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Curative intent therapy in oligometastatic lung cancer with an unresectable primary with N3 nodes: case report and review of the literature

Vanita Noronha¹, Amit Joshi¹, Vijay M Patil¹, Sunny Jandyal¹, Neha Mittal², Nilendu Purandare³, Jaiprakash Agarwal⁴, Nandkumar Kadam¹ & Kumar Prabhash^{*1}

Practice points

- Untreated NSCLC patients with brain metastases have a median survival of approximately 2 months.
- Locally advanced stage III NSCLC patients treated with chemoradiation have a median survival of 16–19 months.
- Select patients with oligometastatic disease may have a prolonged survival if managed aggressively.
- We present the case of a 47-year-old woman with lung adenocarcinoma, cT2aN3M1a, (supraclavicular lymph node, solitary brain metastasis), who was treated with brain metastasectomy, whole brain radiation, induction chemotherapy and concurrent chemoradiotherapy. She relapsed in the brain and locoregionally and was treated with brain re-irradiation, and systemic chemotherapy.
- Her progression-free survival was 32 months and she is alive with recurrent disease 63 months after diagnosis.
- Predictive factors for deciding therapy in patients with oligometastatic disease include small tumor size, absence of lymph node metastases or N0/N1 status, synchronous rather than metachronous metastases and adenocarcinoma histology.
- Systemic therapy is an important tool in the multimodality management of patients with oligometastatic disease.

Untreated NSCLC patients with brain metastases have a median survival of approximately 2 months; locally advanced stage III NSCLC patients treated with chemoradiation have a median survival of 16–19 months. Select patients with oligometastatic disease may have a prolonged survival if managed aggressively. We present the case of a 47-year-old woman with lung adenocarcinoma, cT2aN3M1a, (supraclavicular lymph node, solitary brain metastasis). She underwent brain metastasectomy, whole brain radiation, induction chemotherapy and concurrent chemoradiotherapy. She relapsed in the brain and locoregionally and was treated with brain re-irradiation, and systemic chemotherapy. Her progression-free survival was 32 months and she is alive with recurrent disease 63 months after diagnosis. Systemic therapy is an important tool in the multimodality management of patients with oligometastatic disease.

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¹Department of Medical Oncology, Tata Memorial Hospital, Parel, Mumbai 400012, India

²Department of Pathology, Tata Memorial Hospital, Parel, Mumbai 400012, India

³Department of Nuclear Medicine, Tata Memorial Hospital, Parel, Mumbai 400012, India

⁴Department of Radiation Oncology, Tata Memorial Hospital, Parel, Mumbai 400012, India

*Author for correspondence: Tel.: +91 022 24177214; Fax: +91 022 24171734; kumarprabhashtmh@gmail.com

KEYWORDS

- brain metastasis • brain neoplasms • chemotherapy • drug therapy • multimodality • NSCLC • oligometastatic

Patients with metastatic NSCLC have a poor prognosis and are treated with palliative intent [1]. Patients with nonmetastatic N3 nodal disease are treated with curative intent concurrent chemoradiotherapy (CRT); however, these patients also have a dismal prognosis with an expected median survival of 15–19 months and 3-year and 5-year survivals of 17 and 15%, respectively [2–4]. However, select patients with oligometastatic disease who have been treated with curative intent may have a long survival [5–7]. The majority of these patients have been treated with surgery for the primary. There are scant data on the management and outcome of patients who have unresectable primary NSCLC with oligometastatic disease. We present the case of a patient with NSCLC with an unresectable primary and N3 supraclavicular nodal involvement (stage IIIB for the intrathoracic disease component) and a solitary brain metastasis who had a prolonged survival after curative intent treatment.

Case report

A 47-year-old woman presented to an outside hospital in November 2010 with a 1-year history of headache, vomiting, memory loss and vertigo. Computed tomography (CT) brain showed a hyperdense lesion in the left occipito-parietotemporal region. The clinical impression was a primary brain tumor; accordingly, she underwent craniotomy with excision. Histopathology revealed metastatic adenocarcinoma; immunohistochemical stains were positive for CK7, p63, HMWCK and CA125, and negative for CK20, WT1 and ER. She then presented to our hospital (a tertiary care oncology teaching hospital), where a PET-contrast-enhanced CT scan (PET-CECT) showed a centrally located 3.3 × 2.9 cm right lower lobe lung mass (SUVmax 31.2) with enlarged suspicious lymph nodes in the subcarinal (1.7 cm; SUVmax 13.6), pretracheal, paratracheal, aortopulmonary (1.3 cm) and right supraclavicular (1.5 cm; SUVmax 15.9) regions (Figure 1A–D). CT-guided biopsy from the lung mass revealed NSCLC with squamoid and glandular traits (Figure 2A–C). Pathologic comparison of the lung lesion and the brain lesion confirmed that they were similar; thus the patient was diagnosed with adenocarcinoma of the lung, cT2aN3M1b, stage IV. The patient received whole-brain radiotherapy (WBRT) 3000 cGy in ten fractions over 13 days using a telecobalt machine [8]. In order to eliminate bias of any one

specialty or single physician bias, management decisions at our hospital are taken in a multidisciplinary disease management group, comprising a variety of specialists including surgeons, radiation therapists, radiologists, pathologists, pulmonologists and medical oncologists. As the intrathoracic disease was localized with no additional systemic metastases (postmetastasectomy and WBRT), it was decided in the multidisciplinary thoracic oncology tumor board to treat the patient aggressively with curative intent. Due to the presence of N3 disease (supraclavicular lymph node involvement), surgery was not an option. She was therefore planned for definitive CRT. Due to bulky nodal disease which would require large radiation portals, she initially received neoadjuvant chemotherapy with three cycles of pemetrexed 500 mg/m² and carboplatin area under the curve (AUC) 6, (calculated by Calvert's formula). A restaging PET-CECT after neoadjuvant chemotherapy revealed a partial response (Figure 3A–D). A repeat MRI brain showed postradiotherapy (RT) and postoperative changes only. She received CRT with external beam RT with 3D conformal radiotherapy with 15 MV photons to a dose of 60 Gy in 30 fractions over 62 days concurrently with seven cycles of weekly paclitaxel 50 mg/m² and carboplatin AUC 2, completed in October 2011 [9]. Following CRT, she received one additional cycle of systemic chemotherapy with pemetrexed and carboplatin. At her 3 monthly follow-up visit, she was asymptomatic, but CECT thorax showed multiple irregular nodules with spiculated margins in the right lower lobe, largest measuring 2.8 × 1.8 cm with a 2.2 × 1 cm subcarinal lymph node. CT-guided biopsy of the lung lesion showed no evidence of malignancy; there was interstitial fibrosis with fibroblastic proliferation and scattered inflammatory infiltrate; the cells lining the alveolar spaces showed cytological atypia which was consistent with response to therapy, rather than neoplasm. A repeat MRI brain also showed only treatment-related changes. Thus, the lung nodules were considered a sequel of RT. After a disease-free interval (DFI) of 32 months, she presented in July 2014 with a 3-month history of headache, vomiting and recent memory loss. MRI brain revealed 3.9 × 3.3 × 2.7 cm heterogeneously enhancing mass lesion in the right temporal lobe and CT thorax and abdomen revealed 4 × 3.7 cm right lower lobe lung mass, pleural thickening and enlarged subcarinal lymph nodes. Molecular

Figure 1. Baseline PET-contrast-enhanced computed tomography demonstrating the right lower lobe lung mass, mediastinal lymphadenopathy and right supraclavicular lymphadenopathy.

(A) Baseline PET-contrast-enhanced computed tomography (PET-CECT) scan of the chest showing right lower lobe mass. (B) Baseline PET-CECT scan of the chest showing pathologically enlarged subcarinal node. (C) Baseline PET-CECT scan of the chest showing left paratracheal mediastinal lymphadenopathy. (D) Baseline PET-CECT scan of the chest showing right supraclavicular lymphadenopathy.

testing on the original specimen revealed that the tumor was negative for ALK, but the tissue was inadequate for *EGFR* mutation testing. She received focal re-irradiation with 25 Gy in ten fractions to the recurrent brain lesion followed by systemic chemotherapy with six cycles of pemetrexed and carboplatin. She tolerated the therapy well without any grade ≥ 3 toxicity. Response assessment scan revealed partial response. She was started on maintenance pemetrexed and as of February 2016, she has completed 18 cycles of maintenance pemetrexed and her disease continues to be in partial remission (Figure 4).

Discussion

Metastatic NSCLC patients are usually treated with palliative systemic chemotherapy. The response rate to platinum-based combination chemotherapy ranges between 20 and 30% and the median survival of such patients is approximately 8–11 months [1]. Brain, bone, liver and adrenal gland are the most common extrathoracic sites of distant metastases [10]. Approximately 7% of patients with metastatic

disease have a solitary site of metastasis and are said to have ‘oligometastatic disease’ [11,12].

In 1995, the term ‘oligometastatic’ was coined by Hellman and Weichselbaum to describe a disease stage that is between localized and widely metastatic stages wherein the metastases are limited to a single or limited number of organs [13]. A subset of such patients with oligometastatic disease have been reported to have prolonged survivals following curative intent therapy [5–7]. Patients with oligometastatic disease comprising a solitary brain or adrenal lesion who undergo resection of the primary and the metastatic site may have a 5-year survival of 25% [14]. In 2013, Griffioen *et al.* retrospectively studied the survival outcome of 61 patients with oligometastatic (1–3 metastatic sites) NSCLC who were treated with curative intent, either surgery or radiotherapy (dose $\geq 13 \times 3$ Gy). The sites of metastasis included brain, adrenal gland, bone, lung, extrathoracic nodes, skin and colon. Nine patients had surgery for the primary, while the majority of the remaining patients (30 of 52) received CRT for the lung disease, and 52 of the 61 patients (85%) had a longer than 2-year

Figure 2. Histopathologic features of the lung mass. (A) Biopsy of the lung mass showing a NSCLC in a fibrotic stroma (x40). (B) High power view (x400) of an area in the tumor showing attempt at gland formation, thus raising the possibility of adenocarcinoma with a predominant solid pattern. (C) High power view (x400) of the tumor also shows large polygonal cells with distinct cytoplasmic borders, deeply eosinophilic cytoplasm, hyperchromatic nuclei and conspicuous nucleoli. These morphological features favor squamous differentiation.

survival after the radical treatment; the median PFS and overall survival (OS) were 6.6 and 13.5 months, respectively; the 1-year and 2-year actuarial survivals were 54 and 38%, respectively. Patients who underwent surgery for the primary tumor had a significantly better OS [15].

In 2012, De Ruysscher *et al.* published a prospective Phase II trial in 40 patients with synchronous oligometastatic (defined as <5 sites of metastases) NSCLC. The sites of metastases included brain (n = 17), bone (n = 7), adrenals (n = 4), liver, lung, ovary and muscle. In total, 11 (28.2%) patients had N3 disease. Therapy for the thoracic disease comprised either RT or CRT; none of the patients underwent resection of the primary lung tumor. The treatment of the brain metastasis included either surgical resection (n = 4) or stereotactic RT (n = 13) depending on the size and the location of the tumor. The median PFS was 12.1 months and

1-, 2- and 3-year PFS was 51.3, 13.6 and 13.6%, respectively. The median OS was 13.5 months, and 1-, 2- and 3-year OS was 56.4, 23.3 and 17.5%, respectively [16]. Recently there are emerging reports on the use of stereotactic ablative radiation therapy (SABR) for patients with oligometastatic NSCLC [17]. In both the studies by De Ruysscher and Griffioen, the metastatic sites were not restricted to brain. There are a few studies that have described the outcome in patients with synchronous brain-only metastasis from NSCLC. In 1996, Shahidi *et al.* reported prolonged survival in three patients with metastatic NSCLC with single brain metastasis who were treated with curative intent. In this small case series, all patients underwent surgical resection of the brain metastasis; all patients had node-negative resectable lung primaries [5].

In 2001, Billing *et al.* performed a retrospective study of 28 patients of NSCLC with

synchronous brain-only metastasis who underwent resection of disease at both the sites. Postoperative adjuvant therapy was given to 24 patients which included WBRT alone in 15 patients, WBRT with chemotherapy in six and WBRT, chemotherapy and thoracic radiation in three patients. The median survival was 24 months and ranged from 2 to 104 months. The most important factor that affected survival was the presence of lymph node metastasis. The authors concluded that resection of isolated synchronous brain metastasis and the primary tumor should be performed in a selected group of patients without mediastinal lymph node involvement [18]. In 2001, Bonnette *et al.* retrospectively studied the outcome and prognostic factors in 103 patients who underwent resection of both the isolated brain metastasis and the primary lung tumor (the largest oligometastatic series to date). They also observed a prolonged survival with the aggressive approach of combined resection of the brain metastasis and the primary lung tumor. Adenocarcinoma histology, small tumor size and no lymph node metastasis were favorable prognostic factors [19].

In both the above studies in patients with brain-only metastases, both the primary site of the disease and the brain metastasis were resected and both studies identified lymph

node metastasis as a poor prognostic factor. There are paucity of data regarding the management of synchronous oligometastatic brain disease with unresectable primary lung tumor and N3 nodal disease. Few authors have reported their results in patients with NSCLC with synchronous brain metastasis treated with RT or CRT to the primary tumor [9,20,21]. In 2006, Hu *et al.* retrospectively studied 84 newly diagnosed patients of oligometastatic NSCLC with brain-only metastasis. All the patients underwent either surgery or stereotactic radiosurgery for the brain metastasis. The treatment of the primary included radiotherapy (n = 44), chemotherapy (n = 23) or both (n = 13). By applying American Joint Committee on Cancer staging system only to the primary site, they observed that those with stage I disease had a better outcome (median survival of 25.6 months) compared with stage II (median OS-9.5 months) and III (median OS-9.9 months), respectively. They concluded that radical treatment with curative intent may be justified in patients with stage I thoracic disease and brain-only metastasis [21]. Thus, traditionally metastasectomy is indicated only in the presence of a resectable or controllable primary neoplasm. However, we could perhaps begin to challenge this convention, based on the case reported in this manuscript. As is

Figure 3. Restaging PET-contrast-enhanced computed tomography images after neoadjuvant chemotherapy. Restaging PET-contrast-enhanced computed tomography scan of the thorax showing partial remission specifically related to (A) right lower lobe lung mass, (B) subcarinal lymph node, (C) left paratracheal lymphadenopathy; (D) right supraclavicular lymphadenopathy.

Figure 4. Latest contrast-enhanced computed tomography thorax showing continuing partial remission.

evident by our case, it is not only patients with resectable or controllable primary neoplasms that benefit from metastasectomy. Our patient had TxN2M1b disease, and is still alive more than 5 years from the primary diagnosis and the patient's disease is 'under control'.

With the availability of newer therapeutic modalities, perhaps the key to management of a patient with oligometastatic disease is multimodality therapy. Systemic therapy should intuitively be used in these patients given that the disease has systemically metastasized, although there is no level 1 evidence for this. To the best of our knowledge, only one study reported the survival outcome in 30 patients of oligometastatic NSCLC with brain-only metastasis (one unresectable brain metastasis or multiple brain metastases not amenable to surgery or stereotactic radiosurgery) treated with induction chemotherapy followed by thoracic CRT [9]. In this study, all patients received WBRT, induction chemotherapy with two cycles of paclitaxel and cisplatin, followed by CRT to the primary lung tumor (weekly paclitaxel and carboplatin concurrent with 60 Gy of RT) in patients with nonprogressive disease. The patients received four additional cycles of chemotherapy in the absence of disease progression. The median PFS and OS were 8.43 ± 1.5 and 31.8 ± 15.8 months, respectively and the 1- and 2-year OS rates were 71.1 and 60.2%, respectively. The authors concluded that select patients with oligometastatic NSCLC with brain-only metastasis, especially patients with N0-N1 disease might benefit from aggressive treatment with WBRT and CRT to the primary.

Recently, Ashworth *et al.* published an individual patient data meta-analysis of 757 patients with oligometastatic NSCLC, with 1–5 synchronous or metachronous metastases who were

treated with surgical metastasectomy, stereotactic radiotherapy/radiosurgery or radical external beam RT and curative treatment of the primary lung disease. Most patients had T1 or T2 primaries and 52% had no evidence of lymph node involvement. Surgery was performed in 83.9% of patients for the primary lung tumor and 62.3% patients for the metastatic disease. Predictive factors for survival included synchronous versus metachronous metastases ($p < 0.001$), N-stage ($p = 0.002$) and adenocarcinoma histology ($p = 0.036$). The authors proposed a risk stratification system in which patients with low-risk metachronous metastases had a 5-year OS of 47.8%, patients with intermediate risk synchronous metastases and N0 disease had a 5-year OS of 36.2% and high-risk patients with synchronous metastases and N1/N2 disease had a 5-year OS of 13.8%. The median OS of the entire cohort was 26 months, the 1-year OS was 70.2% and the 5-year OS was 29.4% [22].

Conclusion

Even patients with locally advanced NSCLC with N3 nodal disease and a solitary brain metastasis can have a long-term survival with aggressive multimodal therapy. Our patient underwent brain metastasectomy, WBRT, induction systemic chemotherapy and CRT to the lung primary. She was relapsed in the brain as well as locoregionally and was treated with re-irradiation to the brain lesion and systemic chemotherapy. Her PFS was 32 months and she is alive with recurrent disease 63 months after diagnosis. The major clinical challenge would be to accurately identify the subset of these patients who will do well with aggressive therapy.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

References

Papers of special note have been highlighted as:

• of interest; •• of considerable interest

- 1 Peters S, Adjei AA, Gridelli C, Reck M, Kerr K, Felip E. Metastatic non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 23(7), 56–64 (2012).
- 2 Albain KS, Crowley JJ, Turrisi AT *et al.* Concurrent cisplatin, etoposide and chest radiotherapy in pathologic stage IIIB non-small cell lung cancer: a southwest oncology group Phase II study, SWOG 9019. *J. Clin. Oncol.* 20(16), 3454–3460 (2002).
- 3 Belderbos J, Uitterhoeve L, van Zandwijk N *et al.* Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC08972-22973). *Eur. J. Cancer* 43(1), 114–121 (2007).
- 4 Phernambucq EC, Spoelstra FO, Verbakel WF *et al.* Outcomes of concurrent chemoradiotherapy in patients with stage III non-small-cell lung cancer and significant comorbidity. *Ann. Oncol.* 22(1), 132–138 (2011).
- 5 Shahidi H, Kvale PA. Long term survival following surgical treatment of solitary brain metastasis in non-small cell lung cancer. *Chest* 109(1), 271–276 (1996).
- This was the paper that first described that the 5-year survival of patients with oligometastatic disease treated with radical intent is 25%.
- 6 Thippeswamy R, Noronha V, Krishna V *et al.* Stage IV lung cancer: is cure possible? *Indian J. Med. Paediatr. Oncol.* 34(2), 121–125 (2013).
- 7 Niibe Y, Chang JY. Novel insights of oligometastases and oligo-recurrence and review of the literature. *Pulm. Med.* 2012, 261096 (2012).
- 8 Kocher M, Soffietti R, Abacioglu U *et al.* Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J. Clin. Oncol.* 29(2), 134–141 (2011).
- 9 Arrieta O, Villarreal-Garza C, Zamora J *et al.* Long-term survival in patients with non-small cell lung cancer and synchronous brain metastasis treated with whole brain radiotherapy and thoracic chemoradiation. *Radiat. Oncol.* 6, 166 (2011).
- This was the only study to report survival outcome in patients with oligometastatic disease who were treated with induction chemotherapy followed by thoracic radiotherapy.
- 10 Quint LE, Tummala S, Brisson LJ *et al.* Distribution of distant metastases from newly diagnosed non-small cell lung cancer. *Ann. Thorac. Surg.* 62(1), 246–250 (1996).
- 11 Luketich JD, Martini N, Ginsberg RJ, Rigberg D, Burt ME. Successful treatment of solitary extracranial metastases from non-small cell lung cancer. *Ann. Thorac. Surg.* 60(6), 1609–1611 (1995).
- 12 Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience. *J. Clin. Oncol.* 9(9), 1618–1626 (1991).
- 13 Hellman S, Weichselbaum RR. Oligometastases. *J. Clin. Oncol.* 13(1), 8–10 (1995).
- This was the original paper to describe the oligometastatic state, and hence is of interest.
- 14 West H. The slippery slope of broadening treatment eligibility and weak end points. Defending the oligo in oligometastatic non-small cell lung cancer. *JAMA Oncol.* 1(9), 1219–1220 (2015).
- 15 Griffioen GH, Toguri D, Dahele M *et al.* Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors. *Lung Cancer* 82(1), 197–203 (2013).
- 16 De Ruyscher D, Wanders R, van Baardwijk A *et al.* Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases. Long term results of a prospective Phase II trial (NCT01282450). *J. Thorac. Oncol.* 7(10), 1547–1555 (2012).
- 17 Rusthoven CG, Yeh N, Gaspar LE. Radiation therapy for oligometastatic non-small cell lung cancer: theory and practice. *Cancer J.* 21(5), 404–412 (2015).
- 18 Billing PS, Miller DL, Allen MS, Deschamps C, Trastek VF, Pairolero PC. Surgical treatment of primary lung cancer with synchronous brain metastases. *J. Thorac. Cardiovasc. Surg.* 122(3), 548–553 (2001).
- 19 Bonnette P, Puyo P, Gabriel C *et al.* Surgical management of non-small cell lung cancer with synchronous brain metastases. *Chest* 119(5), 1469–1475 (2001).
- This is the largest oligometastatic series to date (103 patients) and the authors identified various prognostic factors that impacted outcome.
- 20 Flannery TW, Suntharalingam M, Regine WF *et al.* Long-term survival in patients with synchronous, solitary brain metastasis from non-small-cell lung cancer treated with radiosurgery. *Int. J. Radiat. Oncol. Biol. Phys.* 72(1), 19–23 (2008).
- 21 Hu C, Chang EL, Hassenbusch SJ *et al.* Non small cell lung cancer presenting with synchronous solitary brain metastasis. *Cancer* 106(9), 1998–1994 (2006).
- This series included patients with brain-only oligometastatic disease, and also identified which patients may benefit from radical curative intent therapy.
- 22 Ashworth AB, Senan S, Palma DA *et al.* An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small cell lung cancer. *Clin. Lung Cancer* 15(5), 346–355 (2014).
- This is an individual patient data meta-analysis of 757 patients with oligometastatic disease, and the authors also proposed a risk stratification system to help decision making.