherapy [7]. Other factors possibly playing a role in microscopic metastasis awakening at the individual patient level, such as concomitant diseases, immune system action fluctuations, metabolic states, are difficult the be considered as a cause of the emergence of a structured hazard pattern in patient population.

The repeatedly evidenced multipeak pattern of breast cancer recurrence dynamics following primary tumor recurrence [3,6,7] and its persistent timing in the emergence of clinical metastases suggests that dormancy states should be considered as a complex system of interrelated biologic phases crossed by subclinical metastases during their development before their emerging to the clinical level. In particular, the vasculature-related dormancy [19], which is conditioned by a missing angiogenic switch, is currently considered the last step of the process preceding the metastatic clinical surfacing. The finding of our analysis, therefore, is relevant for the approach to therapy for late disease relapses. Indeed, while the already recognized persistent recurrence risk [11] suggests the need of prolonged systemic treatments (e.g. hormone therapy), its structured character from the present evidence, calls for focused investigations aimed at identifying the possibility of targeted therapies.

A potential limitation of this investigation is the focus of our analysis on patients with T1 tumors. This restriction was dictated by the fact that patients with T2 tumors display metastasis dynamics with a definite trend to early recurrence, which results in a lower frequency of late events, thus preventing to reliably estimate late hazard rates. Moreover, our estrogen receptor positive patients were given adjuvant chemotherapy only. Yet, their recurrence risk patterns should be considered meaningful and can reasonably be extended to the patients receiving prolonged adjuvant endocrine treatment, based on findings from suitable randomized clinical trials [20]. Although it is expected that other factors (age, menopausal status, proliferation index, etc.) impact on the baseline recurrence risks, our long lasting experience showed irrelevant effect on the stability of hazard rate peak dynamics, which cannot be deconvoluted, leading to survival models based on unexplained heterogeneity [21].

In conclusion, we support that tumor dormancy is an indispensable component of any explanation aimed at understanding the behavior of breast cancer, and we hope that it will finally move from bench to bedside. Also, we advocate the position that the complex phenomenon of breast cancer progression, eventually resulting in clinical metastases, needs a comprehensive framework including data from both laboratory investigation and clinical research. Such a framework may result only from the integration of the two exploratory levels. The former should renounce, at least in part, to its widely extended reductionist approach and the latter should break out of the simplistic investigation about treatment efficacy (effective vs. not/less effective). We desperately need to assemble a comprehensive novel paradigm of the disease, a reliable picture of its behavior according to the dormancy evidence, since the new paradigm would substantially change the therapeutic perspectives. We treat patients not according to what tumors are, but rather according to our theories about them.

Availability of data and material

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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