**Is it too early to recommend local treatment in oligometastatic NSCLC: a plea for equipoise**

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**Abstract**

Oligometastatic Non-Small Cell Lung cancer (OMD NSCLC) has been proposed to bridge the spectrum between non-metastatic to widely metastatic states and is perceived as an opportunity for potential cure if removed. Twelve clinical trials on local treatment have been reported, yet none are conclusive. These trials informed the development of a joint clinical practice guideline (CPG) by the American & European societies for radiation oncology, which endorses local treatment for OMD NSCLC. However, the heterogeneity between and prognostic factors within these trials likely influenced outcomes and can only support guidance at this time. Caution against an uncritical acceptance of the guideline is discussed, as strong recommendations are offered based on expert opinion and inconclusive evidence. The guideline is also examined by a patient’s caregiver, who emphasizes that uncertain evidence impedes shared decision-making.

**Introduction**

Oligometastatic disease (OMD) is perceived as an opportunity to theoretically cure patients by treating all detectable metastases.1 This opportunity builds upon the inductive reasoning of colorectal metastasectomy.2 However patient selection itself (tumour type, disease-free interval and number of metastases) exerts a strong influence on survival outcomes, because criteria for minimum estimated survival time and surgical fitness were met.3

A recent clinical practice guideline (CPG) on the local treatment of OMD non-small cell lung cancer (OMD NSCLC) recommends considering local treatment using stereotactic ablative radiation therapy (SABR) or surgery.4 A clear distinction between guidance and guideline is necessary for clinicians as the terms are often used inter-changeably.5 Guidance addresses topics with insufficient high-quality evidence, often based on expert opinion/experience. Guidelines are based on a substantial body of moderate- to high-quality evidence from phase 3 clinical trials with an aim to establish standard clinical practice, and therefore avoid areas where evidence is sparse, *because* it requires invoking expert opinion.5,6

While expert opinion offers valuable perspectives, it occupies the lowest tier in the evidence pyramid. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework explicitly cautions against treating expert opinion as a form of evidence, and emphasises the evaluation of the evidence itself, not just the opinions formed from it.7 We suggest clinicians critically appraise the strength of this guideline’s recommendations based on the following assertions:

**1. Concerns about methodology and taskforce composition.**

The taskforce recommends local treatment for all OMD scenarios based on small phase 2 trials, retrospective analyses, and in some instances expert opinion alone, yet state: "Beyond other cancers, the findings from NSCLC have led the way to build towards high-quality evidence and confidence in the use of local therapies for advanced disease in the curative setting”.4 Given the level of evidence, this statement suggests *a priori* agreement that local treatments are an undisputed way of treating patients with OMD NSCLC.5 And having established the goal of resource-intensive local treatment as cure, it provides no evidence on cure rates in any OMD scenario.

These recommendations for intervention don’t align with the GRADE framework, which discourages strong recommendations based on low-quality evidence, except in the following paradigms8:

1. Recommend *for* Intervention
   1. Low-quality evidence of benefit in life-threatening situations, irrespective of harm
   2. Low-quality evidence of equivalence + high-quality evidence suggesting less harm
   3. High-quality evidence of equivalence + low-quality evidence of less harm
2. Recommend *against* Intervention
   1. Low-quality evidence of benefit + high-quality evidence suggesting harm
   2. High-quality evidence of modest benefit + low-quality evidence of catastrophic harm

A majority of taskforce members were already involved in treating OMD NSCLC, and five (including both co-chairs) have reported key evidence on which the recommendations are based.4,5 This is of concern because:

1. The CPG development literature demonstrates that group composition influences recommendations. Those performing a procedure have a lower threshold for recommending it (prior belief effect), also rate more indications as appropriate without substantial evidence (confirmation bias), and in contrast expect a higher level of evidence to deem it inappropriate (disconfirmation bias).9,10
2. An intellectual conflict of interest exists. Experts who have built their expertise by reporting key evidence on a topic, are disincentivised to generate recommendations which contradict their results.11 The inclusion of a methodologist in the taskforce could have counter-balanced this potential conflict.12

The resources available to the taskforce could have facilitated an individual patient data analysis and provided a quantitative estimate of the benefit with local treatments in OMD NSCLC.

**2. Concerns about the quality of evidence and reported end-points.**

Twelve clinical trials (8 single-arm phase II trials, 3 phase II RCTs, and one phase III RCT) have explored local treatment in OMD NSCLC (Figure 1; Table 1), but none are conclusive based on an examination of the following:

1. Was the initial distribution of metastases defined and was upfront systemic therapy delivered?
2. Were only patients responding to systemic therapy chosen and what distribution of residual metastases were actually treated?
3. Were patients selected by mutational status and CNS Involvement?

Eight trials specified initial extra-thoracic involvement, permitting up to five lesions.13–20 In the five trials that provided details, the median number of accrued lesions were ≤ 2.14,16,18–20 Low initial extra-thoracic involvement is a feature of indolent disease and predicts better outcomes.21 Two of these five trials selected patients responding to systemic treatment, thereby reducing disease burden and further improving prognosis.14,16 In fact one trial required elimination of extra-thoracic disease, demonstrating the most remarkable outcomes.16 In trials which didn’t specify initial disease distribution, the number of extra-thoracic lesions treated were one (or none) after systemic treatment, while one trial treated only the locoregional extent of disease.22–25

Within the trials there is a wide variation of OMD counts and sites which were treated (table 1). Overall, the proportion of patients with partial response or stable disease was also not reported in the majority of trials that delivered systemic treatment and selected responding patients.13,16,17,23,24 Recent trials also selected patients with EGFR mutations (*mut*EGFR), which is independently prognostic for better progression-free survival, despite brain involvement.17,19,26,27

In trials not selecting *mut*EGFR patients, most included brain metastases within their OMD definition.13–16,18,20 Across these trials, the extra-thoracic lesions in accrued patients were already low, implying that most harboured solitary brain metastases, a sub-group experiencing better outcomes than those with visceral metastases (whether limited or extensive).21 It is also highly likely that the paradigm of locoregional disease with OMD has a different prognosis to OMD occurring in the setting of well-established locoregional control.

Local treatments prolonged progression-free survival (PFS) in controlled trials, which is expected. Assuming an arbitrary time unit "T" is required before cancer becomes detectable at a volume "V" on imaging, ablating this volume adds another time unit "t" before it becomes detectable again.28 Control arms of these trials lacked this addition of time "t", therefore PFS was significantly longer, but whether this translated to curing patients remains unproven. The enthusiastic reception of these trials has shifted oncologists’ perception of oligometastases, where a majority now believe that OMD is curable and up to a third use ‘cure/curative’ when discussing prognosis with patients.29

Since improved PFS does not warrant the description of ‘curative’, the favourable toxicity profile of SABR should not influence clinicians decision to offer treatment.30 The reported toxicity outcomes are based on the low lesion count in these trials. Treating fewer and smaller lesions, permits a sharp 50% prescription dose drop-off and lesser dose beyond PTV+2cm volume, thus reducing toxicity.31 With the guideline recommending treatment for up to 5 lesions, the expected toxicity outcomes may be worse, especially in community practices. NRG-BR001 demonstrated that irradiating 3-4 metastases or two proximate metastases (within 5cm) led to 21% (9/42 patients) experiencing grade 3-4 toxicity (18 grade 3-4 events).32 Finally, absence of quality-of-life data with SABR in OMD and its unproven role in other clinical situations (oligo-progressive, oligo-residual, oligo-persistent states) merits further investigation.

**3. Uncertain benefit impedes shared decision-making. (section by a patient’s caregiver)**

When cancer teams offer treatment, patients usually assume there is supportive evidence and this CPG formalises the hope that local treatments for OMD NSCLC work.33 Hope drives the patient’s journey with metastatic NSCLC, and this guideline might propel patients/caregivers to seek and demand treatment. When the option of removing all metastatic disease is offered, the implicit expectation is of cure, of permanence - an unachievable expectation which cancer teams have reinforced repeatedly.29,34 Communicating the ambiguity of removing all metastatic disease for some period of time, longer for some, shorter for others, may not be sufficient. Patients often latch onto any ambiguity and respond by making an emotional rather than a cognitively-based decision. Thus reappearance of disease after its temporary eradication by local treatment will be accompanied by disappointment in proportion to the hope offered.

The guideline explicitly acknowledges limited evidence supporting local treatment and instead suggests shared decision making.4 Involvement of the patient/caregiver in making decisions ranges from deferring to the cancer team to seeking a collaborative/proactive role.35 However, a common tendency is to overestimate the benefits and underestimate the risks, often influenced by optimism and emotional reasoning.34,36 Given the knowledge asymmetry between patients/caregivers and health care professionals, an accurate assessment of the evidence underpinning the recommendations of *any* guideline is infeasible.37 Guidelines with equivocal evidence widen this asymmetry further and actually impede the goal of shared decision-making.

**Conclusion**

The guideline on OMD NSCLC is based on the premise that the practice precedes the evidence and that the recommendations for the practice are justified not because trials supporting it are complete, but because of expert opinion.4 And while it is evident that SABR or surgery can remove detectable metastases, we would remind colleagues that the biology of cancer often contradicts strong beliefs when phase 3 trials are performed.38 Nearly three decades after the oligometastatic hypothesis was first proposed (based on breast cancer data), the NRG-BR002 trial didn’t find any benefit of treating oligometastatic breast cancer.39,40 We therefore urge clinicians to maintain scientific equipoise when considering these recommendations.

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**Figure 1:** Visual summary of trials on local treatments for oligometastatic NSCLC. For details, please see Table 1.

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Description automatically generated with medium confidence

*Abbreviations*: CNS, Central Nervous System; *mut*EGFR, Epidermal Growth Factor Receptor mutation present; mPFS, median Progression Free Survival; mOS, median Overall Survival; followed by; NR, not reported; PD, Progressive Disease; PR, Partial Response; RT, Radiotherapy; SD, stable Disease.

**Table 1:** Summary of prospective clinical trials on local treatments for oligometastatic NSCLC

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author [Ref] →  ↓ Characteristics | Petty et al  [13] | Arrieta et al  [14] | Collen et al  [15] | Blake-Cerda  et al [16] | Peng et al [17] | De Ruysscher et al [18] | Wang et al [19] | Bauml et al  [20] | Su et al  [22] | Gomez et al [23] | Iyengar et al [24] | Iyengar et al [25] |
| Year † | 2018 | 2019 | 2014 | 2020 | 2023 | 2018 | 2021 | 2019 | 2015 | 2019 | 2018 | 2014 |
| Phase | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 |
| *n* (Investigational Arm) | 27 | 37 | 26 | 47 | 30 | 39 | 68 | 45 | 198 | 25 | 14 | 24 |
| Exclusively Mutation Positive mNSCLC | No | No | No | No | Yes | No | Yes | No | No | No | No | No |
| Investigational Arm | SABR | InvC Loco-Regional + Metastatic Treatment f/b InvC Maintenance/  Observation ‡ | SABR | SABR | SABR +  EGFR TKI  (1st Gen) | InvC Loco-Regional + Metastatic Treatment ‡ | SABR f/b EGFR TKI  (1st Gen) | InvC Metastatic Treatment f/b Pembrolizumab | RT ▼ + Chem | InvC Loco-Regional + Metastatic Treatment f/b InvC Maintenance/  Observation ‡ | InvC RT f/b InvC Maintenance Chem | SABR + Erlotinib |
| Control Arm | - | - | - | - | EGFR TKI  (1st Gen) | - | EGFR TKI  (1st Gen) | - | - | InvC Maintenance/  Observation | InvC Maintenance Chem | - |
| Was the initial distribution of Extra-Thoracic lesions specified? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | No | No |
| No. of initial Extra-Thoracic lesions permitted | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 | NR | NR | NR | NR |
| Median No. of initial Extra-Thoracic lesions accrued | NR | 2  (Range: 1-NR) | NR | 1  (Range: 0-NR) | NR | 1  (Range: 1-3) | 2  (Range: 1-5) | 1  (Range: 1-4) | NR ❖ | NR ❖ | NR ❖ | NR ❖ |
| Induction Treatment received prior to Investigational Treatment | 1st Line Chem with  PR/SD | 1st Line Chem/TKI (1st Gen) with PR/SD | 1st Line Chem (65%)\* | 1st Line Chem/TKI (1st Gen) with CR of Extra-Thoracic lesions | 3 months of EGFR TKI (1st Gen) with  PR/SD | No | No | No | No | 1st Line Chem/TKI (1st Gen) with PR/SD | 1st Line Chem with  PR/SD | Upto 3 lines of systemic therapy with PD\*\* |
| Only patients responding to Induction Treatment included | Yes | Yes | No | Yes | Yes | NA | NA | NA | NA | Yes | Yes | No |
| Lung Primary counted as site | No | No | Yes | Yes | Yes | No | No | Unspecified | No | No | Yes | Unspecified |
| Lung Primary (+ Regional Nodes) treated | Unspecified | Yes (NR) | Yes (Yes) | Yes (Yes) | Yes (Yes) | Yes (Yes) | Yes (Yes)\*\*\* | Unspecified | Yes (Yes) | No (Yes) | Yes (Yes) | Unspecified |
| CNS counted as site | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No |
| No. of total Metastatic lesions permitted after Induction Treatment | 5 | 5 | 5 | NR | 5 | NA | NA | NA | NA | 3 | 6 | 6 |
| Median No. of Extra-Thoracic lesions accrued after Induction Treatment | 2  (Range: 1-4) | 1  (Range: 0-NR) | 1  (Range: 1-5) | CR at all Extra-Thoracic Sites | Unspecified ❖❖ | NA | NA | NA | NA | 1  (Range: 0-3) | 0  (Range: 0-3) | 2  (Range: 1-5) |
| Treated GTV Median Volume (cc) [Equivalent Sphere (cm)] | NR | NR | 7.2  [1.2] | NR | 36.1  [2.1] | Primary = 51.9 [2.3],  Node = 23.5 [1.8] | NR | NR | NA | NR | NR | NR |
| Investigational Arm mPFS [*vs* Control] (mo) | 11.2 | 23.5 | 11.2 | 34.3 | 17.3  [*vs* 9] | 12.1 | 20.2  [*vs* 12.5] | 19.1 | 9.0 | 14.2  [*vs* 4.4] | 9.7  [*vs* 3.5] | 14.7 |
| Investigational Arm mOS [*vs* Control] (mo) | 28.4 | Not Reached | 23.0 | NR | 33.6  [*vs* 23.2] | 13.5 | 25.5  [*vs* 17.6] | 41.6 | 13.0 | 41.2  [*vs* 17] | Not Reached  [*vs* 17] | 20.4 |
| Grade 3 or higher toxicity rate in Investigational Arm ▼▼ | Nil | 18% (Unclassified)  3% (Pneumonitis);  3% (Hemorrhage) | 4% (Pneumonitis); 4% (Cough) | 8% (Pneumonitis) | Nil | 15% (Dysphagia);  3% (Cough) | 15% (Rash);  7% (Pneumonitis);  1.5% (Rib Fracture) | 7% (Pneumonitis);  2% (Dyspnea, Pain, Nausea) | 40% (Hematological); 11% (Gastrointestinal);  7% (Esophagitis); 2.5% (Pneumonitis) | 8% (Esophagitis); 4% (Anemia); 4% (Rib Fracture) | 21% (Unclassified)  14% (Respiratory); 7% (Hematological); 7% (Infectious) | 100% (Unclassified) |

† Year of updated results (if applicable); ‡ Both surgery and RT were permitted as local and metastatic treatment; \* Rest proceeded directly to Investigational Treatment; \*\* 63% , 29%, 8% accrued after progressing on 1st, 2nd and 3rd Line Systemic Therapy, respectively; \*\*\* Regional nodes included with primary disease, but was not counted as contributing towards total initial involved sites; ❖ Su et al [22] defined oligometastases on the basis of number of organs (rather than lesions) involved, which were 3 or less, while Iyengar et al [24] reported median initial sites (including primary) which were 3 (Range: 2-6); ❖❖ Authors reported median number of organs involved: 1 (Range: 1-3); ▼ Conventional Fractionation followed by Accelerated Hyperfractionation; ▼▼ In trials with investigational arm containing local treatments and systemic treatment (Chemotherapy, TKI or Immunotherapy), the composite toxicity is reported, ignoring the assessment of toxicity attributable to local treatment alone. Toxicities labelled as unclassified did not provide sufficient details about individual toxicities. None reported overlapping toxicities.

**Abbreviations:** Chem, Chemotherapy; f/b, followed by; ICI, Immune Checkpoint Inhibitors; InvC, Investigator’s Choice; LCT, Local Consolidation Treatment; NA, Not Applicable; NR, Not Reported; PR, Partial Response; RT, Radiotherapy; SABR, Stereotactic Ablative Body Radiation Therapy; SD, stable Disease; TKI, Tyrosine Kinase Inhibitors