Review Article

Surgical management of oligometastatic non-small cell lung cancer

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Abstract: The oligometastatic stage IV non-small cell lung cancer (NSCLC) offers a new surgical opportunity. New reported data is showing that surgery can offer a reasonable benefit, in terms of long-term survival, to some patients. The advantages of surgical treatment rely on a more adequate patient selection and a better understanding of the biology of these tumors. Currently, mediastinal involvement of the primary tumor can be identified as the most important prognostic variable after curative-intent of synchronous or metachronous metastasis. It seems clear that the routine use of combined FDG-PET and CT will help to detect the more favorable cohort of oligometastatic patients. As expected, pathological T staging of the primary tumor and the completeness of its resection are also crucial factors influencing final results. The real benefit of the local treatment over synchronous or metachronous metastasis is controversial with series showing better outcomes for metachronous lesions than for synchronous and others offering equal results. Also non conclusive results appear when analyzing different sites of metastasis. Retrospective series tend to show different outcomes depending on the affected organ while usually no differences are found in prospective ones. Most of the current evidence is based on retrospective studies on patients collected along extended periods of time. That represents a great limitation to the knowledge on this topic. Some prospective analyses have added some insight, but still the quality of the evidence is too low to allow drawing robust conclusions. As frequently concluded, prospective well designed investigation is requested to ascertain the value of surgery in this specific population of patients with extended NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); stage IV; oligometastasis; oligometastatic stage; surgical treatment

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Introduction

Since modern therapeutic modalities, including surgery, are available for non-small cell lung cancer (NSCLC) with distant metastasis, it is currently a fact that the current stage IV does not include a homogeneous subset of patients, as the authors of the 7th TNM classification have already underlined (1). The future 8th classification will differentiate a new category, M1b, corresponding to extrathoracic distant oligometastasis, different to the M1c category that will include patients with multiple distant lesions (2). Systemic cytotoxic chemotherapy remains the first-line treatment for most patients in stage IV. But for oligometastatic patients, surgery can be an important tool to improve long-term survival. Some retrospective analyses of series of cases have addressed this topic in the past; but now, new prospective data are available (3). Currently, it is accepted that local oligometastasis localized in the brain, adrenals or lungs can be treated with curative intention (4).

What is considered to be an oligometastatic stage IV NSCLC?

The prevalence of metastatic disease at diagnosis of NSCLC

ranges between 30% to 50% of the patients depending on the series. About 7% of these will show just a solitary or a limited number of metastasis after complete evaluation (5). The term oligometastatic stage suggests a restricted capacity of the tumor for distant spread since a limited number of metastasis can be found. Therefore, in these cases, the possibility of an indolent progression of the illness opens the opportunity to an aggressive local approach to control the disease (6). There is not a clear consensus on the amount of lesions defining the oligometastatic stage but most groups consider three to five metastases as the cut-off point. It seems reasonable that the larger the number, the worst the prognosis. Recently a study (7) presented the 5-year survival probability of 50.3% for patients with single and of 16.7% for those with 2 or more surgically treated lesions.

Accordingly, the oligometastatic stage can occur in a number of clinical situations (6): patients with a limited number of metastasis at diagnosis; patients with multiple metastasis that have a limited residual lesion after systemic treatment or those in whom only one lesion progresses after general treatment (oligoprogression) or those in whom a limited disease recurs after treatment (oligorecurrence). In all these situations surgery seems to offer survival benefits.

The potential role of PET-CT/FDG

The introduction of this tool in the routine staging of NSCLC patients has proved to have a substantial impact on planning their treatment planning. PET-CT/FDG has demonstrated acceptable accuracy in mediastinal staging (8) and in the diagnosis of distant metastasis (9). In this recent study (9), the authors compared the survival rate for stage IV NSCLC oligometastatic patients staged using only traditional CT versus FDG-PET/CT. All patients were treated with curative intent. They showed a 5-year survival rate of 58% for the FDG-PET/CT staged patients significantly superior to the 33% observed in the CT only staged cases (P=0.01). These data support that the results from series published before the routine introduction of PET-CT/FDG in the management of cancer patients should be revisited.

Surgical treatment

The role for a proper selection of patients

The resection of any accessible NSCLC metastasis within any organ should be currently considered with curative intention. As reported in the majority of the series, one of the keys for a favorable outcome is the absence of mediastinal lymph node involvement. A recently published retrospective study including 761 patients collected over a 13-year period (10), reported that cN0 stage IV patients had statistically significant longer survival (11.9 months) compared to 7.2 months for cN1–3 (P<0.001). This survival difference was maintained also in the group of patients who received active treatment including surgery in 2.4% of the patients (18.3 months for the cN0 versus 11.4 months for the rest; P<0.001) but did not reached a significant statistical difference when EGFR mutation was present (37.9 months for cN0 versus 27.0 months for cN1–3). The study of Tönnies *et al*. (11) was designed to describe the criteria for selecting patients in oligometastatic stage IV who would benefit from surgical treatment of both the primary tumor and the synchronous metastasis. In their retrospective series, factors such as lung metastasis opposite to extrapulmonary metastasis, low grade primary tumor (G1, G2) opposite to G3 and, over all, pN0/pN1 lymph node metastasis versus pN2/pN3 positive lymph nodes offered statistical significant differences in survival after treatment. Probably the Memorial Sloan-Kettering prospective trial published in 2002 was the best study to asses this issue (12). They recorded a short median survival time (11 months; range, 1–104 months) in patients undergoing induction therapy, surgical resection of the primary and the metastasis followed by adjuvant therapy. Despite a poorly tolerate treatment strategy, half of the series (12 out of 23) were cN2 positive probably explaining in part the low overall survival.

Another important idea is that survival benefit is also related to the extension of the primary tumor (4,13,14). The authors of this paper (13) identify the pT stage as a predictor of survival, being patients with the lower pT stage the ones having most favorable prognosis. In this series, pT1–2 had a median survival of 26 months compared to 8 months for the patients with pT3–4 tumors. Their 36% 5-year median survival rate confirms that multimodality treatment including surgical resection of the primary tumor should be considered in the therapy of single-metastasis stage IV patients.

As expected, completeness of the resection is a strong determinant of survival. In this retrospective series of cases including 53 patients collected over a 13-year period (15), patients who underwent complete resection showed better long-term survival (HR 4.75; 95%CI, 1.87–12.1), and freedom from local (HR 7.43; 95% CI, 2.32–17.62) and

distant relapse (HR 4.58; 95% CI, 1.76–11.92) compared to those with R1 orR2 resection.

Is the timing of the metastasis relevant? Synchronous vs. metachronous lesions

Most retrospective evidences support a better prognosis of metachronous oligometastatic stage IV patients when compared to patients with synchronous oligometastatic lesions (4,16). Ashworth and colleagues attempted an interesting approach to analyze this problem (16). After a systematic review of the literature collecting data from different series of cases, they identified synchronous versus metachronous metastasis (P<0.001) and adenocarcinoma histology (P=0.036) as the main factors influencing survival in oligometastatic patients. Using the recursive partitioning analysis, authors created 3 groups of risk being longer the probability of 5-year survival for cases with metachronous metastasis (47.8%), while patients with synchronous metastasis and N0 disease and patients with synchronous metastasis and N1/N2 disease had 36.2% and 13.8%, respectively. In contrast, Endo *et al*. (3), in their prospective series, did not find any survival difference between patients with synchronous or metachronous metastasis treated surgically.

Also in some retrospective series, the real benefit of the surgical treatment of both the primary and the metastatic tumors detected synchronically is controversial. In a Chinese series of cases (14), the authors analyzed the mean survival time (MST) achieved in synchronic metastatic tumors. Those patients with surgically treated metastasis achieved the best survival on all subgroups compared to non-surgical treatments for lesions on the same location. The authors remarked that survival time are deeply dependent on the organs affected by the metastasis. For example, the MST for surgically treated brain metastasis was 15.4 months (only 11.5 months in those non-surgically treated, P=0.002) and it was better after adrenal removal (31.1 months after surgery *vs*. 11.3 months if no surgery was indicated, P=0.001). Nevertheless, another study (17) including a series of synchronous metastatic patients collected along a long period of 23 years, failed to find any survival benefit of metastasis resection.

Patients with postoperative distant recurrences (metachronous metastasis) constitute a heterogeneous group and within them, the oligometastatic patients are, again, a subset with favorable prognosis (2,4,18). According to Shimada *et al*. (18), who studied the factors related to post-recurrence survival in a retrospective series of surgically treated NSCLC patients, variables such as male sex, positive smoking history, non-adenocarcinoma histology and shorter disease free interval were negative factors influencing long-term survival after systemic and/or local curative-intent treatment. It should be remarked that systemic treatment and the use of EGFR-TKI, when appropriated, resulted in significantly increase of the post-recurrence survival, whereas applying only local therapies did not show differences in survival outcomes. In their series, lung and brain were the sites most frequently affected by recurrences. For patients with lung oligometastasis, a positive smoking history (HR 5.15; 95% CI, 1.69–15.74) and adenocarcinoma histology (HR 0.18; 95% CI, 0.06–0.55) were the factors influencing survival. On the other hand, for patients with brain metastasis, male sex (HR 3.6; 95% CI, 1.16–11.22), short disease-free interval (HR 5.96; 95% CI, 1.3–27.02) and systemic treatment (HR 0.32; 95% CI, 0.11–0.93) were the influencing factors for survival in multivariate analysis.

Is the site of metastasis a prognostic factor per se?

The answer is not uniform. According to the authors of the vast majority of retrospective studies, the answer is yes but, again, Endo *et al*. (3), found no significant difference among patients with brain, adrenal or lung metastasis.

Brain, adrenal glands, lung and bone are the most frequent sites of NSCLC metastasis. Nevertheless, metastasis at the gastrointestinal tract (19), pancreas (20), breast (21), muscle (22), omentum (23) spleen (24), kidney (3,25), liver (26) and skin (17) had been reported as short series of cases or just as simple case-reports. Despite the probable presence of a publication bias, the curative-intent surgery applied to treat these lesions provided an unexpected prolonged survival. Salah *et al*. (27) assessed this issue in an interesting study collecting data from extra-cranial and extra-adrenal cases. They found that the overall survival for the entirely cohort of 62 patients was 50%. In this study, patients with non-visceral metastasis had a 5-year survival of 63% compared to 39% for those with visceral lesions.

Brain metastasis

The brain is the most common site of extrathoracic distant metastasis for NSCLC patients. They can be detected up to 30% to 55% of the cases at autopsy (28). Sakamoto *et al*. (29) reported that 3.2% of the patients will develop only metachronous brain metastasis after surgery for the primary tumor. The survival after recurrence is poor. A recent study analyzed the median survival time after lung

resection for these patients and it was 25 months (30) with an overall survival rate of 79.1% at 1-year, 38.6% at 3-year and 22% at 5-year, being the recorded median survival time after the treatment of the brain metastasis only 11 months. In another study (14), the median survival time after diagnosis of synchronous brain metastasis was 12.3 months; 15.4 months for those who received complete surgical resection compared to 11.5 months for those who received whole brain radiotherapy (P=0.002). Bae *et al.* (30) found that adenocarcinoma histology, non-pneumonectomy required for treating the primary tumor, disease free interval longer than 10 months from the lung resection, solitary metastasis and size less than 3 cm are positive factors related to a good post-recurrence survival. Systemic and local treatment of the lesion using surgical resection or stereotactic radiation surgery also improved survival. It is interesting that some series show a benefit for the systemic treatment despite the existence of the blood-brain barrier (18,30). At present, the mechanism of action is unknown. The treatment strategy in all cases of synchronous metastasis was to operate on the brain first (15).

Adrenal metastasis

Less than 10% of the patients with NSCLC will present an adrenal oligometastasis (31). Tamura *et al.* (10) suggested that certain type of adrenal metastasis may result from a lymphatic spread as adrenal metastasis are more frequent in those with cN1–3. On the contrary to the brain metastasis, for synchronous adrenal metastasis, the treatment strategy is to operate the primary tumor in the lung first and after, the adrenal lesion (15). According to a systematic review published in 2008 (32), for an isolated adrenal metastasis, patients with a synchronous lesion had a shorter median overall survival than those with a metachronous lesions. However, the 5-year survival estimates are equivalent (26% and 25%, respectively). It is interesting to remark that Barone *et al.* (33) found a 13.5% of bilateral metastasis in their series. In this study, the median overall survival time of those who underwent adrenalectomy was 31 months (3-year OS 48% and 5-year OS 29.3%) compared to 13 months for those who only received medical therapy. In this retrospective study of 37 patients, the authors showed that the overall survival was significantly worse for bilateral cases (11 months) compared to ipsilateral (27 months) and contralateral metastasis (29 months).

Bone metastasis

Recently, a German series (11) analyzed the presence of bone metastasis and reported very low median survival compared to other sites (5 versus 40 months). Previously, Xu *et al.* (14) reported a median survival time of 13.9 months for those patients who had bone surgery or fixation followed by radiotherapy and 11.6 months for those who only received radiotherapy (P=0.251). Other studies (17,18) also reported worse survival data even after surgical resection, concluding that bone metastasis were never associated with favorable long-term survival. No differences were found even when the bone metastasis was on a rib ipsilateral to the tumor and easily accessed from the thoracotomy. The authors suggested that bone metastasis cannot be considered an oligometastatic stage in any situation.

Lung metastasis

Although lung is a frequent site of relapsing NSCLC, no unique analysis of the surgical treatment of lung lesions can be found. Most data are collected from studies including multiple affected sites. As a group, the median survival time for patients with intrapulmonary metastastic disease is better (56 months; 95% CI, 37.2–74.8; P=0.001) than the expected one for patients with extrapulmonary metastasis (18 months; 95% CI, 8.5–27.5) (11). Metastasis seems to be more frequent at the ipsilateral lung (13). When synchronous single contralateral lesions are diagnosed, most patients undergo bilateral staged lobectomies achieving favorable long-term survival (5-year survival time: 45%). This curative-intent strategy (13) is recommended (4) due to a high probability to have two independent primary tumors.

Who can benefit from the surgical resection?

We have reviewed that patients with N2–N3 disease at whom complete resection of the primary tumor is not possible or patients that present with multiple lesions or advance pT stage are probably non-eligible candidates for surgical curative-intent of the tumor and/or metastasis. Probably being the mediastinal lymph node involvement the most important independent prognostic factor. For that reason, some authors recommend complete mediastinal assessment before considering metastasectomy.

On the other hand, it has been recommended that patients with oligometastatic stage should be treated with curative intent after a period of observation of 6–12 months; patients who remain oligometastatic after that observation time are the best candidates as they should be the ones with the more favorable biology (34).

Conclusions

Probably, thanks to the more accurate staging of the tumor with the routine use of combined FDG-PET and CT scan, the role for an aggressive local treatment on oligometastatic lesions will be clarified and it will benefit a large group of patients with a favorable biology still poorly understood. Meanwhile, strict selection of patients according to T and N status, completeness of resection of the primary tumor, adenocarcinoma histology and location of the metastatic lesion will allow us to delimit a group of favorable response to a curative-intent surgical treatment.

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Footnote

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