Journal of BUON **17:** 712-718, 2012

ORIGINAL ARTICLE

Solitary metastasectomy in non-small cell lung cancer

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Summary

Purpose: *Stage IV disease at initial presentation accounts for approximately 41% of newly diagnosed cases with non-small cell lung cancer (NSCLC). Although the majority of these patients have disseminated metastatic disease at diagnosis, a small percentage of them are found to have a solitary site of extrathoracic metastasis. In addition, patients who have received surgical or multimodality treatment with curative intent may experience metachronous solitary distant recurrences during the natural course of their disease. Our aim was to review the possible role of surgical resection in the management of NSCLC with solitary hematogenous metastasis.*

Methods: *We performed electronic literature search of PubMed, EMBASE and the Cochrane Library for articles in English using a number of key words.*

Results: *All identified studies reported survival benefit for patients operated for their single metastatic lesion. Patients with metachronous disease had slightly better prognosis than those with synchronous metastatic lesions. We found no prospective randomized trials comparing surgical and non-surgical treatment modalities for NSCLC with solitary hematogenous metastasis.*

Conclusions: *Available evidence supports the presumption that in highly selected patients with isolated synchronous or metachronous hematogenous metastasis surgical resection as part of an aggressive approach positively affects patients' survival. Factors that are in favor of a satisfactory outcome include control of primary site, confirmed solitary metastatic disease, good performance status (PS), metachronous lesions and longer disease-free interval (DFI). Prospective randomized trials are necessary to provide stronger evidence. Finally, it is worth investigating the biology of these tumors presenting with single-site distant metastasis.*

Key words: adrenal metastasis, brain metastasis, non-small cell lung cancer, surgery

Introduction

Stage IV disease at initial presentation accounts for approximately 41% of newly diagnosed cases with NSCLC [1]. The standard of care for this stage is chemotherapy or palliative care according to the patient's PS [1]. Despite the progress in anticancer therapy, prognosis for metastatic NSCLC remains dismal. Although the majority of these patients have disseminated metastatic disease at diagnosis, a small percentage of them are found to have a solitary site of pulmonary or extrapulmonary metastasis. In addition, any patient previously subjected to surgical or multimodality treatment with curative intent may experience metachronous solitary distant recurrence during the natural course of the disease. This poorly understood state of limited metastatic burden has been described as oligometastatic disease and it seems to run a more indolent course [2,3]. Retrospective clinical studies [3] focused on the definitive surgical management of solitary (synchronous or metachronous) extrapulmonary metastases have reported favorable results, raising the question: is there any place for therapeutic strategies with curative intent in metastatic NSCLC?

The aim of this study was to review the published data concerning the surgical management of solitary brain or adrenal metastases from NSCLC, since they represent the most frequent surgically treated sites of isolated metastatic disease. Sporadic reports describing

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Received 27-02-2012; Accepted 19-03-2012

the surgical management of solitary metastasis in other extrapulmonary sites (including bone, small bowel, spleen, muscle, kidney, pancreas) exist but they will not be discussed herein.

Methods

We conducted an electronic literature search of the major medical databases (PubMed, EMBASE and the Cochrane Library) for articles in English, published until November 2011. The search terms that were used included: lung, pulmonary, bronchogenic, cancer, carcinoma, metastases, metastasis, metastatic, oligometastatic, solitary, single, brain, cerebral, and adrenal. Search terms were selected based on common keywords during a preliminary search of the literature. Reference lists were also checked to ensure that all relevant articles had been identified.

Results

Brain

Metastatic involvement of the brain is commonly detected in patients with NSCLC. The incidence of brain metastases in patients who died with lung cancer has been reported to be 14-45% [4], whereas 48% of metastatic brain lesions are estimated to be originating from lung primaries [5]. Quint et al. (1996), studying the distribution of distant metastatic disease at initial diagnosis of NSCLC found that brain metastases were detected in 9.7% of patients [6]. Metastases were isolated to the brain in 41% of those (representing the 4% of the total cohort). In addition, brain has been demonstrated as the most frequent site of initial extrathoracic recurrence in NSCLC [7,8].

The earliest attempts of surgical excision of brain metastases from lung cancer have been reported in 1930 [9]. Fried and Buckley performed brain metastasectomies in 11 patients without removal of the primary lesion. Operative mortality was high (45%) and interestingly there was one long- term survivor, who lived 7 years after craniotomy. The first resection of an "apparently" solitary cerebral metastasis combined with pneumonectomy for the primary lung cancer was reported by Ballantine and Byron (1948) [10]. Prompted by these initial attempts and observations from autopsy studies, that brain metastases were often single and harbored in accessible areas [11], Magilligan et al. pioneered in the field of cerebral metastasectomy in lung cancer patients [12]. Results of their 25-year experience were published in 1986 in an updated series of 41 patients [13]. Survival rates at 1, 2, and 5 years were 55, 31 and 21%, respectively. Operative mortality was 2%. Patients with small peripheral primary tumors, amenable to wedge resection, were found to have a survival benefit over others. Similar were the results of Read et al. (1989) in 27 out of 92 patients with NSCLC and solitary brain metastases, who were offered a curative lung and brain resection (1, 2 and 5-year survival rates estimated at 52, 35 and 21%, respectively) [14]. Macchiarini et al. (1991) reported another series of 37 patients submitted to combined resection of both primary NSCLC and solitary brain metastasis [15]. A median survival of 27 months and a 5-year survival of 30% was achieved with complete resection. They noted that an interval between operations greater than 12 months positively affected both 5-year overall survival and DFI, whereas adjuvant chemotherapy affected only DFI. Wronski et al. (1995) conducted a retrospective study of the Memorial Sloan-Kettering Cancer Center experience on brain metastasectomy in 231 patients with lung cancer [16]. This analysis was the largest published series and included patients from previous reports from the same institution [17-20]. Overall median survival was 11 months and survival rates were 46.3% at 1 year, 24.2% at 2 years and 12.5% at 5 years. Median survival was found to be greater (14.4 months) in patients with complete resection of the primary tumor. Patients with metachronous metastases had a longer median survival than those with synchronous ones (13 vs 9.2 months; $p=0.03$). Separate analysis for the subgroup of patients with solitary and single brain metastasis submitted to complete resection of both primary and metastatic lesions was not conducted. The following year Mussi et al. failed to demonstrate a statistically significant difference in survival between synchronous and metachronous presentation of metastatic disease in 45 patients with solitary brain metastasis from NSCLC submitted to combined resection [21]. Concerning the entire cohort, they found that only the type of pulmonary resection (reflecting the locoregional extent of NSCLC) and N status affected survival. For the subgroup with metachronous disease, an interval between operations equal or greater than 14.5 months positively affected survival. The positive impact of N0 disease on treatment outcomes had been already highlighted in two previous series of Torre et al. (1988) and Hankins et al. (1988) [22,23].

Subsequent retrospective studies reported similar results regarding survival rates and attempted to investigate further the prognostic value of several parameters. Saitoh et al. (1999) trying to identify prognostic factors in surgically treated NSCLC patients with solitary metachronous brain metastasis reviewed 24 cases [24]. In their series 1-,2- and 3-year survival improved when the interval between operations was>360 days. Lobectomy vs. pneumonectomy was another independent prognostic factor favoring prolonged survival. In a large multicenter series, including 103 patients with synchro-

nous brain metastases (single in 99 cases) from NSCLC, median survival was 12.4 months and 5-year survival 11% [25]. Adenocarcinomatous histology was associated with improved survival. A trend in patients with N0 disease to present better survival than those with N1-2 lymphadenopathy was also noted, though without statistical significance. Likewise, in the Granone et al. series (2001) prognosis was significantly better in patients with N0 status and in adenocarcinomas as it was demonstrated in univariate analysis [26]. Whether synchronous or metachronous, the onset of brain metastatic disease was not found to be correlated with survival in this study. Billing et al. (2001) published another retrospective study where among 8 parameters assessed in multivariate analysis only lymph node status was recognized as an independent prognostic factor [27]. It is worth mentioning that from the cohort of 28 patients in the Billing's study with synchronous brain metastases from NSCLC submitted to complete resection of both sites, those with N0 disease reached a 5-year survival rate of 35% whereas those with N1-2 disease had a 3-year survival rate of 0%. The most recent large series of patients, who were offered combined resection of primary NSCLC and solitary brain metastasis, was that of Furák et al. (2005) [28]. Sixty-five patients were retrospectively studied, 19 of whom with synchronous and 46 with metachronous presentation. None of the assessed parameters (pathology, N status, stage at time of diagnosis, DFI) was found to affect survival. The authors noticed that the total cohort homogeneously displayed survival rates close to that of stage IIIA (1997 revision) irrespective of their stage at initial diagnosis, indicating an unexpectedly favorable prognosis for this subgroup of patients. The reported 5-year survival from the first surgical intervention was 22, 20, 22 and 24% for stages I, II, IIIA and IV, respectively (stage at the time of lung resection).

Different modalities have been studied as adjuvant modalities after solitary brain metastasectomy. The landmark study assessing the efficacy of postoperative whole brain radiation therapy (WBRT) after surgical resection of brain metastasis was that of Patchel et al. (1998) [29]. In this prospective randomized trial, 95 patients (57 with NSCLC) with resected single brain metastasis from different, non radiosensitive, primaries were assigned to postoperative WBRT or observation. Despite that this trial included patients with variable extent of disease, from true solitary metastasis without other neoplastic foci to single brain metastasis in the context of disseminated disease, it was demonstrated that postoperative WBRT was associated with reduction of recurrence rates in the brain, both at initial and distant intracranial sites. Differences in overall survival between the two groups were not evident. Recently Kocher et al. (2011) published the results of the EORTC 22952-26001 study [30]. Although this trial assessed the role of adjuvant WBRT after the definitive management (surgery or stereotactic radiosurgery) of limited (1-3) brain metastases, the reported results were confirmatory of the Patchel's conclusions. The role of adjuvant chemotherapy after resection of solitary brain metastasis remains unclear. Downey et al. (2002) conducted a phase II trial of chemotherapy and surgery for NSCLC with synchronous solitary M1 disease (including brain, adrenals, bone, spleen, lung and colon metastases) in 23 patients, 14 of whom with isolated brain metastasis [31]. Outcomes of this trial were inconclusive. The authors failed to demonstrate that the addition of chemotherapy is beneficial, whereas the feasibility of such a therapeutic strategy, combining induction chemotherapy, surgical resection of primary and metastatic sites and adjuvant chemotherapy proved questionable. In an attempt to overcome the neurotoxic complications assigned to WBRT, tumor bed stereotactic radiosurgery (SRS) have been applied in order to achieve sufficient local control after resection of brain metastases [32]. The authors reported a local control rate of 73%, as assessed by magnetic resonance imaging during a median follow up period of 13 months. Maybe the effectiveness of such an approach should be investigated further.

Surgical resection and the attractive alternative technique of SRS have never been compared in prospective randomized trials as treatment options for patients with solitary brain metastasis from NSCLC [33]. Recently a randomized controlled trial was conducted to define whether SRS plus adjuvant WBRT has superior or equivalent impact on both survival and quality of life with surgery in patients with solitary brain metastasis [34]. After a 6-year period of recruitment only 21 patients with solitary brain metastasis from non radiosensitive primaries including NSCLC were finally analyzed. Investigators failed to confirm or reject the initial hypothesis owing to the small number of patients. Based on the available data, we cannot assess which modality is more efficient in the definitive management of this subset of patients.

Despite the apparent limitations issued from the retrospective nature of most published studies, it is evident that patients with a solitary brain metastasis amenable to combined resection (both the primary tumor and metastasis) exhibit improved survival compared with the predicted survival in customary stage IV (Table 1). Pursuing the attainment of optimal results such patients should be considered as candidates for surgical resection. Good PS, controlled or controllable primary tumor and absence of extracranial metastatic disease should guide proper selection of surgical candidates.

Table 1. Median survival and 5-year survival rates after surgical resection of solitary brain metastasis from NSCLC. All studies were retrospective

Study	*Year*	*No of patients*	*Median survival (mo)*	*5-year survival (%)*
Magilligan et al [13]	1986	41 (14 synchronous - 27 metachronous)	13.2	21
Torre et al [22]	1988	27 (21 synchronous - 6 metachronous)	NR	15
Hankins et al [23]	1988	19 (14 synchronous - 5 metachronous)	20.04	45
Read et al [14]	1989	27	NR	21
Macchiarini et al [15]	1991	37 (10 synchronous - 27 metachronous)	27	30
Mussi et al [21]	1996	52 (19 synchronous - 33 metachronous)	19	16
Saitoh et al [24]	1999	24	6.8	8.3
Bonnette et al [25]	2001	103 (synchronous)	12	11
Granone et al [26]	2001	30 (20 synchronous - 10 metachronous)	23	NR
Billing et al [27]	2001	28 (synchronous)	24	21
Furak et al [28]	2005	65 (19 synchronous - 46 metachronous)	19.3	19

mo: months, NR: not reported

Complete resection, N0 status and a long interval between operations (in metachronous presentation) might represent predictors of better outcomes.

Adrenals

The adrenal glands represent one of the commonest sites of extrathoracic metastatic spread in patients with lung cancer. In autopsy series, adrenal metastases were found in 25.2% and 43% of patients who died with lung cancer [4,35]. On the other hand, the incidence of truly isolated adrenal metastases has been reported to be low (2.4%) among patients undergoing initial staging workup [36]. The prominent selectivity of lung cancer to metastasize to the adrenals, along with observations on the higher incidence of ipsilateral metastases [35,37,38] especially in the early stages of the neoplastic process generated the hypothesis that early ipsilateral adrenal metastases might be of lymphogenous origin [35,37- 39]. Based on this presumption, solitary ipsilateral adrenal metastases tend to be considered as a form of locoregional disease rather than disseminated metastatic spread justifying more aggressive management strategies [37].

The first published report of adrenalectomy for lung cancer metastases was that of Twomey et al. (1982), where two cases of adrenal metastases from NSCLC were treated surgically, achieving a remarkable long-term survival (over 6 and 12 years respectively) [40]. Since then, several retrospective studies have been published in favor of surgical resection for adrenal metastases, trying to define selection criteria and prognostic factors whilst in few of them surgical and conservative approaches have been compared. The earlier published data were case reports and small series, including 2-5 patients each, with few long-term survivors among them [41-45]. Those preliminary reports were followed by larger series. The largest retrospective multicenter study was that of Porte et al. (2001) [46] with 43 patients (including 11 from a previous prospective study published by the same author [47]). They reported a mean survival rate of 16.2 months and a 4-year actuarial survival of 11%. These values were almost the same for the synchronous and metachronous groups whereas they were not affected by the location of the metastases (ipsilateral vs. contralateral). Other factors affecting outcomes failed to be recognized. On the contrary Mercier et al. (2005) reporting a series of 23 patients who had undergone adrenalectomy for NSCLC metastases stated that a DFI greater than 6 months between resection of the primary and diagnosis of the adrenal metastasis was the only predictor of increased survival [48]. The 5-year survival rate of patients with a DFI>6 months was 38% whereas there were not 5-year survivors in the DFI<6 months group. The overall 5-year survival was 23.3%. Pfannschmidt et al. (2005) came synchronously to the same conclusion in a study including 11 patients [49]. They found that median survival was better in the metachronous group than in patients with synchronous adrenal metastases (30.9 vs. 10.3 months), defining as metachronous those metastases occurring >6 months after the pulmonary resection. The only prospective trial studying the management of solitary NSCLC metastases, included only 3 patients with adrenal involvement (in a total of 23). The small number of patients hindered the extraction of particularized conclusions concerning the management of adrenal metastases [31].

Beitler et al. (1998) performed a collective review, analyzing data from 11 previously published articles [50]. A total of 60 patients with solitary adrenal metastases were split into two groups. In the first group of 32 patients, where enough details were available, the median survival was 24 months and the 5-year survival rate 33%. No parameter affecting survival was recognized.

Table 2. Median survival and 5-year survival rates after surgical resection of solitary adrenal metastasis from NSCLC. Results from a recent metaanalysis

Study	*No. of patients*	*Presentation*	*Median survival (mo)*	*5-year survival rate (%)*
Tanvetyanon et al [51]	48	Synchronous	12	26
	66	Metachronous	31	25

mo: months

In the second group of 28 patients (retrieved from series studying adrenal metastasis from various primaries) results were less favorable. Recently, a systematic review was conducted by Tanvetyanon et al. (2008) comparing the outcomes of adrenalectomy between patients with synchronous and those with metachronous metastasis [51]. In this study 114 patients were included (42% in the synchronous group). A significant difference in median survival between the two groups emerged (12 months for patients with synchronous metastasis and 31 months for those with metachronous disease). Interestingly the 5-year survival rates were almost equal for both groups (approximately 25%) (Table 2). This remarkable 5-year survival led to the conclusion that both groups of patients with solitary adrenal metastasis from lung cancer might be benefited from adrenalectomy.

Few studies comparing adrenalectomy with conservative management exist. Luketich et al. (1996) treating 8 patients with chemotherapy plus adrenalectomy and 6 patients with chemotherapy alone found that the median survival was higher in the first group (31 vs. 8.5 months, respectively) [52]. Similar results had been reported in a smaller previous study by Higashiyama et al. (1994) also [53]. Currently, in a retrospective study of 37 patients, Raz et al. compared the results of operative vs. non operative management of NSCLC with solitary adrenal metastasis [54]. Five-year survival was significantly higher in those with adrenalectomy (38 vs. 0%). Ipsilateral metastasis and absence of mediastinal node involvement were recognized as factors predictive of better outcome.

Reports concerning the role of adjuvant chemotherapy in addition to surgical resection are limited and discordant. In a retrospective literature analysis of 18 patients with metachronous disease, it was found that median survival was longer in patients who had received adjuvant chemotherapy (19 months) than in those submitted to surgical resection alone (14 months) [55]. Other studies where adjuvant therapy was among the analyzed variables failed to demonstrate an impact on survival [48,49]. Due to the obvious minimum existing data, conclusions regarding the role of adjuvant therapy deemed insecure.

Adrenalectomy could be performed through several approaches. Apart from the traditional retroperitoneal and transperitoneal (laparotomy) routes, the transdiaphragmatic adrenalectomy has been described as an attractive alternative [46,56]. Through this approach adrenalectomy could be performed via phrenotomy during thoracotomy in combination with the pulmonary resection in cases of ipsilateral and synchronous adrenal metastases. Other authors have advocated in favor of laparoscopic adrenalectomy [57,58] that seems to combine the advantages of minimally invasive surgery (shorter operative time, shorter length of hospitalization and lower complication rates) with equivalent oncologic outcomes [58]. Regardless of the type and timing of the procedure, adrenalectomy seems to be accompanied by minimal added morbidity, rendering a surgical approach to adrenal metastases feasible and safe [51].

In light of this evidence, in lung cancer patients with a solitary adrenal metastasis adrenalectomy appears as the only available option that offers increased survival and a chance for cure. Selection of the appropriate patient for adrenalectomy is of utmost importance and should be guided by a controlled primary tumor, a negative further metastatic workup and the feasibility of a complete resection of the metastatic lesion. Patients with metachronous disease, ipsilateral metastasis and lack of mediastinal node involvement might be more benefited from a surgical approach.

Conclusion

Though derived mostly from retrospective studies, available evidence supports the presumption that in patients with solitary hematogenous metastasis, surgical resection is associated with favorable results. Comparison of surgical vs. non-surgical modalities in the management of solitary metastatic disease in prospective randomized studies seems to be very difficult. Recruitment problems were common in such trials [34]. Evaluation of possible candidates should include a thorough staging workup (including PET-CT and brain MRI). The role of tumor biology in both the distinct metastatic presentation as solitary deposits and the response to surgical therapy, when clarified, might further facilitate proper selection of surgical candidates.

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