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Current Perspective

# Are rapidly growing cancers more lethal?

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**Abstract** The view, that rapidly growing tumours are more likely than slow-growing tumours to metastasize and become lethal, has remained almost axiomatic for decades. Unaware of any solid evidence supporting this view, we undertook an exhaustive system-level analysis of intra- and intercellular signalling networks. This analysis indicated that rapid growth and metastasis are often different outcomes of complex integrated molecular events. Evidence from humans can be derived chiefly from screening interventions because interval cancers that surface clinically shortly after a negative screening test are, on average, more rapidly growing than cancers not detected by screening. We reviewed all available data limited to cancers of the breast, cervix and large bowel. The evidence from humans provides no support for the theory that rapidly growing cancers are more prone to metastasize. These findings indicate that the prevailing view should be reconsidered, as should the impact of length-biased sampling in cancer screening, and the findings provide no support for treating interval cancers more aggressively than non-interval cancers.


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## 1. Introduction

Cancer screening has been described as a clash between science and intuition [1]. The same might hold for the almost axiomatic long-held view that rapidly growing tumours are more likely to metastasize and become lethal than slow-growing tumours [2–4]. This view seems to be integrated into daily thinking among doctors treating cancer patients but is also conveyed in the scholarly literature (e.g.: [5–7]). Evidence to support or refute this theory may come from molecular biology, because cancer is a system-level disease, and somatic mutations and signalling pathways that entail accelerated tumour growth would also promote dissemination of malignant cells that create distant metastases. But the ultimate proof must come from human studies investigating the prognosis of individuals with cancer. There is now compelling evidence to indicate that cancer growth rate and metastases are not related phenomena. This challenges the assessment of screening interventions [2–4] and possibly also the management of cancer patients.

## 2. Evidence from tumour biology

Already in 1958, in an exhaustive review of the natural history of cancer, Foulds discussed growth rate and metastatic potential as separate, distinct features of a malignant tumour [8]. Foulds emphasised that '*growth rate, local invasion, spread to regional lymph nodes, and dissemination to the blood stream are independently variable characteristics*'. He concluded that '*a survey of varied types of neoplasia reveals patterns of development common to all of them*', suggesting that the evidence from one or a few cancer sites might be generalisable to others. The explosive expansion of knowledge from molecular biology may now allow a deeper understanding of the signalling complexity that governs growth rate and the metastatic process.

Tumour growth and metastasis were defined as separate hallmarks of cancer, implying that their molecular background is different. However, somatic mutations occurring in related genes often have overlapping functions [9]. In addition, cross-talk between various signalling pathways makes it difficult to clearly distinguish between 'tumour growth pathways' and 'metastasis pathways'. Nevertheless, an increasing amount of recent scientific evidence demonstrates that the development of the rapid growth versus metastatic phenotypes can be distinguished as separate, context-dependent outcomes of the whole signalling network [10–12].

Cancer stem-like cells and cancer cell dormancy are special examples of this context-dependent duality. Cancer stem-like cells may reside in one of the two basic states in their signalling network: namely, either in a rapidly proliferating state or in a quiescent, metastasis-inducing state [13]. Rapid proliferation or metastasis-prone phenotypes of both states develop as a result of a finely tuned balance between signalling pathways.

Primary tumours have an extremely great cellular heterogeneity [14,15]. In addition to the various mutational DNA rearrangement, DNA copy number, gene expression, proteome, phosphoproteome and other 'omic' differences of individual cancer cells, they display different signalling (and metabolomic) activation patterns and are surrounded by different stromal cells [14]. The behaviour as either rapid tumour growth or metastasis formation depends on the intercellular signalling network of the cancer cell community. In the rapidly proliferating state of individual cancer cells, stable intercellular interactions are less likely to develop. Thus, ongoing rapid proliferation can be described as growth which is more or less independent of cellular context. On the contrary, the development of the state of metastasis requires a stabilising niche even during cell migration; thus the metastatic switch is promoted by the development of a robust and resilient network of intercellular signalling cooperation [13,16–19].

Metastasis is the cause of nine out of ten deaths in cancer patients. The system-level analyses of intra- and intercellular signalling networks indicate that rapid growth and metastasis formation are often different outcomes of complex integrated molecular events.

## 3. Evidence from human studies

The theory that patients with a rapidly growing cancer have a poor prognostic outlook may have remained so persistent not only because it makes intuitive sense but also because empirical evidence to refute the theory is so hard to generate. Indeed, in an individual patient, the growth rate of the primary tumour is usually impossible to measure, whereas indirect estimates—such as time between onset of symptoms and diagnosis—are notoriously difficult to retrieve and interpret.

The only valid scenario that allows the identification of groups of cancers with different growth rates is in cancer screening. Patients who surface clinically with interval cancers between two screening examinations, or shortly after a negative screening (so-called interval cancers), make up one group. Interval cancers have, by definition, a detectable preclinical phase (sojourn time) which is shorter than the interval between two screening examinations [20]. The preclinical phase, as a measure of growth rate, would be shorter the sooner the cancer is detected after a negative screening. The valid comparison group comprises patients unaffected by screening, diagnosed in routine clinical practice due to symptomatic disease; because of length-bias sampling and overdiagnosis bias—and thus over-representation of slowly growing tumours—screen-detected cancer patients do not make up a valid comparison group [20].