

Oligometastatic NSCLC: the changing role of surgery

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Abstract: There is a very limited role for pulmonary resection in the management of NSCLC that has already metastasized systemically. Well selected individuals who present with limited metastatic disease (oligometastases) to a single organ may be considered for resection or an alternative local therapy to both the lung and the extrapulmonary site in rare instances where a thorough metastatic evaluation fails to reveal other foci of disease. This evaluation must include a negative mediastinoscopy.

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Two developments will potentially contribute to a changing role of surgery in the treatment of oligometastatic NSCLC disease in the near future.

One may lead to an increasing role for surgery in this patient population and relates to the improvement in systemic therapy we have recently witnessed, particularly for patients with stage IV adenocarcinomas whose tumors harbor a mutation that is actionable and in whom dramatic and prolonged responses are seen. Anecdotal experiences describe instances where such patients are left with minimal volume disease not responding or progressing where surgery may be brought in to render these patients “without evidence of disease” (NED) and/or to obtain additional tissue for analysis.

In the opposite direction, new stereotactic radiation platforms may potentially lead to a decreasing role for surgery in patients with oligometastatic disease in whom historically surgery was considered, as these radiotherapies are often considered less morbid than surgery short term though cost comparisons of the two “local” modalities are lacking. To set the stage for these upcoming developments, one may want to briefly review the established literature on this topic.

First and foremost, it is important to realize that there is no randomized data to date that has addressed this population of patients and that the data consists almost exclusively of retrospective series that usually span long periods of observation. As such the reported populations

are highly selected and the true denominators are unknown. Such a selection is, in a way, reflected in comparing patients who present with synchronous M1 disease, arbitrarily defined by many as those presenting within a disease free interval (DFI) of 6 months or less from initial diagnosis and those presenting later i.e. metachronous disease. In general the reported prognosis of the latter is better than with the former, as time and longer DFIs allow better identification of the true oligometastatic patient (1).

Synchronous presentation

In potential candidates where apparent oligometastatic disease is identified at initial diagnosis, one of the dilemma is deciding the timing of surgery vis-à-vis that of chemotherapy. Theoretical arguments in favor of proceeding with surgery first are: obtain ample tissue for analysis/genomics, treatment-naïve patients have a better performance score at the time of surgery and the efficacy of chemotherapy is potentially better after resection, when all visible disease has been removed. In this scenario, one should favor a minimally invasive approach to the resection if possible to hopefully allow for a quicker recovery and early initiation of the systemic therapy. Arguments in favor of proceeding with chemotherapy first are: “*in vivo*” testing of the systemic therapy, absence of delay in the initiation of the systemic treatment, better compliance/delivery of chemotherapy before surgery and “buying time” to tease

out individuals who may have additional occult M1 disease at presentation. For example, in one of the few prospective phase II experiences reported in this population, Downey *et al.* from Memorial described in 2002 that 5 patients out of 11 with apparent oligometastatic disease at diagnosis progressed while receiving induction chemotherapy (2).

Cerebral metastases

Patients with apparent isolated brain metastases dominate the reported experiences supporting a possible role for pulmonary resection in the face of known M1b disease. In the evaluation of such patients one must obtain a complete metastatic evaluation with at least a CT/PET scan and the brain imaging should be with MRI with and without contrast as up to 50% of patients with an apparent solitary brain metastases on CT will have multiple brain lesions when reimaged by MRI (3). As well, these candidates should have a negative mediastinoscopy evaluation before lung resection as in many series there is no 3-year survival in the presence of N2 involvement (4,5). In patients identified as having isolated brain oligometastases at initial diagnosis, the clinical dilemma is to decide whether one treats the brain or the chest first. The rule is generally to treat the symptomatic site first (usually the brain). In cases where both sites are asymptomatic, the brain is often treated first as neurologic symptoms are more likely to develop; the exception being when the presence of the brain metastases is equivocal radiologically where one would resect the pulmonary lesion and reevaluate the brain later. Five-year survival rates of 11% to 35% have been reported in this population, with patients with N0 stage disease and adenocarcinoma histology faring better (4-7). The debate as to whether to treat these patients with additional whole brain radiation therapy or simply establish close imaging follow up with repeated stereotactic interventions as needed is unsettled and beyond the scope of this discussion (8).

Adrenal metastases

There are less numerous series addressing the role of surgery in the presence of isolated adrenal metastases but in general the principles reviewed above are identical: patients with longer DFIs possibly do better and the absence of regional nodal involvement (N0) is a key predictor of better results (9,10). One series suggested laterality of the adrenal involvement as an important prognostic factor with contralateral involvement negatively affecting survival (10).

Long-term survival of 25% can be achieved in well selected patients (11).

Case reports have also described long-term survival of patients with oligometastatic involvement at other sites (bone, skin and kidney).

M1a pleural involvement

Small series have evaluated the role of extrapleural pneumonectomy in the treatment of ipsilateral pleural implants associated with otherwise favorable lung cancers but this remains experimental and cannot be recommended outside of a trial setting.

M1a lung

When dealing with two separate lesions of same apparent histology in the lung or lungs, the diagnostic challenge is to determine whether we are dealing with metastatic disease or multifocality of a still localized process. Radiological clues on CT or CT/PET may be as useful as histological analysis of the different lesions, though modern day tissue profiling is not entirely error proof in such a scenario. The Martini-Melamed criteria described in 1975 remain very useful as well (12). If in doubt, for a patient with good cardiopulmonary reserves who has undergone a full metastatic evaluation including a negative mediastinoscopy, one will usually err on the side of multifocality and treat accordingly. In such a scenario, surgical sparing anatomical resections should be encouraged. The identification of regional nodal involvement on one side (N1-2) may make one reconsider the intended contralateral intervention, an argument to tackle the most worrisome lesion first. These cases should always be reviewed at a multidisciplinary conference and in some instances we have offered parenchyma sparing resection on one side and stereotactic ablation on the other. The presence of carcinoma-in-situ in the vicinity of both resected lesions confirms multifocality, additional information that stereotactic ablation cannot provide.

Conclusions

With either synchronous or metachronous presentations, in well evaluated patients there is a role for a “local therapy” approach to both the primary and the secondary sites in a very well selected group of patient. In reality, when working up potential patients with such apparent

oligometastatic disease for “dual local therapy”, one often identifies additional disease that rules them out from such interventions.

The favorable biology of these unusual malignancies is what drives their prognosis and the impact that our “local” interventions have on this prognosis remains unclear... but a lack of “clarity” should not translate into a lack of intervention as long as the morbidity of the interventions is reasonable.

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