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Extracranial Oligometastasis in Non-Small Cell Lung Cancer

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Abstract

Classically, the main treatment approach to metastatic non-small cell lung cancer (NSCLC) has been chemotherapy, achieving a mean survival time of only 8 to 11 months. However, a subset of these patients has a better prognosis and could benefit from radical local treatment. At present, the evidence to support SBRT in oligometastatic NSCLC is limited, despite the increasing number of clinical trials being carried out to evaluate SBRT as monotherapy or in combination with immunomodulatory therapies. Based on the available data, it appears that only 10-15% of patients with oligometastatic disease are likely to benefit from local radical treatment. This subset of patients who are likely to respond well to SBRT should meet certain criteria.

Introduction

Classically, the main treatment approach to metastatic non-small cell lung cancer (NSCLC) has been chemotherapy, achieving a mean survival time of only 8 to 11 months [1]. However, a subset of these patients have a better prognosis and could benefit from radical local treatment [2]. In a report published in 1996, Hellmann and Weichselbaum [3] found that patients with a limited number of metastatic lesions (from 1 to 5) present a more indolent disease course than those with ≥ 5 metastases. Those authors called this intermediate stage "oligometastasis" to differentiate it from localized NSCLC and from widespread metastasis.

Materials and Methods

We have conducted a descriptive review about extracranial oligometastasis In non-small cell lung cancer as we think is important to clarify which subset of patients are likely to respond to SBRT.

Results

Niibe and Hayakawa [4] later updated this definition by introducing the concept of oligo-recurrence to describe patients whose primary tumor is controlled but who develop metastatic lesions during the disease course. Oligometastasis is not uncommon in patients with NSCLC: it is estimated that 20% of patients with stage IV disease are oligometastatic at diagnosis [5]. Treatment of oligometastatic disease has classically included surgery, with overall survival (OS) rates at one year ranging from 56% [6] to 73% [7], and a median survival time of 20 months [7].

In recent years, studies have shown that the use of Stereotactic Body Radiation Therapy (SBRT) to treat oligometastatic lesions can achieve results that are comparable to surgery, with one study reporting two-year rates of local control and OS of 74% and 39%, respectively [8]. Consequently, interest in SBRT for this indication has continued to grow. To increase the probability that local treatment with SBRT will favourably impact the course of disease in this subset, it is essential to select the patients likely to be good responders and/or those with less aggressive disease [9-11].

At present, the evidence to support SBRT in oligometastatic NSCLC is limited, despite the increasing number of clinical trials being carried out to evaluate SBRT as monotherapy or in combination with immunomodulatory therapies [12]. The only randomized trials that have been published to date are phase II trials (several phase III trials are underway NRG LU 002 NCT 03137771, SARON NCT02417662) and the reported OS rates vary widely, ranging from 18% to 90%

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at 2 years [13]. Four reviews have been carried out [13-16], and the findings of these reviews suggest that there are several clinical factors that may be useful in identifying patients who are suitable for radical local treatment, including the following: 1) metachronous lesions (oligoprogression); 2) limited nodal involvement (N0-N1); and 3) disease-free interval (DFI) ≥ 6 months.

To date, five phase II prospective studies assessing oligometastatic disease in primary lung cancer have been published [17-21]. The first of these, carried out by De Ruysser et al. [17], was published in 2012. In that study, 39 patients with NSCLC underwent radical treatment of the primary tumour. Nearly all (95%) of the patients received systemic treatment and most (87%) presented a single synchronous metastatic lesion at diagnosis. Median survival was 13.5 months (range, 7.6-19.4), with OS and progression-free survival (PFS) rates, respectively, of 56% and 51.3% at one year, and 23% and 13.6% at two years.

A second prospective phase II study, conducted by Collen et al [18], reported results in 2014. In that study, 26 patients with stage IV NSCLC and ≤ 5 lesions were treated with SBRT after systemic treatment or as primary treatment. At a mean follow-up of 16.4 months, 30% of patients showed a complete response at all tumour sites, and an additional 30% presented a partial response. At one year, the OS rate was 63% and median survival time was 23 months. It is worth noting that the mediastinal lymph nodes received the same dose (50 Gy in 10 fractions) as the primary lung tumor, which could explain the 8% rate of grade 3 (G3) toxicity in the sample.

The third phase II study was conducted by Iyengar et al [19] and also published in 2014. The study evaluated 24 patients with NSCLC with < 7 metastatic lesions (maximum of 3 hepatic or pulmonary lesions) who progressed to first-line of chemotherapy. The main outcome measure was 6-month PFS. A novel aspect of the study was the combination of SBRT with concomitant erlotinib (150 mg/day), which was initiated one week before treatment and continued until progression. EGFR determination was not mandatory. The results were promising, with 6-month PFS of 69% and a median survival of 20.4 months. However, note that two patients developed severe pneumonitis (grades G3 and G4), a known adverse effect of anti-EGFR drugs.

Gomez et al. [20] published the results of a phase II trial in NSCLC patients with synchronous oligometastatic disease (defined as ≤ 3 lesions, including the primary tumor) at diagnosis. The treatment scheme was at least four cycles of chemotherapy or, in patients with EGFR mutations or ALK rearrangements, 3 or more months of EGFR or ALK inhibitors, respectively. Following treatment, the tumour was reassessed by CT scan and if the Oligometastasis persisted, the patients (49 cases) were randomized to receive either maintenance treatment (24 cases) or local radical treatment (25 cases). The study was closed prematurely, at a median follow up of 12.39 months, after the interim analysis revealed a median PFS of 11.9 months in the local treatment group versus only 3.9 months in the maintenance group (hazard ratio, 0.35 [90% CI 0.18–0.66], log-rank p = 0.0054). That study demonstrated that patients who respond well to systemic treatment clearly benefit from local treatment.

The group of Iyengar et al. [21] recently published the results of similar trial published by Gomez et al. Patients with an oligometastatic disease at diagnoses were enrolled. Interestly they include patients with 6 metastatic extracraneal sites (including the primary), and the results showed that patients with local treatment achieved better progression free survival than patients without SBRT.

Discussion

Based on the available data, it appears that only 10-15% of patients with oligometastatic disease are likely to benefit from local radical treatment. This subset of patients who are likely to respond well to SBRT should meet certain criteria. In patients with synchronous disease, these factors include: 1) the possibility of radical treatment of the primary tumor; 2) limited nodal involvement (N0-N1); 3) maximum of 1-2 metastatic lesions amenable to radical treatment; and 4) good response to systemic treatment. In these cases, the asymptomatic metastatic lesions can be treated with SBRT; if the metastatic lesions are symptomatic, treatment of these lesions should be prioritized provided that this does not compromise initiation of systemic treatment. In metachronous disease, the oligoprogression may be treated when the disease-free interval is longer than 6 months and there are less than three metastatic lesions.

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