Editorial

Role of consolidative stereotactic ablative radiotherapy in patients with oligometastatic non-small cell lung cancer

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Oligometastatic non-small cell lung cancer (NSCLC), presenting with one to five synchronous or metachronous metastatic lesions, has recently been considered a distinct disease state (1). In this setting, three different clinical conditions can be identified: (I) *de novo* oligometastatic—patients with a synchronous diagnosis of primary and metastatic lesions naive from oncological treatments; (II) oligorecurrent—patients with a controlled primary tumor after loco-regional treatment but with new and limited metastatic sites; (III) oligoprogressive—patients with a limited metastatic progression during systemic therapy (one or few sites), but with a control of the primary tumor and most of metastatic disease (2).

Locally ablative therapies are often used for such clinical presentations, alone or in combination with systemic chemotherapy/molecular target therapies/immunotherapy; however, the subset of patients who may benefit from these interventions at metastatic sites or at the primary lesion has not been conclusively identified. These issues are reflected by the heterogeneous survival outcomes reported in several retrospective and a limited number of prospective studies on oligometastatic lung cancer (3).

Stereotactic ablative radiotherapy (SABR) has been considered an emerging therapeutic approach: recent technological improvements, including high accuracy in patient positioning verification systems, image guidance and intensity modulated radiation delivery, allow clinicians to focus ablative radiation doses on small cancer volumes, maximising the sparing of surrounding normal tissues, and promote the potential role of SABR in oligometastatic settings, with high rates of local control for different anatomical districts from various primary tumor sites in absence of relevant toxicity (4).

A recent study in *Lancet Oncology*, reported a randomised, controlled, phase 2 trial, including patients with oligometastatic NSCLC (5). Patients were randomized to receive a local consolidative treatment to all metastatic sites (radiotherapy or surgery), followed by a maintenance systemic therapy or an exclusive maintenance systemic approach.

After a median follow-up of 12.4 months, median progression-free survival in the local consolidative therapy group was 11.9 *vs.* 3.9 months in the maintenance treatment group (HR =0.35; 90% CI, 0.18–0.66; P=0.0054).

Authors concluded that local consolidative treatments for metastatic NSCLC patients with limited number of metastatic sites is able to improve progression-free survival compared to exclusive maintenance therapy. Moreover, a phase 3 randomized clinical trial was recommended to confirm this hypothesis, encouraging a new therapeutic approach in oligometastatic NSCLC patients. In an editorial published by *CA: A Cancer Journal for Clinicians* in March 2017, Barton underlined the importance of this design that reflects real-world treatment approach, and will make clinicians and patients more comfortable with the approach of consolidative local therapy (6).

Several aspects should be considered when radiotherapy as local treatment is offered to oligometastatic patients: the appropriate patient selection, the radiation dose prescription

and the treatment tolerability. Moreover, clinical outcomes seem to be influenced by several factors, including a longer disease-free interval between cancer diagnosis and prescription of local treatment, adenocarcinoma histology, absence of lymph nodal involvement, lower overall tumor burden, and primary tumor control (7,8). Other additional elements could impact on OS in this scenario are a good performance status, limited nodal disease, presence of epidermal growth factor receptor (EGFR) mutation, and metastases limited to a single organ (9). Moreover, as reported by Rusthoven *et al.*, the predominant pattern of failure in advanced NSCLC after first-line systemic therapy is local recurrence, justifying SABR treatment to improve time to disease progression and postpone the prescription of second-line systemic therapies (10).

The patients enrolled in Gomez *et al.* study met several criteria, including the presence of three or less metastatic lesions, no progression after front-line chemotherapy, no malignant pleural effusion, and the ability to tolerate aggressive local treatment, representing ideal candidates for locally ablative therapy (5). Patients randomized to local consolidate therapy group were treated with various kind hypofractionated regimens, including from palliative schedules to ablative treatment, but specific details about biologically effective dose (BED), total dose prescription and fractionation have not been reported (5).

Another limitation of this study pointed out by Mary Kay Barton is the lacking of data about overall survival (OS). In fact, the marked PFS advantage led to early study closure with OS data not yet mature at the time of reporting (6).

In this study, no patients in either group had a grade 4 adverse event nor died from an adverse event (5). Nevertheless, local ablative treatment in combination with systemic therapy can increase severe toxicities; on the other hand, the probability to discontinue the maintenance therapies, promoting a potential disease progression, could certainly affect QoL. Unfortunately, in Gomez *et al.* study QoL data collection was lacking, limiting a critical opinion about this issue.

Currently, from similar ongoing trials focused on NSCLC and other primary histologies such as SARON (NCT02417662) and ROLE (NCT01796288), or inclusive of multiple oligometastatic tumor types, such as CORE (NCT02759783) and SABR-COMET (NCT01446744) results are awaited.

Finally, another intriguing prospective is represented by the combination of SABR and immunotherapies.

Historically, tumoricidal effect correlated to radiotherapy has been justified by a direct and non-repairable damage of DNA. Conversely, recent literature has started to report a relationship between ablative radiation doses, microenvironment alteration and immune system activation (11). Apparently, local and systemic tumor control seems to depend on a balance between immunosuppressive and immunostimulatory signals generated within the tumor and the immune surveillance. Immune surveillance system is a complex process concerning several immune system cells (i.e., CD8 and CD4 lymphocytic cells, natural killer cells, B lymphocytes and macrophages).

Specifically, radiation seems to be able to create an "in situ" vaccine phenomenon. In fact, it has been reported that different radiation techniques and dose schedules influenced immune system response to tumor through several pathways, including changes in different cytokine expressions, leading to alteration in tumor microenvironment (12). Theoretically, the combination of hypofractionated schedules and immune checkpoint inhibitors could contribute to tumor rejection (13), to prolong survival (14), and rarely to realize abscopal effect (15). Hence, a combination of immunotherapies and SABR may play a role in the treatment of metastatic NSCLC patients.

In conclusion the inclusion of local treatment, such as SABR seems to be a promising treatment option in oligometastatic NSCLC patients. Dr. Gomez says that planned expansion phase 3 studies trials will use OS as the primary endpoint, enroll a larger number of patients, and incorporate novel agents such as immunotherapy into the design (6). Strong coordination, interaction, and collaboration among all professional figures, including medical and radiation oncologists, are crucial to select patient eligible to local treatment in order to offer the most appropriate oncological perspective.

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Footnote

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

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