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Discrepancies between primary tumor and metastasis: A literature review on clinically established biomarkers

Stéphane Vignot [a,*], Benjamin Besse [b], Fabrice André [b], Jean-Philippe Spano [a], Jean-Charles Soria [b]

[a] *Service d'Oncologie Médicale, Groupe Hospitalier Pitié Salpêtrière, Paris, France*
[b] *Unité INSERM U 981, Université Paris Sud, Département de Médecine, Institut Gustave Roussy, Villejuif, France*

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Contents

Abstract

The identification of predictive factors of response is critical for the development and appropriate use of anti-cancer agents. The evaluation of biomarkers is usually performed by analyzing the primary tumor tissues but this approach does not take into account potential discrepancies between primary tumor and secondary lesions. This review proposes to describe currently available data regarding differential expression of established biomarkers between primary tumor and matched metastasis. In light of recent data, the need of iterative biopsies in metastatic setting has been suggested but technical and methodological limits in such analyses should not be ignored and this strategy cannot be definitively validated. Complementary studies are still needed since the question of spatial and temporal variability of biomarkers in solid tumors is clearly a key issue in an era where personalized therapy is strongly advocated by clinicians, researchers and patients.

Keywords: Primary tumor; Metastasis; Discrepancies; Personalized oncology

1. Optimal tumoral tissue to be analyzed in the era of personalized oncology

Should a biopsy of a metastatic lesion be considered, even when samples from primary tumor are available and exploitable for any molecular analysis? This question often occurs in daily practice and biopsies are usually proposed for some clinical situations where it is important to prove

* Corresponding author at: Oncologie Médicale – Groupe Hospitalier Pitié Salpêtrière, 47-83 boulevard de l'Hôpital, 75651 Paris Cedex 13, France. Tel.: +33 1 42 16 05 09; fax: +33 1 42 16 04 98.
E-mail address: stephane.vignot@psl.aphp.fr (S. Vignot).

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metastatic progression or to discriminate between metastases or new primary tumors. A pulmonary lesion for a smoking patient with bladder cancer may for example represent a frequent example of this approach. Beyond this diagnostic question, a new aspect has recently emerged since the determination of molecular predictors of response is now critical for the development and clinical implementation of anti-cancer agents, both for conventional chemotherapy and molecular targeted therapies. Some biomarkers are now established (hormone receptors, amplification of HER2, mutation of KRAS, mutation of EGFR) while others are emerging with new agents development (EML4-ALK, mutation of BRAF). The evaluation of such biomarkers is usually performed using the primary tumor tissues which are used for histological diagnosis but this approach does not take into account potential discrepancies between primary tumor and secondary lesions, nor evaluates the potential lethal disease (i.e. the metastasis). Such discrepancies may enlighten the molecular process underlying metastatic progression. These data must be considered with attention as they may lead to the identification of new prognostic and predictive factors, to the discovery of putative new molecular targets and to determine whether biomarker evaluation on metastasis in addition to primary tumor is really informative for therapeutic decision, thereby leading to validate or not the relevance of a new biopsy for each metastatic progression. Multiple biopsies in a patient life-time represent a usual practice for indolent lymphoma where a new biopsy is considered at progression to exclude transformation but has to be studied and criticized more precisely for solid tumors. Many limits and barriers have to be considered in this setting and this review aims to discuss these questions in the purpose to guide future practice.

2. Known discrepancies and potential consequences on treatment decision: focus on breast, colon and non-small cell lung cancer

Many manuscripts have been published regarding this question, in many tumor types. We have deliberately chosen to focus here on biomarkers (and their respective tumor-type) which are actually associated with a conditional approval in Europe (Table 1).

2.1. Breast cancer

Multiple groups have studied the potential discrepancies between primary breast cancer and metastasis for ER, PR and HER2 (Table 2, with a focus on most recent publications, and Fig. 1) [1–13].

Definitive conclusions cannot been drawn since data are not consistent. If HER2 expression could be considered as stable between primary tumor and metastasis, previous works reported a more important variation for HER2 testing compared with recent data and this finding may be limited to bone metastases [14]. It is difficult to assess if this variation

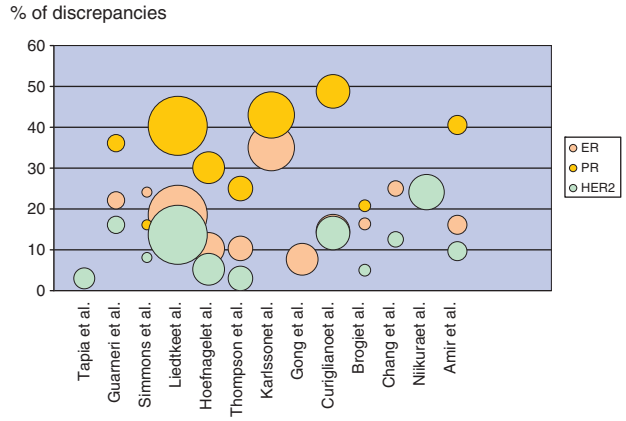

Fig. 1. Schematic representation of ER, PR and HER2 discrepancies between primary tumor and metastasis in breast cancer based on Table 2.

is clinically relevant or is due to technical interference linked to decalcification precluding reliable immunohistological analyses. HR expressions may vary between primary tumor and metastasis, as reported in the largest studies presented here. The discrepancies are especially marked for PR expression (loss of expression) and the therapeutic impact of this finding may be limited since hormonal therapies could be proposed depending on ER status which seems more stable. Few studies have reported treatment modifications based on the analysis of the metastatic lesions [3,6,9,10]. In the pooled analysis of prospective studies BRITS and DISCOVERY, biopsy results altered management in 14.2% (95% CI 10.4–18.8) but the clinical impact is unknown [15].

2.2. Colorectal cancer

The first studies about discrepancies between primary tumor and metastasis for colon cancer focused on EGFR status by IHC as this biomarker was initially included in conditional approval of cetuximab (indeed expression of EGFR in IHC for more than 1% of tumoral cells was required) [16,17]. Complementary studies showed that EGFR expression was not correlated to cetuximab sensitivity and this biomarker was abandoned in colon cancer [18]. KRAS mutational status value was identified more recently and a wild type status is now required for prescription of cetuximab or panitumumab in metastatic colorectal cancer. On the contrary, mutated KRAS is associated with resistance to EGFR inhibitors [19–21]. Initial data relative to KRAS mutational status frequency and type were in favour of a consistent KRAS status during neoplastic dissemination with no significant difference in mutation frequencies between a group of 879 tumor specimens derived from primary tumor sites and a group of 139 metastases [22]. This hypothesis was confirmed by numerous studies with paired analyses of primary tumor and matched metastases (Table 3 and Fig. 2) [23–34]. In clinical practice, these data support analysis of KRAS mutational status indifferently either on primary tumor or metastatic lesion. It is important to highlight that