Editorial on Thoracic Surgery

A new race against lung cancer

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In 2017 lung cancer is still worldwide the huge nightmare among cancers with a tribute in terms of incidence and deaths ceiling 1.8 and 1.6 millions of patients respectively (1,2).

The main reasons are linked to time lead bias phenomenon reducing the magnitude of benefit of screening programs in high risk populations. The high incidence and deaths of this tumor in non-smokers patients or with scarce recognized risk factors and the modest efficacy of old fashion chemotherapeutic agents makes this tumor a challenge.

Two major axes regarding targeted agents and immunotherapies seem to improve the prognosis of lung cancer patients but resistance mechanisms and immunoescape are the main weakness of these breakthrough agents. However, new therapeutic approaches leading to becoming chronic in some cases lung cancer have improved the number of the so called 5 years long-term survival (3,4).

The real reason of failure of all treatments in lung cancer is due to the Darwinian principle of species evolution: cancers are composed by heterogeneous tumor cells and their evolution is not linear but branching evolutionary trajectories that are the main ways leading to uncontrolled growth and metastatic spreading of this tumor.

Recently, Cancer Research UK is supporting an ambitious program investing £14 million in studying the evolutionary genetic landscape in non-small cell lung cancer (NSCLC). Swanton and colleagues have reported preliminary results of the whole-exome sequencing of 100 early-stage NSCLC in order to correlate the heterogeneity towards the study of clonal and subclonal events to meaningful clinical outcome named recurrence-free survival (5).

Tracking Non-small Cell lung cancer Evolution through Therapy (TRACERx) trail started its activity in April 2014 and more than 800 tumors from completely surgical resected patients affected by NSCLC stage IA through IIIA have been collected in order to deeply fathom heterogeneity through whole exome sequencing.

In summary, the authors have found that a few driver mutations like EGFR, MET, BRAF were almost exclusively clonal whereas PIK3CA, NF1, KRAS, TP53 and NOTCH family members were represented as subclonal mutations. Also gene amplification seemed to follow the same pattern of variability with little allelic imbalance being clonal (TERT, 8p loss, 5p gain, FGFR1) while the majority were subclonal. Clonal mutations were sometimes histotype-oriented while subclonal lost that dependency being expression of heterogeneity per se.

This aspect has an immediate effect in clinical practice: subclonal driver alterations may appear as clonal in a small biopsy leading to a therapeutic choice that could be unsatisfactory giving an underperformance than expected. On the contrary, we risk to consider a passenger mutation as driver.

Another aspect that clearly emerges from this trial regards the importance to intervene earlier with target agents. In fact, true driver mutations are present at the beginning of clonal evolution in the so called "trunk" of clonal evolution and the probability to purge neoplastic cells is higher when we target mutation in the trunk instead of blocking a subclonal mutation in a side branch of this evolutionary clone.

During the evolution of the trunk there is a point of no return in which the genome doubling phenomenon accelerates the clonal diversification sprouting many branches with many other subclonal mutations/amplifications.

Regarding the clinical aspect the TRACERx trial demonstrated that elevated subclonal heterogeneity was associated with worse outcomes with a meaningful higher

risk of recurrence and cancer death (HR 4.9).

TRACERx trial had also a translational analysis conducted on plasma analyzing ctDNA in the same patients resected and studied from a tissue source. The plasma of the first 100 patients enrolled in TRACERx and 1 patient co-recruited to the PEACE (Posthumous Evaluation of Advanced Cancer Environment) were collected and analyzed in order to correlate ctDNA release, their level in plasma at the time of surgery and in the follow-up time, with recurrence risk, chemotherapy resistance and death. The clear benefit of this technique is to monitor ctDNA profile with a no invasive method in order to guarantee an accurate detection of preclinical recurrence and to intervene earlier with new therapeutic strategy to eradicate tumors as first biomolecular appearance (6).

Using a multiplex-PCR NGS platform the authors have analyzed the clonal and subclonal single nucleotide variants (SNV) matching the results to tissue. A median of 94% of clonal SNV and 27% of subclonal SNV were detected within individual essay-panel. The variant allele frequency (VAF) correlates more with clonal SNV than subclonal SNV, this discover shows a better sensitivity between ctDNA and the possibility to detect clonal SNV than subclonal SNV.

The most important finding was the relationship between mean clonal VAF and volume of primary lung tumor. A linear relationship was detected and with the improvement of sensitivity of the techniques employed to unravel lower plasma VAF quantity may lead to anticipating the detection of neoplastic small lung nodule when single tumor is 0.034 cm^2 corresponding to a 4 mm of diameter in low-dose CT scan screening.

The implication in clinical practice of that discovery is really intriguing. In fact, in a longitudinal part of this study ctDNA detection in plasma, considered positive if at least two SNV were detected, allows to anticipate the clinical relapse showed by traditional CT scan 70 days before (range 30–365 days). Notably in 30% of relapsed patients ctDNA detection may predict clinical relapse with a lead-times more than 6 months.

The second implication is the prediction of adjuvant chemotherapy refractoriness. In all patients in which ctDNA arises during adjuvant chemotherapy did a local or distant relapse while the clearance of high level of post-surgical ctDNA was related to relapse free occurrence.

Even if the clinical implication of this technique is quite outstanding in clinical practice due to a reliable method to anticipate earlier the relapse detection still some issues remain due to higher costs currently fixed around 1,800$ and maybe some methodological issues regarding this technology not widely validated in all hospitals.

The preliminary results arising from TRACERx trial and its ctDNA counterpart detection in plasma have many implications in decision making of early disease and also in metastatic setting. However, it is important to wonder if something could be changed in the surgical approach in the era of minimal invasive surgical techniques.

The tumor heterogeneity and complexity in biology coupled with better understanding of phylogenesis of lung cancer lead to a shift the paradigm also in some indication of surgical intervention in locally advanced lung cancer.

One example that anticipated the wider analysis conducted in TRACERx trial is the experience described in an elegant model about the genomic profiles of lung cancer primitive nodules (7).

The authors analyzed the tumor gene profiles of 15 lung adenocarcinoma from 6 patients affected by multiple synchronous lesions. What it is a challenging in order to consider the multiple synchronous lesions as different separate tumors or intrapulmonary metastatic spread was clarified after performing a whole genomic sequencing of such single nodule of these patients.

The results are quite astonishing: all genomic signatures of these nodules are totally different suggesting their independence so excluding a metastatic process behind this peculiar clinical situation.

It is risky to generalize the results of this experience but after the discovery of extreme heterogeneity of lung tumors in TRACERx trial we can conclude that in selected cases a surgical intervention with a curative intent must be offered to cT3 (same lobe) or cT4 (different lobe) clinical entity due to multiple lung nodules.

Regarding contralateral nodule, especially if alone, in the same way a surgical approach could be possible. Obviously technical constraint and estimated respiratory condition of the patient may limit this possibility.

Another exciting chapter that transforms the indication of minimally invasive surgery is that about the clinical management of oligometastatic disease.

This entity is nowadays more studied and even if the definition is not fully accepted, the importance to correctly evaluate these patients is crucial for their survival.

Oligometastatic feature is defined as a disease with a low amount of site of disease involvement and low metastatic burden usually no more than 5 lesions overall even in different organs (8).

Together with low metastatic spread a second definition is to be applied: indolent behavior or longer time free to progression disease after first line systemic treatment. About one fifth of lung cancer patients seems to be affected by this situation and the understanding of biological mechanism unravel by TRACERx trial may be permitted in the near future to empower the activity of multidisciplinary team and surgical approach in those patients.

The management of these patients should be different and handled by a multidisciplinary team and with a mini-invasive surgery in order to prolong progression free survival.

Recently, in a randomized multicenter phase II clinical trial the issue regarding a right way to manage these patients is correctly answered (9).

Seventy-four non-progressive oligometastatic advanced NSCLC patients both EGFR mutated/ALK translocated or wild-type were enrolled after the completion of the first line of therapy consisting of four cycles of chemotherapy or 3 months of targeted agents. Patients were randomized to receive a local consolidative therapy on residual site (stereotactic radiotherapy or surgery) with or without maintenance therapy or maintenance treatment alone. After a median follow-up of 12.4 months the primary end point median progression free survival was statistically significantly higher in the consolidative arm respect to maintenance alone: 11.9 *vs.* 3.9 months respectively with a reduction of the risk of progression of 65% (HR 0.35; 90% CI: 0.18–0.66).

The main bias of this study regards the selection of the population with oncogene driver mutation tumors that may drive this positive and meaningful effect of the consolidative strategy. This population is effectively recognized as a good prognosis with a great impact of targeted treatment that allows a better control, reducing the probability of progression and in some cases even prolonged beyond progression due to a slow non-symptomatic progressive disease.

Beyond criticisms (10) this trial is the first attempt to address a personalized strategy in stage IV NSCLC but, again, the main reason of this success is due to the peculiar biology of the oligometastatic status. When the technology employed in TRACERx trial could be applied to this population becomes evident the difference between phylogenesis of these cancers respect to the more aggressive and usual stage IV NSCLC.

In conclusion, the evidence of tumor heterogeneity will exploit a large employment of personalized strategy in order to manage every single clinical situation.

The mini-invasive surgery will help to capture this heterogeneity performing lung nodulectomy in particular in synchronous multinodular disease. Furthermore a particular role could be assumed by surgeons in order to manage oligometastatic disease. Finally, ctDNA monitoring preoperatively in suspect lung cancer nodules open the doors to a new concept of oncologic surgery in which other biological factors may guide the scalpel more than the anatomy of the tumor.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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