A 66-Year-Old Woman With Newly Diagnosed Oligometastatic Non–Small Cell Lung Cancer

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Key Words
Non–small cell lung cancer, adrenal metastasis, oligometastatic disease

Abstract
A 66-year-old woman presented with newly diagnosed stage IV non–small cell lung cancer (NSCLC) and a large adrenal metastasis. Five weeks before presentation, she developed low-grade fevers and shortness of breath with minimal activity. After 3 weeks of symptoms, she reported to her primary care physician. Her lung examination was normal and she was given a course of doxycycline for presumed bronchitis. A chest radiograph showed a right upper lobe (RUL) lung nodule. Chest CT 1 week later (Figure 1) showed a 1.4-cm spiculated RUL lung nodule, peripheral right lung nodule, right perihilar mass, and a 10.9-cm left adrenal mass. PET/CT showed enhancement of the RUL nodule, hilar mass, and left adrenal mass. She presented for evaluation of treatment options. This case was thought to represent an instance of oligometastatic stage IV NSCLC. Literature suggests that a select patient population with otherwise resectable disease may benefit from surgical resection of a lung primary and the isolated metastasis with improved survival. This seems to be most effective in patients who have undergone a complete staging evaluation with PET scan; CT of the chest, abdomen, and pelvis; and a brain MRI revealing T1–2, N0–1, M-oligo disease. This radical approach should be reserved for patients with potentially curative disease based on the staging evaluation and who are otherwise good surgical candidates. (JNCCN 2012;10:297–301)
activity. The left adrenal mass showed peripherally increased fluorodeoxyglucose (FDG) uptake at an SUV of 19.6. The right adrenal nodule was not FDG-avid. The patient was then referred to the authors’ institution for further evaluation and care.

The patient currently feels well and has returned to her baseline functional state with ECOG performance score of 0. Her presenting shortness of breath resolved. She has occasional transient pain along her left flank. Her past medical history is notable for a greater than 40 pack-year tobacco history before she quit 5 years ago. She had a hysterectomy and 10 years of hormone replacement therapy. She reported an episode of pneumonia as a child and another episode 5 years before her recent presentation. Her only current medication is warfarin. Her family history is negative for cancer. On physical examination, she looks well without dyspnea and with normal vital signs. She had no abnormal cardiopulmonary or abdominal findings. Her flank pain was not elicited on examination. She had no palpable lymph nodes or organomegaly. Her recent laboratory results showed normal blood counts, electrolytes, renal and liver function, and therapeutic international normalized ratio.

Discussion

After the initial clinical visit, this case was thought to potentially represent an instance of oligometastatic stage IV NSCLC. The RUL parenchymal lesion was thought to be the primary and the perihilar lesion to represent N1 regional lymph node involvement. The peripheral pleural nodule was small and did not have increased FDG uptake, suggesting a lower likelihood for it to be malignant. The right adrenal nodule was read as not having increased uptake and was thought to be a benign finding. With this interpretation (T1, N1, M-oligo), her case was considered for treatment with curative intent for oligometastatic disease.

The TNM staging guidelines for NSCLC were revised recently to account for better-understood prognostication based on disease involvement. A rare subset of patients with oligometastatic disease was not separately delineated as part of the current staging system, but these patients may benefit from treatment with curative intent. According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC [NSCLC-11], patients with oligometastatic disease, specifically a single adrenal or brain lesion, may benefit from a different treatment approach compared with those with advanced or widespread metastases (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). Some literature suggests that patients with a solitary adrenal metastasis may be amenable to curative intent therapy through treating the lung and adrenal lesions with local surgery, resulting in improved overall and 5-year survival.

Diagnosis and treatment of oligometastatic NSCLC is a shifting area of research as imaging technique quality and sensitivities evolve. A se-
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ries published in the 1970s, before the availability of PET/CT scans, reported that 9% of 202 patients undergoing curative resection had clinically unsuspected adrenal metastasis when examined at autopsy within 1 month of pulmonary surgery. In a prospective analysis of 246 patients with otherwise operable NSCLC according to CT staging, 10 (4.1%) were found to have a suspicious adrenal metastasis, 4 of which were found malignant on biopsy. PET/CT has become the standard of care, noting clinically significant changes in staging in 20% of patients compared with staging using CT alone, and detecting occult metastases in 6% of patients. Thus, to pursue an oligometastatic approach to treating NSCLC, patients must be fully staged using current modalities before treatment.

A retrospective review by Khan et al. examined all patients with NSCLC presenting to their institution’s radiation oncology clinic between 1989 and 2004. They focused on the subset of patients with oligometastatic disease who received systemic therapy and otherwise curative-intent locoregional management. All but one patient had a PET scan as part of the staging workup. Brain imaging was performed only if patients developed neurologic symptoms. Of the 371 charts reviewed, only 23 patients (6%) met these criteria. All had an ECOG performance status of 0 to 1. Most had oligometastatic brain metastasis (14/23), but 2 had an adrenal metastasis. Of the 23 patients, 7 had T3/4 disease and 17 had N2/3 disease, suggesting that what was considered “curable” surgery at that time might now be considered non–resectable disease, and that the locoregional disease burden was high. Median survival was 20 months (range, 9–148 months), with 5 patients (22%) surviving beyond 36 months.

In the only published prospective phase II trial by Downey et al., patients with NSCLC and a solitary synchronous metastasis were treated with neoadjuvant mitomycin, vinblastine, and cisplatin (MVP) and resection of the lung primary and metastasis, followed by MVP adjuvant treatment. Of the 23 patients studied, 3 had adrenal metastases, but only 1 of these eventually underwent adrenalectomy. Conclusions regarding whether an oligometastatic approach could be beneficial could not be made from this study. The results were heterogeneous and the protocol chemotherapy regimen was poorly tolerated, limiting the ability to extrapolate their results.

Beitler et al. reviewed the role of adrenalectomy for oligometastatic lung cancer. Sixty patients from 11 published reports were included and were subdivided into patients pooled from case reports and small series versus those from 2 large series. Of the 32 patients from the small series and case reports group, the median overall survival was 24 months. The 28 patients summed from the 2 large series had an overall survival of 14 months. The discrepancy of overall survival between the subgroups suggests a publication bias of small studies highlighting patients who did well with a metastasectomy approach.

Multiple retrospective analyses and reviews have attempted to define which patients with oligometastatic disease are likely to benefit from a potentially curative approach. A retrospective review of 43 patients treated with resection of both the lung primary and a solitary adrenal metastasis reported a median overall survival of 11 months. Disease recurrence was seen in 80% of patients, half within 6 months, but 3 patients were still alive at 5 years. The study was too small to identify any predictive indicators of who would benefit most from oligometastatic treatment. Specifically, no difference was seen when patients were subdivided by histology; TNM stage; synchronous metastasis (concurrent diagnosis of lung primary and metastasis) versus metachronous metastasis (subsequent diagnosis of the metastasis); or time to metachronous metastasis. A later literature review of 10 publications addressed definitive surgery in oligometastatic NSCLC in 114 patients who were divided retrospectively into synchronous or metachronous adrenal metastasis. Median overall survival was 12 months for synchronous disease and 31 months for metachronous disease. However, the estimated 5-year survival rates were 26% in the synchronous group and 25% in the metachronous disease, suggesting equivalent longer-term outcomes.

A single-institution review reported equivalent overall survival for synchronous and metachronous disease, but improved overall survival for ipsilateral disease. Both ipsilateral metastases (those occurring on the same side of the body as the lung primary) and contralateral metastases are considered distant sites of disease. Researchers have conjectured that ipsilateral metastases are the result of lymphatic spread from the lung primary to the adrenal gland, whereas contralateral disease develops via hematogenous spread. The ipsilateral survival benefit was not shown in most other studies.
A recent retrospective review by Mordant et al. evaluated patients with NSCLC and a solitary extrathoracic metastasis who had undergone curative intent surgery for the lung primary between 1983 and 2006. Ninety-four patients met their criteria, 12 of whom had a metastasis in the adrenal gland. PET/CT was included in the staging workup for later cases. In this review, surgical resection of the metastasis was not associated with a survival benefit (P = .67). However, N0 staging (compared with N1 or N2) did confer a 5-year survival benefit (31.2% N0 vs. 0% N1 vs. 4% N2; P < .01). This reinforces the idea that nodal disease burden can greatly influence the potential success of an oligometastatic approach.

Although most of the published literature is retrospective, improved outcomes with adrenalectomy are possible. The authors advocate for applying this technique in patients who meet appropriate selection criteria (i.e., staging with CT, PET, and brain MRI showed otherwise resectable disease and only an isolated metastasis [T1–2, N0–1, M-oligo]; and surgical candidate). Using this approach, surgery for oligometastatic disease may be indicated for a very small subset of patients (only 0.7% in one study). However, with improving technologies, currently labeled “medically inoperable” patients may have new treatment options, such as stereotactic ablative lung radiotherapy. As these opportunities evolve, the criteria for appropriate treatment candidates will need to be amended.

Conclusions
The NCCN Guidelines for NSCLC specifically detail the pretreatment evaluation of patients with a potentially solitary site of metastatic disease (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org [NSCL-11]). To confirm that a patient only has a single site of metastasis, complete staging should include mediastinoscopy, bronchoscopy, brain MRI, and a PET/CT scan. As the authors were considering using a potentially curative approach to treat their patient with presumed oligometastatic disease, this case was discussed at the multidisciplinary tumor board with representation from surgical oncology, radiology, radiation oncology, and medical oncology. On detailed review, concern was expressed that her disease was actually more extensive than originally described. Reviewing the original images, increased FDG avidity was seen in all 3 lung lesions (including the peripheral RUL lesion) and in both the left and right adrenal lesions. Comparatively, the right adrenal lesion had a lower SUV than the large left lesion, but it was noticeably increased from the background. The authors elected not to pursue a tissue diagnosis of either of the adrenal lesions, given the overall picture of more than a solitary metastatic site. This underscores the importance of careful review of the primary data, both as a primary provider and as a consultant.

This case also reinforces the need for expertise in imaging acquisition and interpretation in a complete staging workup before initiating a treatment plan. An oligometastatic approach might be beneficial in certain patient populations, but only after an extensive evaluation to confirm that the metastatic site is truly solitary. Once it became clear that this patient did not have oligometastatic disease, the authors treated the patient in concordance with NCCN Guidelines for NSCLC recommendations for disseminated metastatic disease (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org [NSCL-13]). Because the patient had adenocarcinoma histology, EGFR mutation testing and ALK fluorescence in situ hybridization testing were ordered.

In the absence of a known sensitizing mutation, the authors pursued first-line therapy with doublet chemotherapy according to the NCCN Guidelines for NSCLC (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org [NSCL-14]). Several acceptable category I options are available for treatment in this setting. Given the adenocarcinoma histology, the authors recommended carboplatin and pemetrexed, because this regimen is well tolerated. This patient was started on this regimen and, after the first cycle, noted a decrease in her left flank pain and improved exercise capacity.

References
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