

Review

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Review

Oligo-Recurrence in Lung Cancer; The Most Curable State Among Advanced Disease?

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Abstract: The introduction of effective systemic therapies, such as immune checkpoint inhibitors and molecular-targeted agents, along with advancements in precision medicine, has significantly improved survival outcomes for patients with advanced non-small-cell lung cancer (NSCLC). However, recurrence or progression remains common, and only a fraction of patients can achieve long-term control. For a subset of patients with more localized metastatic disease—referred to as oligometastases—emerging evidence suggests that a multimodal approach combining systemic therapy with local ablative therapies (LAT), such as radiotherapy or surgical resection, may offer curative potential. The concept of oligo-recurrence is defined by the presence of a limited number of metastases and recurrences in patients with controlled primary lesions. A key distinction between oligometastasis and oligo-recurrence lies in the status of the primary lesion: whether it is controlled or uncontrolled. In cases of oligo-recurrence, all gross recurrent or metastatic sites are potentially treatable with LAT. According to a European consensus, oligo-recurrence is regarded as the most favorable subgroup among various oligometastatic classifications, showing a promising response to LAT. However, this classification remains a topic of ongoing debate and requires further exploration. In addition to an ongoing randomized clinical trial on oligo-recurrent NSCLC, further rigorous studies focusing specifically on oligo-recurrence could help refine treatment strategies for this advanced but potentially curable state. These investigations are essential for developing effective, tailored approaches to optimize outcomes for patients within this prognostically favorable subgroup.

Keywords: Oligo-recurrence; Local ablative therapy; Radiotherapy; Surgery

1. Introduction

Lung cancer is the leading cause of cancer-related deaths globally, largely due to its aggressive nature and tendency to metastasize to other organs [1]. The extensive blood and lymphatic networks surrounding the lungs facilitate this metastatic spread, making it particularly challenging to control. In recent years, immune checkpoint inhibitors and molecular-targeted therapies have emerged as promising treatments for metastatic non-small cell lung cancer (NSCLC). However, despite their effectiveness, these therapies often show limited success in the later stages of the diseases or after recurrence, often due to acquired resistance or the presence of a more aggressive tumor biology.

For a subset of patients with more localized metastatic disease, there is growing evidence that a multimodal treatment approach, combining systemic therapy with local ablative therapy (LAT), such as radiotherapy or surgical resection, may offer curative potential. One concept gaining attention is oligometastases. The concept of oligometastases was proposed by Hellman and Weichselbaum in 1995 [2]. It refers to an advanced stage of cancer with a limited number of metastatic lesions, and represents an intermediate disease state between locally advanced cancer and widespread systemic metastasis. More than ten years later, the concept of oligo-recurrence was defined by Niibe and colleagues, as the state in which cancer patients have five or fewer metastatic lesions with controlled primary lesions [3-5].

In this review, we provide a comprehensive introduction of the evidence supporting lung cancer oligometastases and oligo-recurrence. We review the efficacy of radiotherapy and surgical resection for treating metastatic lesions and, finally discuss whether oligo-recurrence can be classified as the most curable state among advanced NSCLC cases.

2. Search Methods

In the narrative review, we collected international guidelines along with retrospective and prospective studies from relevant articles and review. The search was limited to English-language publications, and the PubMed database was queried using the terms “lung cancer” and “oligo-recurrence”.

3. Definition and Classification

The term “oligometastases” refer to a condition of metastatic disease that is limited in the number of metastatic sites and the extent of disease, making it potentially amenable to metastatic-directed surgical and radiotherapeutic treatments with curative intent for select patients, as outlined in an editorial written by the aforementioned two radiologists [2]. On the other hand, Niibe et al. defined the concept of oligo-recurrence in the mid-2000s as the presence of one to five metastases and recurrences (excluding local recurrence) with controlled primary lesions [5]. The key difference between oligometastases and oligo-recurrences lies in the status of the primary lesion-whether it is controlled or uncontrolled-indicating that all gross recurrent or metastatic sites can be treated with LAT.

However, it is important to note that in past clinical trials on oligometastatic NSCLC, the definition of oligometastases varied across studies, making it difficult to compare and interpret the results. To address this issue, several consensus guidelines have been proposed, primarily by North American and European radiotherapy groups, aiming to establish standardized definitions, diagnostic criteria, and classifications for oligometastatic NSCLC. In 2019, the European Organization for Research and Treatment of Cancer Lung Cancer Group (EORTC LCG) proposed a consensus aimed at standardizing eligibility criteria in clinical trials and facilitating the comparison of clinical trial data [6]. A survey was distributed to the consensus group, as well as to national societies and members of the EORTC LCG and radiation oncology group (ROG). A total of 423 physicians from 34 countries completed the survey, and their responses helped shape the questions for the consensus meeting. According to this consensus, synchronous oligometastatic NSCLC is defined as having up to five metastases in a maximum of three organs, all of which are treatable with local therapy [6].

In 2020, the European Society for Radiotherapy and Oncology (ESTRO) and the American Society for Radiation Oncology (ASTRO) produced a consensus on the definition of oligometastatic disease, emphasizing the importance of ensuring that all metastatic lesions can be safely treated [7]. Furthermore, the 2023 edition of the Japanese Lung Cancer Society Guidelines for non-small cell lung cancer includes a section on oligometastatic disease, recommending that local therapy should be considered for patients with stage IV NSCLC who have a limited number of synchronous oligometastatic lesions and whose disease is stable with drug therapy [8]. In 2020, ESTRO and EORTC consensus introduced a decision tree that uses five questions to classify oligometastatic disease into nine different categories based on factors such as the presence or absence of polymetastatic disease, whether the primary tumor was diagnosed within six months, whether systemic therapy was ongoing at the time of oligometastatic disease diagnosis, and whether there were progressing lesions during systemic therapy [9]. This decision tree facilitates the development of treatments specific to each disease state and is also valuable for the efficient conduct of clinical trials. This consensus detailed oligo-recurrence, separating it into three subclassifications; metachronous, repeat, and induced oligo-recurrence. “Metachronous” refers to the first-time diagnosis of new oligometastases more than 6 months after the initial diagnosis of cancer. “Repeat” indicates patients with a previous diagnosis of oligometastatic disease, and the subsequent diagnosis of new, growing, or regrowing oligometastases. “Induced” refers to patients with a history of polymetastatic disease, where active systemic therapy induces oligometastases. Thus, when considering all the evidence, oligo-recurrence is currently defined as a state characterized by a limited number of metastases and recurrences with controlled primary lesions and is classified into the subtypes metachronous, repeat, and induced.

4. Clinical Trials for Oligometastatic and Oligo-Recurrent NSCLC

As of October 2024, no randomized clinical trial results have been published for oligo-recurrent lung cancer. On the other hand, several important randomized phase II trials are underway, comparing LAT to all metastatic sites with maintenance therapy or observation for stage IV oligometastatic NSCLC. In a 2016 randomized phase II trial by Gomez et al., the effects of adding maintenance drug therapy and local treatment were evaluated in NSCLC patients with three or fewer metastatic lesions who had stable disease for three months after initial chemotherapy [10]. Interim analysis of the 49 patients enrolled showed a significant improvement in progression-free survival (PFS) for the local treatment group, with a hazard ratio of 0.35 (11.9 months vs. 3.9 months, 90% confidence interval 0.18-0.66, $p = 0.006$). Long-term follow-up further indicated that median overall survival (OS) in the local treatment group was 41.2 months, notably longer than the 17.0 months observed in the maintenance therapy group [11]. Additionally, adverse events were comparable between both groups.

In a 2018 single-institution randomized phase II trial by Iyengar et al., patients with NSCLC who demonstrated stable disease after 4 to 6 cycles of platinum-based chemotherapy, were negative for epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) fusion genes, and had up to five metastatic lesions (with no more than three in the lungs or liver) were enrolled [12]. The study compared maintenance drug therapy alone to the addition of stereotactic body radiotherapy (SBRT). Interim analysis of the 29 patients showed a significant improvement in PFS in the local treatment group, with a hazard ratio of 0.30 (9.7 months vs. 3.5 months, 95% confidence interval 0.11-0.82, $p = 0.01$).

In the randomized phase II SABR-COMET trial, which included patients with solid tumors and up to five metastatic lesions (including the primary tumor), the additional effect of SBRT was compared to maintenance therapy in patients whose disease had remained controlled for more than three months with drug therapy [13]. Among the participants, 18% had NSCLC. Results from the 99 randomized patients indicated a significant extension in OS in the SBRT group, with a hazard ratio of 0.57 (41 months vs. 28 months, 95% confidence interval 0.30-1.10, $p = 0.009$). However, grade 2 or higher adverse events were observed in 29% of patients (19 individuals) in the SBRT group, compared to 9% (3 individuals) in the maintenance therapy group. Additionally, treatment-related deaths occurred in 3 patients (4.5%) in the SBRT group, while no such events were reported in the maintenance therapy group [13].

The SINDAS trial studied first-line TKI therapy with or without upfront radiotherapy in EGFR-mutated synchronous oligometastatic NSCLC [14]. Between 2016 and 2019, 133 patients with up to five extra-cranial metastases were enrolled. Median PFS was 12.5 months with TKI alone versus 20.2 months with TKI plus SBRT, and median OS was 17.4 months versus 25.5 months, respectively.

Currently, several phase III trials targeting lung cancer oligometastases are ongoing. While no final reports have been published, Iyengar et al. presented findings at the 2024 American Society of Clinical Oncology annual meeting from a randomized phase II/III trial (NRG-LU002) comparing maintenance therapy alone to local consolidation therapy plus maintenance therapy in oligometastatic NSCLC [15]. The phase II results showed no significant difference in PFS between the groups, leading to the study's closure for further enrollment. This outcome may be due to the heterogeneous study population, which included both true oligometastasis cases with fewer initial metastatic sites and induced oligometastasis cases, where systemic therapy initially controlled widespread metastasis to create an oligometastatic state.

The JCOG2108 trial, conducted by the Japan Clinical Oncology Group (JCOG), is the only ongoing multicenter randomized phase III study comparing systemic chemotherapy followed by maintenance therapy versus local consolidation therapy for postoperative oligometastatic recurrent NSCLC [16]. This study focuses on patients with completely resected, non-EGFR/ALK mutated NSCLC with three or fewer distant recurrent lesions, with OS as the primary endpoint. After initial chemo-immunotherapy, patients with reduced or stable metastases are randomized to receive either maintenance therapy or LAT (radiotherapy or surgery) targeting all recurrent lesions. The results of this study could help establish a dedicated treatment framework, including LAT, for oligo-recurrent NSCLC.

Targeted next-generation sequencing is now a routine part of clinical practice for cancer. The clinical trials discussed here, along with ongoing phase III trials on oligometastatic NSCLC, are designed to incorporate multiple molecular targeted therapies and immune checkpoint inhibitors as systemic treatments. The advent of effective drug therapies and precision medicine has improved outcomes for patients with advanced NSCLC and even for those with oligometastatic disease. Combining systemic therapies with LAT is crucial in pursuing a potential cure for oligometastatic NSCLC.

5. Surgery For Oligo-Recurrent NSCLC

In consensus and clinical practice guidelines, curative local treatment generally refers to metastasis-directed therapy, primarily focusing on radiotherapy. Among the randomized phase II trials discussed earlier, only the study by Gomez et al. permitted surgical treatment as a form of local ablative therapy (LAT), with surgery used in just 28% of cases [10]. Clear criteria for selecting radiotherapy versus surgical treatment as the preferred local therapy remain undefined. Even in ongoing randomized phase III trials for oligometastatic NSCLC, only a few allow surgery as a local therapy option. Notably, the JCOG2108 trial incorporates both surgery and radiotherapy as LAT options for oligo-recurrent NSCLC [16]. This does not imply that radiotherapy is preferred over surgery as LAT for oligometastatic NSCLC. In fact, reports on surgical treatment for oligometastatic lung cancer are increasing.

Mitchell et al. conducted a retrospective study on patients with NSCLC (cT1-3N0-2M1) and three or fewer synchronous metastases, comparing LAT by pulmonary resection or radiotherapy for the primary lesion [17]. Of 88 patients, 63 (71.6%) received radiotherapy, while 25 (28.4%) underwent surgery (lobectomy in 80%, pneumonectomy in 12%, sublobar in 8%). Ninety-day mortality was low (0% for surgery; 1.6% for radiotherapy). Median survival was 55.2 months in the surgery group and 23.4 months in the radiotherapy group, suggesting that pulmonary resection is feasible and may offer long-term survival for selected patients, though selection bias may exist.

Deboever et al. retrospectively analyzed patients with oligometastatic NSCLC (>3 synchronous metastases) who underwent primary tumor resection. Among the 52 patients meeting the criteria, there were no deaths at 30 or 90 days [18]. Median postoperative PFS was 9.4 months (5.5–11.6), and OS was 51.7 months (22.3–65.3), indicating that pulmonary resection for locoregional control in oligometastatic NSCLC is feasible, safe, and may offer durable long-term survival benefits.

Regarding LAT modalities, retrospective studies on oligo-recurrent NSCLC vary in focus: many examine both surgery and radiotherapy, others focus on radiotherapy alone and a few evaluate surgical resection alone. Ishige et al. reported on seven patients with liver oligo-recurrent NSCLC who underwent hepatectomy [19]. All patients achieved complete tumor resection without complications. The median survival following hepatectomy was 24.0 months (range 15.2–30.2), and they concluded that hepatectomy may be as effective as multidisciplinary therapy for oligo-recurrent NSCLC in the liver. Raz et al. compared surgical and non-surgical approaches for patients with oligometastatic adrenal metastasis from NSCLC [20]. The five-year overall survival rate was 34% for the 20 patients who received operative treatment, compared to 0% for the 17 patients treated nonoperatively ($p = 0.002$), despite the presence of selection bias.

Table 1 summarizes retrospective studies on patients with oligo-recurrent NSCLC after curative control of the primary lung tumor, treated with radiotherapy and/or surgery for recurrence [21–32]. Hishida et al. analyzed 768 NSCLC patients with postoperative recurrence after complete resection [23]. Among the 162 patients with three or fewer metastases, the 5-year post-recurrence survival rate was 32.9%, significantly higher than in those with more than three lesions. Multivariate analysis showed that initial local therapy (radiation or surgery) for recurrent disease was associated with improved post-recurrence survival (odds ratio [OR] 0.44; 95% confidence interval [CI] 0.29–0.68). Sonoda et al. examined post-recurrence survival in 118 NSCLC patients with oligo-recurrence after complete resection, stratified by EGFR mutation status [30]. They found that local treatment of metastatic lesions significantly improved survival in patients without or with unknown EGFR

mutations, but not in those with EGFR mutations. These studies suggest that postoperative oligo-recurrence, accounting for 21% to 53% of all recurrences, is not uncommon.

When assessing postoperative oligo-recurrence in the ESTRO/EORTC consensus, it classifies as "synchronous oligometastatic disease" because it involves patients with no prior systemic treatment for recurrence (genuine oligometastatic disease), represents a first diagnosis of oligometastases (de novo oligometastatic disease), and is characterized by metachronous metastasis. These homogeneous states facilitate establishing objective criteria for choosing between surgical treatment and radiotherapy.

6. Radiotherapy for Oligo-Recurrent NSCLC

In 2006, Niibe et al. published a landmark multi-institutional study that introduced the concept of oligo-recurrence. In this study, 84 patients with isolated oligo-recurrent para-aortic lymph nodes received conventional radiotherapy, with or without chemotherapy, achieving a 5-year overall survival rate of 31.3% [4]. Niibe et al. further explored conventional radiotherapy for isolated osseous metastasis in breast cancer in 2008, treating seven patients with solitary osseous metastases and controlled primary and other sites with doses of 30 to 50 Gy [33]. Only one patient experienced a recurrence of pain, having received the lowest dose of 30 Gy. These findings suggest that radiation therapy for solitary osseous metastasis may be effective, and higher doses could provide long-term pain relief.

Retrospective studies on lung cancer oligo-recurrence are summarized in Table 2 [34-40]. Yamashita et al. classified oligometastases into sync-oligometastases and oligo-recurrence [35]. Sync-oligometastases refer to cases with ≤ 5 metastatic or recurrent lesions alongside active primary tumors. In their study of 96 patients (10 with sync-oligometastases, 79 with oligo-recurrence, and 7 unclassified), the median follow-up for survivors was 32 months. Median OS was 23.9 months for sync-oligometastases and 66.6 months for oligo-recurrence ($p = 0.0029$). Multivariate analysis identified sync-oligometastases and multiple metastatic tumors as significant unfavorable factors for both OS and relapse-free survival.

In a separate analysis, Niibe et al. examined the prognostic impact of pulmonary oligo-recurrence versus sync-oligometastases [38]. Among 1,378 patients with 1,547 tumors (1,016 oligo-recurrence, 118 sync-oligometastases, and 121 unclassified), the three-year OS was 64.0% for oligo-recurrence and 47.5% for sync-oligometastases ($p < 0.001$). Multivariate analysis showed a hazard ratio (HR) of 1.601 for sync-oligometastases compared to oligo-recurrence ($p = 0.014$). Collectively, these results suggest that OS is better for oligo-recurrence patients than for those with sync-oligometastases.

Kissel et al. evaluated outcomes for lung cancer patients with extracranial metastases across various oligometastatic settings—oligometastatic, oligorecurrent, oligopersistent, and oligoprogressive (the "oligometastatic spectrum")—using SBRT (stereotactic body radiation therapy) with or without systemic treatments [41]. They found that initial nodal stage and the specific oligometastatic spectrum category were prognostic factors for distant progression-free survival (d PFS), while age, initial primary stage, and oligometastatic spectrum were prognostic factors for OS in multivariate analysis. Among the oligometastatic spectrum, oligoprogression was identified as an unfavorable prognostic factor.

Niibe et al. examined the prognostic significance of oligo-recurrence in NSCLC patients with brain-only oligometastases treated with stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) [36]. The median OS for all 61 patients was 26 months (95% CI: 17.5–34.5 months). When categorized by oligostatus, the sync-oligometastases group had a median OS of 18 months (95% CI: 14.8–21.1 months) with a five-year OS of 0%, while the oligo-recurrence group had a median OS of 41 months (95% CI: 27.8–54.2 months) with a five-year OS of 18.6%. In multivariate analysis, oligo-recurrence was the only significant independent factor associated with a favorable prognosis.

Aoki et al. evaluated the feasibility of salvage SBRT for patients who had undergone surgery and subsequently developed local failure or intrathoracic oligo-recurrence [37]. In total, 52 patients with 59 tumors were analyzed. The median OS following salvage SBRT was 32 months, with one-

and three-year OS rates of 84.4% and 67.8%, respectively. Only 4 patients (7.7%) experienced local failure. The study concluded that post-operative salvage SBRT is a promising therapeutic option for NSCLC patients with local failure or intrathoracic oligo-recurrence.

Radiotherapy is essential for the local treatment of oligometastases, serving not only curative purposes but also playing a critical role in complementing and enhancing systemic therapy. In Japan, SBRT for oligometastases became covered by health insurance in April 2020. Further prospective studies or larger cohort studies are needed to establish robust evidence supporting radiotherapy as the primary modality of LAT for oligo-recurrent NSCLC.

7. Other Treatments for Oligo-Recurrent NSCLC

Local therapeutic options for oligo-recurrent NSCLC are limited primarily to radiotherapy and surgery. However, Hiraki et al. reported promising results for radiofrequency ablation (RFA) in treating NSCLC patients with pulmonary metastasis from various primary cancers, including colorectal, lung, hepatocellular carcinoma, renal cell carcinoma, and sarcoma, suggesting RFA's potential to provide long-term survival for patients with oligo-recurrence or oligometastasis of lung cancer [42]. Regarding oligo-recurrence of NSCLC, Kodama et al. conducted a notable study involving 44 patients who underwent lung RFA for recurrent NSCLC post-surgery [43]. Of these, 43 had no extrapulmonary metastasis, while one patient with liver and splenic metastasis also received RFA. They treated single or multiple intrapulmonary recurrences, with an average follow-up of 29 months showing overall survival rates of 98% at one year, 73% at two years, and 56% at three years. Recurrence-free survival rates were 77% at one year and 41% at three years, with tumor size and sex identified as independent significant predictors in multivariate analysis. This study suggested that RFA could offer a potential for long-term survival in patients with oligo-recurrent primary lung cancer.

Ni et al. conducted a retrospective analysis of 103 patients with pulmonary oligo-recurrence following radical surgical resection of NSCLC, performing 143 sessions of microwave ablation (MWA) to treat all nodules [44]. The median PFS and OS were 15.1 months and 40.6 months, respectively. After MWA, 15 patients (14.6%) experienced local recurrence as the first event, while intrathoracic oligo-recurrence and distant metastases were observed in 45 (43.7%) and 20 (19.4%) patients, respectively.

However, advancements in radiotherapy and surgical techniques may have further improved the curability of oligo-recurrent NSCLC, potentially reducing the role of RFA or MWA for oligo-recurrence today.

8. Conclusions

With advancements in both systemic and local therapies, there is increasing interest in exploring the curative potential for oligometastases and oligo-recurrence in lung cancer. Among the various oligometastatic subclassifications outlined in the ESTRO-EORTC consensus, oligo-recurrence stands out as the subgroup with the most favorable prognosis, showing significant potential for benefit from LAT. However, this classification is still subject to ongoing debate and requires further investigation.

Beyond the ongoing JCOG2108 trial, additional rigorous clinical trials specifically focusing on oligo-recurrence could provide valuable insights into refining strategies for treating this advanced but potentially curable state of NSCLC. These studies will be crucial in determining the most effective, tailored approaches to maximize outcomes for patients within this prognostically favorable subgroup.

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