CASE SERIES

Imaging in thoracic oncology: case studies from Multidisciplinary Thoracic Tumor Board (part 2 of 2 part series)

Leslie E. Quint[a,b], Rishindra M. Reddy[b], Jules Lin[b], Douglas A. Arenberg[d], Corey Speers[e], James A. Hayman[e], Fengming P. Kong[e], Mark B. Orringer[b], Gregory P. Kalemkerian[c]

[a]*Department of Radiology,* [b]*Department of Surgery (Section of Thoracic Surgery),* [c]*Department of Internal Medicine (Medical Oncology),* [d]*Department of Internal Medicine (Pulmonary Medicine) and* [e]*Department of Radiation Oncology, University of Michigan Medical Center, Box 0030, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0030, USA*

Corresponding address: Leslie E. Quint, MD, Professor of Radiology, Department of Radiology, University of Michigan Medical Center, Box 0030, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0030, USA.
Email: lequint@med.umich.edu

Abstract

Multidisciplinary tumor board conferences foster collaboration among health care providers from a variety of specialties and help to facilitate optimal patient care. Generally, the clinical questions revolve around the best options for establishing a diagnosis, staging the disease and directing treatment. This article describes and illustrates the clinical scenarios of three patients who were presented at our thoracic Tumor Board, focusing on management issues and the role of imaging. These patients had invasive thymoma; concurrent small cell lung cancer and non-small cell lung cancer; and esophageal cancer with celiac lymph node metastases, respectively.

Keywords: *Lung cancer; small cell lung cancer; non-small cell lung cancer; esophageal cancer; invasive thymoma; tumor board.*

Background

Part 1 of this two part series described and illustrated the clinical scenarios of three patients who were presented at the weekly Multidisciplinary Thoracic Tumor Board conference at our institution. These patients (cases 1–3) had non-small cell lung cancer (NSCLC) and mediastinal lymph node metastases; a small, growing ground glass nodule; and oligometastatic NSCLC, respectively. This article constitutes part 2, which presents three additional patients (cases 4–6) with invasive thymoma; concurrent small cell lung cancer (SCLC) and NSCLC; and esophageal cancer with celiac lymph node metastases, respectively. The discussions focus on management issues and the role of imaging for each patient.

Case 4: invasive thymoma

History and imaging findings

A 67-year-old woman with a 6-year history of myasthenia gravis presented to the emergency room with worsening dyspnea on exertion. Her past medical history included coronary artery disease with coronary stent placement, diabetes, and intermittent shortness of breath with previous oxygen dependence due to her myasthenia gravis. Her family history was notable for a sister who recently died from complications of myasthenia gravis. She had a 60 pack-year smoking history, although she quit 10 years ago. She presented with poor pulmonary function tests, including an FEV_1 (forced expiratory volume in the first second of expiration) of 1.16 L (49% predicted) and a D_{LCO} (diffusing capacity of lung for carbon monoxide) of 47% predicted. A chest radiograph showed a lobulated anterior mediastinal mass; mild elevation of the left hemidiaphragm suggested involvement of the ipsilateral phrenic nerve (Fig. 1a). A computed tomography (CT) scan of the chest from an outside hospital revealed a lobulated 8-cm diameter left-sided anterior mediastinal mass (Fig. 1b). On subsequent re-evaluation of the scan by the Tumor Board, a 1-cm left-sided pleural nodule was noted, consistent with a drop metastasis in the pleural space.
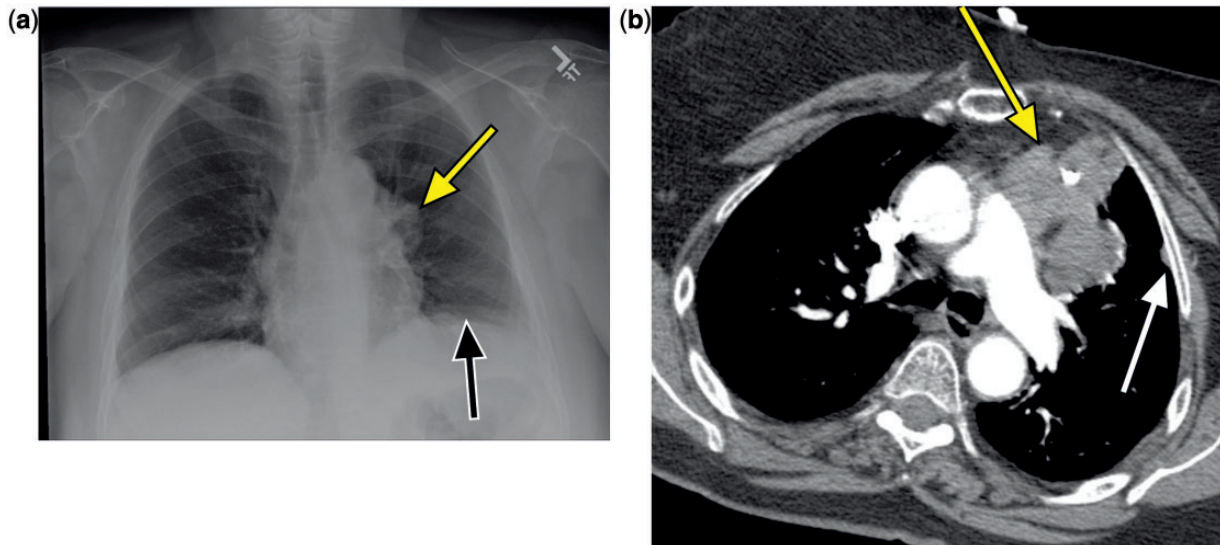
Figure 1 A 67-year-old woman. Chest radiograph (a) showed a lobulated anterior mediastinal mass (yellow arrow) with mild elevation of the left hemidiaphragm (black arrow). CT scan (b) demonstrated a lobulated, left-sided anterior mediastinal mass (yellow arrow) and a 1-cm left-sided pleural nodule (white arrow).

A CT-guided biopsy was performed and pathology revealed epithelial cells consistent with a thymoma, type B2. Due to the patient's comorbidities, she was referred to a tertiary care center for surgical evaluation.

Tumor Board input and clinical course

During presentation at the Tumor Board, it was determined that the patient had not been seen by her cardiologist or neurologist in the previous year, and she appeared to be a borderline surgical candidate at best. Due to her comorbidities, she was not deemed an optimal candidate for chemotherapy, and therefore radiotherapy was recommended for both the primary tumor and the presumed solitary metastasis.

Management Issues

When should an anterior mediastinal mass be biopsied?

The diagnostic evaluation of an anterior mediastinal mass depends on the initial radiologic interpretation. If the appearance is strongly suggestive of a non-invasive thymoma, resection is generally recommended. Percutaneous biopsy of potentially encapsulated thymomas should be avoided in order to prevent extracapsular tumor seeding. If the radiographic appearance suggests lymphoma, a positron emission tomography (PET) scan may be helpful in revealing other sites of disease that are more accessible for tissue sampling; in any case, a tissue biopsy is needed to confirm the diagnosis of lymphoma. A core biopsy may be obtained, or an anterior mediastinotomy may be performed to access tissue directly, without potentially seeding the lateral pleural spaces. If a

germ cell tumor is high in the differential diagnosis, β-human chorionic gonadotropin and α-fetoprotein levels should be checked, and a needle biopsy may be performed to confirm the diagnosis[1].

Is surgery the best treatment option for thymomas?

For suspected thymomas, surgery should only be offered if complete surgical resection is possible. Patients should be evaluated routinely for the risks of general anesthesia, including an evaluation for possible myasthenia gravis, which, if present, should be optimally controlled before surgery. Also, pulmonary function testing is critical before surgery, as phrenic nerve involvement is not always apparent on radiologic scans, and baseline pulmonary status may affect intra-operative decision making if a phrenic nerve is involved.

Resection is typically performed through a median sternotomy, although minimally invasive options utilizing a lateral approach are possible for small, fat-encapsulated lesions that do not appear to abut any major structures. In general, an approach through a median sternotomy is favored as it allows full access to the anterior mediastinum and removal of all the fat between the chest wall and the pericardium. Thymic tissue deposits can extend down to the level of the diaphragm. Care is taken to avoid entering the bilateral pleural spaces in order to minimize droplet metastases. Patients with thymomas that extend into the pericardium, a single phrenic nerve, or into the innominate vein or other branch vessels may still be surgical candidates, but patients with advanced local disease should be carefully selected. For a patient with normal lung function, the resection of a single phrenic nerve can be performed with minimal comorbidity, and some

surgeons favor performing a diaphragm plication of the affected side in the same setting. However, tumors that involve both phrenic nerves should not be resected, as loss of both phrenic nerves would require permanent diaphragm pacing or ventilator dependence. Tumors involving the pericardium may be removed en bloc with the involved portion of the pericardium, although a pre-operative echocardiogram should be considered to rule out cardiac involvement, which would indicate unresect-ability; resection of the anterior pericardium rarely requires mesh reconstruction. Tumor involvement of the pericardium does lead to a higher future incidence of pericardial metastases. Thymomas that grow into the innominate artery or vein may also be resected for cure, as vessels may be repaired with a small Dacron patch or completely replaced with a graft. Careful patient selection is critical in these cases, and this extensive resection should only be performed at a center with experience in complex resections and reconstruction[2].

Disease that has spread into the pleural space is con-sidered metastatic and not amenable to surgical cure, although in select patients with isolated metastases and long disease-free intervals, resection for local control may be considered. Usually, the favored treatment is systemic chemotherapy, although in our patient's case, this was not recommended due to her extensive comorbidities. Radiotherapy provides a potential alternative for local postoperative control in the setting of residual disease. No matter what treatment is chosen, the long-term prog-nosis is most often related to the inherent biology and rate of growth of the tumor[3].

Role of imaging

CT imaging suggested the diagnosis of thymoma due to the lobulated appearance of the mass protruding off to one side of the mediastinum, the presence of calcifica-tion, and lack of additional lymph node enlargement. Furthermore, the detection of a separate pleural nodule in the ipsilateral hemithorax was crucial in indicating tumor spread outside the capsule of the gland[4].

Case 5: concurrent SCLC and NSCLC

History and imaging findings

A 74-year-old man with a 60 pack-year history of cigarette smoking presented with a 3-month history of uninten-tional weight loss, exertional dyspnea, and occasional non-productive cough. Chest CT at an outside hospital showed a 2.6-cm diameter irregular nodular opacity along the pleural surface of the right upper lobe (Fig. 2a) that was slightly larger compared with a scan from 3 years earlier, as well as a new, separate, 4-cm diameter right upper lobe perihilar mass (Fig. 2b). Both lesions showed intense fluorodeoxyglucose (FDG) avidity at PET scan-ning (Fig. 2c,d). Endobronchial ultrasound-guided biopsy of the right hilar mass revealed SCLC (TTF-1, CD5/6,

synaptophysin positive, and chromogranin A, napsin A negative).

Tumor Board input and clinical course

Review of the images by the Tumor Board indicated that the peripheral right upper lobe lesion likely represented NSCLC due to its relatively indolent course over a 3-year period and its morphologic features. Given biopsy proof of SCLC in the hilar mass, the Tumor Board thought that the patient probably had two different malignancies. A CT-guided biopsy of the peripheral lesion was recom-mended and showed adenosquamous NSCLC. He was thus diagnosed with two synchronous primaries and staged as limited stage (T2a N1 M0) SCLC and stage IA (T1b N0 M0) NSCLC. After a CT of the brain revealed no evidence of intracranial metastasis, he went on to receive definitive chemoradiotherapy with cisplatin and etoposide and twice daily radiation therapy for SCLC treatment, with plans for subsequent resection or stereotactic body radiotherapy (SBRT) to the stage IA right upper lobe NSCLC.

Management issues

Why did the patient undergo both a diag-nostic CT and a PET/CT?

CT scanning is generally the initial imaging modality obtained in clinical situations such as this, because it shows excellent anatomic detail and may elucidate both neoplastic and non-neoplastic disease processes account-ing for the patient's signs and symptoms. In addition, the precise anatomic information obtained from CT may aid in surgical treatment planning of tumors. PET is per-formed only after there is a presumed or proven diagnosis of cancer, in order to stage the tumor; it is particularly helpful in identifying previously occult sites of metastatic disease. Other imaging modalities, such as magnetic res-onance imaging, are reserved for specific problem sol-ving, such as the evaluation of indeterminate liver or adrenal lesions or assessment for brachial plexus invasion from superior sulcus tumors.

How common are synchronous primary cancers of the lung?

Synchronous primary lung cancers are relatively uncom-mon, with the reported prevalence ranging from 0.3% to 4.6%[5]. The simultaneous discovery of additional pulmo-nary nodules in a patient with proven lung cancer raises the clinical dilemma of whether this finding represents multifocal disease, synchronous multiple primary lung cancers (of similar or dissimilar histologic subtype, which can potentially be treated with curative intent), or metastases. Furthermore, the co-incidence of SCLC and NSCLC in the same patient is uncommon and repre-sents a particular treatment dilemma[6]. A combination of diagnostic imaging, understanding of patterns of
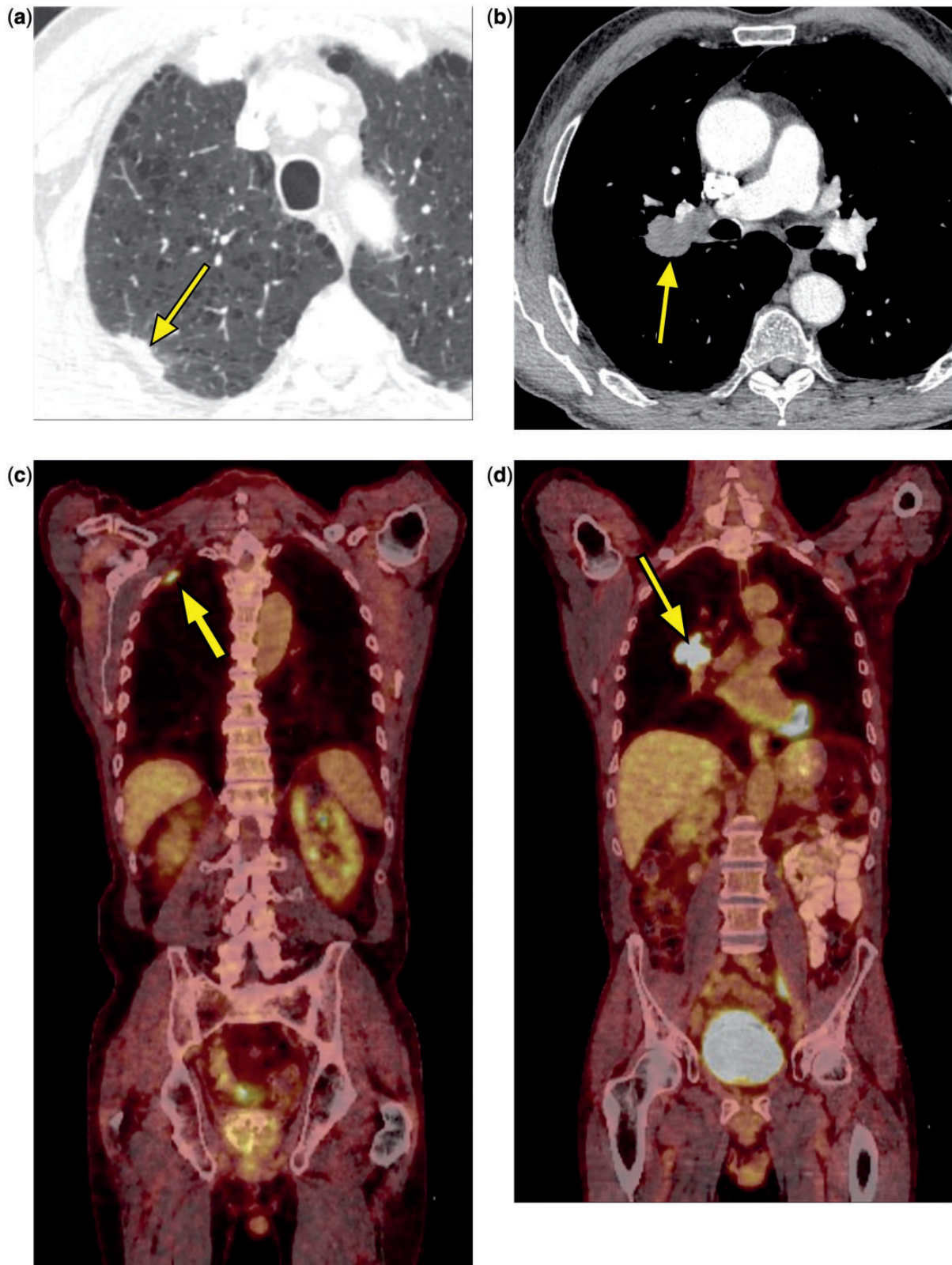
Figure 2 **A 74-year-old man. Chest CT showed a 2.6-cm diameter irregular nodular opacity along the pleural surface of the right upper lobe (a, arrow) and a separate 4-cm diameter right upper lobe perihilar mass (b, arrow). Both lesions showed intense FDG avidity at PET scanning (c,d, arrows).**

spread and tumor characteristics, and clinical experience may raise or lower the level of clinical suspicion for synchronous primaries. Ultimately, however, confirmatory biopsies, sometimes with molecular analyses that are not available at all institutions, are required to establish the diagnosis of synchronous primaries versus metastatic disease.

Is PET scanning helpful in distinguishing synchronous primary lung cancers from metastatic disease?

Recent work using FDG signatures from PET scans showed that the difference in the measured standardized uptake values (SUVs) of lung lesions may be useful in differentiating metastatic from synchronous primary lung cancers. In a retrospective analysis in which not all sites were biopsied, the relative difference between the SUVs of lung lesions was significantly higher in patients with second primary cancers than in those with metastatic disease[7]. In our patient, however, both lesions were similarly intensely FDG avid.

How did the diagnosis of two different primary cancers change the treatment approach?

Treatment of extensive stage SCLC (the original diagnosis in this patient) generally involves combination platinum-based chemotherapy with consideration of the addition of intrathoracic radiation therapy in select patients with a partial/complete response locally and a complete response distantly[8]. In addition, prophylactic cranial radiation therapy has shown an overall survival benefit in patients with partial to complete response to chemotherapy[9]. Despite these interventions, however, the prognosis for extensive stage SCLC remains dismal, with a median survival of 10 months and a 5-year overall survival rate of 1%. Conversely, treatment of limited stage SCLC involves a combination of cisplatin and etoposide chemotherapy and routine use of early radiation therapy either to a dose of 45 Gy with 1.5 Gy twice daily treatments or 60 Gy in 30 daily fractions[10–12]. With a good response to therapy, the addition of prophylactic cranial irradiation to 25 Gy in 10 fractions has been shown to improve overall survival[13]. Compared with extensive stage SCLC with its associated poor median and overall survival, the median survival of patients with limited stage SCLC is 20 months with 5-year overall survival rates reported between 20 and 25%.

Treatment of stage IA NSCLC involves either resection (in those patients deemed surgical candidates) or SBRT in those patients who are not surgical candidates. Control rates with either modality remain extremely high with 3-year overall survival rates of 50–70% with resection and 40–88% in unresectable patients treated with SBRT[14–16].

Thus, the treatment and prognosis of a patient with extensive stage SCLC is markedly different than for a patient with synchronous limited stage SCLC and stage IA NSCLC. Accurate diagnosis and staging leads to more appropriate treatment selection, and, in our patient, a much better potential prognosis for someone initially diagnosed with a universally fatal disease.

Role of imaging

The morphologic features of the peripheral lesion at CT and the slow growth of this lesion on serial CT scans suggested the correct diagnosis, leading to a confirmatory CT-guided biopsy.

## Case 6: esophageal cancer with celiac lymph node metastases

History and imaging findings

A 45-year-old man with a past medical history of gastroesophageal reflux and hiatal hernia presented in March 2009 with a 3-week history of hematemesis. Endoscopy revealed a fungating mass in the distal esophagus, and biopsy demonstrated a poorly differentiated invasive adenocarcinoma arising in the Barrett mucosa. At endoscopic ultrasonography, the primary esophageal tumor appeared to be invading the adventitia, and a nearby enlarged lymph node showed an abnormal echotexture; the tumor was staged as T3N1Mx.

A barium esophagram showed an irregular mass in the distal esophagus and a small hiatal hernia (Fig. 3a). CT scans showed thickening of the distal esophagus (Fig. 3b) and an enlarged lymph node in the region of the gastrohepatic ligament, extending to the border of the celiac axis (Fig. 3c,d). Both the distal esophagus and the lymph node were intensely FDG avid at PET scanning (SUV 6.2 and 8.3, respectively) (Fig. 3e,f).

Tumor Board input and clinical course

Due to the location of the abnormal lymph node at the celiac axis on CT scanning, the tumor was thought to be stage T3N0M1a (stage IVa) according to the 6th edition of the American Joint Committee on Cancer (AJCC) staging classification, and the Tumor Board recommended definitive, combined radiation therapy and chemotherapy. The patient subsequently received definitive radiation therapy with 56 Gy and concurrent 5-fluorouracil and cisplatin. After completion of chemoradiotherapy, no residual neoplasm was detected on a follow-up PET scan. Endoscopic biopsy at 15 sites showed Barrett mucosa and high-grade dysplasia without evidence of invasive carcinoma. Despite the potential morbidity and mortality associated with surgery, the patient was still interested in undergoing esophageal resection. After discussion by the Tumor Board, a transhiatal esophagectomy and cervical esophagogastric
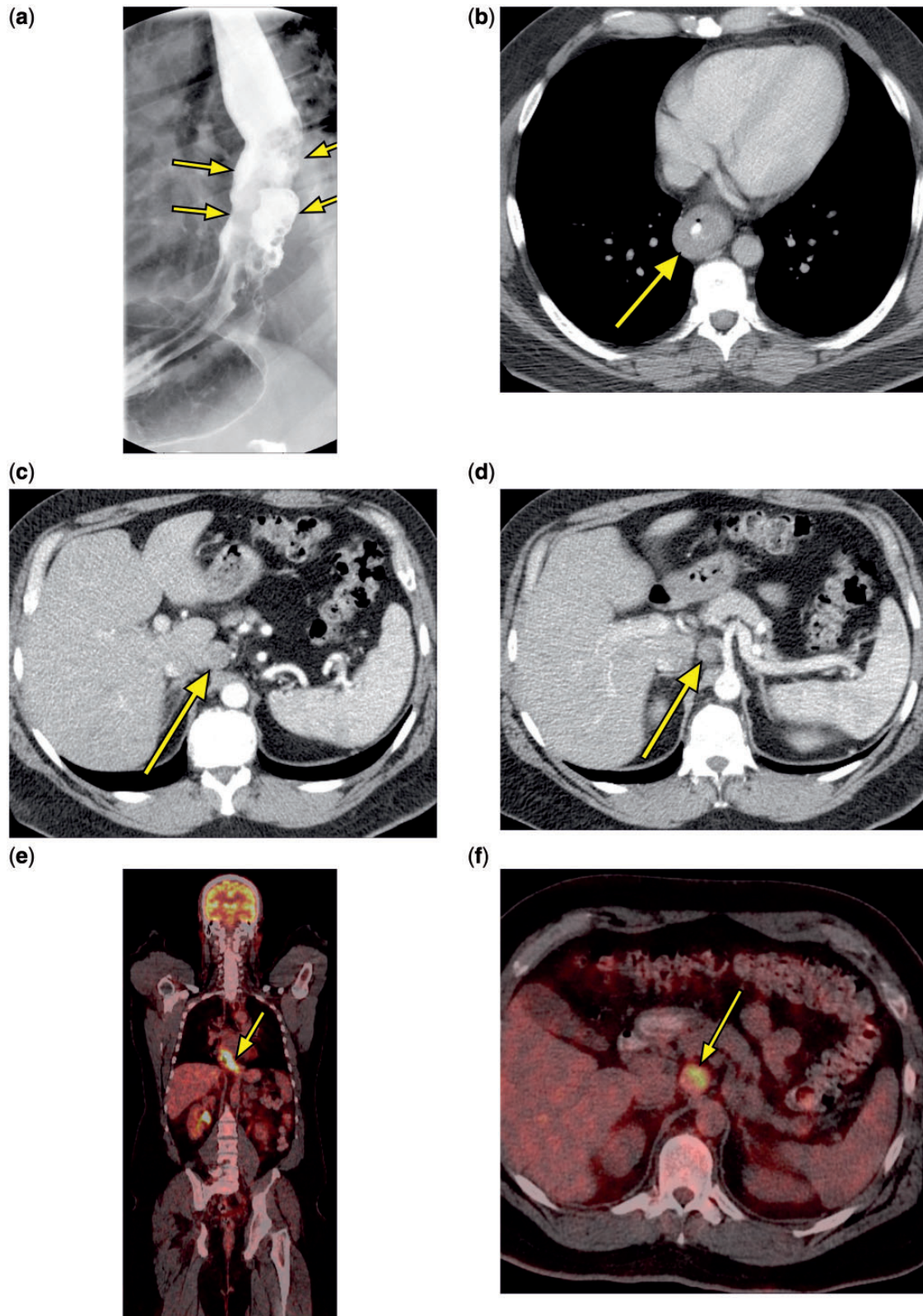
Figure 3 **A 45-year-old man. A barium esophagram showed an irregular mass in the distal esophagus (a, arrows) and a small hiatal hernia. CT scans showed thickening of the distal esophagus (b, arrow) and an enlarged lymph node in the region of the gastrohepatic ligament, extending to the celiac axis (c,d, arrows). Both the distal esophagus and the lymph node were intensely FDG avid at PET scanning (SUV 6.2 and 8.3, respectively) (e,f, arrows).**

anastomosis were performed. The final pathology report showed no residual cancer in the resected esophagus or the removed lymph nodes. The patient is currently doing well, without evidence of disease, 3.5 years after initial treatment.

Management issues

How did updates to the 7th edition of the AJCC staging system (2010) affect the staging of this patient's disease?

When this patient was staged in 2009, involvement of celiac axis lymph nodes was deemed M1a (stage IV) disease according to the 6th edition of the AJCC staging system, and this tumor was considered unresectable. In the 7th edition of the staging system, which was published in 2010, involvement of celiac lymph nodes was reclassified as regional nodal disease, and thus potentially amenable to resection, albeit after preoperative chemoradiation. This reclassification was based on survival data showing that patients with celiac nodal metastases often fared as well as those with regional nodal disease at other sites and considerably better than those with distant organ metastases. Thus, using the newer staging system, this patient's disease would have been classified as T3N1M0 (stage IIIA), compared with T3N0M1a (stage IVa) using the older system, and neoadjuvant rather than definitive chemoradiotherapy would have been indicated.

What is the value of neoadjuvant chemoradiotherapy before esophagectomy?

There are several advantages of neoadjuvant chemoradiotherapy before esophagectomy. Chemoradiotherapy frequently results in downstaging by reducing the size of the primary tumor and sterilizing regional lymph nodes that contain metastatic disease. As a result, the required extent of the esophagectomy may be reduced. Surgical evidence has demonstrated that patients with good responses to chemoradiation show significantly better survival after esophagectomy compared with those who have responded poorly to chemoradiation[17,18]. Our published data indicated that among 583 patients who received chemoradiation before a transhiatal esophagectomy, 125 (21%) were complete responders (ypT0N0). Their 2- and 5-year survival rates were 80% and 58%, respectively. Among the remaining patients with residual cancer in the resected specimen, the 2- and 5-year survival rates were 45% and 32%, respectively[17]. Even these latter survival data compare favorably with historic control patients who had no chemoradiation before esophagectomy and had 2-year survival rates in the single digits.

What is the value of an esophagectomy after chemoradiotherapy, particularly in those who are complete responders to chemoradiotherapy?

Published randomized trials have demonstrated a limited survival benefit of surgery after chemoradiation[19,20]. Patients enrolled in these two trials had esophageal squamous cell carcinomas, which show distinctly different biological behavior compared with adenocarcinomas, the most common form of esophageal cancer in the United States. Unfortunately, there is no randomized trial investigating the additional role of surgery after chemoradiation in patients with adenocarcinomas of the lower esophagus and esophagogastric junction.

The consensus opinion of the National Comprehensive Cancer Network (NCCN) is that esophagectomy is the preferred treatment after evidence of a complete response to chemoradiotherapy for adenocarcinoma of the lower esophagus/gastroesophageal junction. Unfortunately, there is currently no definitive test, short of analysis of the resected esophagus, that can conclusively identify a complete response to chemoradiation. Roughly 21–30% of patients with esophageal carcinoma have had a complete response when the resected esophagus is examined histologically[17,21]. Conversely, approximately 70–80% still have residual carcinoma. Until we have treatment that results in a complete response in most patients so treated, an esophagectomy and regional nodal dissection is the best means of insuring removal of residual local tumor, and, if there is no residual cancer in the specimen, identifying those who are truly complete responders. This distinction has obvious implications on the recommendation for adjuvant therapy.

What is the role of radiation therapy in the treatment of esophageal cancer?

Although the role of radiation in providing local tumor control has been clearly defined in the management of esophageal cancer, some questions remain regarding the most appropriate radiation dose. In general, as stated in the NCCN guidelines, a dose of 45–50.4 Gy is recommended for neoadjuvant chemoradiation followed by esophagectomy. However, it is worth noting that 41.4 Gy in 1.8 Gy fractions was used in the recently reported CROSS study, which demonstrated the superiority of neoadjuvant radiation and concurrent weekly carboplatin and paclitaxel over surgery alone[21]. Although higher doses have been used in Japanese and European multicenter studies, the NCCN guidelines still recommend 50–50.4 Gy in 1.8–2.0 Gy fractions for definitive chemoradiotherapy. This recommendation is largely based on an intergroup randomized study that showed no benefit of 64.8 Gy on survival or locoregional control over 50.4 Gy[22]. At our institution, a total dose of 50–50.4 Gy for chemoradiotherapy is typically used in both the

neoadjuvant and definitive settings, with fractionation depending on the patient's tolerance. Future studies to identify biomarkers for intrinsic tumor sensitivity to chemoradiation would be ideal, in order to individualize the dose prescription.

Role of imaging

The findings on PET scanning were highly suspicious for metastatic disease within the celiac axis lymph node, due to the similarly high FDG activity within the primary esophageal tumor and the lymph node. On the other hand, CT enabled precise anatomic localization of the lymph node, which influenced tumor staging and, consequently, patient treatment.

Conclusion

Input from the entire multidisciplinary oncology group facilitates integration of imaging findings into the larger clinical context, thereby optimizing patient management.

Conflict of interest

The authors have no conflicts of interest to declare.

References

[1] Duwe BV, Sterman DH, Musani AI. Tumors of the mediastinum. Chest 2005; 128: 2893–2909. doi:10.1378/chest.128.4.2893. PMid:16236967.

[2] D'Andrilli A, Venuta F, Rendina EA. Surgical approaches for invasive tumors of the anterior mediastinum. Thorac Surg Clin 2010; 20: 265–284. doi:10.1016/j.thorsurg.2010.02.002. PMid: 20451137.

[3] Spaggiari L, Casiraghi M, Guarize J. Multidisciplinary treatment of malignant thymoma. Curr Opin Oncol 2012; 24: 117–122. doi:10.1097/CCO.0b013e32834ea6bb. PMid:22143371.

[4] Quint LE. Imaging of anterior mediastinal masses. Cancer Imaging 2007; 7(Spec No A): S56–62. doi:10.1102/1470-7330.2007.9014. PMid:17921091.

[5] Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975; 70: 606–612. PMid:170482.

[6] Hiraki A, Ueoka H, Yoshino T, et al. Synchronous primary lung cancer presenting with small cell carcinoma and non-small cell carcinoma: diagnosis and treatment. Oncol Rep 1999; 6: 75–80. PMid:9864405.

[7] Dijkman BG, Schuurbiers OC, Vriens D, et al. The role of (18)F-FDG PET in the differentiation between lung metastases and synchronous second primary lung tumours. Eur J Nucl Med Mol Imaging 2010; 37: 2037–2047. doi:10.1007/s00259-010-1505-2. PMid:20533031.

[8] Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. J Clin Oncol 1999; 17: 2092–2099. PMid:10561263.

[9] Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007; 357: 664–672. doi:10.1056/NEJMoa071780. PMid:17699816.

[10] Miller KL, Marks LB, Sibley GS, et al. Routine use of approximately 60 Gy once-daily thoracic irradiation for patients with limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 2003; 56: 355–359. doi:10.1016/S0360-3016(02)04493-0. PMid:12738309.

[11] Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992; 327: 1618–1624. doi:10.1056/NEJM199212033272302. PMid: 1331787.

[12] Turrisi AT, 3rd. Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999; 340: 265–271. doi:10.1056/NEJM199901283400403. PMid:9920950.

[13] Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999; 341: 476–484. doi:10.1056/NEJM199908123410703. PMid:10441603.

[14] Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009; 75: 677–682. doi:10.1016/j.ijrobp.2008.11.042. PMid:19251380.

[15] Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004; 101: 1623–1631. doi:10.1002/cncr.20539. PMid:15378503.

[16] Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010; 303: 1070–1076. doi:10.1001/jama.2010.261. PMid:20233825.

[17] Orringer MB, Marshall B, Chang AC, Lee J, Pickens A, Lau CL. Two thousand transhiatal esophagectomies. Ann Surg 2007; 246: 363–374. doi:10.1097/SLA.0b013e31814697f2. PMid: 17717440.

[18] Chang AC, Ji H, Birkmeyer NJ, Orringer MB, Birkmeyer JD. Outcomes after transhiatal and transthoracic esophagectomy for cancer. Ann Thorac Surg 2008; 85: 424–429. doi:10.1016/j.athoracsur.2007.10.007. PMid:18222237.

[19] Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007; 25: 1160–1168. doi:10.1200/JCO.2005.04.7118. PMid:17401004.

[20] Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005; 23: 2310–2317. doi:10.1200/JCO.2005.00.034. PMid:15800321.

[21] van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012; 366: 2074–2084. doi:10.1056/NEJMoa1112088. PMid:22646630.

[22] Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94–05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002; 20: 1167–1174. doi:10.1200/JCO.20.5.1167. PMid:11870157.