Abstract
Lung cancer is not simply a single disease, but a collection of several phenotypically very diverse and regionally distinct neoplasias. Its natural history is complex and not yet fully understood. Stem cells and the complex interaction with the microenvironment of the tumor and the immune system play an important role in tumor progression and metastasizing capacity. This finding explains why lung cancer does not always follow the multistep carcinogenetic and exponential growth model and why small lesions do not always equate to early-stage disease. Despite the fact that volume doubling times are increasingly used as surrogate markers for the natural history of lung cancer and as estimates for the proportion of overdiagnosed cases, it is only a momentary impression. At baseline screening especially, screen-detected lung cancer cases are preferably detected when they are in the indolent phase of their growth curve (length-biased sampling), from which it can by no means be concluded that they may not progress or metastasize at a later stage. Because the natural history of lung cancer is only partly elucidated, conclusions on the impact of overdiagnosis in lung cancer screening are premature.

The Current Paradigm of Lung Cancer Development
Lung cancer is a collection of several phenotypically diverse and regionally distinct neoplasias. In the absence of screening, lung cancer patients present only when they become symptomatic. At that time, the disease is usually incurable due to its advanced stage with local or distant metastases. Although chest X-ray screening trials in the 1970s were negative, recent advances in technology have lead to new observational and randomized trials with low-dose, multidetector CT techniques (1–4). These trials try to answer the question of whether it might be possible to detect smaller and therefore more curable lesions by CT and to reduce lung cancer mortality.

Based on West’s universal law of growth in living organisms, it has been demonstrated that tumor size correlates with clinical outcome (5). Guiot and colleagues showed that tumors follow a universal exponential growth curve under unrestricted dietary conditions (6). Adjustments to these growth dynamics have been made due to the effect of lack of nutrient supply, increases in mechanical stress, growth promotorm/inhibitor interaction, and the impact of interactions with the microenvironment (7). Based on many experimental and clinical observations, it has now been accepted that tumors initially grow rapidly (exponentially or superexponentially), but, according to the Gompertzian growth curve model, increasingly slow their growth as they become larger so that the tumor size trends to a constant level as time increases (8, 9). According to this model, metastatic dissemination, tumor cell invasion, and angiogenesis will start once a tumor reaches a “critical” volume, due to the rising mechanical stress exerted by the microenvironment (6). This threshold has been investigated for breast cancer and lung cancer in which a strong relationship between, respectively, tumor size and axillary and mediastinal lymph node involvement and survival has been observed (2, 10–12). A consequence of the current paradigm of lung cancer development is that there is a threshold before which treatment (surgical resection) can be curative, whereas, later, it can only be locally effective.

The question remains as to whether this multistep carcinogenetic model always reflects the observed natural history of lung cancer. The validity of predictions on survival time based on the exponential growth model, including the assumption that death occurs, on average, after 40 to 41 tumor doublings, has been questioned because the estimated survival times based upon these models are much longer than those observed in reality (13). So far, there is no evidence that size always correlates with biologic behavior and that small lesions are always equivalent to early-stage disease (Fig. 1) (ref. 14). In patients with lung cancer who undergo surgical resection for early Stage I or II disease, only 60% to 70% will be cured, whereas the other patients, despite having early-stage disease and complete surgical resections, have recurrence of their
disease and ultimately die. Another consequence of adherence to the current growth paradigm is that malignant nodules will continue to develop and grow unless they are surgically removed. Yet it may be the case that some will stabilize, shrink, or grow so slowly that even if left in situ they will not all develop into lethal lesions (15). Finally, multistep carcinogenesis may not be able to account for dramatic cases of lung cancer that develop in very short intervals (Fig. 2). The low-interval cancer rate observed in lung cancer screening trials might argue against the frequent occurrence of this type of rapidly evolving cancers, but, given the lack of long-term follow-up on negative screens in the published series so far and the lack of individual nodule history tracking, current available data should be interpreted with caution.

This evidence suggests that although the current paradigm is well supported and might be applicable for a certain subset of cancer cases, it does not explain all lung cancer biology.

**Volume Doubling Time and the Natural History of Lung Cancer**

Based on the observation that tumor size at the time of detection is not always consistent with the biological behavior of a tumor, it has been proposed that the volume doubling time (VDT) could serve as a surrogate maker for lung cancer biology. With the conduct of CT lung cancer screening trials and the use of computerized volumetric software, new information on the natural history of screen-detected lung cancer is rapidly accumulating. It has been found that CT-screen-detected lung cancer has markedly longer VDTs, and that a substantial portion has substantially longer VDTs (> 400 days) compared to those detected in routine medical care (13). Based on this observation, it has been hypothesized that screen-detected lung cancer might represent a disease entity of its own and not be the precursor of advanced-stage disease (16). Hence, advanced-stage lung cancer may not have had detectable and curable disease in the past. Based on this hypothesis, two different types of lung cancer have been proposed: screen-detected and advanced-stage disease lung cancer (16). Evidence for this view has been derived from the comparison of the pooled data of three observational CT screening trials with the Bach’s lung cancer risk model (17). In this comparison, lung cancer screening led to the detection of more early-stage disease than expected, without a reduction in the proportion of advanced-stage disease.

However, the use of the VDT as a surrogate marker for lung cancer biology has several limitations. Due to the fact that the VDT data are so far largely based on 2D manual measurements, VDT assessments are subject to measurement errors. In addition, the VDT is not a reflection of the total growth curve of the tumor, but merely a momentary impression. Nodule growth may be absent for a certain period of time, and tumors may even shrink or show very slow growth (VDT > 400 days) with a sudden acceleration in growth and metastasizing.

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**Fig. 1.** A 52-year-old man with a 14-mm nodule in the right upper lobe (left). A 3-month repeat scan showed no growth (middle), but an evaluation 1 year later showed significant growth and the detection of an adenocarcinoma of the lung with mediastinal lymph node involvement (pT2N2Mx) (right).

**Fig. 2.** A 63-year-old man with a small pulmonary nodule <5 mm in the right upper lobe. At the 1-year follow-up, the nodule had significantly grown and upon work-up appeared to be a stage IV adenocarcinoma of the lung with brain metastases.
behavior. In addition, indolent or even absent tumor growth may be associated with the development of distant metastasis.

Therefore, we believe that it is inappropriate to assume that lung cancer cases with a VDT > 400 days are, per definition, overdiagnosed cases based on the argument that it would take more than 30 years to grow from a 1 cm lesion to a size that is usually lethal, because it is based on the simplified assumption that cancers double at a constant rate, which is, without doubt, inaccurate. Recent advances in knowledge regarding the potential role of cancer stem cells in the natural history of lung cancer and its interaction with the microenvironment and the immune system may provide alternative explanations for the observed biological behavior of lung cancer that does not always fit into the multistep carcinogenetic model.

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**Cancer Stem Cells and Lung Cancer Development**

Cigarette smoke results in epithelial damage and signaling events that elicit wound repair and a proinflammatory state. The presence of proinflammatory cytokines and chemokines released from healing wounds may be responsible for the recruitment of differentiated cells such as neutrophils and macrophages, and it may also lead to organ-specific stem cell proliferation and the recruitment and proliferation of bone-marrow-derived stem cells (18, 19). Respiratory stem cells and bone-marrow-derived stem cells have the function to repair injured or destroyed tissues within the lung by their capability to self-renew and differentiate into mature cells (20, 21). Most adult tissues harbor stem cells, and, in lung cancer tissue, a rare population of cancer-stem-like cells has been identified (22–24).

There is mounting recent evidence that there are two different processes of (lung) cancer development: a localized and a systemic one (22). The prevailing view is that lung cancer development starts as a localized process in which the disease originates from the transformation of lung epithelial cells or lung cancer progenitor cells by carcinogens. The metastatic potential in progenitor cells could be acquired by accumulating genetic and/or epigenetic alterations occurring during cancer progression (multistep carcinogenesis). Alternatively, they may also arise from transformed stem cells through genetic mutation or from epithelial cells, which acquire stem-cell physiology through activation of distinct gene expression profiles (22, 25, 26), although validation of this cancer stem cell concept in solid tumors is still lacking (Fig. 3). Kim and colleagues have been the first to identify a rare population of bronchioalveolar cancer stem cells (BASCs) in lung cancer mouse models, and they hypothesized that BASCs might be the putative precursor cells of lung adenocarcinomas, although without definitive evidence so far (27). Stem cells appear to be prototumorigenic and must first receive at least one permanent genetic mutation to destabilize their growth prior to cancer initiation. Once mutated, cancer stem cells have limitless proliferative capacity and give rise to daughter progenitor cancer cells that have limited proliferative capacity (22, 25, 26).

In the systemic route of lung cancer development, stem cells have the ability to circulate and home to different organs without acquiring their metastatic potential. A stem-cell-derived lung cancer might thus, from the very beginning, be a systemic disease and be incurable with local resection. There is indeed evidence that the presence of cancer stem cells in human tumors, including lung cancer, correlates with clinical outcome (28). The functional properties of cancer stem cells may also be influenced through external signals mediated by further differentiated cancer cells and host stroma cells, including activated fibroblasts and infiltrating immune cells such as macrophages and endothelial cells, and cancer stem cells may remain dormant, without metastasizing capacity, for a certain period of time. So far, the metastatic phenotype has been regarded as a cell-autonomous alteration specified by the genome of the cell. However, there is also evidence that cancer cells acquire their metastatic phenotype due to exposure of epithelial cancer cells to paracrine signals that they receive from mesenchymal cell types within the tumor-associated stroma (29). Recent reports propose that bone-marrow-derived mesenchymal stem cells are recruited in large numbers to the stroma of developing tumors through the release of various endocrine and paracrine signals. Upon interaction with the cancer cells, the metastatic potential is largely increased, but it may revert to a lower metastatic state once they are no longer in contact with these stem cells (30). These data illustrate that the tumor microenvironment facilitates metastatic spread by eliciting reversible changes in the phenotype of cancer cells and highlights the recently discovered critical role of chemokine networks in malignant progression. Certain tumors recruit, at a certain moment, bone-marrow-derived endothelial progenitor cells, which appear to be pivotal for the progression of avascular, dormant or micrometastatic tumors to lethal macro-metastatic ones. They do so by producing distinct proangiogenic chemokines, which interact with these endothelial progenitor cells to initiate and possibly maintain nascent vessels within specific primary and metastatic lesions. These data suggest that bone-marrow-derived hematopoietic progenitor cells initiate metastatic colonization, the so-called angiogenic switch (31, 32). When these events occur in the natural history of cancer development is yet unknown, but this process might be independent of tumor size.

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**Fig. 3.** Schematic representation of lung cancer development. *A*, the localized, multistep carcinogenetic model and *B*, the hypothesized systemic, bone marrow-derived stem cell model. Screening for lung cancer could potentially be effective in model *A* when the disease is detected before it has metastasized, but not in *B*.
Conclusion

The natural history of lung cancer is complex, diverse, and not yet fully understood. So far, lung cancer evolution has been interpreted according to the exponential growth model, but there is increasing evidence that the natural history of lung cancer does not always fit this model. Bone-marrow-derived stem cells and the complex interaction with the microenvironment of the tumor and immune system may play an important role in tumor progression and the achievement of metastasizing capacity. There is, in our opinion, no biological rationale why CT-detected early-stage lung cancer should be regarded as a distinct group of cancer. The only appropriate conclusion is that screen-detected lung cancer cases are preferably detected when they are in the indolent phase of their growth curve (length-biased sampling), from which it can by no means be concluded that they may not progress or metastasize at a later stage. As the natural history of lung cancer is only partly elucidated, conclusions on the impact of overdiagnosis in lung cancer screening are premature.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References
