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Fifteen important questions for oncology to be addressed from 2015

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Summary

Cancers can now be classified by multidimensional criteria including tumour site, histology, primary - "driver" - molecular alterations, secondary molecular alterations, characteristics of the immune stroma, and genetic profile of the patient. The development of tools for the characterisation of the cancers, as well as novel molecular and immune therapeutics are evolving at an unprecedented pace. In 2012, a list of future challenges was identified at the occasion of the European Organisation for Research and Treatment of Cancer (EORTC) 50th anniversary. Three years after, it is interesting to look back at the questions addressed then and to assess the progress of these questions. We propose here a novel set questions which have emerged from the recent publications in this area.

Mots clés
Caractérisation moléculaire des tumeurs
Défis pour l'oncologie
Médecine personnalisée

Résumé

Quinze questions importantes à se poser en oncologie en 2015

Les cancers peuvent maintenant être classés selon des critères multidimensionnels tels que le site primitif, l'histologie, les altérations moléculaires primaires *driver*, les altérations moléculaires secondaires, les caractéristiques du stroma immunitaire et le profil génétique du patient. Les outils pour la caractérisation des cancers ainsi que les nouvelles thérapies moléculaires et immunitaires évoluent à un rythme sans précédent. En 2012, une liste des défis à venir a été identifiée à l'occasion du 50e anniversaire de l'*European Organisation for Research and Treatment of Cancer* (EORTC).Trois ans après, il est intéressant de revenir sur les questions posées et les progrès accomplis. Nous proposons ici une nouvelle série de questions issues des avancées récentes.

In 2015, the rapidly evolving tools for molecular characterisation of tumor cells enables refinement of the nosological classifications at an unprecedented pace, in a growing number of cancers [1-16]. These alterations are more frequently used for treatment decision purposes, and often guide molecular treatments in end stage patients initially, and now more and more frequently in first line setting [17-23]. In addition, the presence, phenotype and topography of specific immune cells in the stroma of cancer are better understood, and their contributions to tumor progression, and value as predictors for response to treatment start to be established [24-29].

Cancers are now classified by multidimensional criteria: 1) tumour site; 2) histology; 3) primary - "driver" - molecular alterations; 4) secondary molecular alterations; 5) characteristics of the immune stroma; 6) genetic profile of the patient. In addition, temporal evolution of the genetic and epigenetic alterations of the tumor cells and composition of the stroma are more and more frequently reassessed. Rebiopsies of the metastatic sites enable to identify secondary resistance mutations induced by Darwinian selection of pre-existing in a minority of clones [30,31].

These molecular and immune characteristics can now be diagnosed not only in tumor samples, but also in the peripheral blood tumor DNA, with the rapid emergence of liquid biopsies [32]. These novel tools offer the opportunity to assess holistically the presence of heterogenous mutations at the initial diagnosis, and to monitor secondary mutations emerging during treatment.

Hence, cancers gathered in previous histological groups are becoming much more fragmented than previously anticipated into a variety of homogenous molecular subtypes, distinguished by sets of genetic and epigenetic alterations [33-36], including "driver" molecular alteration. In lung cancer, tumours with mutations in *ALK* (4% of lung cancer), ROS1 (1% of lung cancer), BRAF V600 or *EGFR* (<10% of lung adenocarcinoma) have specific clinical presentations and are now proposed for specific targeted treatments [22]. The precise sequence of the driver mutation may have specific biological consequences, may determine outcome of the patients and the selection of treatment [18-20]. This is well illustrated in GISTs, a model which also shows that the fragmentation of cancers also observed in rare tumours: The recently identified (1998) entity of gastrointestinal stromal tumours (GIST) comprises at least 10 different subtypes (mutated on KIT exon 11, exon 9, other, PDGFRA exon 12, 14, 18, the latter being split between D842V and others, SDH gene mutations, NF1, BRAF...). Even within GIST mutated on *KIT* exon 11, the nature and topography of mutation (point mutation, deletion, codons involved) has a major impact on long term outcome after surgery as well as in metastatic setting. These different GIST require distinct treatments in advanced or adjuvant phase [20]. The complexity further increases as we are recognizing that heterogeneity may even occur within a single tumour and patient: Complex, Darwinian, branched evolution of mutations is occurring from primary tumour cells to metastastic cells [30,31].

Secondary resistance to targeted agents develops in many patients with solid tumours in advanced phase [4,5]. Whether the emergence of resistant clones, is proportional to tumour cell mass is likely but not completely demonstrated in all tumors. Novel pieces of evidence point to the fact that physical removal of tumour cells in advanced cancers may reduce the risk of emergence of secondary resistance [37].

These refinement in nosological classifications, with an intense fragmentation of "old school" organo-histological classifications have therefore consequences for the prognosis of cancers in localized phase, as well as for cancers in advanced phase. Whether very long - maybe lifelong - targeted therapy in advanced and adjuvant setting is needed is now being studied in carefully designed trials exploring homogenous molecularly well defined disease entities [38]. Finally, whether the curative local treatments in localized phase, surgery and radiotherapy, should be adapted to these refined nosological classifications remains a topic of research. Whether the efficacy of treatment in metastatic phase predicts efficacy in adjuvant setting has been challenged in colorectal cancers [39].

In the last three years, the development of tools for the characterisation of the cancers, as well as novel molecular and immune therapeutics has been evolving at an unprecedented pace. The state of the art of "personalized", "precision", "molecular" medicine requires therefore a periodical assessment of the general questions remaining to be addressed. At the occasion of the European Organisation for Research and Treatment of Cancer (EORTC) 50th anniversary, a list of future challenges was identified and presented in a publication [40,41]. In "hard" sciences such as Mathematics [41], set of key questions are periodically established for the scientific community. There is a similar need in medical science, with the major difference that the current pace of the evolution of technologies and therapeutic tools requires a much more frequent reassessment of questions and needs. A list of questions was set after in 2012. Three years after this publication [42] it is interesting to look back at the questions addressed then and their potential answers.

One of the questions was how to integrate the increasing knowledge of hundreds of genomic alterations of each individual tumour for diagnostic, prognostic and predictive purposes in daily clinical practice. This important question remains largely a work in progress, as construction of clinical databases integrating massive datasets obtained from molecular tools are in progress. Interaction of clinical researchers, with molecular biologists and databases with bio-informaticians will be critical in the coming years. The strategy for the identification of driver mutations in a given tumour for a given patient has also been refined? Clinical research programs of simultaneous identification of a variety of genomic alterations are underway in many countries, including France. Clinical trials with molecular inclusion criteria, leaving histology as secondary parameter, are underway (eg, NCT01524978, NCT01414933, NCT01774409...). Some of these trials are successful, eg with a 100% tumor control rate shown with vemurafenib in Erdheim-Chester disease in a recent presentation at the American Society of Haematology. This points out to the ongoing paradigm changes that put organ origin as a secondary criteria. Whether adjuvant treatment with targeted therapies enables to prevent or postpone relapse is still unclear. Trials are in progress in a variety of tumour types with TKIs as well as for immune checkpoints inhibitors. In GIST, the paradigmatic model, novel surrogate markers for overall survival have proposed. EORTC 62024 proposed an innovative criteria for the assessment of the benefits of adjuvant imatinib in high risk and intermediate GIST: This criteria is defined as the time to the development of resistance to imatinib in advanced phase, and integrate the possible emergence of an earlier resistance under the adjuvant therapeutic pressure, which was not observed reassuringly in the first report [43].