

Management of patients with lung cancer is classically based on histologic diagnosis and staging definition at initial presentation and on physiological assessment mainly based on spirometry and, when indicated, ergometric tests. Goal of physiological assessment is providing estimation of risk of interventional procedures, especially resective surgery, whereas histologic typing, and, at a more important extent, staging, are the mainstay of prognostic assessment and definition of management.

Surgery is generally regarded as the best treatment option of NSCLC and 5-year survival is around 60% in operated patients. Yet, only about 30% of tumors are suitable for potentially curative resection at the time of initial diagnosis, because of advanced stage, poor performance status or cardio-respiratory reserve. There is no doubt that efforts have to be made to improve patient outcome by: (I) increasing the number of patients amenable to a local treatment including surgery or SBRT; (II) improving post-operative outcome; (III) better understanding of biologic mechanisms of tumor progression.

SBRT is a promising local treatment modality of NSCLC, whose relative indications as compared to surgery needs to be refined; ongoing randomized trials are designed to answer the question. Pending these results, SBRT should be used as local treatment in patients unfit for or refusing surgery; in the others, surgery remains the mainstay. Video assisted thoracic surgery (VATS) has quickly applied to complex procedures such as major lung resection, because of its benefits in terms of less postoperative pain, shorter hospital stay, earlier resumption of normal activities, allowing resection in marginally fit patients; however limitations of the technique prompted to development of novel surgical strategies (e.g., the fissure-less techniques) and were at the origin of complications rarely seen at open surgery, requiring specific intraoperative management and possibly impacting postoperative outcome.

Even in the era of VATS, mortality of lung resection for malignancy is as high as approximately 2.5% and this figure is even higher when only pneumonectomy is analyzed, underlining the need of interventions to reduce post-operative mortality and morbidity. Classically, mortality of lung-cancer resection has been attributed to bronchial fistula and post-operative acute respiratory distress syndrome, but it is now known that post-operative pneumonia is a major determinant of postoperative mortality; age, underlying respiratory disease, mainly COPD, and extent of resection are the main determinants of occurrence of postoperative complications. Although significant efforts have been made to improve management when complications occur, prevention remains the best treatment tool. Intraoperative protective ventilation and optimal fluid administration are key measures, but probably optimization of nutritional status and improvement of sarcopenia through specifically designed prehabilitation programs are underemployed measures.

In the era of mini-invasive diagnostic and therapeutic strategies, programs of early recovery after surgery (ERAS) have been set in different institutions, with reduction of occurrence of postoperative complications as compared to historical controls. Final aims of such programs usually are to reduce postoperative morbidity and mortality while simplifying and shortening the hospital course with a positive impact on costs. All these promising results need to be validated in large cohorts and in a more comprehensive setting including every aspect of optimized perioperative care; furthermore, in thoracic surgery usefulness of ERAS actually relies on a relatively low level of evidence and an important challenge remains to evaluate the real benefit of these programs in the different subsets of lung cancer patients.

Furthermore, it has been underlined that every proposed step of such programs is not always feasible. Thus, another challenge is implementing programs in real life; possibly more direct patient participation and tailoring intervention to patients, with respects to risk factors, nutritional and cardiorespiratory reserve, would allow developing strategies of comprehensive management applying to lung cancer surgery modern concepts of predictive, personalized, participatory, and preventive medicine.

Better understanding of biologic mechanisms of tumor progression is another key factor to accelerate toward better outcome of lung cancer patients. It has long been believed that tumor stage was the main determinant of outcome of NSCLC in patients with limited, operable disease and in those with locally advanced disease or metastatic spread; research in this setting is currently ongoing and some paradigms are also matter of debate. Recent works showed that properly selected patients with oligo-metastatic disease can benefit of lung surgery integrated with systemic chemotherapy or targeted-therapies together with local treatment of selected type of metastasis (brain and adrenal). Thus, heterogeneity in patients outcome within the same stage and after the same treatment modality led to the search for other tumor-related histopathological factors possibly influencing survival. Thus, vascular or lymphatic emboli, spread through air spaces, and, among adenocarcinomas, tumor grade, have been recently identified as outcome determinants. Similarly, molecular

phenotype (which constitutes the basis for most targeted therapies) of cancer cells has been evaluated as a possible prognostic indicator, with different gene mutations associated to more favorable or, conversely, unfavorable outcome. Although less extensively studied, deregulation of cellular energetics, enabling replicative immortality, invasion and metastasis has also been suggested as potentially determine cancer progression. Thus, most of biological, translational, and clinical research of recent years aiming at understanding mechanisms of aggressiveness of NSCLC dealt with factors related to tumor itself and research in therapeutic approach was targeted toward tumor-related factors.

Contrary to tumor-related factors, host-related factors have been much less extensively evaluated until recently. Pro-inflammatory cytokines responsible of systemic inflammation and associated growth factors are involved in carcinogenesis through their effects on tumor cell growth, survival, proliferation and migration. The interactions between systemic inflammation and tumor immune microenvironment have also been investigated; the tumor immune microenvironment has been shown to be an important determinant of long-term outcome in primary and metastatic lung tumors. It has been observed that tumor immune microenvironment is directly correlated with nutritional status (as measured mainly by pre-albumin levels) and inversely correlated with preexisting systemic inflammation, but correlations exist also between immune cell densities in the operative specimen and several associated conditions and clinical features (such as stroke, COPD, usual body weight), suggesting that preexisting systemic inflammation/poor nutritional status could impact the intra-tumor immune contexture and the patient outcome.

Globally, a more large and comprehensive vision including assessment of patient phenotype (morphomic), physical performance (in particular assessed by respiratory tests and low or high technology exercise test), inflammatory and nutritional status provide additional discriminatory information for predicting outcome after surgery. Knowledge of the strong and independent prognostic values of these parameters authorizes a shift of mentality from a clinical and scientific reasoning mainly based on tumor characteristics to a reasoning taking into account together with tumor characteristics, the host's ones and their continuous interactions which are represented on one side by tumor immune microenvironment, and on the other by tumoral and, probably more importantly, global metabolism. This understanding allows implementation of new strategies aiming at counteracting cancer growth and systemic inflammation, improving nutritional status, promoting physical exercise, in the idea of restoring patient fitness. These patient-directed strategies are to be regarded as important therapeutic tool to be added to tumor-directed strategies, (surgery, chemotherapy, targeted therapies and radiotherapy). This evolution in mentalities requires accumulation of new, sometimes counterintuitive, evidences. In this perspective, this *Key Leaders' Opinion on Peri-Operative Risk Factor and Therapeutic Strategy in Lung Cancer Surgery* (FIRST EDITION) is a collection of papers, recently published by experts in this fields working in renowned Centers all over the world, which provides an exhaustive review of most of the above described topics. I am glad and honored of providing a preface to this textbook, which is the result of the effective cooperation between researchers. Enjoy the interesting reading!



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