Chapter

Challenges in the Treatment of Oligometastatic Non-small Cell Lung Cancer

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Abstract

Since 1995, when the concept of oligometastatic non-small cell lung cancer was first described, no high-level evidence has been introduced for management of those patients subset. Data from retrospective reports and analysis and from every-day clinical practice revealed that some of the non-small cell lung cancer patients with a few metastases could benefit significantly with local radical treatment approach of primary and metastatic lesions. Recent advances in modern local treatment approaches with minimally invasive surgery and stereotactic radiotherapy, as well as introduction of immunotherapy, open new field of interest for personalized treatment of limited metastatic non-small cell lung cancer. In this report, we are summarizing limited data of case reports, retrospective studies and few randomized studies of patients with oligometastatic non-small cell lung cancer and discuss challenges of treatment in the era of molecular targeted therapy and immunotherapy.

Keywords: oligometastases, non-small cell lung cancer, ablative treatment, stereotactic body radiation therapy, immunotherapy, molecular targeted therapy

1. Introduction

Lung cancer is the leading cause of cancer mortality worldwide, with over 1.7 million deaths and over 2 million newly diagnosed cases annually [1]. More than a half of all new diagnosed patients with non-small cell lung cancer (NSCLC) presents in stage IV disease with a median overall survival (OS) of 10–12 months. Stage IV NSCLC is generally considered incurable disease with a 5-year survival ranged from 0 to 10% [2]. However, the sub segment of patients in stage IV was recognized years ago with different clinical presentation and prolonged survival that overcomes expected for metastatic disease [3]. Oligometastatic disease was first described in 1995 as a state of limited systemic metastatic burden in which treatment of oligometastases with radical local therapies could be curative in selected patients [3, 4]. For decades, no high-level evidence has been introduced for management of these patients subset. Moreover, no uniform definition and staging requirements for usage the term oligometastatic NSCLC have been accepted until recently. Clinical data indicate that the number of patients with oligometastatic disease that undergo ablative local treatment is increasing at a great rate [5]. With the extension of imaging diagnostic methods like 2-deoxy-2-[fluorine-18]fluoro-D-glucose

positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and magnetic resonance imaging (MRI), oligometastatic NSCLC patients who benefit most from radical treatment could be selected precisely [6]. On the other hand, development in technical improvement of modern local treatment approaches and advances in new systemic treatment options for NSCLC patients offer new hope for improvement of outcomes in oligometastatic NSCLC. In this chapter, we present most relevant scientific evidence regarding oligometastatic NSCLC and discuss future perspectives in treatment of these patients in the era of molecular targeted treatment and immunotherapy.

2. Definition

Even the oligometastatic disease was first described in 1995, no uniform and clear definition has been accepted for years [3]. Most past clinical trial protocols have used an upper limit of metastases between one and eight as inclusion criteria; however, 90% of included patients actually had one metastasis [5, 7].

The concept of oligometastatic NSCLC include different clinical scenarios of limited number of metastatic lesions that are feasible to local ablative treatment. Regarding the time of presentation, in synchronous oligometastatic disease metastatic lesions are detected at the time of diagnosis of the primary tumor. In metachronous oligometastatic disease new metastatic lesions not present at the time of the primary diagnosis develop [8, 9]. Other related terms are currently used, like oligorecurrence, in which limited number of metastatic lesions develop in otherwise controlled primary tumor site followed radical treatment. Oligoprogression describes metastatic disease with controlled primary tumor and most metastases due to systemic therapy followed by progression of one or few metastatic lesions. Oligoressistance follows systemic therapy of patients with widespread metastases who have a near complete response but limited number of persistent lesions remains. First attempt to unify the oligometastatic state was inclusion oligometastatic disease in the 8th edition of the Tumor, Node, Metastasis (TNM) published by the International Association for the Study of Lung Cancer (IASLC). In the assessment for M descriptor, 225 (22%) of the 1025 metastatic patients were reported with a single metastasis in a single organ that had significantly better prognosis than those with multiple metastases in one or several organs [10]. Accordingly, single metastatic lesion in a single distant organ was assigned to the new M1b category [2, 10].

Recently, a pan-European multidisciplinary consensus statement on the definition and staging of synchronous oligometastatic NSCLC was formulated [11]. As it was concluded, the definition is relevant when a radical treatment is technically feasible with acceptable toxicity, with all sites being amenable to local treatment modality that may result in long-term disease control. A maximum of 5 metastases and 3 organs is proposed for definition of oligometastatic NSCLC. The presence of diffuse serosal metastases (meningeal, pericardial, pleural, and mesenteric) or bone marrow involvement excludes cases from the definition, as these cannot be treated with radical intent. For pulmonary metastases, the eight TNM classification should be followed. Metastasis in the same lobe (T3) or in the same lung (T4) should not be counted as a metastatic site, but it can influence the possibility of treatment with radical intent. Mediastinal lymph nodes must be considered as regional disease, but their involvements are of importance in the decision of feasibility for radical treatment of locoregional disease. The recommendations for staging include ^{18}F-FDG PET/CT and brain imaging, preferably magnetic resonance imaging (MRI), that are mandatory. Besides mediastinal lymph node staging with ^{18}F-FDG PET/CT, pathological confirmation is

required if this influences the treatment decision. In addition, pathological confirmation at least of one metastasis is required unless the risk outweighs the benefit.

3. Incidence

Oligometastatic disease used to be reported sporadically [12]; however, with the improvement in diagnostic imaging, mainly ^{18}F-FDG PET/CT and MRI, oligometastases appear relatively frequent. While available data on incidence of oligometastatic NSCLC at diagnosis remains limited, even when published mostly in retrospective reports, the diversity of inclusion criteria about the maximum number of metastatic lesions accepted for study, makes it more difficult to compare. However, it has been estimated that aproximatelly 20–50% patients with metastatic NSCLC at diagnosis present with oligometastatic disease [10, 13, 14]. As mentioned before, in the IASLC TNM classification of lung cancer, 22% of all metastatic patients had a single metastatic lesion [10]. The most frequent site of a single lesion was bone, followed by brain, adrenals and liver. In an analysis of 725 NSCLC patients with metastatic disease at diagnosis, 186 (26%) were recognized with oligometastatic disease defined as ≤5 lesions [13]. Of those, 51% of the patients had a single metastatic lesion and in 81% of patients, metastases were limited to one organ site. As in previous analysis, the most common site of a single lesion appearance was brain, bone and adrenal glands. In the group of oligorecurrent NSCLC patients after treatment of the primary site, 50–60% were reported to present with only one to three metastatic sites [4, 15]. The majority of patients who have been treated with surgery, at recurrence presented with metastases in the brain, contralateral lung or adrenal gland. The pattern of oligoprogression in advanced or metastatic NSCLC patients after first-line chemotherapy has been barely reported. In a study of Rusthoven et al., local progression only, was the predominant pattern of failure in 64% of patients after systemic therapy, mostly platinum-based chemotherapy, suggesting that consolidation local therapy after first-line systemic treatment could potentially alter the patterns of failure and prolong time to progression in a substantial proportion of those patients [14]. With the introduction of new systemic treatment possibilities that prolong survival, like tyrosine kinase inhibitors (TKI) in patients with epidermal growth factor receptor (EGFR) mutation/anaplastic lymphoma kinase (ALK) rearrangement, oligoprogression has been reported more often. Molecular targeted therapy with TKI enable higher response rates and better progression-free survival (PFS), however, progression inevitably develops in most cases after 1 to 2 years of molecular targeted treatment due to acquired resistance [16]. Data from literature reveals that the proportion of patients progressing with an oligoprogressive pattern of disease ranges from 15 to 47% during EGFR TKI treatment [17–19]. Few series also suggest that as many as 25% of patient treated with TKI progress with single metastases and 50% with four or less lesions [17, 20]. For those patients with oligoprogressive or oligoresistance disease, local ablative therapy and continuation of molecular targeted therapy could result in more than 6 months of additional clinical benefits [20].

4. Prognostic factors

Oligometastatic disease is highly divers in prognosis, ranged from rapid progression with demise during treatment to long-term survivals. It is assumed that about 25% of oligometastatic patients will have prolonged disease-free interval [7, 12, 21]. Therefore, the identification of oligometastatic patients that will benefit most from aggressive local treatment is of the crucial importance.

As already mentioned, results from IASLC 8th TNM classification validation study revealed significantly longer OS in patients with a single extrathoracic metastasis than in those with multiple metastases [10]. In the individual patients data meta-analysis of Ashworth et al. 757 oligometastatic NSCLC patients were included from 1985 to 2012 and managed with ablative treatments to all sites of disease, however, half of the patients had only a single metastasis [7]. Surgery was the most commonly used treatment for the primary tumor (83.9%) and metastases (62.3%). Factors predictive for OS were synchronous versus metachronous metastases ($P < .001$), N-stage ($P = .002$), and adenocarcinoma histology ($P = .036$). In recursive partitioning analysis, three risk groups were identified: low-risk, metachronous metastases (5-year OS, 47.8%); intermediate risk, synchronous metastases and N0 disease (5-year OS, 36.2%); and high risk, synchronous metastases and N1/N2 disease (5-year OS, 13.8%). In the analysis of Parikh et al., 186 patients with five or fewer distant metastatic lesions at diagnosis were included, of whom 52% patients had a single metastatic lesion [13]. On multivariable analysis, Eastern Cooperate Oncology Group (ECOG PS) performance status, nodal status N2–3, squamous pathology, and metastases to multiple organs were associated with a greater hazard of death (all $P < .01$). However, the number of metastatic lesions and radiologic size of the primary tumor were not associated with OS. Definitive local therapy to the primary tumor was associated with prolonged survival. Data from twenty-four studies that included altogether 1935 patients with oligometastatic NSCLC were analyzed in a meta-analysis by Li et al. [22]. Among patients with oligometastatic disease, defined as 5 or fewer lesions, they identified several factors associated with improved survival, including aggressive treatment to the primary lung tumor, female gender, lower nodal stage, adenocarcinoma histology and thoracic stage. Other retrospective publications reported importance of aggressive local treatment [23, 24]; moreover, the major predictors of OS were the extent of intra-thoracic disease including nodal status and possibilities for resection or radical radiotherapy [25–27]. In the trial by Gomez et al. besides treatment type (local treatment versus no local treatment) presence of driver mutations were associated with improved PFS [28, 29]. Aside of the number of metastases, mediastinal node involvement, time until onset of metastases, histology, PS, T stage, treatment of the primary and metastatic lesions, diagnosis-specific graded prognostic assessment (DS-GPA classification, and Lung-molGPA) is well known for patients with brain metastasis.

Additionally, a specific genetic or epigenetic alterations ("initiation," "progression," and "virulence" genes) have been described so far that together with failures in immunosurveillance impact patients'clinical outcomes. The oligometastatic tumors are believed to have more indolent biology [3]. Initial investigations of the mechanisms running occurrence of oligometastases identified a central role of microRNAs (miRNAs). Lussier and colleagues evaluated miRNA profiles in an analysis of patients with five metastases manageable for RT. They found that overexpression of the miR-200 family was correlated with polymetastatic progression [30]. Moreover, they observed a specific microRNA expression that identified the patients most likely to remain oligometastatic after metastases directed treatment and therefore associated with a better prognosis.

5. Treatment

Since oligometastatic NSCLC is considered as intermediate state between localized lung cancer and widespread metastatic disease, the therapeutic approaches used for treatment of these patients besides standard systemic therapy include aggressive local therapy.

Several early case and retrospective reports showed that a subset of NSCLC patients with mostly solitary metastasis that were radically treated to all known metastatic sites, could achieve long-term survival [31–33]. Following years, more retrospective reports of oligometastatic patients treated with radical intent were published that demonstrating better-than-expected prolonged survival with median OS between 13.5 to 26 months and 5-year survival between 10 to 36% [13, 23–25, 34–37]. In an individual patient data meta-analysis on 757 oligometastatic NSCLC treated between 1985 and 2012 with surgical metastasectomy, stereotactic radiotherapy/radiosurgery, or radical external-beam radiotherapy for metastases and with curative treatment of the primary lung cancer, median OS was 26 months, 1-year OS 70.2%, and 5-year OS 29.4% [7].

While the last decade use of effective local treatment with minimally invasive surgery or advanced radiation technics for oligometastatic lesions in NSCLC patients has risen, the evidence from prospective studies has been lacking. The first prospective single-arm phase II trial of oligometastatic NSCLC patient with up to five metastases at primary diagnosis amendable for radical local treatment was published in 2012 [27]. Forty patients were enrolled with brain, bone and adrenal gland metastases. Of all included, 87% had a single metastatic lesion and 95% of all received chemotherapy as part of their primary treatment. Median OS was 13.5 months and two- and three- year survival rates were 23.3% and 17.5%, respectively. In 2016, Gomez et al. published the results of a prospective multicentre randomized phase 2 trial that enrolled 74 oligometastatic NSCLC patients with the maximum of 3 metastatic lesion [28]. All patients received standard first-line systemic therapy including platinum-based chemotherapy or TKI in patients with EGFR mutations or ALK rearrangements. Patients were randomly assigned to either local consolidative therapy consisting of resection or (chemo) radiotherapy or to maintenance treatment alone. The study was terminated early after randomization of 49 patients as part of the annual analyses due to substantial efficacy improvement in the local consolidative group compared with the maintenance group. At a median follow-up time of 12.39 months, the median PFS in the consolidative group was significantly longer with 11.9 months versus 3.9 months in the maintenance group. Importantly, time to appearance of a new lesion was longer in the consolidative group arm (11.9 months vs. 5.7 months) suggesting that local consolidative treatment may have altered the natural course of the disease, either by limiting the potential for subsequent dissemination or by altering systemic anticancer immune response. In 2018, the updated survival data at a median follow-up of 38.8 month, confirmed the PFS benefit in consolidative group with 14.2 months compared to 4.4 months in the maintenance group and median OS of 41.2 months in the consolidative arm versus 17.0 months in the maintenance arm [29].

In a phase II randomized clinical trial conducted by Iyengar et al., a total of 29 patients with oligometastatic NSCLC were included [38]. Inclusion criteria allowed up to six sites of extra cranial lesions (including primary) and exclude patients receiving first-line molecular targeted therapy with EGFR/ALK TKI. Fourteen patients were assign to the stereotactic body radiation therapy (SBRT)-plus-maintenance chemotherapy arm, and 15 patients to the maintenance chemotherapy–alone arm. In the SBRT group, all residual disease sites were treated with SBRT. A total of 31 lesions were treated in 14 patients with intrathoracic sites the most common locations of SBRT treatment. Likewise, the trial was stopped to accrual early after an interim analysis found a significant improvement in PFS in the SBRT-plus-maintenance chemotherapy arm with 9.7 months vs. 3.5 months in the maintenance chemotherapy–alone arm (P = .01).

A third completed randomized phase II trial, SABR (stereotactic ablative radiotherapy)-COMET international trial included patients with a controlled

primary malignancy of different solid cancers and 1–5 metastatic lesions manageable for SABR treated between 2012 and 2016 [39]. Ninety-nine patients, of those 18% NSCLC patients, were randomly assigned in a 1:2 ratio between standard-of-care treatments and standard-of-care treatments plus SABR. Median OS was 28 months in the control group versus 41 months in the SABR group. Adverse events of grade 2 or worse were significantly higher in SABR group (29% vs. 9%) with three deaths after SABR. Recently, results of extended follow-up were published [40]. With the median follow-up of 51 months, median OS was 28 months in the control arm versus 50 months in the SABR group. Five-year OS rates were 17.7% versus 42.3%, respectively. There were no new grade 2–5 adverse events.

All three randomized studies have contributed increasingly in the evidence that radical local treatment approach added to standard therapy may yield prolonged survival in selected oligometastatic NSCLC. However, last decade most studies have still been retrospective in nature and biased with respect to definition of oligometastatic disease. Systematic review by Schanne et al. included 54 studies that were published between 1987 and 2018 with altogether 1994 patients with oligometastatic NSCLC [5]. Even with a wide range of oligometastatic definitions, 90% of patients were treated for a single metastasis. 60% of patients were diagnosed with adenocarcinoma and 55% of the metastases were located in the brain, 17% in the lung, 11% in the adrenal gland and 17% in other organs. Systemic therapy was used in 68% of patients in a variety of settings, mostly adjuvant/maintenance or neoadjuvant but also combined with RT. Molecular targeted therapy was used in 5% of cases; however, immunotherapy was not used treatment modality in any of analyzed studies. Surgical resection was the most common local treatment modality used in 76% of patients for primary tumor and in 65% of patients for distant metastases. RT was used as neoadjuvant/adjuvant or definitive treatment of primary tumor in 9% and 22%, respectively. Adjuvant RT after surgical resection for metastatic lesions was used in 27% of patients, mostly after resection of brain metastases. Radiation as primary treatment modality was more common for treatment of metastases than for primary tumors (69% vs. 35%). Median OS in the analyzed studies was 19.6 months (6.2–52.9 months) with an observed plateau and possible long-term survival of 20%. Importantly, this analysis also gives us insight in time trends of management oligometastatic NSCLC patients for the last three decades. Relating to time analysis, in the studies published after 2011 radiotherapy has almost surpassed surgical approaches. Local treatment changed in favor to wider use of radiotherapy for primary tumors from 23 to 41%. Moreover, wider adoption of SBRT instead of conventionally fractionated RT with an increase from 0 to 23% for primary tumors and from 15 to 60% for distant metastases was reported. Additionally, the number of patients receiving no systemic therapies was reduced from 45% before 2011 to 24% afterwards. Notably, a trend for improved median OS over time was observed: patients from reports published after 2011 revealed better OS compared to the earlier period: 28.1 months versus 17.2 months, respectively. Comparing the effect of different type of local treatment, when only studies after 2011 were included, no significant effect on median OS was detected neither for primary tumor nor for metastases.

Despite the lack of evidence for optimal treatment of patients with oligometastatic NSCLC, the concept of delivering local radical treatment in patients with oligometastatic NSCLC was incorporated in NSCLC guidelines. The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines due to the limited available evidence propose preferred inclusion in clinical trials [41, 42]. The National Comprehensive Cancer Network (NCCN) guidelines state that patients with NSCLC with limited metastases can receive local radical treatment [43].

6. Challenges in the era of molecular targeted and immunotherapy

The management of oligometastatic NSCLC has changed significantly over the past decades. While surgery, radiotherapy, stereotactic radiotherapy and systemic therapy are the cornerstones of current treatment strategies, treatment modalities have varied over time with respect to the advantages of local treatment techniques as introduction of new systemic treatment possibilities. According to the literature, surgery has been mostly used in oligometastatic NSCLC patients for resection of brain, contralateral lung and adrenal gland metastases [5, 23, 35, 44] Considering the significant morbidity associated with surgical resection of multiple sites of metastatic disease, SBRT has become an alternative treatment approach for achieving local ablation. The highest level of evidence for incorporation of local treatment in oligometastatic NSCLC patients based on small randomize phase II clinical trials, which regularly reported higher PFS and OS with the use of SBRT compared with no SBRT [28, 29, 38–40]. However, the efficacy of SBRT in potentially curable patients with the stage I NSCLC is already confirmed [45]. The broader adoption of SBRT in clinical practice reflects its non-invasive nature, ability to simultaneous treatment of multiple sites in a short time, feasibility of concurrent local and systemic treatment, utility to treatment in the outpatient setting and relatively low toxicity profile [46, 47]. Moreover, SBRT to the progressing lesions may delay the need to start or change systemic therapy that might reflect in prolonged PFS, OS and quality of life for the patients [48–50]. In a systematic review by Tsao et al., reported median OS ranged from 13.5 to 55 months and PFS from 4.4 to 14.7 months. [50] SBRT has currently become a treatment option for tumors in almost any body site, with many publications documenting its efficacy for lung, liver, adrenal, and bone/spine metastases, achieving high as much as 70–90% of local control [51].

Systemic therapy is the backbone treatment for metastatic NSCLC patients; though it is not well defined in management for oligometastatic NSCLC [41–43]. Despite potentially successful local treatment, the majority of oligometastatic NSCLC patients will develop distant progression due to undetectable micrometastases at the time of diagnosis. Therefore, all recent prospective trials combined local treatment with addition of systemic therapy standardly used at the time of the study. However, the therapeutic sequence of systemic therapy might be important for oligometastatic disease, as usually only the patients who do not progress with induction systemic treatment were capable for aggressive local treatment. We are currently not able to reliably predict the course of oligometastatic disease at the time of diagnosis, therefore upfront local therapy colud represent an overtreatment due to rapid progression to multimetastatic disease. Although studies with oligometastatic NSCLC have included patients treated with systemic therapy, mostly chemotherapy and minority molecular targeted therapies, current clinical practice and guidelines for treatment of metastatic NSCLC include molecular targeted agents, immunotherapy or combination of immunotherapy and chemotherapy in first-line setting [52–64]. The introduction of new agents as molecular targeted and immunotherapy has resulted in the improved survival in patients with metastatic and locally advanced NSCLC. As a result, the first line systemic therapies used in most retrospective and prospective studies of oligometastatic NSCLC do not reflect those currently used. With onset of new systemic therapies in the management of NSCLC patients, great interest has risen in exploring the safety and efficacy of combined SBRT with new agents to improve the therapeutic outcomes in metastatic NSCLC as well as in oligometastatic disease.

6.1 Molecular targeted therapy in oligometastatic NSCLC

Patients with actionable tumor mutations have high response rates and long PFS times when treated with molecular targeted therapy [54–62]. However, progression inevitably occurs due to either insufficient CNS passage of the drug in some cases of CNS progression, or to acquired resistance with biological change in the tumor cells. The concept of oligoprogression supports the idea of disease progression due to the development of TKI-resistant clones with subsequent distant progression [65]. Different scenarios of progression in patients with actionable tumor mutations including oligoressistance, oligoreccurence or oligoprogression requiring consideration for local treatment. In the analysis of Guo et al. the majority of progressive disease on osimertinib was reported within residual lesions in initially involved sites, thus consolidative SBRT may prolong time to progression in a selected subgroup of patients [66]. In a retrospective study of Xu et al., 145 patients with oligometastatic EGFR-mutant NSCLC diagnosed from 2010 to 2016 were enrolled [67]. According to consolidative local treatment with surgery or radiotherapy, patients were grouped in three category, 51 in the all-local therapy group (consolidative to all residual disease, including primary tumor, lymph nodes, and metastatic sites), 55 in the part-local therapy group (consolidative to either primary tumor or oligometastatic sites), and 39 in the non-local therapy group (not receive any local therapy). Radiotherapy included standard-fractionation radiotherapy (60 Gy in 2-Gy fractions), aggressive palliation radiotherapy (45 Gy in 3-Gy fractions, a biologically equivalent dose of approximately 60 Gy) or stereotactic radiosurgery (SRS), with curative intent when possible. The median PFS in all-local, part-local, and non-local groups were 20.6, 15.6, and 13.9 months, respectively ($p < 0.001$). The median OS in all-local, part-local, and non-local groups were 40.9, 34.1, and 30.8 months, respectively ($p < 0.001$). The difference was significant between the all-local group and part-local or non-local group. The median OS was significantly better with consolidative local therapy for primary tumor (40.5 versus 31.5 months, $p < 0.001$), brain metastases (38.2 versus 29.2 months, $p < 0.002$), and adrenal metastases (37.1 versus 29.2 months, $p < 0.032$). Radiation toxicity was acceptable, included grade ≥ 3 pneumonitis (7.7%) and esophagitis (16.9%). No grade 5 toxicity was reported. A retrospective multi-institutional analysis by Magnuson et al. explored the optimal management of patients with EGFR-mutant NSCLC who developed brain metastases and have not received EGFR TKI [68]. A total of 351 patients from six institutions were included. Patients were treated with SRS followed by EGFR-TKI, WBRT followed by EGFR-TKI, or EGFR-TKI followed by SRS or WBRT at intracranial progression. The median OS for the SRS, WBRT, and EGFR-TKI cohorts was 46, 30 and 25 months, respectively ($P < .001$). On multivariable analysis, SRS versus EGFR-TKI, WBRT versus EGFR-TKI, age, performance status, EGFR exon 19 mutation, and absence of extracranial metastases were associated with improved OS. SRS followed by EGFR-TKI resulted in the longest OS and allowed patients to avoid the potential neurocognitive sequelae of WBRT.

In a retrospective analysis of Elamin et al. 129 patients with EGFR-mutant NSCLC who were treated with first-line TKI and 12 that were treated with TKI followed by local consolidation therapy were included [69]. Among the 12 patients treated with TKI plus local consolidative treatment, 8 patients had oligometastatic disease (defined as 3 metastases), and 4 patients had >3 metastases. Local consolidative treatment regimens were hypofractionated radiotherapy or SBRT for 11 patients and surgery for 1 patient. TKI followed by local consolidative treatment resulted in a significantly longer PFS (36 months) compared with TKI alone (14 months). Recently, Wang et al. presented an interim result of a randomized

phase III, open-label clinical trial of first-line tyrosine kinase inhibitor with or without upfront local RT in patients with EGFR oligometastatic NSCLC [70]. From January 2016 to January 2019, 133 participants were enrolled, including 65 in the TKI arm who received standard of care TKI alone and 68 in the SBRT arm who received SBRT and TKI. At a median follow-up of 19.6 months, the median PFS for TKI alone was 12.5 months, and for TKI and SBRT was 20.20 months, respectively ($P < .001$). The median OS in the TKI alone arm was 17.40 months, and for TKI and SBRT arm was 25.50 months, respectively ($P < .001$).

Concerning the safety profile for combining EGFR or ALK TKI inhibitors and high dose RT, treatment was well tolerated and none of the available studies reported a significant increase in side effects [66–69]. To conclude, SBRT in combination with molecular targeted agents in actionable mutations NSCLC patients seem rationale for improving long-lasting disease control in synchronous oligometastatic oncogene addicted NSCLC patients; however no prospective data are available to confirm this.

6.2 Combining immunotherapy and radiotherapy

Immunotherapy with immune checkpoint inhibitors has revolutionized the management of stage IV NSCLC. In recent years, the blockade of programmed cell death 1 (PD-1) / programmed cell death ligand 1 (PD-L1) axis which served as a mechanism for tumor evasion of host tumor antigen-specific T-cell immunity, has demonstrated evident benefit in PFS and OS in metastatic and locally advanced NSCLC [61–64, 71, 72]. The indications for PD-1/PD-L1 blockade with immune checkpoint inhibitors (ICI) currently include most metastatic NSCLC patients without actionable tumor mutations, either as a single agent or combined with cytotoxic chemotherapy. The anti-PD-1/PD-L1 drugs approved at the moment for NSCLC are pembrolizumab, nivolumab, atezolizumab and durvalumab. Despite this paradigm shift, most patients present some kind of resistance to ICI, therefore arise the interest of researchers to combine multiple therapies. According to growing preclinical data describing mechanistic synergy between radiotherapy and immunotherapy, the most promising investigated combination is ICI with RT [73, 74]. Rational for combining radiotherapy and immunotherapy arises from the significant immune-stimulatory effects they both possess increasing the natural antitumor immune response through synergistic potentiation of an immunomodulatory effect [75, 76]. Increasing evidence indicates that cancer cells killed by radiation release tumor-associated antigens and immunoregulatory cytokines that serve as a kind of in situ vaccine against cancer [77, 78]. Cytokines also activate systemic tumor-specific immune response to eliminate tumor cells even outside the radiation field, so called abscopal effect [79]. This radiation-induced immune-mediated systemic antitumor phenomenon has high therapeutic potential, but is rare and relating to preclinical data more probable induced by high ablative doses, combined with checkpoint inhibitors [80, 81]. SBRT, through released neo-antigens and consequent maturation and proliferation of naive T-cells, and immunotherapy through activation and amplification of naive T-cells, may reciprocally potentiate each other amplification of T-cells-mediated tumoricidal effects [82–84]. Due to the lack of evidence, most "immunogenic" time sequencing of radio-immunotherapy and radiation dose-fractionation is not determined. Some data indicate that concurrent treatment or close sequencing of immunotherapy following radiotherapy may be the most effective [82]. However, according to data the radiation dose for the optimal antitumor immune response should be sub-tumoricidal. Several preclinical studies suggested that 8 to 10 Gy per fraction in 1–3 fractions represent optimal immunogenic dose [82–84].

Clinical interest for the combination of ICI and RT in NSCLC started to arise after the results of the KEYNOTE-001 study that enrolled progressive locally advanced or metastatic NSCLC [85]. A secondary analysis of the phase I trial revealed that of 97 included patients, 43% had been treated with RT prior to the administration of pembrolizumab. Those patients had significantly longer PFS (4.4 vs. 2.1 months) and OS (11.6 vs. 5.3 months) comparing patients with no RT. A single-arm phase 2 study of Bauml et al. included 45 patients with oligometastatic NSCLC with up to 4 metastatic sites [86]. Pembrolizumab was administered 4 to 12 weeks after prior comprehensive locally ablative therapy consisting of radiotherapy, chemoradiotherapy, surgery, or radiofrequency ablation, but most received ablative radiotherapy. Median PFS was 19.1 months, significantly greater than the historical median of 6.6 months (P = .005). OS at 12 months was 90.9% and at 24 months 77.5%. Even not conducted in oligometastatic NSCLC patients, the results of a multicetre, randomized phase 2 study (PEMBRO-RT) are interested. 92 patients were enrolled with advanced NSCLC after at least one regiment of chemotherapy with at least two metastases but upper limit was not specified [87]. Altogether, 76 patients were randomized to the pembrolizumab alone (control, 40 patients) or pembrolizumab after radiotherapy (3 fraction of 8 Gy) that was applied to a single metastatic site (experimental, 36 patients) to increase the likelihood of abscopal effect. The overall response rate at 12 weeks was 18% in the control arm vs. 36% in the experimental arm (P = .07). Median PFS was 1.9 months vs. 6.6 months (P = .19), and median OS was 7.6 months vs. 15.9 months (P = .16). Although a doubling of overall response rate was observed, the results did not meet the study's prespecified end point criteria for meaningful clinical benefit. Interestingly, subgroup analyses showed the largest benefit of radiotherapy in patients with PD-L1 – negative tumors. In a retrospective study of Samstein et al. 758 patients treated with ICI and RT were analyzed [88]. Median OS was 9 months in the entire cohort. Subanalysis regarding sequencing ICI and RT revealed increased OS in patients who received ICI and RT simultaneously. Median OS was 20 months for patients who started with ICI for at least 1 month before RT and continued throughout RT compared with 11 months for those that started ICI less than 30 days prior to RT and continued ICI throughout RT. In the cohort of patients who received concurrent therapy, hypofractionated radiotherapy (dose >4.00 Gy per fraction) and ICI greater than 30 days before RT was associated with improved OS.

Prospective data for management of patients with oligometastatic NSCLC in the era of immunooncology is scarce. Most of the available data on combining ICI and SBRT has been retrospective experiences on patients with metastatic NSCLC; however the benefit of combined treatment has been persistently demonstrated [89–91]. Importantly, the available data suggest that toxicity profile from the combination treatment has not increased in comparison to immunotherapy alone in the metastatic setting. A recent systematic review from prospective studies revealed grade ≥ 3 median toxicity rates of 14.5% with anti-PD-1/L1 plus SABR and 26% with anti-CTLA-4 plus SABR [92]. Concerning toxicity, no increased rates of immune-related adverse events using SBRT in the different organs or tissue types have been reported. However, reports from the studies that combined dual ICI therapy with SBRT in different cancers in prospective trials detected more toxicity.

In the future management of oligometastatic NSCLC patients, more questions should be answered. In the era of immunooncology, local treatment still presents the backbone of management with adding ICI to improve outcome of oligometastatic NSCLC patients. However, future prospective studies should give us answers to what sequence of local treatment and ICI is the most optimal combination, which radiation technique and fractionation would offer the best results, which patients should be selected for radical-intent treatment regarding biomarkers.

A great number of trials combining ICI and RT are ongoing. Regarding oligometastatic NSCLC, one is of particular interest, a randomized trial of consolidative immunotherapy with vs. without thoracic radiotherapy and/or SBRT after first-line systemic therapy for metastatic NSCLC comparing PFS as primary objective (NCT03867175).

7. Beyond progression: oligoprogression in NSCLC patients

An important growing subsegment of NSCLC patients is a group with oligoprogressive disease. With more effective systemic therapies that offer high response rates and long PFS times in patients with metastatic NSCLC, the oligoprogressive disease has become more and more common clinical scenario. Oligoprogressive disease, presented in oncogene driven NSCLC mostly occur due to the isolated emergence of well-described resistance mutations [65]. According to the literature, the occurrence of oligoprogression during TKI treatment seems to be quite frequent, reported in the range of 32–49% [17, 19, 20]. However, the optimal therapeutic approach in these patients is still unclear. Three main treatment options include changing systemic therapy, continuing the same systemic therapy beyond progression or using local therapy for eradicate the resistant clones while continuing the same systemic therapy [41]. The evidence supporting local treatment is limited to small retrospective reports. Weckhard et al. reported that 49% of ALK or EGFR positive metastatic NSCLC patients are treated with TKI presented with intracranial or extracranial oligoprogression suitable for local treatment [20]. Of 25 patients, 24 were treated with RT and one underwent surgery; however, 19 of 25 locally treated patients progressed again with PFS of 6.2 months. Yu et al. reported on 184 patients with EGFR mutation, of these 42 progressed with intracranial and 18 with extracranial oligometastases. These 18 were treated with local therapy, including surgery, radiofrequency ablation or RT with the median TTP of 10 months. Gan et al. reported on 33 ALK+NSCLC patients treated with crizotinib that had extracranial oligoprogression. Of these, 14 were suitable for local treatment with SBRT. Median overall time on crizotinib among those treated with SBRT versus those who progressed but were not suitable for SBRT was 28 and 10.1 months, respectively. Patients remaining on crizotinib for >12 months vs. ≤12 months had a 2 year OS of 72% vs. 12%, respectively ($p < 0.0001$) [93]. Xu et al. reported on 206 EGFR-mutant NSCLC patients included in the analysis of the survival benefit of adding local ablative therapy after oligoprogression during first-line TKI. With the median follow-up time of 42 months, the median PFS1, median PFS2 and median OS were 10.7 months, 18.3 months and 37.4 months, respectively. Survival rates of 1 year, 2 years and 3 years were 94.1%, 78.9%, and 54.7%, respectively. Altogether, the data suggest that local ablative treatment of progressive lesions in actionable mutations NSCLC patients can prolong treatment with first-line TKI without reported unacceptable excess toxicity. Moreover, despite the paucity and the heterogeneity of clinical data the use of local therapy in oligoprogressive oncogene driven NSCLC is already considered as standard clinical practice [94].

Currently, a few prospective randomized clinical trials are ongoing researching the benefit of local ablative treatment in oligoprogressive NSCLC. A Canadian trial, the STOP-NSCLC (NCT02756793) is a randomized phase II trial with estimated enrolment of 54 patients with oligoprogressive NSCLC during TKI or maintenance chemotherapy that evaluate either SBRT with continuation of current systemic agents or standard of care that may include continuation of current systemic agent, observation or switch to next-line treatment. Primary end-point will be PFS, while secondary end-points will be OS, local control, toxicity, quality of life and patterns

of further progression. Similarly, European HALT study (NCT03256981) is a phase II/III, randomized study with question whether the use of SBRT to ≤3 sites of oligoprogressive disease in mutation positive advanced NSCLC patients with continuation of TKI improves PFS compared to continuation of TKI alone. The study aims to recruit 110 patients with oligoprogressive mutation positive advanced NSCLC following initial response to TKI. Third ongoing randomized trial is PROMISE-004 (NCT03808662) study with heterogeneous cohort including breast and NSCLC patients and estimated enrolment of 160 patients with either no targetable mutations upfront or targetable mutations after progression on first-line TKI. The purpose of the study is to evaluate the role of SBRT when metastatic lesions have just begun to grow with PFS as primary end-point.

In the context of immunotherapy in NSCLC patients, which includes the majority of lung cancer patients currently, tumor escape is not uncommon, but studies of oligoprogression are lacking. According to mechanism, oligoprogression might represent local immune tolerance due to stromal or tumor changes. Recently, in order to specify oligoprogression in NSCLC patients treated with immunotherapy, the results of a retrospective analysis of the failure pattern of 297 on ICI and 75 patients treated combined with chemotherapy and ICI were published [95]. Under ICI monotherapy in the first-line treatment, oligoprogression was more frequent (20% vs. 10%, $p < .05$), occurred later (median 11 vs. 5 months, $p < .01$) and affected fewer sites (mean 1.1 vs. 1.5, $p < .05$) compared to oligoprogression in patients treated with ICI monotherapy in later lines. Lymph nodes (42%, manly mediastinal) and the brain (39%) were mostly affected, followed by the lung (24%) and other organs. Compared to multifocal progression, oligoprogression occurred later (11 vs. 4 months, $p < .001$) and was associated with longer survival (26 vs. 13 months, $p < .001$) and higher tumor PD-L1 expression ($p < .001$). Chemoimmunotherapy showed a similar incidence of oligoprogression as ICI monotherapy (13% vs. 11% at 2 years). Local treatments were applied regularly for brain but only in 50% for extracranial lesions. However, oligoprogression in NSCLC patients is less common under ICI treatmnet than under TKI and its frequency descent with time. Few prospective trials evaluate the value of RT in oligoprogressive NSCLC treated with ICI, with one randomized phase II study designed to evaluate the effect of local consolidative RT to all sites of oligoprogressive disease in patients with metastatic NSCLC who have progressed through first-line systemic therapy containing an ICI (NCT04485026).

8. Conclusion

The number of patients with oligometastatic NSCLC has increased significantly over the last decade as well as the use of the locally ablative therapy to treat these patients. The evidence supporting this approach includes three randomized phase II clinical trials and substantial retrospective data; however, the inclusion criteria in these trials were mostly incomparable. Oligometastatic NSCLC has recently been defined by a consensus of multidisciplinary group of European thoracic oncology experts and this was the first step to unify future researching regarding diagnostic procedures and inclusion criteria. Recently, the therapeutic landscape of metastatic NSCLC has dramatically changed with the introduction of new systemic agents as molecular targeted and immunotherapy resulting in the prolonged survival and changing the field of oligometastatic framework significantly. A new concept that emerged with more effective systemic therapy is oligoprogression, frequently presents in patients treated with TKI. Additionally, combining radiotherapy and immunotherapy represent an increasing filed of interest due to synergistic

potentiation of an immunomodulatory effect as a way to overcome the resistance of immunotherapy that exist in a substantial part of metastatic NSCLC patients. Especially for oligometastatic NSCLC patients, this integration might be meaningful due to a low tumor burden that seems to be one of the most important predictive factors for the benefit of SBRT-immunotherapy combination. In the future, further studies are needed to assess different treatment variables in order to optimize management of oligometastatic NSCLC in the way that the intent of treatment might not be just prolonged survival but cure.

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