Editorial

Postoperative radiotherapy and lung cancer in stage III: helpful or harmful

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Comment on: Billiet C, Peeters S, Decaluwé H, *et al.* Outcome after PORT in ypN2 or R1/R2 versus no PORT in ypN0 Stage III-N2 NSCLC after Induction Chemotherapy and Resection. J Thorac Oncol 2016;11:1940-53.

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Despite the continued improvement in knowledge the treatment of Non Small Cell Lung Cancer (NSCLC) patients in III stage is still, today, an ongoing challenge.

Billiet and colleagues (1) reported the results of a retrospective study of disease control for biopsy and radiological proven III-N2 NSCLC. The main objective was to describe the ability to trimodality therapy using induction chemotherapy before surgery and postoperative radiotherapy (PORT) in patients ypN2 status and/or with incomplete resection.

As a result, it was seen similar outcomes in patients with these worse prognostic features respect to patients without (ypN0 or complete resection). It is like radiotherapy may impact, principally, on patients with nodal involvement. In the 51 patients with N2 it was obtained directly comparable outcomes to patients with chemotherapy nodal regression (ypN0).

It is controversial whether operable patients with III-N2 stage should be candidates for surgery and trimodality therapy.

Firstly, it is important to understand if downstaging or downsizing after induction treatment is a prognostic factor for better long term survival. If that were true, radiotherapy could have a very important role with therapeutic consequences in preoperative or postoperative setting. In fact, radiotherapy is an ideal complement to systemic therapy as a spatially confined, non-invasive approach of controlling the eradication of microscopic residual disease and/or gross tumor. Nowadays, the role of PORT is still very controversial.

Large-scale retrospective study and a recent meta-analysis demonstrated an improved overall survival in patients with N2 NSCLC who underwent PORT and chemotherapy after radical resection (2,3).

In the light of this studies, ASTRO guideline (4) recommends PORT in the setting of gross primary/nodal residual disease or positive margins.

Nevertheless, a recent revision of PORT meta-analysis by Cochrane group (5) confirms detrimental effect of PORT for patients with completely resected NSCLC and did not provide evidence that the relative effect of PORT was smaller or larger for patients of any category defined by age, sex, histology or stage.

Obviously, meta-analysis does not allow to consider all factors that may interfere or otherwise affect the efficacy or safety of PORT in NSCLC. Simply, the number of patients needed to harm (NNH) is superior to the number of patients needed to treat (NNT). Differently from PORT meta-analysis, in Billiet *et al.* study (1) and in other "real world" studies (2,3), radiotherapy does not increase the number of deaths non–cancer-related and the rate of lung and cardiac toxicity. In fact, in the last twenty years, advances in radiation techniques significantly increase spatial precision with conformality of the dose to the target, sparing critical normal structures.

This translates into a gain in therapeutic window of radiotherapy, and so, it can permit feasibility of a tri-modality strategy.

Differently from studies analyzed in meta-analysis, furthermore, the role of accurate staging of mediastinal lymph nodes, both at diagnosis and after induction

chemotherapy, it is now emphasised.

Both improvement of radiotherapy and a better staging of patients can help to understood the greater benefits of PORT.

Despite everything, a criticism toward radiotherapy can be related on strategy of prescription based, nowadays, on morphological data and on site of anatomical origin of disease. Radiotherapy, hardly, uses the genomic determinants of the cellular response to radiation deriving from radiobiology studies (6).

Obviously, a personalized molecular staging may help to guide the evolution from a modern radiotherapy with a generic and technological approach, to one in which its therapeutic window is modulated on the molecular alterations in an individual patient's tumor.

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Footnote

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