Are rapidly growing cancers more lethal?

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Running head: Growth rate and prognosis

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1

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Abstract

The view that rapidly growing tumors, compared to those who grow slowly, are more likely 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 signaling networks. This analysis indicate that rapid growth and metastases formation often are 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 detected unaffected by screening. We reviewed all available data which are limited to cancers of the breast, cervix, and large bowel. And the human evidence 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 well as the impact of length biased sampling in cancer screening and they provide no support for treating interval cancers more aggressively than non-interval cancers.

Introduction

Cancer screening has been described as a clash of science and intuition. [1] The same might hold for the almost axiomatic long-lasting view that rapidly growing tumors, compared to those who grow slowly, are more likely to metastasize and become lethal. [2-4] This view seems integrated to the 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 signaling pathways that entail accelerated tumor 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 knowledge to believe that cancer growth rate and metastases are not related phenomena. This challenges the assessment of screening interventions [2-4] and possibly the management of cancer patients.

Evidence from tumor 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 tumor.[8] Foulds emphasized "*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 generalizable to others. The explosive expansion of knowledge from molecular biology may now allow a deeper understanding of the signaling complexity that governs growth rate and the metastatic process.

Tumor 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 signaling pathways make a clear dissection of 'tumor growth pathways' *versus* 'metastasis pathways' difficult. However, an increasing number of recent scientific evidence demonstrates that the development of the rapid growth *versus* metastatic phenotypes can be discriminated as separate, context-dependent outcomes of the whole signaling network. [10-12]

Cancer stem-like cells and cancer cell dormancy give special examples of this context-dependent duality. Cancer stem-like cells may reside in one of the two basic states of their signaling 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 fine-tuned balance between signaling pathways.

Primary tumors have an extremely large 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 signaling (and metabolomic) activation patterns and are surrounded by different stromal cells. [14] The behavior as either rapid tumor growth or metastasis formation depends on the inter-cellular signaling network of the cancer cell community. In the rapidly proliferating state of individual cancer cells, stable inter-cellular interactions are less likely to develop. Thus, ongoing rapid proliferation can be described as a more-less cellular context-independent growth. On the contrary, the development of the metastasis state requires a stabilizing niche even during cell migration, thus the metastatic switch is promoted by the development of a robust and resilient network of inter-cellular signaling cooperation. [13, 16-19]

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

Evidence from human studies

The theory that patients with a rapidly growing cancer have a poor prognostic outlook may have remained so long-lived not only because it makes intuitive sense. A more important reason may be that empirical evidence to refute the theory is so hard to generate. Indeed, in an individual patient, the growth rate of the primary tumor is usually impossible to measure. And 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: One group comprises patients who surface clinically as interval cancers between two screening examinations or shortly after a negative screening (so-called interval cancers). Interval cancers have, by definition, a detectable preclinical phase (sojourn time) which is shorter than the interval between two screening examinations. [20] And 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 (due to length-bias sampling and overdiagnosis bias, and thus overrepresentation of slowly growing tumors, screen-detected cancer patients are not a valid comparison group). [20]

Hence, valid assessment of the theory that rapidly growing tumors are more lethal can be undertaken only within populations where interval cancers can be compared with cancers detected unaffected by prior or ongoing screening. To prevent confounding, a valid study also

requires that interval cancers have been treated according to the same principles as non-interval cancers. All these methodologic challenges limit the number of informative studies substantially. Below, we provide an overview of evidence from high-quality studies for different cancer types.

Cervical cancer

We are aware of only one informative study based on an audit of the National Swedish Screening Program. [21] To eliminate lead-time and length-bias sampling, the investigators analyzed symptomatic cervical cancers diagnosed following a negative smear. These case patients were divided into those who progressed rapidly and were detected before the next scheduled screening (interval cancer); and those who were overdue and detected after the recommended screening interval.

As shown in Figure 1, those who surfaced clinically during the screening interval had a higher (rather than lower as the prevailing theory predicts) disease specific survival than women diagnosed after the recommended screening interval. The difference in cure proportion was 14%. [21] The investigators also compared cancers detected at screening within the recommended interval with those detected later, but found no appreciable difference in the overall excellent prognostic outlook (Figure 1). Thus, this large, population-based study provided no evidence that rapidly growing cervical cancers have a poor prognosis.

Breast cancer

A few small studies with suboptimal design have analyzed prognosis of interval cancer (cf. ref [22]). An early study with an ideal (randomized) design but low statistical power provided no

support for the theory of a worse prognostic outlook among interval cancers. [23] A more recent and much larger observational study took advantage of the stepwise introduction of the nation-wide mammography screening program in Norway. [22] Authors compared prognosis among 1,816 women with interval cancers and 5,300 diagnosed before they had been invited to mammography screening. After ten years of follow-up, survival was virtually identical in women with interval cancer (79.1%) and women in the non-screened group (76.8%) (p=0.53) (Figure 2).

Colorectal cancer

We found no data in the published literature that could elucidate, whether patients with rapidly growing colorectal cancers (CRC) had a different prognostic outlook than those with slowly growing cancers. We therefore used existing, population-based databases in Sweden, to identify individuals with a negative colonoscopy. We included colonoscopies performed between 1997 and 2013. We excluded individuals with earlier CRC and those with CRC diagnosed within six months from colonoscopy, assuming that they were overlooked at the colonoscopy (false negative) or underwent a lengthy diagnostic work-up.

During follow-up through 2013, we identified 1,957 eligible individuals with a CRC diagnosed more than 6 months after the first negative colonoscopy of whom 426 died from colorectal cancer. We fitted a multivariate Cox regression model with time since colonoscopy to CRC detection as a continuous determinant of CRC death, adjusting for age, sex, calendar time, interaction terms between the covariates and quadratic terms for age and continuous interaction terms. The hazard ratio for time from negative colonoscopy to cancer detection was 1.00 (95% confidence interval 0.999-1.002, p=0.65). In another Cox regression, where time since negative examination was categorized in yearly intervals and outcome was set to

CRC death within five years (restricted to colonoscopies performed in 1997-2008 to allow for at least five years of follow-up), HR was 0.95 (p=0.68). Hence, our analyses do not support the theory that growth rate and prognosis are related phenomena.

Other cancers

The clinical landscape of prostate cancer has changed more dramatically than that of any other malignancy following introduction of screening. Yet, a valid comparison of the prognosis among men with interval cancers and those unaffected by screening is difficult because opportunistic PSA-testing with overdiagnosis of non-lethal cancer has profoundly influenced the recorded incidence at the population level. [24] Even in randomized trials, contamination due to PSA-testing among those assigned to no screening, would bias prognostic analyses. For other cancer sites, data are sparse and confounded by opportunistic screening and overdiagnosis, and available screening modalities have too poor performance to allow informative analyses.

Conclusion

The theory that rapidly growing cancers are more lethal than those who grow slowly cannot be definitely dismissed, because the null hypothesis can never be proven scientifically, only refuted. With this caveat, our summary of the human evidence shows a lack of support for the prevailing idea that rapidly growing cancers are more prone to metastasize. These data are consistent with almost 70 year old evidence from tumor biology, as well as with recent system-level analyses of intra- and inter-cellular signaling networks.

Our findings might have at least two practical consequences. Firstly, the concern that length-bias sampling influence survival analyses when screened- and non-screened detected cancers are compared [3, 4] may be unfounded although bias can arise due to lead-time and overdiagnosis of non-lethal cancer. Secondly, the empirical support for treating interval cancers more aggressively than non-interval cancers is currently lacking.

Conflict of interest:

None declared.

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Figure legends:

Figure 1: Relative survival ratios of cervical cancer in Sweden for women diagnosed 1999-2001 (all histological types and all ages), by screening history and mode of detection. Reproduced from "Screening and cervical cancer cure: population based cohort study. Andrae B, Andersson TM, Lambert PC, Kemetli L, Silfverdal L, Strander B, Ryd W, Dillner J, Törnberg S, Sparén P, 2012;344:e900", with permission from BMJ Publishing Group Ltd., 2016".

Figure 2: Cumulative breast cancer survival plot for women with breast cancer by group. Reproduced from "Prognosis of interval breast cancer: population-based observational cohort study, Kalager M, Tamimi R, Bretthauer M, Adami HO, 2012;345;e7536", with permission from BMJ Publishing Group Ltd., 2016".
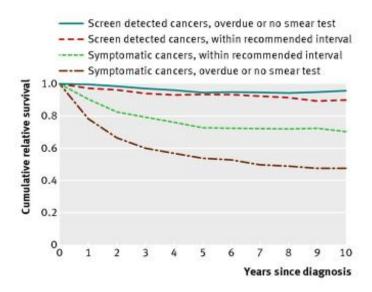
Fig. 1

Legend:
- Screen detected cancers, overdue or no smear test
- Screen detected cancers, within recommended interval
- Symptomatic cancers, within recommended interval
- Symptomatic cancers, overdue or no smear test

(y-axis: Cumulative relative survival; x-axis: Years since diagnosis)

Fig. 2

Legend:
- Interval breast cancer
- Non-screened breast cancer

(y-axis: Breast cancer survival (%); x-axis: Years of follow-up)