PERSPECTIVES IN SURGERY OF OLIGOMETASTATIC NON-SMALL-CELL LUNG CANCER

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ABSTRACT

20-50% of patients with newly diagnosed non-small-cell lung cancer (NSCLC) have synchronous metastases. This dramatically affects survival and traditionally excludes patients from the spectrum of curative therapies. Nonetheless, studies have been performed to assess the role of surgery in Stage 4 NSCLC with metastases circumscribed to a single or limited number of organs, proposing the definition of oligometastatic NSCLC to enlarge the possibility of curative resection. Aggressive treatments have shown promising results; however, the great heterogeneity of survival outcomes implies the bias of selection of patients who can benefit from surgery. The new molecular-targeted systemic therapies, cytotoxic regimens, and radiant treatments can complement surgery in metastatic NSCLC, leading to optimal control of the disease. Retrospective series can help us to design prospective trials, selecting patients with positive prognostic determinants to undergo intensive resective and pharmacologic treatments. Molecular and gene profiling will probably be the most accurate method to elect candidates to sanative therapy in Stage 4 NSCLC.

Keywords: Oligometastatic non-small-cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR), Stage 4 NSCLC, thoracic surgery.

INTRODUCTION

Non-small-cell lung cancer (NSCLC) remains one of the primary causes of cancer-related death, and accounts for approximately 80% of all lung cancer (LC) histotypes. 20-50% of patients have metastatic disease at presentation, according to the findings of current imaging methods. Stage 4 NSCLC has an overall median survival time of 7-11 months from time of diagnosis, and it is not traditionally considered suitable for curative therapies.[1] In this context, surgery has always had a marginal role. Nonetheless, the advent of systemic targeted agents and the amelioration of local control of metastases impose the re-evaluation of the pointlessness of surgical treatment in Stage 4 LC. A number of studies have shown promising results for an aggressive approach, including surgery and combined systemic treatments for patients suffering from NSCLC with distant secondarisms; however, the heterogeneity of outcomes points out the lack of election of patients. Pursuant to the characteristics of the patient and the disease, several authors proposed criteria to select candidates for intensive sanative therapy. Weak evidence prevents the ordinary inclusion of the encouraging paradigms described to attempt the cure of Stage 4 NSCLC.

DEFINING OLIGOMETASTATIC NSCLC

Hellman and Weichselbaum[2] in 1995 proposed the consideration for Stage 4 cancers with metastases circumscribed to a single or limited number of organs. The definition of oligometastatic disease aims for the election of candidates to aggressive curative treatments, on the basis of the conception of an intermediate disseminated tumour stage characterised by the confined involvement of organs. In the aforementioned editorial, the metastatic potential is supposed to be correlated to the macroscopic and histological features of the tumour, with special regard to size

and grade, as well as the 'seed and soil' crosstalk of aberrant cells. Furthermore, 5-year survival rates (5SRs) of NSCLC remain unsatisfactory after surgery with curative intent, and disease recurrences, including distant metastases, are frequent.[3] These findings suggest a common subtle micrometastatic pattern in patients undergoing restorative resection. In effect, the definition of Stage 4 disease, subtending the presence of secondarisms, is based upon imaging features with recognised sensitivity and detection limits.

The definition of oligometastatic NSCLC, according to prognostic and therapeutic implications, is challenging, even though the majority of authors include patients with 1-5 metastases in this category. Oligometastases are distinct from oligo-recurrences, which envisage a metachronous pattern. The increase in sensitivity of diagnostic tools and the perspective of local control of tumour masses lead to the augmentation of diagnosis of occult Stage 4 NSCLC while simultaneously inciting new therapeutic solutions for patients. In addition, it is evident that there is a lack of prognostic accuracy of the actual staging criteria based upon macroscopic characteristics. Gene expression and molecular profiling could represent the leading indicators in the future, as well as in selecting patients with Stage 4 NSCLC who are amenable for curative surgery. The importance of microRNA expression in oligometastatic patients treated with high-dose radiotherapy has been assessed, revealing that microRNA-200c enhancement in an oligometastatic cell line can predict the polymetastatic progression. These findings suggest the biological, genetic, and molecular bases of the oligometastatic stage.[4]

THE ROLE OF SURGERY

Surgery has been performed with success for Stage 4 NSCLC. Resection of synchronous brain metastases improves the outcome in patients with an adenocarcinoma and small lung tumour, without abnormal mediastinal lymph nodes seen on the computed tomography (CT) scan or during mediastinoscopy.[5-7] Prognostic factors also include controlled primary tumour site, the absence of extracranial disease, a good performance status, and an age of <60 years. Surgical resection of the brain masses or stereotactic radiosurgery combined with adjuvant whole-brain radiotherapy prolongs survival by approximately 8-11 months. Radiosurgery can be used for the local control of metastases, avoiding the postponement of resection of the primitivity. Surgery is the best treatment to reduce intracranial pressure, therefore it is privileged in case of mass effect. Palliative radiosurgery can be performed in patients with NSCLC with poor prognosis to improve neurological deficits.[8]

Concerning isolated suprarenal gland secondarisms from NSCLC, adrenalectomy is the treatment of choice, significantly improving long-term survival in both synchronous and metachronous patterns.[9] A 2013 review emphasises the heterogeneity of survival outcomes, discussing the definition of the oligometastatic stage.[10] The authors argue the need for randomised trials. The series included 49 studies, with 2,176 patients with 1-5 metastases treated with surgical metastatectomy, stereotactic ablative radiotherapy, or stereotactic radiosurgery, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Only one study reported randomised data, referring to patients with brain metastases as comprising 60% of the articles. 82% of patients had a controlled primary tumour. 1-year overall survival (OS) was 15-100%, 2-year OS was 18-90%, and 5-year OS was 8.3-86%. This variability among survival outcomes implies a fragmentary knowledge of prognostic determinants in patients included in the diagnosis of Stage 4 NSCLC, underlining the lack of patients who can benefit from aggressive treatments.

Pfannschmidt and Dienemann[11] emphasise the difficulty in evaluating the effectiveness of surgical resection, mainly due to the selection bias. The reported overall 5SR is about 28% for patients with satellite nodules and 21% for patients with ipsilateral nodules. In the case of resected brain metastasis, the 5SR is 11-30%, similar to the benefit observed in the case of adrenalectomy, in which the 5SR is 26%.[11] In a series of 84 newly diagnosed NSCLC patients presenting with a solitary brain metastasis, the survival outcome was found to be comparable to Stage 1 NSCLC. The median survival was 25.6 months for Stage 1, 9.5 months for Stage 2, and 9.9 months for Stage 3. Primary LC was treated in half of the cases by thoracic radiation therapy, chemotherapy, or both. 53 patients underwent craniotomy and 31 stereotactic radiosurgery. 1-year OS was 49.8%, 2-year OS was 16.3%, and 5-year OS was 7.6%. The authors concluded that intensive treatment during the early stages is justified for a thoracic

Stage 1 NSCLC with a solitary brain metastasis, contrary to locally advanced cancers.[12]

PROGNOSTIC FACTORS

The number of metastatic sites is a potential predictor of survival. The Southwest Oncology Group published the data collected from 1974-1988 of 2,531 patients with extensive stage NSCLC, indicating a sole metastatic site as a favourable determinant.[13] A retrospective series of 1,284 patients with a diagnosis of Stage 4 NSCLC at presentation revealed that OS without brain secondarisms is significantly correlated with the number of metastatic sites. Brain metastases conferred a worse prognosis (median OS of 7 months versus 9 months; 95% confidence interval, 7-8 months versus 8-10 months), with an inverse correlation with the volume of all metastases or the largest lesion.[14]

Ashworth et al.[10] reported that definitive treatment of the primary tumour, N-stage, and a disease-free interval of at least 6-12 months are significant prognostic factors for surgery in Stage 4 NSCLC on multivariate analyses. The median OS range was 5.9-52 months (overall median 14.8 months; for patients with a controlled primary tumour 19 months). The median time to any progression was 4.5-23.7 months (overall median 12 months). The statistical dispersion observed in 1-year, 2-year, and 5-year OS was confirmed. In a retrospective series of 53 patients with oligometastatic NSCLC, mainly with a single metastatic brain lesion, treated with curative intent in the period from January 1997 to May 2010, weight loss and the use of a positron emission tomography-CT scan in pre-operative staging had an independent positive prognostic value. The need for radical pulmonary resection was confirmed.[15]

SYSTEMIC THERAPIES

The current guidelines from the American Society of Clinical Oncology (ASCO) and Cancer Care Ontario[16] recommend adjuvant cisplatin-based regimens for patients with Stage 2 or 3A NSCLC who have undergone radical resection. Neoadjuvant therapy has demonstrated effectiveness in the case of satisfactory pathological response and negative surgical resection margins,[17] but exclusively cytotoxic drugs have been used in the majority of trials. Patients with Stage 3 NSCLC obtain benefit in terms of progression-free survival and OS by neoadjuvant and adjuvant treatment; on the other hand, the need for complementary systemic therapies for patients with Stage 2 NSCLC is still debated. Concerning Stage 4 NSCLC, early surgery and the local control of metastases, in addition to the aspecific cytotoxic regimen, could act in synergy with biological agents. These compounds could represent a cancer signalling-targeted strategy to control masses' overgrowth,[18] regulated by the crosstalk with macro and microenvironment. Molecular-targeted agents could reduce the prolonged dissemination of secondarisms and the 'seed and soil' reciprocity between aberrant cells and the destination tissues. Indeed epidermal growth factor receptor (EGFR) is involved in the haematogenous and lymphatic spread of malignant cells, in their pro-metastatic interdependence with stromal tissue[19] as well as in the evasion of tumour immunosurveillance.[20]

EGFR inhibitors have shown efficacy in selected non-surgical patients with a disseminated disease characterised by a mutated gene, in spite of the heterogeneity of survival outcomes. The variability of mutations among cancer cell lines, acquired resistances, and the mitogenic pathways' redundancy are probable reasons for the inter and intra-individual differences in response.[18] The solution to the development of resistance is one of the major therapeutic objectives of modern pharmacology, and could be reduced by three new third-generation compounds presented at the 2014 ASCO meeting.[21] Preoperative anti-EGFR molecules have been administered with weak benefits. In these trials the study population was not selected for EGFR mutations, but retrospectively analysed; the genetic alteration was the strongest predictor of response,[22,23] as expected. However, mutations affect a minority of patients with specific epidemiologic characteristics: non-smokers, adenocarcinoma histologies, and Asian ethnicities. A few authors have developed randomised trials in a selected population. Adjuvant administration of anti-EGFR designed for mutated receptors seem to have promising applications.[24-26] Furthermore, studies demonstrate that EGFR inhibitors are safe and active on brain metastases of NSCLC.[27]

Several trials have investigated the role of cetuximab in an unselected population reporting weak advantages, as seen for bevacizumab, the anti-vascular endothelial growth factor compound which could contraindicate resection for the risk

of bleeding.[28] Nevertheless, the monoclonal antibody has demonstrated a high safety profile as well as an anti-proliferative action on NSCLC and its active brain metastases.[29] In addition, crizotinib has been used for echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase translocation and *ROS1*-rearranged NSCLC with success.[30,31] In these terms it is legitimate to apply the concept of neoadjuvant or adjuvant systemic treatment to oligometastatic stages amenable to surgery. Molecular-targeted agents could have a synergistic activity to surgery, as argued for radiotherapy.[32] Cytotoxic and biological drugs could strengthen surgery in selected patients before and after, with an acceptable toxicity.

CONCLUSION

LC is the most lethal tumoural disease in the world. The cause of the poor survival is that the vast majority of LCs are diagnosed at an advanced stage, owing to the limited role of screening programmes and the absence of early symptoms in most cases. In spite of the fact that low-dose tomographic screening has demonstrated efficacy for reducing mortality in persons at high risk for LC,[33] this practice is not routinely performed yet. The current tumour, node, metastasis (TNM) classification, based upon macroscopic features, defines prognosis and permits the election for curative or palliative treatments. Limitations of the TNM staging are pointed out by the great heterogeneity existing among survival outcomes in patients included in specific staging categories. The most important variability is observed in Stage 4 NSCLC, which regrettably comprises a large component of all newly diagnosed LCs. Several efforts have been accomplished for these patients with questionable results. Nonetheless, a non-negligible aspect of Stage 4 NSCLCs is their positive response to aggressive treatments, including surgery.

Controversy exists regarding the selection of Stage 4 candidates for sanative therapies; the definition of oligometastatic has been proposed on the grounds that a limited number of secondarisms involving a confined number of organs could represent a prognostic advantage, therefore a spur to indicate aggressive treatments. Surgery has already been performed with success in several Stage 4 cancers, and this success was attributed to systemic therapies and the local control of metastases.[34,35] Nowadays it is legitimate to attempt surgery of Stage 4 NSCLC with curative intent if the initial lesion is radically resectable, as well as the single site metastasis, in a patient with a good performance status. The benefit of surgery for patients having a locally advanced lesion or an oligometastatic disease (generally defined by a number of 1-5 metastases) is debatable. Also in this nosographic category, survival outcomes are heterogeneous; the need for prospective trials based upon the retrospective findings will help to select the patients most likely to benefit from intensive therapy. Furthermore, molecular and gene profiling could summate sensitivity to the election criteria, in consideration of the prognostic value of genetic or proteomic alterations and also the available molecular-targeted agents which can strengthen surgical resection.

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