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Revolutions in cancer treatment:
how can they be integrated?

Pathways to therapeutic progress in oncology

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Abstract

Therapeutic progress in clinical oncology results from identifying new classifiable entities characterised by specific molecular alterations, (i) resulting in a comprehensive reclassification of a number of cancers and (ii) acting as predictive biomarkers. These advances allow us to understand the subclonal evolution of cancers and development of primary and secondary resistance in patients. The future of oncology should integrate this routine information; however, the multiplicity of different biomarkers makes integration into simple algorithms difficult. Bioinformatics and artificial intelligence are becoming essential in clinical decision-making. This change in our understanding of cancers and the way they are classified is essential in order to effectively develop targeted treatments. The quality of initial management of cancer continues to be one of the keys to improving survival in patients with these diseases. Recent successes in molecular medicine in the field of cancer are presented here, along with possible strategies for future developments.

AN EVOLVING CLASSIFICATION SYSTEM

The histological classification of cancers, which is used as a basis for all our clinical practice recommendations, is being challenged. The histological entities that used to be considered relatively homogeneous in their clinical behaviour are being fragmented into a huge number of heterogeneous diseases based on insights from molecular biology, particularly high-throughput tumour cell genome sequencing systems. This molecular classification of cancers is associated with the characterisation of immunological subgroups of cancers, causing further fragmentation of these new nosological entities. This is having a significant impact on the development of clinical research as cancer is beginning to resemble a collection of rare diseases.[1-5] Previously, phase III trials compared cancer treatments in very large groups of patients, but now trials are recruiting patients based on histological and molecular subgroups of cancers. Furthermore, clinical research and translational research are not progressing at the same pace. For example, profiles predicting the risk of recurrence in localised breast cancer were described in the early 2000s,[6] but the MINDACT EORTC trial did not clarify the use of biomarker-guided treatment until 12 years later.[7] During these years of clinical research, a myriad of technological developments and the generation of a considerable amount of scientific evidence have further altered existing classification frameworks. The challenge in this context is to create a more effective match between the pace of clinical research and the pace of fundamental research.

EXPERT NETWORK AND LOCOREGIONAL TREATMENTS

The first revolution in oncology was to change the quality of surgery. Improving the quality of management in early neoplastic disease phase is one of the keys to improving patients' survival; rigorous adherence to clinical practice recommendations for locoregional treatments provides greater survival improvements than the benefit offered by many new drugs.

The National Cancer Institute wanted to identify the rare cancers that account for 20% of all cancers and 30% of mortality. One of their aims was to improve the management of these patients within expert networks. In the past 10 years, a project has been undertaken in collaboration with the French Sarcoma Group. The NetSARC network has created a database unlike any other in the world, recording all the sarcoma diagnoses in France since 2010 and subjecting them to a second expert pathological review. Analysis of this database, which includes almost 50,000 patients, has shown that only a third of cases were presented at multidisciplinary team (MDT) coordination meetings. Yet, patients whose care was coordinated by an MDT received treatment that was more compliant with clinical practice recommendations (imaging of the tumour before treatment/surgery, biopsy before the first resection).[8] Organising the management of patients in this way also had an impact on the quality of surgery, particularly when patients had operations in specialist centres.[9] Specialist centres had a 40% better survival rate, and their surgical management cost less because the rate of re-operation at these centres was much lower. These benefits were shown, for example, in patients with retroperitoneal sarcomas.[10] The coverage of the French national territory provided by the expert network also has a beneficial impact on reducing inequality; all patients, regardless of their geographical distance from the specialist centre, have a similar life expectancy, as long as they are managed in a specialist centre.[11]

DEEP LEARNING AND MEGADATA

The third revolution in oncology is the use of megadata generated by bioinformatics and artificial intelligence to assist with clinical decision-making. One reason why the prognosis for French sarcoma patients was worse for those managed outside specialist centres was that the diagnosis was incorrect. Yet, it may be possible to improve the quality of the diagnosis using artificial intelligence tools. For example, does the reading of whole-slide images that have been divided into small 112 × 112 µm squares (called 'tiles') using a deep learning algorithm (**Figure 1**) make it possible to improve our diagnostic performance? It seems that in the case of mesothelioma the answer is yes: tiles recognised by a deep learning tool have made it possible to improve both the diagnosis and prognosis for patients with this type of cancer.[12] These tools should make it possible not only to refine molecular and prognostic classification, but also to improve identification of patients at high risk of recurrence, catalogue molecular subgroups and link molecular biology or immunological subgroups to image analysis.

Figure 1. Deep learning models make it possible to identify new characteristics that will predict patient survival, leading to the discovery of new biomarkers. A machine learning model has made it possible to predict the overall survival of patients with mesothelioma through histological analysis of a database of histology slides (MESOPATH/MESOBANK). The method of reading the slides using a computer with a deep learning algorithm was tested on 681 slides by MESOBANK and validated using 56 reference slides from the cancer genome atlas. The whole-slide image was divided into 112 × 112 µm squares or 'tiles', and a predictive score was given to each tile of interest that was positively or negatively associated with survival.
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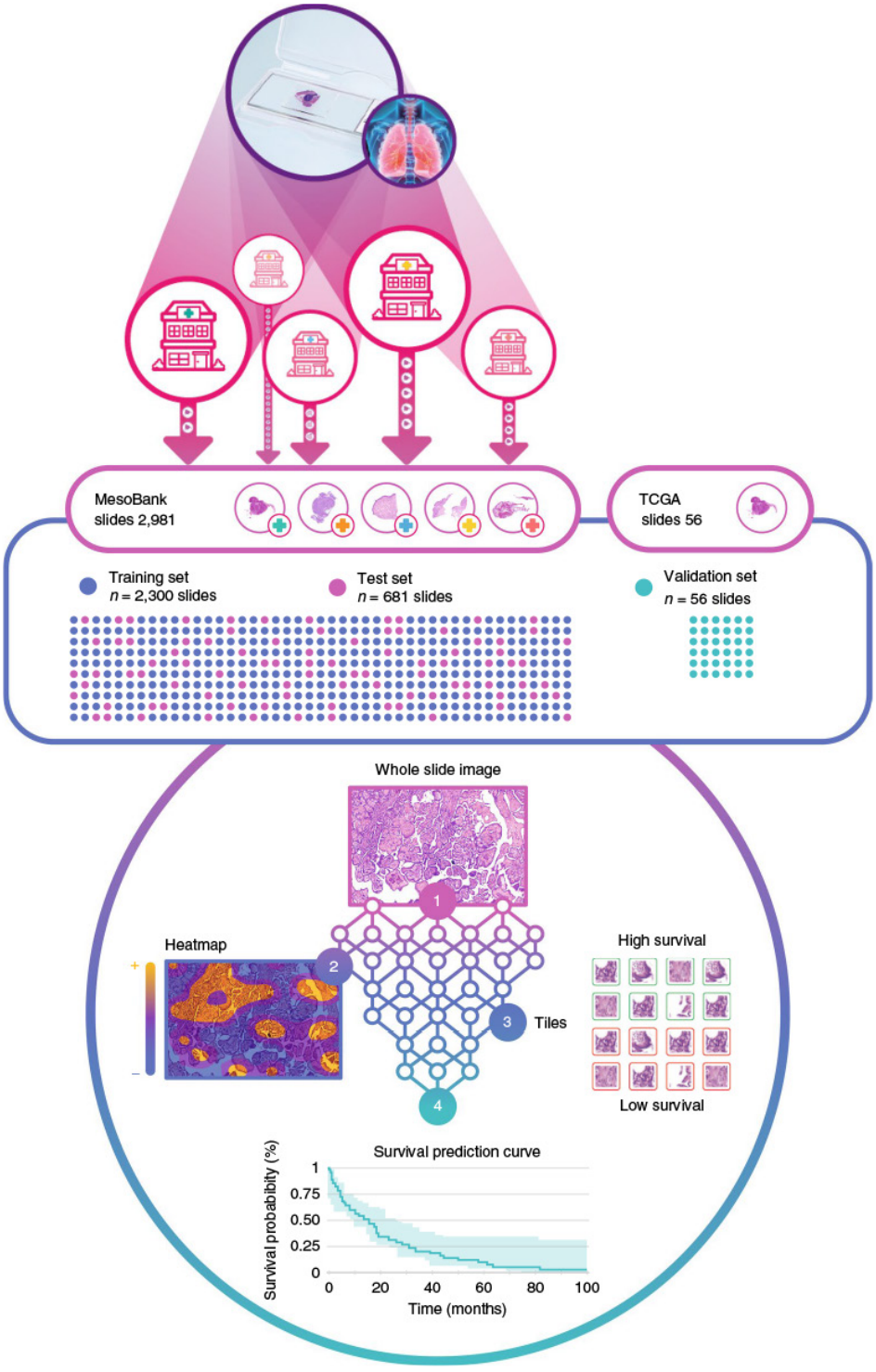

At the Léon Bérard Centre in Lyon, patient records have been computerised for about 25 years, providing a database of 300,000 patients. This large database has made it possible to (i) determine that about 8% of patients report with a second cancer, and (ii) create a detailed table describing cancers that are linked, in ways that are well known in some cases but completely unknown in others. Megadata has also made it possible to analyse the time within which a second cancer occurs based on the patient's sex, or depending on whether or not chemotherapy is used (personal communication).

Today, due to the fragmentation of classification frameworks and the rarity of individual molecular diseases, new statistical strategies are needed to demonstrate the efficacy of new drugs. These analytical approaches to deep learning and data mining will probably find their way into our health care system because they make it possible to better use our current data.

PRECISION MEDICINE

Precision medicine is the result of understanding the biology of disease and the genetic alterations that play a key role in disease progression. This allows us to describe not only the molecular alterations that are shared by all cancer cells, but also those of subclones of cancer cells that respond differently to treatments, cytotoxic drugs, radiotherapy or targeted therapy, so that we can explain the development of primary and secondary treatment resistance. Driver mutations – or strong oncogenic drivers – have been identified (e.g. KIT, BRAF) making it possible to develop targeted therapies, but these may have very different impacts, depending on the type of cancer.[13] This is a general phenomenon; all of the molecular characterisation studies, such as the ProfilER study in a cohort of 4000 patients,[14] have shown a wide variety of molecular abnormalities and only 7% of the patients are actually treated with targeted therapy. Strong oncogenic drivers have been identified, but only in a small number of cancers. It is therefore not yet known how to define, from the outset, precisely what will be a strong driver in a way that would make it possible to predict the performance of a targeted therapy.[15] Two current studies are attempting to find answers to this question. The ProfilER 2 study (NCT03163732) is evaluating the added value of a large molecular profiling panel (370 genes) in comparison with a limited molecular profiling panel (70 genes) in solid tumours; the results will allow us to determine which approach is more effective for managing patients. The first indications of the answer to this will be available when the France Genomic Medicine Plan 2025 issues its first complete genome sequencing data. The MOST study (NCT02029001) is also evaluating the clinical benefit of treatment targeting molecular alterations in cancer (using sorafenib, everolimus, nilotinib, pazopanib, olaparib, durvalumab or tremelimumab) in patients with advanced or metastatic solid tumours with local progression. The purpose of this study is to be able to identify the most appropriate treatment for patients with a specific molecular abnormality and evaluate the response to that treatment.

BRINGING THE CONTEXT TOGETHER

Although the developments in molecular medicine have considerable potential, the available treatments are not yet adequate. In future, oncology practice will need to routinely bring this information together, but it is currently difficult to integrate the large number of biomarkers (e.g. mutations, expression levels) into simple algorithms that can be used to guide the decision-making process. Translational research is at the heart of efforts to develop future treatments and identify the cancer-specific responses and resistance mechanisms. Progress can only come through close collaboration between basic science researchers and clinical researchers. This type of collaboration sometimes bears fruit: one research programme has made it possible to identify a drug, known as NP-137, which is currently undergoing phase I clinical research in patients with progressive locally advanced or metastatic solid tumours (NCT02977195). NP-137 is a monoclonal antibody that blocks netrin, a growth factor that interacts with dependent receptors and is generally over-expressed in a large proportion of cancers. The initial results of this trial are encouraging and responses are being seen in patients who received it as monotherapy, with limited toxicity.

Numerous challenges need to be overcome to integrate all the sources of information and fields of research into one cohesive pathway towards therapeutic progress in oncology. Changes are needed in our administrative and legal frameworks so that we can make progress together, in a setting classification systems are becoming more and more fragmented, but where the opportunities at the interface of fundamental research and clinical research are greater than ever.

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