Complex situations in lung cancer: multifocal disease, oligoprogression and oligorecurrence

Raphael Werner[1], Nina Steinmann[1], Herbert Decaluwe[2], Hiroshi Date[3], Dirk De Ruysscher[4,5] and Isabelle Opitz[1]

[1]Department of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland. [2]Department of Thoracovascular Surgery, Ziekenhuis Oost-Limburg, Genk, Belgium. [3]Department of Thoracic Surgery, Kyoto University Hospital, Kyoto, Japan. [4]Department of Radiation Oncology (MAASTRO), GROW School for Oncology and Reproduction, Maastricht University Medical Center+, Maastricht, The Netherlands. [5]Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands.

Corresponding author: Isabelle Opitz (Isabelle.schmitt-opitz@usz.ch)

Shareable abstract (@ERSpublications)
Complex situations in lung cancer such as multifocal disease, oligoprogression and oligorecurrence are expected to become more common with the emergence of novel treatment options and require an interdisciplinary and personalised treatment approach. https://bit.ly/49uOfJF

Cite this article as: Werner R, Steinmann N, Decaluwe H, *et al*. Complex situations in lung cancer: multifocal disease, oligoprogression and oligorecurrence. *Eur Respir Rev* 2024; 33: 230200 [DOI: 10.1183/16000617.0200-2023].

Received: 10 Oct 2023
Accepted: 23 Feb 2024

Abstract

With the emergence of lung cancer screening programmes and newly detected localised and multifocal disease, novel treatment compounds and multimodal treatment approaches, the treatment landscape of non-small cell lung cancer is becoming increasingly complex. In parallel, in-depth molecular analyses and clonality studies are revealing more information about tumorigenesis, potential therapeutical targets and the origin of lesions. All can play an important role in cases with multifocal disease, oligoprogression and oligorecurrence. In multifocal disease, it is essential to understand the relatedness of separate lesions for treatment decisions, because this information distinguishes separate early-stage tumours from locally advanced or metastatic cancer. Clonality studies suggest that a majority of same-histology lesions represent multiple primary tumours. With the current standard of systemic treatment, oligoprogression after an initial treatment response is a common scenario. In this state of induced oligoprogressive disease, local ablative therapy by either surgery or radiotherapy is becoming increasingly important. Another scenario involves the emergence of a limited number of metastases after radical treatment of the primary tumour, referred to as oligorecurrence, for which the use of local ablative therapy holds promise in improving survival. Our review addresses these complex situations in lung cancer by discussing current evidence, knowledge gaps and treatment recommendations.

Introduction

The treatment landscape of non-small cell lung cancer (NSCLC) is rapidly evolving. Novel treatment compounds and the recent improvements in lung cancer surgery and radiation therapy allow for multimodal treatment approaches and have contributed to the major improvement in survival [1]. In the past years, the implementation of national lung cancer screening programmes has improved the early detection of pulmonary nodules and comprehensive genomic profiling is providing pivotal information for the assessment of early-stage and advanced-stage NSCLC. In view of the increasing complexity of lung cancer treatment, this review aims to address the current evidence and knowledge gaps of frequently encountered complex situations in NSCLC, including multifocal disease, oligoprogression and oligorecurrence.

Search methods

For this narrative review, international guidelines and retrospective and prospective studies published from inception to August 2023 were identified by searches of PubMed, as well as references from relevant

articles and reviews. English language was used as a restriction and the PubMed search included the following search terms: “multifocal synchronous lung cancer”, “second primary lung cancer”, “multifocal lung adenocarcinoma”, “pneumonic-type lung adenocarcinoma”, “oligoprogressive disease”, induced oligoprogression”, “oligorecurrence” and “local ablative therapy”.

Multifocal disease

Summary

The recent advances in imaging techniques such as low-dose computed tomography (CT) and the establishment of lung cancer screening programmes have improved the early detection of pulmonary nodules but also increased the number of patients in whom multiple nodules are synchronously detected [2, 3]. The radiological finding of multiple synchronous lung cancers (MSLCs) can either represent multiple primary NSCLCs that are potentially curable, or locally or haematogeneously spread intrapulmonary metastases. This results in a clinical dilemma, because the relationship between two nodules essentially determines the correct therapeutic approach [4].

Based on clinico-pathological and molecular findings, the International Association for the Study of Lung Cancer (IASLC) proposed revisions in the staging of MSLC and presented four patterns of lung cancer that may synchronously manifest in multiple pulmonary sites [4–7]: 1) second primary lung cancers, 2) separate tumour nodules, 3) multifocal lung adenocarcinoma with ground-glass/lepidic (GG/L) features and 4) pneumonic-type lung adenocarcinoma (figure 1). Each of these patterns require a distinct approach to staging and treatment and further research is required to identify the origin of separate lesions and the role of local treatment approaches.

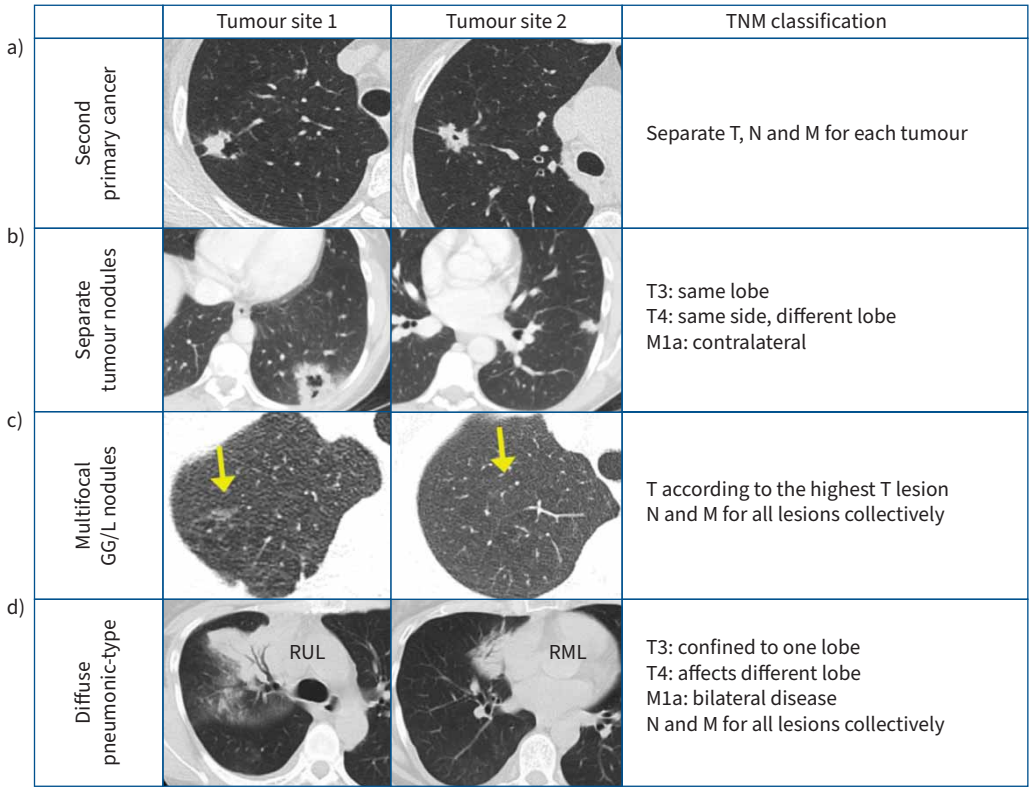

FIGURE 1 Radiological appearance of the four different patterns of multifocal disease according to the classification proposed by the International Association for the Study of Lung Cancer Multiple Pulmonary Sites Workgroup. a) Second primary lung cancer, b) separate tumour nodules, c) multifocal lung adenocarcinoma with ground-glass/lepidic (GG/L) features (yellow arrows) and d) pneumonic-type lung adenocarcinoma. These different patterns represent different disease stages or different entities that require a distinct approach to staging and treatment. RUL: right upper lobe; RML: right middle lobe. Reproduced and modified from Detterbeck *et al.* [4], with permission.

Definition

In the past decades, many efforts have been made to distinguish these clinical entities and to determine the adequate treatment. The first empirical criteria were published by Martini and Melamed in 1975 [8] and included clinical characteristics such as the presence of nodal disease, systemic extrapulmonary metastases or a latency of ⩾2 years to distinguish primary tumours from intrapulmonary metastases. Together with the American College of Chest Physicians (ACCP) guidelines, these criteria were widely applied in multidisciplinary tumour boards to guide treatment decisions [9]. However, modern pathological and molecular techniques, including targeted sequencing, whole-exome or whole genome sequencing, have recently revealed that many of these synchronous lesions represent multiple different primary tumours rather than metastases [10].

Synchronous second primary lung cancers

If two nodules show different lung cancer histology (including subtype grading and cytological features) in representative tissue specimens, they can easily be distinguished as second primary lung cancers. In contrast, the presence of nodules with identical histomorphological features does not necessarily imply that these are manifestations of the same tumour. The clonal relationships between different tumours in the same patient have recently been investigated by comprehensive genomic profiling of resected nodules. In the study by Liu *et al.* [10], 15 lung adenocarcinoma cases from six patients showed that all same-patient lung cancers harboured distinct genomic profiles and were classified as second primary lung cancers. Even identical oncogenic driver genes showed different mutations in different tumours from the same patient. Notably, according to the ACCP guidelines, all nodules would have been classified as separate tumour nodules or intrapulmonary metastases [10]. Findings from clonality studies therefore indicate that most nodules with the same histological type are likely to be second primary cancers. The radiological and histological classification should thus always be combined with a detailed genetic assessment to accurately identify the origin of MSLCs [4]. However, defining criteria that conclusively identify two lesions as identical is far more challenging than defining criteria that distinguish two lesions as separate [4]. In the IASLC proposals for revisions in the staging of MSLC, the presence of a different histology, different breakpoints in genomic hybridisation and the simultaneous origin from carcinoma *in situ* are mentioned as affirmative factors to identify two lesions as separate. Other criteria that speak for a separate origin, *e.g.* the absence of nodal and systemic metastases, different growth rates, different biomarker patterns and different radiographic appearances, are considered relative criteria and should be used with caution.

In case of second primary lung cancers, both cancers should be classified with a separate tumour, node, metastasis (TNM) staging and treated individually according to the current guidelines [4]. This approach is supported by a recent meta-analysis of the IASLC Multiple Pulmonary Sites Workgroup, which confirmed that the median 5-year survival in patients with synchronous second primary lung cancers treated by definitive local therapy (defined by lobectomy or segmentectomy in stage I tumours) is comparable irrespective of matching histology (45% in patients with same-histology tumours and 46% in patients with different histologies) [6].

Separate tumour nodules (intrapulmonary metastases)

In contrast to second primary lung cancers, which are unrelated tumours, separate tumour nodules are a single tumour with intrapulmonary metastasis. The terminology “satellite nodule” was abandoned in 2010. In the IASLC database for the 8th edition of TNM staging, 3.5% of all patients showed an ipsilateral or contralateral separate malignant nodule of the same histological type. Most commonly, only one separate nodule was present and overall survival (OS) decreased progressively depending on the location of the separate nodule. The best outcomes were for same-lobe nodules (*i.e.* T3), followed by same lung but different lobe nodules (*i.e.* T4), with the shortest OS in contralateral nodules (*i.e.* M1a) [4, 11]. However, OS was primarily confounded by the treatment administered and no survival differences were present among surgically managed and among non-surgically managed patients. Owing to these confounding factors, the TNM classification of the 8th edition for separate tumour nodules was left unchanged: synchronous nodules in the same lobe are classified as T3 and show a median 5-year survival of 38% (52% in N0 disease) and synchronous nodules of the same lung but different lobe are classified as T4 with a median 5-year survival of 30% (43% in N0 disease) [11].

Multifocal lung adenocarcinoma with GG/L features

Radiologically, multifocal adenocarcinoma with GG/L features present with either pure ground-glass morphology or part-solid morphology (figures 1 and 2). They are separate tumours like second primaries, but owing to the distinct clinical, pathological and biological characteristics and similarities, they are considered a separate entity that is associated with an indolent behaviour and a favourable outcome. Patients with multifocal GG/L adenocarcinoma are often female never-smokers and have a reduced risk for

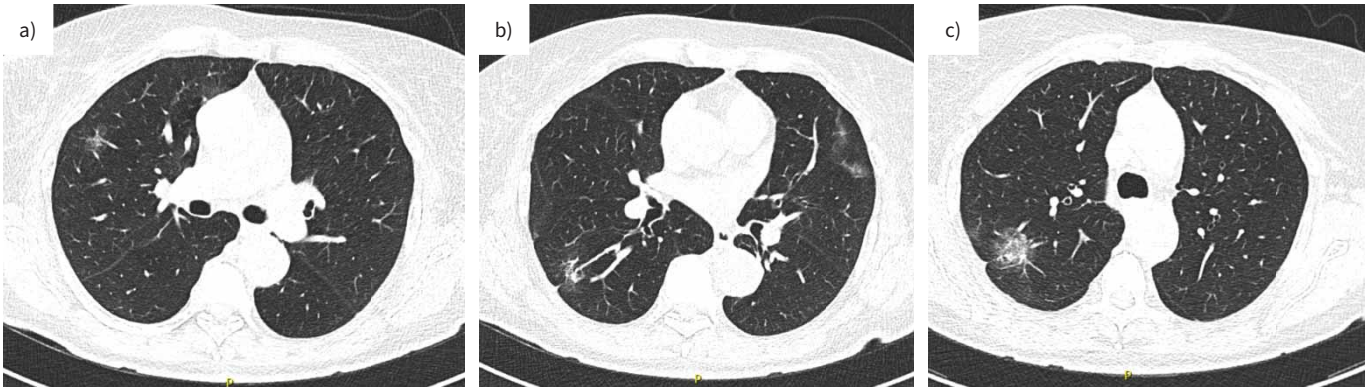

FIGURE 2 Computed tomography (CT) in a 74-year-old female patient with a smoking history of 25 pack-years revealed multiple ground-glass lesions in the right upper (a and b) and lower lobe, as well as the left lower lobe but without signs of enlarged mediastinal lymph nodes. Follow-up CT after 6 months revealed the growth of a lesion in the right lower lobe (c) with a new solid component of 3 mm diameter, while all other lesions remained stable. After multidisciplinary tumour board discussion, a wedge resection of the lesion in the right lower lobe was performed. The histological and genetic analysis revealed a well-differentiated lepidic adenocarcinoma harbouring a Kirsten rat sarcoma virus (*KRAS*) G12C mutation. The Tumour, Node, Metastasis (TNM, 8th edition) staging was considered pT1b cN0 cM0. The patient made an uneventful recovery and in the latest follow-up 2 years after surgery, all remaining ground-glass lesions were stationary. The patient was treated at the University Hospital Zurich.

nodal or distant metastatic spread, but an increased risk for the development of additional subsolid cancerous lesions [3, 4]. The 5-year survival rates reported in the literature range between 64% and 100% [5]. The radiological GG/L appearance correlates with the pathological subgroups of lepidic-predominant adenocarcinoma, minimally invasive adenocarcinoma, adenocarcinoma *in situ* or atypical adenomatous hyperplasia. The origin and molecular nature of these lesions are currently not fully understood and clonality studies have shown conflicting results. In a study including targeted sequencing of multiple synchronous multifocal adenocarcinomas with GG/L features, Park *et al.* [12] showed that while many mutation profiles of paired lesions were different, 68.7% of all patients had lesions that carried mutations in the same genes. This suggests that although these are different tumours, a common molecular abnormality may form the basis of tumorigenesis in these patients [3, 12].

Regarding the treatment of synchronous second primary lung cancers, many questions remain unanswered. To date, there are no uniform recommendations. A multidisciplinary team approach is essential. According to the recent guidelines of the American College of Radiology, GG lesions that remain stable in size or do not exceed the threshold of >1.5 mm growth per year are classified as Lung Imaging Reporting and Data System (RADS) 2 (<30 mm) or Lung-RADS 3 (>30 mm) and can thus be followed-up by low-dose CT in 6- or 12-month intervals, respectively [13]. By contrast, for lesions that show accelerated growth or develop a solid component, treatment should be considered [13]. Parameters that determine the treatment modality include the location (peripheral *versus* central, unilateral *versus* bilateral, single or multiple lobes involved), the morphology of each lesion (size, growth rate, solid areas), the patient's functional reserve to tolerate surgical resection and the patient's treatment preference. The ACCP guidelines recommend sublobar resection of all lesions if feasible [13]. However, these cases must be evaluated individually by a multidisciplinary tumour board [14]. Most centres follow a "whack-a-mole" strategy, in which the largest growing lesion is anatomically resected by segmentectomy or lobectomy to obtain a definitive histological diagnosis and perform molecular analyses [15]. If ipsilateral lesions are increasing in size or density as well, synchronous limited resection of these lesions may provide valuable additional information, especially when considering targeted systemic treatment [3]. Further lesions that are suspected to be malignant and are located contralaterally or difficult to access surgically, or that require large parenchymal resections, are commonly treated by stereotactic body radiation therapy (SBRT), as are patients who do not have sufficient functional reserve to undergo surgery [16].

Pneumonic-type adenocarcinoma

Typically, CT of patients with pneumonic-type adenocarcinoma shows a diffuse consolidative pattern that includes ground-glass as well as solid components [17]. Histologically, these findings commonly correspond to mucinous adenocarcinoma with highly heterogeneous areas. The IASLC Multiple Pulmonary Sites Workgroup proposes that the staging in these patients is performed according to the TNM classification. Tumours confined to one lobe are thus staged as T3, tumours involving multiple lobes of

one side as T4 and tumours with bilateral spread as M1a [4]. While the rate of progression is usually slow and nodal or systemic metastases are rare, the prognosis is significantly poorer than in patients with multifocal GG/L adenocarcinoma [4]. Owing to the rare occurrence of this disease entity, treatment recommendations are mainly based on expert opinions and individual decision-making by a multidisciplinary tumour board is essential. Because of the diffuse spread of the disease, surgery is commonly only performed if a single lobe is affected. In selected patients, the use of double-lung transplantation is reported in the literature with a 5-year survival rate of 39% [18].

Conclusion

Implementation of low-dose CT screening for lung cancer is increasing the diagnosis of numerous pulmonary nodules, ranging from preinvasive to invasive types. Future studies including pathological and molecular assessment of matched tissue samples from multiple lesions may hopefully elucidate the lineage connections of these lesions and thereby offer valuable understanding into their development as cancers. This knowledge will help to guide multidisciplinary tumour board decisions on well-informed treatment strategies for this increasingly common clinical scenario. With regards multifocal lung adenocarcinoma with GG/L features, parenchymal-sparing surgical resection of the lesions with accelerating growth or solid components remains the gold standard in patients who are eligible for a definitive local treatment.

Induced oligoprogression

Summary

With the current standard-of-care systemic treatments, many patients with widespread stage IV NSCLC show disease control and partial or complete responses, but a majority will face disease progression [19]. However, a significant proportion of the latter will present with induced oligoprogressive disease (OPD), which describes cancer progression in a limited number of sites with otherwise controlled disease (figure 3).

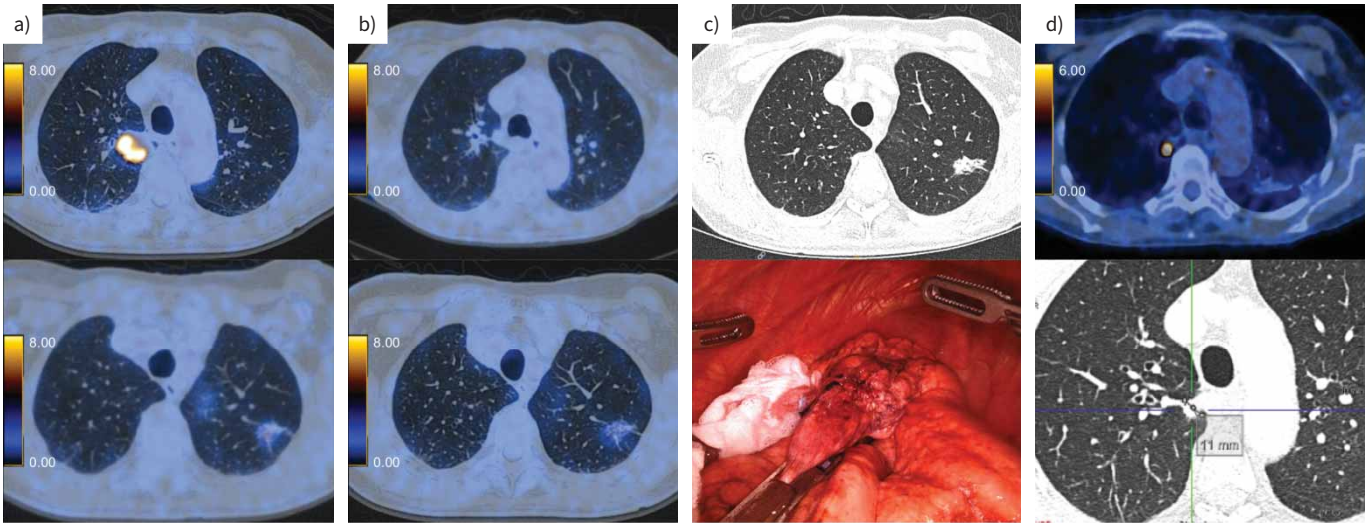

FIGURE 3 Chest computed tomography (CT) was performed in a 75-year-old female patient owing to a persistent cough and elevated inflammatory markers. The CT showed a large tumour in the right upper lobe and multiple bilateral pulmonary lesions. A subsequent bronchoscopy and endobronchial ultrasound-guided biopsy confirmed a thyroid transcription factor-1 (*TTF-1*)$^{+}$ adenocarcinoma with hilar lymph node metastases. Next-generation sequencing revealed an epidermal growth factor receptor (*EGFR*) exon 19 mutation. The subsequent fluorodeoxyglucose positron emission tomography-CT (PET-CT) showed the primary tumour in the right upper lobe with pulmonary metastases (a). A brain magnetic resonance tomography (MRT) showed no intracranial metastases. Therefore, a clinical Tumour, Node, Metastasis (TNM, 8th edition) stage cT4 cN1 cM1a was assumed. The patient underwent targeted treatment with osimertinib and, after 3 months, a metabolic and morphologic partial response was seen (b). The patient continued osimertinib and, after another 3 months, oligoprogression occurred in the left upper lobe (upper panel, c). A robotic-assisted wide wedge resection was performed (lower panel, c) and histological analysis confirmed that the adenocarcinoma metastasis maintained the identical *EGFR* exon 19 mutation without additional resistance mutations. Targeted therapy with osimertinib was thus continued and, after another 6 months, a follow-up PET-CT showed oligoprogression at the site of the primary tumour in the right upper lobe (upper panel, d). The patient then underwent stereotactic body radiation therapy of the progressive lesion in the right upper lobe with eight fractions of 6 Gy (65% isodose) using a volumetric modulated arc therapy technique (lower panel, d). Osimertinib was again continued beyond progression and, to date, regular clinical and radiological follow-up 5 years after initial diagnosis has not shown any signs of relapse. The patient was treated at the University Hospital Zurich.

Currently, there are many knowledge gaps in the definition and treatment of OPD. Based on the evidence available, local ablative therapy (LAT) by minimally invasive surgery and/or SBRT to moderate doses are promising options to address localised treatment resistance. The ideal time for a switch in systemic treatment currently remains uncertain, but treatment continuation beyond progression is often recommended in OPD because it preserves further treatment options.

Definition

Over the course of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment, an oligoprogressive pattern is seen in 15–47% of all patients [20–22]. OPD is less common under immune checkpoint inhibitor (ICI) treatment when compared to TKI treatment, with an approximate incidence of 20% [23]. The initial state of disseminated or polymetastatic disease is what sets apart the concept of induced OPD from the better-established concept of oligometastatic disease (OMD). A European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus report recently defined the scope of OMD and distinguished the state of induced OPD (discussed within this review) from metachronous oligoprogression [24]. The latter was defined by new appearance of oligometastases >6 months after systemic treatment for a non-metastatic disease and its treatment goes beyond the scope of this review [24]. The concept of induced OPD is supported by multiple studies that assessed the genetic evolution of tumours at sites of localised progression by re-biopsy: once treatment resistance is acquired in a tumour subpopulation, this subpopulation is selected in a Darwinian manner and may systemically re-seed to cause widespread disease progression [21, 25, 26].

The development of localised treatment failure and acquired resistance to systemic treatment is believed to involve diverse mechanisms that depend on the tumour's genetic profile and the applied treatment modalities. In patients with acquired resistance to TKI treatment, a re-biopsy should thus be performed whenever possible to identify the molecular driver of resistance [27]. Under ICI treatment, different mechanisms, *e.g.* tumour-associated loss of neoantigens, expression of alternate immune checkpoints, defective interferon-receptor signalling or antigen presentation pathway, and changes in the tumour microenvironment are assumed to induce treatment resistance [28–30]. From a clinical perspective, the induced OPD setting offers the meaningful opportunity to regain short- or even long-term control of a disseminated disease by the use of local treatments [31]. The local eradication of de-differentiated subclones in this intermediate stage of disease aims to restore the status of treatment sensitivity that subsequently enables re-initiation of the previous systemic treatment [26]. In various retrospective analyses, the oligoprogressive state was associated with a favourable prognosis with significantly improved progression-free survival (PFS) and OS when compared to multi-progressive disease (defined as more than five metastases) [30, 32, 33]. Different oncogenic driver mutations result in a distinctive pattern of metastatic spread, with a higher incidence of liver and brain metastases in *EGFR*-mutant NSCLC and an increased risk of liver, pleural and pericardial metastases in anaplastic lymphoma kinase (*ALK*)-mutant NSCLC [26, 34, 35]. Nevertheless, the most common site of treatment failure remains the lung itself [26, 34].

Currently, there is very limited evidence to guide local salvage therapies and systemic treatment decisions for induced OPD. And while several prospective phase 2 and 3 trials, including local, systemic and combined approaches, are ongoing (ClinicalTrials.gov: NCT03256981, NCT04405401, NCT04892953, NCT04549428, NCT04767009, NCT02759835, NCT03410043), the recommendations discussed here are based primarily on low-quality evidence and expert opinions.

Systemic treatment for induced OPD

In patients under TKI treatment presenting with OPD in the follow-up, the options are either to switch to a next-generation TKI (*e.g.* osimertinib after first-line erlotinib or afatinib after first-line gefitinib) or to continue the established treatment beyond radiological progression until clinical progression occurs [26]. If no further targeted treatment option is available, a switch to conventional chemotherapy can be performed. However, the termination of TKI treatment in oncogene-addicted NSCLC may result in a rapid disease flare and hyperprogression within a short time after discontinuation [36]. In addition, each change in treatment means that further treatment options become more and more limited and, based on current data, an established TKI treatment should be continued beyond radiological progression [26]. The results of the ASPIRATION phase 2 study confirm that a continuation of erlotinib despite radiological progression is feasible and associated with a potential improvement in OS [37]. However, in contrast, the IMPRESS phase 3 study assessed the efficacy of continuing gefitinib with platinum-based chemotherapy for gefitinib-resistant NSCLC and did not find significantly prolonged PFS when compared to platinum-based chemotherapy alone [38]. Unfortunately, there are currently no robust clinical data about the management of OPD after ICI therapy. However, there are several ongoing clinical phase 2 studies that evaluate a

continuation of ICI beyond progression (UMIN-CTR: UMIN000041778; ClinicalTrials.gov: NCT04767009) or an ICI switch to atezolizumab (ClinicalTrials.gov: NCT04549428) in combination with local treatment. Considering the remaining uncertainty about the ideal time for a treatment switch, the decision about continuing an established treatment should always be discussed individually by a multidisciplinary tumour board.

Local therapy for induced OPD

While there are a few prospective trials assessing the application of local treatment options in oncogene-addicted NSCLC and induced OPD, there are currently no prospective data evaluating the addition of local treatments in patients with non-oncogene-addicted NSCLC under ICI [39, 40]. Based on the available evidence, the current guidelines of the European Society of Medical Oncology (ESMO), as well as the current guidelines of the National Comprehensive Cancer Network, suggest LAT to the oligoprogressive sites as a reasonable treatment option that may extend the duration of benefit of the current line of systemic therapy [39–41]. However, due to the lack of evidence there are no specific recommendations concerning the modality of LAT (surgery *versus* radiotherapy) [39–41].

Surgical treatment

In a selected group of patients with either induced OPD or residual disease after first-line systemic treatment, surgical resection within a salvage concept is under evaluation as an additional treatment option. Currently, clinical data on the outcome of this approach are scarce and candidate selection remains a central challenge. In case of OPD at the site of the primary tumour and especially after ICI treatment or in patients with central tumours, hilar dissection may be complicated and extended resections including sleeve-resections or intrapericardial resections are common. Prospective, randomised trials are thus necessary to evaluate the benefit of this approach. At the University Hospital Zurich (Switzerland), the salVage trial, an investigator-initiated randomised phase 3 trial comparing maintenance with the addition of LAT in stage IV NSCLC and induced oligopersistence after standard-of-care first-line systemic treatment, started recruiting in February 2024 (ClinicalTrials.gov: NCT06114108). The trial features two co-primary end-points in a predefined hierarchy, first PFS and second quality of life as measured by patient-reported outcome measures.

Radiotherapy

The use of SBRT in induced OPD is supported by several retrospective cohort analyses. Qiu *et al*. [42] report a retrospective series of 46 patients with oligoprogressive *EGFR*-mutant NSCLC under TKI treatment who underwent LAT (radiotherapy in 44 patients, radiofrequency ablation of lung metastases in two patients). All patients continued the established TKI treatment and median PFS and OS were 7.0 and 13.0 months, respectively. Grade 3 pneumonitis was encountered in two patients (4.3%). A retrospective analysis by Rossi *et al*. [20] reported on 13 patients with induced OPD during first-line afatinib or gefitinib. LAT was performed by SBRT and TKI treatment was continued in 30 patients. Median OS was longer in the group receiving LAT compared to patients who continued TKI beyond progression without LAT (37.3 months *versus* 20.1 months, $p<0.001$) [20].

To date, there is evidence on local therapy for induced OPD from four prospective phase 2 or 3 trials (table 1). In the multi-institutional phase 2 trial by Iyengar *et al*. [43], 24 patients with OPD NSCLC under conventional chemotherapy received SBRT and concurrent erlotinib. Notably, none of the tumours tested harboured an *EGFR* mutation. With a median PFS of 14.7 months, and median OS of 20.4 months, the survival was longer than historical values for patients who received systemic agents only [43]. Kim *et al*. [44] conducted a single-arm phase 2 trial in oligoprogressive *EGFR*-mutant NSCLC in the era of osimertinib. All 24 patients received LAT by different modalities, including SBRT and/or surgery, and osimertinib was continued beyond progression. PFS was 11.2 months, and ever longer in a cohort of T790M-positive cases (15.8 months) [44]. Another phase 2 study on oligoprogressive *EGFR*-mutant NSCLC was conducted by Weiss *et al*. [45]. Patients who showed OPD under treatment with erlotinib underwent LAT by SBRT and osimertinib was continued beyond progression. After SBRT, the median PFS was 6 months. Owing to poor accrual with upcoming third-generation TKI alternatives, the trial was closed early [45]. An interim analysis of the only randomised trial in OPD to date, the CURB trial, showed a significantly longer PFS in the cohort of NSCLC patients treated by SBRT (median PFS of 44 weeks *versus* 9 weeks with standard of care) [46]. Unfortunately, the interim analysis does not provide insights into the administered systemic treatment that may fundamentally influence the outcome. In the population of induced OPD, there are currently several trials underway that assess different LAT approaches, such as the randomised NORTHSTAR (ClinicalTrials.gov: NCT03410043) and HALT (ClinicalTrials.gov: NCT03256981) trials. In general, when planning SBRT in patients under TKI treatment, the risk for flare-up of the disease when stopping the TKI should be balanced against the risk of toxicity. And last but

https://doi.org/10.1183/16000617.0200-2023

TABLE 1 Clinical phase 2 and 3 trials on induced oligoprogression in NSCLC

First author [ref.], year	Trial	Subjects (n)	Cohort	OPD definition	New systemic treatment	New local therapy	Primary end-point	Outcome	Additional findings
Iyengar [43], 2014	Single-arm phase 2	24	Unselected patients with stage IV NSCLC and oligoprogression under first-line systemic chemotherapy	⩽6 lesions (extracranial)	Erlotinib	SBRT	PFS (6 months)	Median PFS: 14.7 months Median OS: 20.4 months	New distant sites were the most common sites of progression
Kim (abstract) [44], 2018	Single-arm phase 2	24	Stage IV *EGFR*-mutated NSCLC and oligoprogression	⩽5 lesions	(Re-)initiate osimertinib	Surgery, RT	PFS PFS at second progression	Median PFS: 11.2 months for patients on first-line TKI 15.8 months for T790M-positive patients	Resistance mechanisms: *MET* amplification, *EGFR* C797S mutation, *EGFR* amplification, transformation to SCLC
Weiss [45], 2019	Single-arm phase 2	25	Stage IV *EGFR*-mutated NSCLC and oligoprogression under erlotinib	⩽3 lesions (extracranial)	Reinitiate erlotinib	SBRT	PFS	Median PFS: 6 months Median OS: 29 months	The serum proteomic signature VeriStrat did not predict PFS Study closed early due to poor accrual
Tsai *et al.* (abstract, interim analysis) [46], 2021	Randomised phase 2	58 NSCLC 44 breast cancer	Stage IV NSCLC or breast cancer and oligoprogression after ⩾1 line of systemic therapy	⩽5 lesions	SBRT to all progressive sites plus SOC *versus* palliative SOC only		PFS	NSCLC: median PFS 44 weeks (SBRT) *versus* 9 weeks (no SBRT)	55% had received immmunotherapy 86% of all NSCLC had no actionable aberrations No difference in median PFS in the breast cancer cohort

NSCLC: non-small cell lung cancer; OPD: oligoprogressive disease; SBRT: stereotactic body radiation therapy; PFS: progression-free survival; OS: overall survival; *EGFR*: epidermal growth factor receptor; RT: radiation therapy; *MET*: MET proto-oncogene; SCLC: small cell lung cancer; SOC: standard of care; TKI: tyrosine kinase inhibitor.

not least, prognostic factors in the setting of advanced malignancies such as fat-free mass index or handgrip strength can provide help in the decision-making process for LAT [47].

Conclusion

Currently, the knowledge gaps in the definition and treatment of OMD and OPD do not allow clinical decisions to be based on high-level evidence. In view of the many uncertainties, minimally invasive surgery and/or SBRT to moderate doses are reasonable options as LAT in OPD. Cases of induced OPD should be discussed by a multidisciplinary tumour board to find a personalised treatment approach. In parallel, the currently ongoing clinical trials on different LAT approaches will help to guide treatment decisions in the future. Finally, in the population of OPD with extensively pretreated patients, quality-of-life considerations should play a central role in the multidisciplinary decision-making.

Oligorecurrence

Summary

Another subgroup of OMD is oligorecurrence, marked by a disease-free interval (DFI) of ⩾6 months and a controlled primary lesion. This subgroup comprises patients with markedly superior survival in comparison to synchronous OMD. While evidence strongly suggests the application of LAT to all metastatic sites, the treatment modality is still subject of ongoing discussions and thus far both surgery and SBRT, and potentially microwave ablation therapy, appear to be suitable therapeutic approaches.

Definition

Oligorecurrent NSCLC is a distinct clinical entity, limited to metastatic sites suited for localised treatment. Oligorecurrence and OMD share similarities, both describing a state of limited distant relapse confined to specific locations (figure 4) [48]. However, oligorecurrence differs by having a controlled primary lesion [48, 49]. This classification stems from the prognostic significance of the primary lesion's status, creating a favourable OMD subgroup [50]. Subsequently, patients with oligorecurrence exhibit better prognosis compared to synchronous oligometastatic or poly-recurrent cases [48, 51–53]. For instance, He *et al*. [54] observed a significant difference in OS, with oligorecurrent NSCLC patients experiencing an OS of 41.5 months compared to 21 months for sync-oligometastases. Similar results emerged from a larger study by Yamashita *et al*. [53], reporting median OS of 66.6 months for oligorecurrence and 23.9 months for sync-oligometastases across various primary tumours, including NSCLC, colorectal cancers, head and neck

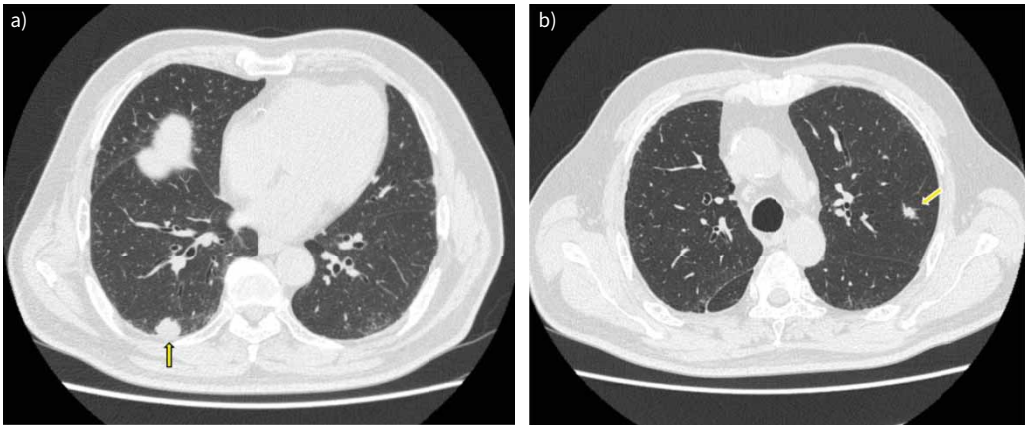

FIGURE 4 Computed tomography (CT) in a 73-year-old male patient revealed a 19 mm pulmonary nodule in the right lower lobe (a, yellow arrow). A video-assisted thoracoscopic surgery (VATS) right lower lobectomy was performed, and histological analysis revealed an adenosquamous carcinoma staged pT2a pN0. An R0 resection was achieved, the programmed cell death ligand-1 (PD-L1) status was negative (<1%) and no targetable mutation was present. Adjuvant therapy with tegafur/uracil followed. After 18 months, a 7 mm nodule was detected in the left upper lobe (b, yellow arrow), initially visible as a small nodule 6 months postoperatively. Both systemic therapies (chemotherapy, immunotherapy and tyrosine kinase inhibitors) and local ablative therapies (surgical resection, stereotactic body radiation therapy and radiofrequency ablation) were discussed. A VATS wedge resection was performed and histology confirmed squamous cell carcinoma without a driver mutation, suggestive of metastasis. The nodule measured 11 mm, and surgical margins were negative. Remarkably, even 2 years and 6 months after the oligo-metastasectomy, the patient remains disease-free. The patient was treated at Kyoto University Hospital.

cancers, uterine cancers and others. It is common to differentiate synchronous from metachronous disease based on a DFI of 6 months [54, 55]. This differentiation is pivotal to discern between progression and true recurrence. Similar to OMD, the absence of a clear consensus on the definition of oligorecurrent NSCLC limits the comparison of outcomes from literature and the formation of treatment guidance. Therefore, establishing a uniform definition is crucial. While most authors have used three metastatic lesions as the threshold for oligorecurrence [51, 56], Sonoda *et al.* [57] proposed two metastatic lesions as the preferred threshold, given the notably better prognosis for one to two recurrences compared to three or more. In the context of oligorecurrence, it is important to mention that metachronous disease should be defined as a DFI of a minimum of 6 months [53]. The topic of oligorecurrence assumes high relevance, because with advances in postoperative surveillance tools an increasing number of patients is being detected with limited recurrence [58]. For instance, Zhang *et al.* [59] reported 60% of locally advanced NSCLC cases with disease progression displaying oligorecurrence. In summary, based on current evidence and expert opinions, we suggest defining oligorecurrence as one to three metachronous metastases in one organ, with a DFI >6 months, that can be treated by LAT, with the condition of a controlled primary lesion [24, 51, 52, 56, 60].

LAT for oligorecurrent NSCLC

LAT has gained significant attention owing to their potential benefits on post-recurrence PFS and even OS [52, 54, 58–61]. However, despite several retrospective analyses suggesting an improvement in OS with LAT, its direct correlation has not yet been proven [61]. Research by Sonoda *et al.* [62] illustrated a significantly higher 5-year post-recurrence survival (PRS) rate of 55.6% for patients undergoing LAT *versus* 31.1% without, underlining LAT's efficacy. Although some prospective trials exist for OMD, evidence for oligorecurrence mainly relies on retrospective studies, demonstrating the need for more prospective trials (table 2) [51, 52, 60, 66]. A recent prospective observational study by Yano *et al.* [51] included 17 postoperative oligorecurrent NSCLC cases. Their findings aligned with prior retrospective research, indicating that LAT should be considered for managing oligorecurrence.

The choice of treatment modality for oligorecurrent NSCLC remains a subject of ongoing discussion and may vary based on the metastatic site and patient factors. In a retrospective study with 97 patients with oligorecurrent pulmonary NSCLC, surgical resection trended towards improved 5-year PRS and post-recurrence PFS compared to radiation therapy, although this was not statistically significant [62]. Additionally, significantly longer PRS for surgical resection has been reported when compared to nonoperative therapy with a similar cohort [54, 67].

Surgical treatment

Surgical resection offers the advantage of providing tissue samples for analysis, which is vital for distinguishing pulmonary oligorecurrence from secondary tumours [10, 68]. In a retrospective study involving a small cohort of 11 patients, He *et al.* [54] demonstrated a significantly longer OS and 5-year survival for patients with oligorecurrent pulmonary NSCLC who received combined surgical treatment and chemotherapy, compared to those who underwent chemotherapy alone. Additionally, the study findings supported the notion that pulmonary wedge resection and segmentectomy should be considered the preferred surgical approaches. Conversely, the authors cautioned against the use of lobectomy owing to its relatively higher operation risk and greater trauma [54]. This aligns with results from Aoki *et al.* [55], which indicated a better prognosis for patients who underwent sublobar resection instead of lobectomy or pneumonectomy. However, secondary surgery for oligorecurrent lesions in the chest may be challenging because of anatomical changes, higher complication rates and patient surgery-fatigue [58]. Furthermore, some patients may not be eligible for surgery owing to poor general condition or limited respiratory function [62]. In such cases, local radiotherapy with or without chemotherapy is an alternative treatment option [58]. Regarding surgical treatment for metastatic sites other than the lung in the oligorecurrent setting, studies have reported favourable outcomes for both adrenalectomy and intracranial metastasectomy [69–71].

Radiotherapy

Radiation therapy presents the advantage of being a viable treatment option for patients with compromised general health and limited lung function. However, it also carries the risk of potential side effects, such as radiation-induced lung injury in case of thoracic radiation [62]. Nevertheless, SBRT has exhibited promising efficacy and excellent tolerance in patients with intrathoracic oligorecurrence of NSCLC [53, 55, 62]. Furthermore, SBRT has also proven to be suitable for treating adrenal and intracranial metastases [69, 72]. In a study conducted by Sonoda *et al.* [62], no significant PSR difference was observed between surgical resection and radiation therapy, highlighting the importance of individualised treatment decisions. Concerning the outcome analysis after SBRT, it is hypothesised that there is a higher occurrence of

TABLE 2 Retrospective and prospective analyses of oligorecurrence in NSCLC

First author [ref.], year	Trial	Subjects (n)	Median follow-up (months)	Cohort	Oligorecurrence definition	LAT modalities	Primary end-point	Outcome	Additional findings
Ni [63], 2021	Retrospective	103	31.8	NSCLC patients with pulmonary oligorecurrence after previous radical surgical resection	Pulmonary oligorecurrence: ⩽5 local or metastatic nodules after surgical resection confined only to the lung (both ipsilaterally and contralaterally)	Microwave ablation	PFS	Median PFS: 15.1 months Median OS: 40.6 months	Local recurrence and intrathoracic oligorecurrence were not significant predictors for OS; however, distant metastasis was predictive of OS
Hishida [52], 2015	Retrospective	162	116.8	Resected NSCLC stage IA–IIIB with recurrence	⩽3 loco-regional or distant recurrent lesions in a single organ	Surgery, SBRT, radiotherapy ⩾45 Gy	PRS PFS	5-year PRS and postoperative PFS rates after DLT: 38.6% and 22.3% 5-year PRS: 32.9% for oligorecurrence *versus* 9.9% for polyrecurrence	Initial DLT was associated with improved PRS (OR 0.44) Recurrence location and initial pathological stage did not affect PRS
Yuan [58], 2020	Retrospective	56	60	Stage I–IIIA NSCLC with thoracic oligorecurrences	Thoracic oligorecurrence: ⩽3 loco-regional confined to lung lobe, hilar/ mediastinal lymph nodes, bronchial stump or chest wall	Surgery, SBRT, radiotherapy ⩾45 Gy, proton radiation therapy	PRS PR-PFS	Median PRS: 31 months Median PR-PFS: 17 months	Time to recurrence ⩾12 months was associated with improved PRS (OR 0.74), and regional lymph node oligorecurrence was associated with poor PRS (OR 1.48)
Sonoda [57], 2022	Retrospective	577	43	NSCLC after complete resection with recurrence	⩽2 recurrences	Surgery, gamma knife, SBRT, radiotherapy ⩾45 Gy, proton beam therapy, radiofrequency ablation, cryotherapy	PRS	Median PRS: 20 months 5-year PRS rate was 33.6% for patients with 1–2 recurrences and 7.1% for those with ⩾3 recurrences	Sex (female), histological type (adenocarcinoma), gene mutation status, recurrence-free interval <1 year and presence of 1–2 recurrences were factors associated with prolonged PRS
Sonoda [62], 2021	Retrospective	97	60	NSCLC after complete resection with recurrence	⩽5 metachronous recurrences limited to the lungs only	Surgery, radiatiotherapy	PRS PR-PFS	5-year PRS rates: 55.6% in patients who underwent LAT *versus* 31.1% for those who did not 5-year PRS rates: 61.5% following resection *versus* 47.6% following radiotherapy 5-year PR-PFS: 30.3% following resection *versus* 24.7% following radiotherapy	

Continued

https://doi.org/10.1183/16000617.0200-2023

TABLE 2 Continued

First author [ref.], year	Trial	Subjects (n)	Median follow-up (months)	Cohort	Oligorecurrence definition	LAT modalities	Primary end-point	Outcome	Additional findings
Zhang [59], 2023	Retrospective	153	26	Stage III NSCLC after radiotherapy	⩽3 extracranial organs and ⩽5 extracranial lesions	Radiotherapy	PFS OS	Median PFS: 11.0 months Median OS: 40.0 months	Additional TKI therapy besides definitive CRT could prolong PFS but not OS among patients with driver mutations
Lee [56], 2017	Retrospective	139	65	Unselected patients with stage I NSCLC who underwent curative resection	⩽3 lesions in one organ	Surgery, SBRT, photodynamic therapy, other radiotherapy	PRS	3-year PRS: 49.1% 5-year PRS: 33.8%	Age at recurrence, adenocarcinoma cell type, disease-free interval, EGFR-TKI treatment and potentially curative local treatment were independent prognostic factors for survival
Matsuguma [60], 2020	Retrospective	406	84	Patients who underwent complete anatomic lung resection for NSCLC that developed recurrence	<3 recurrent foci	Surgery, radiotherapy of ⩾45 Gy, SBRT	PR-OS PR-PFS	5-year PR-OS: 14.0% 5-year PR-PFS: 5.9%	Female sex, longer disease-free interval, specific targeted therapy, recent recurrence, oligorecurrence and DLT were found to be independent favourable prognostic factors for both PR-OS and PR-PFS Recent recurrence, oligorecurrence and DLT were associated with improvement in both the median PR-PFS time and 5-year PR-PFS rate
Aoki [55], 2020	Retrospective	52	25	Patients with NSCLC recurrence that was treated with SBRT, and who previously underwent curative surgical resection	Limited number of recurrent lesions and controlled primary lesions	SBRT	OS PFS Local control Toxicity	Median OS following salvage SBRT: 32 months 1-year PFS rate: 80.8% 3-year PFS rate: 58.7% Median LC: 71 months 1- and 3-year LC rates: 97.9% and 94.9%	Central tumour location and the possibility of reoperation were independent prognostic factors for OS 4 patients experienced grade 3 or higher AEs and two experienced grade 5 AEs (pneumonitis and haemoptysis)

Continued

https://doi.org/10.1183/16000617.0200-2023

TABLE 2 Continued

First author [ref.], year	Trial	Subjects (n)	Median follow-up (months)	Cohort	Oligorecurrence definition	LAT modalities	Primary end-point	Outcome	Additional findings
Jin [61], 2022	Retrospective	81	65.8	NSCLC stage I–III patients who had extracranial single-organ oligorecurrence after receiving radical treatment	Oligometastatic disease characterised by well-controlled primary lesion	SBRT, surgery, radiotherapy ⩾50 Gy, microwave ablation, seed implantation	PFS	Median PFS: 16.2 months for no DLT *versus* 16.0 months for the DLT group Median OS rate was 36.3 months for no DLT *versus* 30.8 months for the DLT group	In the subgroup without specific TKI therapy, the PFS of patients receiving DLT was significantly superior, but there was no significant difference in OS
Sonoda [64], 2023	Retrospective	34	58	Completely resected *EGFR*-mutated NSCLC stage IA–IIIB with oligorecurrence	⩽2 metachronous recurrences	Surgery, SBRT, stereotactic radiosurgery, gamma knife, other curative irradiation, proton beam therapy	PRS	5-year PRS rates: 59.4% for *EGFR*-mutated oligorecurrence with radical local therapy *versus* 45.5% without radical local therapy 5-year PRS rates: 39.3% in patients with no or unknown *EGFR* mutations who received radical local therapy *versus* 15.7% for those who did not receive radical local therapy	
Kim [65], 2022	Retrospective	71	41.2	NSCLC stage I–IIIC without oncogenic driver mutations with metachronous brain-only oligorecurrence who received LAT	⩽5 metastatic or recurrent lesions with controlled primary lesions, DFI ⩾6 months	Surgery, SBRT, whole-brain radiation therapy	OS PFS	Median OS: 38.9 months Median PFS: 25.5 months	ECOG ⩾1 was associated with poor survival No significant difference in OS between patients with local therapy and those with local plus systemic therapy (18.5 months *versus* 34.7 months)
Yano [51], 2013	Prospective	13	48	Completely resected NSCLC with postoperative recurrence, excluding second primary lung cancer	⩽3 metastases	Surgery, radiotherapy	PFS	Median PFS: 20 months for patients who received LAT *versus* 5 and 15 months for two patients receiving chemotherapy only	

NSCLC: non-small cell lung cancer; LAT: local ablative therapy; PFS: progression-free survival; OS: overall survival; SBRT: stereotactic body radiation therapy; PRS: post-recurrence survival; DLT: definitive local therapy; PR-OS: post-recurrence overall survival; PR-PFS: post-recurrence progression-free survival; TKI: tyrosine kinase inhibitor; CRT: chemoradiotherapy; *EGFR*: epidermal growth factor receptor; LC: lung cancer; AE: adverse event; DFI: disease-free interval; ECOG: Eastern Cooperative Oncology Group.

non-cancer-related deaths due to the allocation of mainly inoperable patients with significant comorbidities to this treatment option. However, there has been limited direct comparison between SBRT and surgery up to this point and conducting prospective trials could offer valuable insights.

Microwave ablation therapy

Another promising option for inoperable patients is microwave ablation, which has shown notable efficacy and safety even for repeated therapy in case of re-recurrence. Ni *et al*. [63] reported a median OS of 40.6 months for pulmonary oligorecurrences treated with microwave ablation and 1-, 3- and 5-year survival rates of 97.1%, 58.7% and 34.3%, respectively. Complications were generally mild, with pneumothorax being most frequent. However, microwave ablation procedures exclude lesions located adjacent to major vessels or in central areas due to the elevated risk of pulmonary puncture and subsequent post-ablation complications [63].

LAT in the setting of positive driver mutation status

Because primary tumour management in NSCLC usually involves surgery, programmed cell death ligand-1 status and gene mutations are available for most cases. This holds especially true for recent times, because the increased adoption of lung cancer screening leads to the identification of more cases at early stages [58], for which upfront surgical resection is the preferred therapeutic approach [73]. While the addition of conventional chemotherapy to LAT showed no clear benefits within the context of oligorecurrence [58], attention should shift to immunotherapies and targeted treatments. The question arises whether LAT should be pursued for oligorecurrence in the case of a present driver gene mutation. Jin *et al*. [61] observed that clinicians are more inclined to perform LAT when there is no targetable driver gene mutation. Given the positive impact of LAT and TKIs on PFS [59, 60], their combined use holds promise as an optimal approach for individuals harbouring targetable mutations [56, 61]. However, a study by Sonoda *et al*. [64] showed no significant PRS difference between *EGFR*-mutated NSCLC patients with or without LAT in addition to TKI treatment and postulated that this absence of significant difference in PRS might be due to the effectiveness of EGFR TKIs in *EGFR*-mutated NSCLC.

Conversely, Matsuguma *et al*. [60] emphasised prioritising LAT over targeted therapy in $EGFR^+$ NSCLC oligorecurrence. They argued that while TKIs show potential, relying solely on them may not ensure stable PFS, often resulting in recurrence within 1–2 years [56, 60]. Furthermore, the ESMO expert consensus for $EGFR^+$ NSCLC, published in 2022, states that for oligorecurrence that occurs during adjuvant osimertinib treatment, LAT should be considered [74].

Patient selection for LAT

The number of metastases, DFI, lymph node involvement and gene mutation status all play pivotal roles in determining the most appropriate therapeutic approach [58, 60, 64]. A significant determinant of patient selection is the DFI, reflecting time between treatment and recurrence [52, 60]. Studies have indicated that a DFI of $\geqslant$12 months is associated with improved PRS [58], highlighting that patients with longer intervals have better treatment responses and prolonged survival rates. Lymph node involvement emerges as another essential factor, with regional lymph node oligorecurrence having been linked to poor PRS [52, 58]. Conversely, a lower initial TNM stage signifies better survival and prognosis [54, 56]. This emphasises the importance of thoroughly assessing lymph node status and TNM stage, including positron emission tomography-CT (PET-CT) and cranial magnetic resonance tomography (MRT). If PET-CT or MRT are not available, though we strongly advise them, we recommend relying on CT scans for staging as a second choice. Furthermore, metastasis count and location matters. Notably, patients with solitary pulmonary oligorecurrence have demonstrated the best survival outcomes [58]. However, as mentioned earlier in the text, it is crucial to exercise caution because second primary tumours are often mistakenly interpreted as pulmonary metastases [10, 68]. Concerning this topic, we refer to Shao *et al*. [68], who proposed a comprehensive algorithm to distinguish between synchronous primary lung cancers and intrapulmonary metastases, and Liu *et al*. [10], who provided insights into the possible diagnostic value of genomic profiling in this context. Generally, patient selection is of great importance, because the patient population with oligorecurrent NSCLC is still highly heterogeneous, with different prognoses for different recurrence sites [58].

Conclusion

LAT has shown considerable potential in the management of oligorecurrent NSCLC. Distinguishing between intrapulmonary metastases and second primary tumours is imperative in the setting of oligorecurrent pulmonary NSCLC to deduct meaningful conclusions from survival analyses. Further research is needed to elucidate the most appropriate treatment modality and patient selection criteria,

especially concerning the interactions between LAT, TKIs and immunotherapies. Future studies should be designed as prospective multi-institutional trials.

Conclusion: complex situations in lung cancer

The implementation of lung cancer screening programmes and the advances in systemic and multimodal treatment options are increasing the complexity of lung cancer treatment. In parallel, the growing knowledge and continued research on genetic cancer characteristics, tumour microenvironment, cancer evolution and development of resistance helps us to elucidate these complex situations and develop treatment recommendations to guide multidisciplinary tumour board decisions. Regarding multifocal disease, understanding lineage connections between lesions is essential for treatment decisions, because this relationship distinguishes independent early-stage tumours from locally advanced or metastatic cancer. Each of the four patterns of multifocal disease described by the IASLC lung cancer staging project require a distinct approach to staging and treatment. Based on the limited evidence on induced OPD, LAT by surgery and/or radiotherapy is a promising approach and quality-of-life considerations should be incorporated into personalised treatment decisions. In parallel, a continuation of systemic treatment beyond progression is often recommended because it preserves further treatment options. While LAT to all recurrent sites has shown promising potential in oligorecurrent NSCLC, patient selection and the choice of treatment modality remain to be assessed in future trials.

Questions for future research

Regarding complex situations in lung cancer, there are many knowledge gaps remaining to date. In multifocal disease, the mechanisms of tumorigenesis for multifocal lung adenocarcinoma need to be further investigated in future research projects to identify common driver aberrations and potential systemic targets. In OMD, including oligoprogression and oligorecurrence, a common definition is still missing; standardised protocols and selection criteria based on prognostic scores are essential to define a uniform treatment approach and to guide multidisciplinary tumour boards. In general, in-depth analyses of matched tissue samples from multifocal or metastatic disease may help improve our understanding of tumour evolution and identify biological characteristics that may determine treatment decisions.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: R. Werner reports advisory board participation from BMS. N. Steinmann has nothing to disclose. H. Decaluwe reports consulting fees from Intuitive Proctor. H. Date reports lecture honoraria from Johnson and Johnson. D. De Ruysscher reports grants and advisory board membership from AstraZeneca, BMS, Beigene, Philips, Olink and Eli-Lilly. I. Opitz reports grants from Roche and Medtronic; consulting fees from Intuitive; lecture honoraria from Roche and AstraZeneca; and advisory board participation from AstraZeneca, MSD, BMS and Medtronic.

References

1 Zhou Y, Xiang Z, Lin W, *et al*. Long-term trends of lung cancer incidence and survival in southeastern China, 2011–2020: a population-based study. *BMC Pulm Med* 2024; 24: 209.
2 Walter JE, Heuvelmans MA, Yousaf-Khan U, *et al.* New subsolid pulmonary nodules in lung cancer screening: the NELSON trial. *J Thorac Oncol* 2018; 13: 1410–1414.
3 Roden AC, Mansfield AS. Multifocal pulmonary adenocarcinoma with ground-glass/lepidic features-exciting times as the mystery is unfolding. *J Thorac Oncol* 2018; 13: 1616–1618.
4 Detterbeck FC, Nicholson AG, Franklin WA, *et al.* The IASLC lung cancer staging project: summary of proposals for revisions of the classification of lung cancers with multiple pulmonary sites of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol* 2016; 11: 639–650.
5 Detterbeck FC, Marom EM, Arenberg DA, *et al.* The IASLC lung cancer staging project: background data and proposals for the application of TNM staging rules to lung cancer presenting as multiple nodules with ground glass or lepidic features or a pneumonic type of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol* 2016; 11: 666–680.
6 Detterbeck FC, Franklin WA, Nicholson AG, *et al.* The IASLC lung cancer staging project: background data and proposed criteria to distinguish separate primary lung cancers from metastatic foci in patients with two lung tumors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11: 651–665.
7 Detterbeck FC, Bolejack V, Arenberg DA, *et al.* The IASLC lung cancer staging project: background data and proposals for the classification of lung cancer with separate tumor nodules in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11: 681–692.
8 Martini N, Melamed MR. Multiple primary lung cancers. *J Thorac Cardiovasc Surg* 1975; 70: 606–612.

9 Shen KR, Meyers BF, Larner JM, *et al.* Special treatment issues in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; 132: Suppl. 3, 290S–305S.

10 Liu Y, Zhang J, Li L, *et al.* Genomic heterogeneity of multiple synchronous lung cancer. *Nat Commun* 2016; 7: 13200.

11 Goldstraw P, Chansky K, Crowley J, *et al.* The IASLC Lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11: 39–51.

12 Park E, Ahn S, Kim H, *et al.* Targeted sequencing analysis of pulmonary adenocarcinoma with multiple synchronous ground-glass/lepidic nodules. *J Thorac Oncol* 2018; 13: 1776–1783.

13 American College of Radiology. Lung-RADS v2022. 2022. Available from www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/Lung-RADS-2022.pdf Date last accessed: 10 October 2023.

14 Ettinger DS, Wood DE, Aisner DL, *et al.* NCCN guidelines insights: non-small cell lung cancer, version 2.2023. *J Natl Compr Canc Netw* 2023; 21: 340–350.

15 Suzuki K. Whack-a-mole strategy for multifocal ground glass opacities of the lung. *J Thorac Dis* 2017; 9: Suppl. 3, S201–S207.

16 Chen C, Huang X, Peng M, *et al.* Multiple primary lung cancer: a rising challenge. *J Thorac Dis* 2019; 11: Suppl. 4, S523–S536.

17 Wislez M, Massiani MA, Milleron B, *et al.* Clinical characteristics of pneumonic-type adenocarcinoma of the lung. *Chest* 2003; 123: 1868–1877.

18 de Perrot M, Chernenko S, Waddell TK, *et al.* Role of lung transplantation in the treatment of bronchogenic carcinomas for patients with end-stage pulmonary disease. *J Clin Oncol* 2004; 22: 4351–4356.

19 Schoenfeld AJ, Hellmann MD. Acquired resistance to immune checkpoint inhibitors. *Cancer Cell* 2020; 37: 443–455.

20 Rossi S, Finocchiaro G, Di Noia V, *et al.* Survival outcome of tyrosine kinase inhibitors beyond progression in association to radiotherapy in oligoprogressive EGFR-mutant non-small-cell lung cancer. *Future Oncol* 2019; 15: 3775–3782.

21 Doebele RC, Pilling AB, Aisner DL, *et al.* Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin Cancer Res* 2012; 18: 1472–1482.

22 Yoshida T, Yoh K, Niho S, *et al.* RECIST progression patterns during EGFR tyrosine kinase inhibitor treatment of advanced non-small cell lung cancer patients harboring an EGFR mutation. *Lung Cancer* 2015; 90: 477–483.

23 Harada D, Takigawa N. Oligoprogression in non-small cell lung cancer. *Cancers (Basel)* 2021; 13: 5823.

24 Guckenberger M, Lievens Y, Bouma AB, *et al.* Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol* 2020; 21: e18–e28.

25 Kuiper JL, Heideman DA, Thunnissen E, *et al.* Incidence of T790M mutation in (sequential) rebiopsies in EGFR-mutated NSCLC-patients. *Lung Cancer* 2014; 85: 19–24.

26 Basler L, Kroeze SG, Guckenberger M. SBRT for oligoprogressive oncogene addicted NSCLC. *Lung Cancer* 2017; 106: 50–57.

27 Amini A, Verma V, Simone CB, *et al.* American Radium Society appropriate use criteria for radiation therapy in oligometastatic or oligoprogressive non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2022; 112: 361–375.

28 Anagnostou V, Smith KN, Forde PM, *et al.* Evolution of neoantigen landscape during immune checkpoint blockade in non-small cell lung cancer. *Cancer Discov* 2017; 7: 264–276.

29 Gettinger S, Choi J, Hastings K, *et al.* Impaired HLA class I antigen processing and presentation as a mechanism of acquired resistance to immune checkpoint inhibitors in lung cancer. *Cancer Discov* 2017; 7: 1420–1435.

30 Heo JY, Yoo SH, Suh KJ, *et al.* Clinical pattern of failure after a durable response to immune check inhibitors in non-small cell lung cancer patients. *Sci Rep* 2021; 11: 2514.

31 Rheinheimer S, Heussel CP, Mayer P, *et al.* Oligoprogressive non-small-cell lung cancer under treatment with PD-(L)1 inhibitors. *Cancers (Basel)* 2020; 12: 1046.

32 Hosoya K, Fujimoto D, Morimoto T, *et al.* Clinical factors associated with shorter durable response, and patterns of acquired resistance to first-line pembrolizumab monotherapy in PD-L1-positive non-small-cell lung cancer patients: a retrospective multicenter study. *BMC Cancer* 2021; 21: 346.

33 Kagawa Y, Furuta H, Uemura T, *et al.* Efficacy of local therapy for oligoprogressive disease after programmed cell death 1 blockade in advanced non-small cell lung cancer. *Cancer Sci* 2020; 111: 4442–4452.

34 Doebele RC, Lu X, Sumey C, *et al.* Oncogene status predicts patterns of metastatic spread in treatment-naive nonsmall cell lung cancer. *Cancer* 2012; 118: 4502–4511.

35 Cagney DN, Martin AM, Catalano PJ, *et al.* Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *Neuro Oncol* 2017; 19: 1511–1521.

36 Chaft JE, Oxnard GR, Sima CS, *et al.* Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. *Clin Cancer Res* 2011; 17: 6298–6303.

37 Park K, Yu CJ, Kim SW, *et al.* First-line erlotinib therapy until and beyond response evaluation criteria in solid tumors progression in Asian patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer: the ASPIRATION study. *JAMA Oncol* 2016; 2: 305–312.

38 Soria JC, Wu YL, Nakagawa K, *et al.* Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. *Lancet Oncol* 2015; 16: 990–998.

39 Hendriks LE, Kerr KM, Menis J, *et al.* Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023; 34: 358–376.

40 Hendriks LE, Kerr KM, Menis J, *et al.* Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023; 34: 339–357.

41 Ettinger DS, Wood DE, Aisner DL, *et al.* Non-small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2022; 20: 497–530.

42 Qiu B, Liang Y, Li Q, *et al.* Local therapy for oligoprogressive disease in patients with advanced stage non-small-cell lung cancer harboring epidermal growth factor receptor mutation. *Clin Lung Cancer* 2017; 18: e369–e373.

43 Iyengar P, Kavanagh BD, Wardak Z, *et al.* Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. *J Clin Oncol* 2014; 32: 3824–3830.

44 Kim C, Roper N, Hoang C, *et al.* Local ablative therapy for oligoprogressive, EGFR-mutant, non-small cell lung cancer (NSCLC) after treatment with osimertinib. *J Clin Oncol* 2018; 36: abstr21080.

45 Weiss J, Kavanagh B, Deal A, *et al.* Phase II study of stereotactic radiosurgery for the treatment of patients with oligoprogression on erlotinib. *Cancer Treat Res Commun* 2019; 19: 100126.

46 Tsai C, Yang J, Guttmann D. Consolidative use of radiotherapy to block (CURB) oligoprogression: interim analysis of the first randomized study of stereotactic body radiotherapy in patients with oligoprogressive metastatic cancers of the lung and breast. *Int J Radiat Oncol Biol Phys* 2021; 111: 1325–1326.

47 Burtin C, Bezuidenhout J, Sanders KJC, *et al.* Handgrip weakness, low fat-free mass, and overall survival in non-small cell lung cancer treated with curative-intent radiotherapy. *J Cachexia Sarcopenia Muscle* 2020; 11: 424–431.

48 Niibe Y, Hayakawa K. Oligometastases and oligo-recurrence: the new era of cancer therapy. *Jpn J Clin Oncol* 2010; 40: 107–111.

49 Niibe Y, Chang JY. Novel insights of oligometastases and oligo-recurrence and review of the literature. *Pulm Med* 2012; 2012: 261096.

50 Niibe Y, Nishimura T, Inoue T, *et al.* Oligo-recurrence predicts favorable prognosis of brain-only oligometastases in patients with non-small cell lung cancer treated with stereotactic radiosurgery or stereotactic radiotherapy: a multi-institutional study of 61 subjects. *BMC Cancer* 2016; 16: 659.

51 Yano T, Okamoto T, Haro A, *et al.* Local treatment of oligometastatic recurrence in patients with resected non-small cell lung cancer. *Lung Cancer* 2013; 82: 431–435.

52 Hishida T, Yoshida J, Aokage K, *et al.* Postoperative oligo-recurrence of non-small-cell lung cancer: clinical features and survival. *Eur J Cardiothorac Surg* 2016; 49: 847–853.

53 Yamashita H, Niibe Y, Yamamoto T, *et al.* Lung stereotactic radiotherapy for oligometastases: comparison of oligo-recurrence and sync-oligometastases. *Jpn J Clin Oncol* 2016; 46: 687–691.

54 He J, Li Y, An J, *et al.* Surgical treatment in non-small cell lung cancer with pulmonary oligometastasis. *World J Surg Oncol* 2017; 15: 36.

55 Aoki S, Yamashita H, Takahashi W, *et al.* Salvage stereotactic body radiotherapy for post-operative oligo-recurrence of non-small cell lung cancer: a single-institution analysis of 59 patients. *Oncol Lett* 2020; 19: 2695–2704.

56 Lee K, Kim HR, Kim DK, *et al.* Post-recurrence survival analysis of stage I non-small-cell lung cancer. *Asian Cardiovasc Thorac Ann* 2017; 25: 623–629.

57 Sonoda D, Matsuura Y, Kondo Y, *et al.* A reasonable definition of oligo-recurrence in non-small-cell lung cancer. *Clin Lung Cancer* 2022; 23: 82–90.

58 Yuan Q, Wang W, Zhang Q, *et al.* Clinical features and prognostic factor of thoracic postoperative oligo-recurrence of non-small-cell lung cancer. *Cancer Manag Res* 2020; 12: 1397–1403.

59 Zhang J, Mao J, Xu D, *et al.* Pattern of failure and clinical value of local therapy for oligo-recurrence in locally advanced non-small cell lung cancer after definitive chemoradiation: Impact of driver mutation status. *Cancer Med* 2023; 12: 6971–6979.

60 Matsuguma H, Nakahara R, Wakamatsu I, *et al.* Definitive local therapy for oligo-recurrence in patients with completely resected non-small cell lung cancer. *Am J Clin Oncol* 2020; 43: 210–217.

61 Jin JN, Yue P, Hao Y, *et al.* Definitive local therapy for extracranial single-organ oligorecurrent non-small-cell lung cancer: a single institutional retrospective study. *Medicine (Baltimore)* 2022; 101: e31918.

62 Sonoda D, Matsuura Y, Kondo Y, *et al.* Comparison of local therapy in patients with lung oligo-recurrence of non-small-cell lung cancer. *J Surg Oncol* 2021; 123: 1828–1835.

63 Ni Y, Peng J, Yang X, *et al.* Multicentre study of microwave ablation for pulmonary oligorecurrence after radical resection of non-small-cell lung cancer. *Br J Cancer* 2021; 125: 672–678.

64 Sonoda D, Kondo Y, Maruyama R, *et al.* Examination of the effectiveness of local therapy for oligo-recurrence of EGFR-mutated NSCLC. *Thorac Cancer* 2023; 14: 766–772.

65 Kim H, Park S, Jung HA, *et al.* Long-term survival in non-small cell lung cancer patients with metachronous brain-only oligorecurrence who underwent definitive treatment. *Cancer Res Treat* 2022; 54: 150–156.

66 Hishida T, Nagai K, Yoshida J, *et al.* Is surgical resection indicated for a solitary non-small cell lung cancer recurrence? *J Thorac Cardiovasc Surg* 2006; 131: 838–842.

67 Han SJ, Cho S, Yum S, *et al.* Surgical treatment of pulmonary oligorecurrence after curative resection for non-small-cell lung cancer. *Interact Cardiovasc Thorac Surg* 2020; 30: 18–23.

68 Shao J, Wang C, Li J, *et al.* A comprehensive algorithm to distinguish between MPLC and IPM in multiple lung tumors patients. *Ann Transl Med* 2020; 8: 1137.

69 Sakamoto J, Sonobe M, Kobayashi M, *et al.* Prognostic factors for patients in postoperative brain metastases from surgically resected non-small cell lung cancer. *Int J Clin Oncol* 2014; 19: 50–56.

70 Mercier O, Fadel E, de Perrot M, *et al.* Surgical treatment of solitary adrenal metastasis from non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2005; 130: 136–140.

71 Gao XL, Zhang KW, Tang MB, *et al.* Pooled analysis for surgical treatment for isolated adrenal metastasis and non-small cell lung cancer. *Interact Cardiovasc Thorac Surg* 2017; 24: 1–7.

72 Casamassima F, Livi L, Masciullo S, *et al.* Stereotactic radiotherapy for adrenal gland metastases: University of Florence experience. *Int J Radiat Oncol Biol Phys* 2012; 82: 919–923.

73 Vansteenkiste J, Crinò L, Dooms C, *et al.* 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. *Ann Oncol* 2014; 25: 1462–1474.

74 Passaro A, Leighl N, Blackhall F, *et al.* ESMO expert consensus statements on the management of EGFR mutant non-small-cell lung cancer. *Ann Oncol* 2022; 33: 466–487.