

# A rare case of squamous cell carcinoma lung with multiple locoregional recurrences and histological transformation

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## ABSTRACT

A 52-year-old female nonsmoker with localized squamous cell carcinoma (T3N1M0) of lung underwent lobectomy with adjuvant chemotherapy. Two years later, the patient had her first locoregional recurrence with adenosquamous cell carcinoma, and pneumonectomy with adjuvant chemotherapy rendered her disease free. Subsequent isolated locoregional recurrence with squamous cell carcinoma 18 months later was treated with chemoradiotherapy and had a complete response. Patient yet again had locoregional recurrence after 4 years and had progressive disease despite subsequent multiple line of treatment with platinum-based chemotherapy, stereotactic body radiation therapy, and nivolumab. This case is unique in presentation due to prolonged survival with multiple line of treatment of recurrent locoregional tumor without distant metastasis and alteration in the histology of tumor during illness.

**KEY WORDS:** Chemoradiotherapy, histological transformation, lobectomy, locoregional recurrence, non-small cell lung cancer, pneumonectomy, squamous cell carcinoma

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## INTRODUCTION

Lung cancer is still the leading cause of cancer-associated mortality worldwide with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all lung cancers. Despite advancements in therapeutic modalities locoregional and distant recurrence remain major problems. Even after complete resection, recurrence occurs in 45% of patients with NSCLC<sup>[1]</sup> and is associated with a reduction in patient's life expectancy sharply.<sup>[2,3]</sup> Any decision on retreatment should take into consideration prior therapeutic strategy, location of recurrence, and physical condition of the patients. Here, we present a challenging case with unique presentation of changing histopathology and multiple locoregional recurrence without distant metastasis despite improved survival with multimodality care.

## CASE REPORT

A 52-year-old female, who was a nonsmoker with no comorbidities presented with cough, right-sided chest pain, exertional breathlessness, and a weight loss of 6 kg for 4 months in July 2007. Physical examination revealed reduced chest movements in the right side of chest anteriorly, and reduced intensity of breath sounds on auscultation. Blood counts and other biochemical analysis reports were within normal limits. The chest radiograph revealed a right perihilar mass with spiculated margins [Figure 1a]. Computed tomography (CT) of chest showed a heterogeneously enhancing mass lesion measuring 3.6 cm × 3.2 cm × 2.9 cm with spiculated margin in right hilar region, 2.9 cm from carina extending

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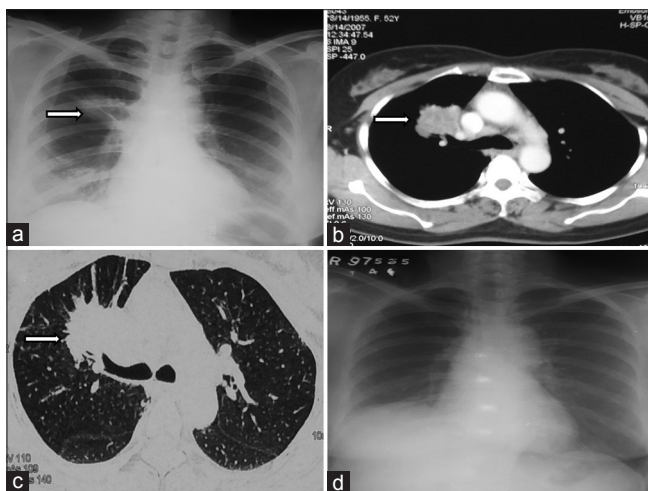
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superolaterally in anterior segment of right upper lobe and abutting the mediastinal pleura, superior pulmonary vein, and interlobar artery [Figure 1b and c]. There was no mediastinal lymphadenopathy. Magnetic resonance imaging (MRI) chest showed invasion of mediastinal pleura. Bronchoscopic biopsy of an intraluminal mass lesion in right upper lobe revealed squamous cell carcinoma lung [Figure 2a] and staging workup with ultrasound of abdomen, bone scan, and MRI brain did not show any distant metastases. Tumor was initially staged to Stage IIB lung cancer (T3N0M0) which was upstaged to Stage 3A (T3N1M0) intraoperatively, as a right hilar lymph node was positive for malignancy. The patient underwent right lung upper lobectomy with peribronchial and hilar lymph node dissection [Figure 1d]. Histopathological examination of resected tumor showed squamous cell carcinoma with an R0 resection and the patient was administered adjuvant chemotherapy with six cycles of carboplatin plus gemcitabine and followed up every 3 months.

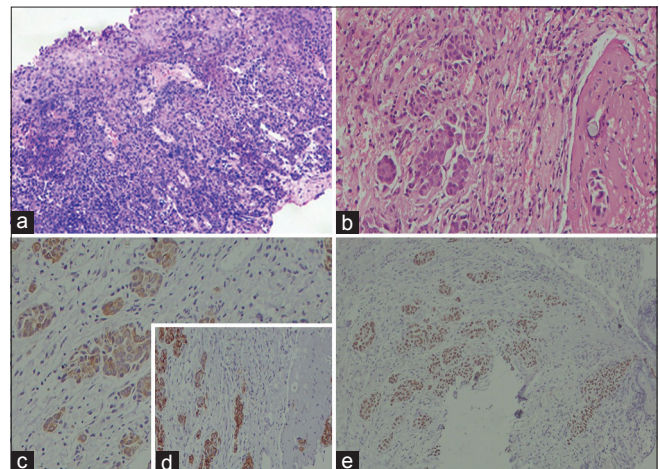
After being asymptomatic for 2 years, the patient presented again in March 2010 with cough and hemoptysis of 1-month duration. The chest radiograph showed a right perihilar lesion with elevated right hemidiaphragm [Figure 3a]. The CT chest was suggestive of locoregional recurrence of bronchogenic carcinoma with a heterogeneously enhancing soft-tissue lesion with largest diameter of 3.9 cm in bronchus intermedius, the mass invading into superior vena cava (SVC) and closely abutting right pulmonary artery and azygous vein with no mediastinal lymphadenopathy. MRI chest revealed partial loss of fat planes at hilar and suprahilar regions notably at confluence of SVC, azygous vein, and right pulmonary artery. A repeat bronchoscopic biopsy of mass in the right bronchus intermedius revealed squamous cell carcinoma and staging workup with fluorodeoxyglucose-positron

emission tomography (FDG-PET)/CT-detected an FDG avid mass in the right perihilar region with no evidence of distant metastasis and mediastinal lymphadenopathy, suggestive of locoregional recurrence [Figure 3b and c]. Pneumonectomy was performed through right posterolateral thoracotomy, and the entire mass and portion of SVC were excised *en bloc* sacrificing right phrenic nerve [Figure 3d]. The SVC was repaired. Subcarinal and paratracheal lymph node clearance was done up to superior mediastinum. Histopathological examination showed squamous cell carcinoma with additional component of adenocarcinoma that was positive for expression of thyroid transcription factor 1, mucin 1, and tumor protein 63 on immunohistochemistry suggestive of adenosquamous carcinoma [Figure 2b-e]. Six cycles of adjuvant chemotherapy of carboplatin and pemetrexed were given postoperatively. A PET-CT that was done 6 months later detected no abnormal area of FDG uptake [Figure 3e and f].

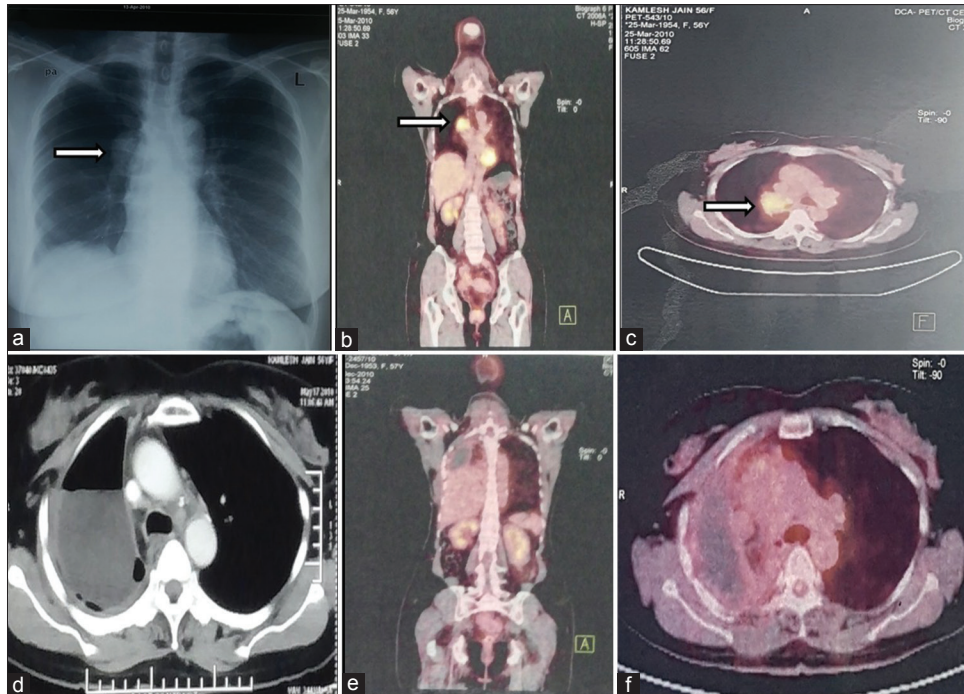
One and a half years following pneumonectomy, the patient had complaints of cough with expectoration and right-sided chest pain, in December 2011 and a repeat PET-CT showed a soft-tissue thickening measuring 2.3 cm × 1.4 cm with increased FDG uptake (SUV 8.5) along the right paratracheal region before bifurcation [Figure 4a and b]. These features once again suggested a locoregional recurrence. Conventional transbronchial needle aspiration (TBNA) revealed squamous cell carcinoma and a repeat surgical option was ruled out by both patients as well as the thoracic oncosurgeon. Concurrent chemoradiation with CT guided, three-dimensional conformal radiotherapy (3D-CRT) of 60 Gy in 30 fractions, over 6 weeks with active breathing



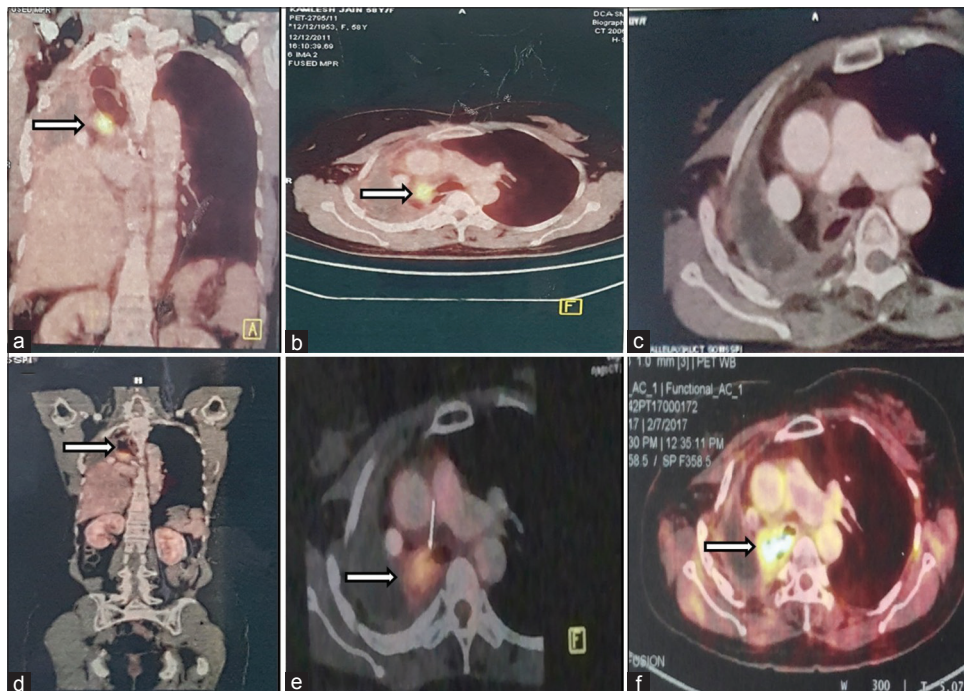
**Figure 1:** (a) Frontal chest radiograph shows a right perihilar mass with spiculated margins. (b and c) Mediastinal and lung windows of axial computed tomography of chest show a heterogeneously enhancing mass lesion measuring 3.6 cm × 3.2 cm × 2.9 cm with spiculated margin in the right hilar region. (d) Chest radiograph after right upper lobe lobectomy



**Figure 2:** (a) Initial biopsy shows sheets and nests of malignant squamous cells displaying mild to moderate nuclear pleomorphism with frequent mitotic figures and intercellular bridges. Focal keratinisation is also present. (b) Histological shift from squamous cell histology to a morphological adenosquamous cell carcinoma which shows scanty tumor tissue arranged in the form of glands and sheets, expressing thyroid transcription factor 1 (c), mucin 1 (insert d), and protein 63 (e) during the first recurrence



**Figure 3:** (a) Chest radiograph shows a right perihilar lesion with elevated right hemidiaphragm. (b and c) Coronal and axial fused positron emission tomography-computed tomography images show a fluorodeoxyglucose avid mass in the right perihilar region with no distant metastasis and mediastinal lymphadenopathy suggestive of locoregional recurrence. (d) Mediastinal window of axial computed tomography after pneumonectomy. (e and f) Postpneumonectomy coronal and axial positron emission tomography-computed tomography images show no abnormal fluorodeoxyglucose avid lesion



**Figure 4:** (a and b) Coronal and axial positron emission tomography-computed tomography images show a fluorodeoxyglucose avid mass in the right perihilar region with no distant metastasis and mediastinal lymph node suggestive of a second locoregional recurrence. (c) Postchemoradiotherapy positron emission tomography-computed tomography monitoring image demonstrates no abnormal fluorodeoxyglucose avid uptake suggestive of complete response. (d) Coronal positron emission tomography-computed tomography image reveal a fluorodeoxyglucose avid lesion in the right perihilar region without distant metastasis suggestive of third locoregional recurrence. (e) Postchemotherapy axial positron emission tomography-computed tomography image reveal an increase in fluorodeoxyglucose avidity. (f) Positron emission tomography-computed tomography after stereotactic body radiation therapy and multiple line chemotherapy demonstrates increase in fluorodeoxyglucose avidity as well as increase in size of the lesion

coordinator was administered with four cycles of carboplatin and paclitaxel. Follow-up of the patient at 3 months interval and review PET-CT after completion of chemoradiotherapy showed significant decrease in size as well as FDG activity and complete resolution of the right paratracheal metabolic active lesion with distant metastases, respectively [Figure 4c].

Around 4 years following chemoradiotherapy, in March 2016, the patient again presented with shortness of breath and cough. The PET-CT demonstrated a heterogeneously enhancing FDG avid (SUV-5.2) mass lesion measuring 2.4 cm × 2.9 cm × 2.3 cm along right paratracheal border at same location suggestive of locoregional recurrence [Figure 4d]. Endobronchial ultrasound TBNA done revealed fibrocollagenous tissue infiltrated with squamous cell carcinoma and patient was administered six cycles of carboplatin and paclitaxel. PET-CT scan after completion of therapy showed mild increase in size, while there was a significant increase in FDG activity (SUV-7.2) of the lesion as compared to previous scan [Figure 4e]. Subsequently, the patient also had progression on stereotactic body radiation therapy (SBRT) which was given with curative intent following chemotherapy with carboplatin and paclitaxel [Figure 4f]. Finally, the patient was initiated on nivolumab, an immune checkpoint inhibitor; however, she developed hospital-acquired pneumonia with septic shock following the first dose of nivolumab and finally succumbed to her infection in February 2017.

## DISCUSSION

Surgery, potentially curative treatment for early-stage NSCLC has a tumor recurrence rate of 30%–77% with a long-term survival of <50%.<sup>[4]</sup> Management of recurrent lung cancer is challenging due to limited treatment options being available and poor performance status of the patient. In the present case, despite lobectomy and adjuvant chemotherapy, the patient had locoregional recurrence with the mass invading into SVC, closely abutting right pulmonary artery and azygous vein. Although complete resection of such a tumor is indicated in the absence of N2 involvement, vascular invasions are technically difficult to operate and are associated with higher risk of complications particularly in patients undergoing concomitant pneumonectomy.<sup>[5]</sup> Outcome of patients with SVC resection and reconstruction in the setting of advanced lung cancer remains dismal with median survival ranging from 8.5 to 40.0 months and a 5-year survival rate up to 30%.<sup>[6]</sup> However, our patient survived for around 7 years with multiple locoregional recurrences despite adjuvant chemotherapy alongside pneumonectomy with R0 resection and SVC resection and reconstruction. Chemoradiotherapy for locoregional recurrent NSCLC is feasible for highly selected patient with better survival.<sup>[7]</sup> Since our patient was not a candidate for third surgery and had yet another locoregional recurrence, curative

intent reirradiation with CT-guided three-dimensional CRT along with adjuvant chemotherapy was tried. This resulted in remission of the tumor. Conformal radiation delivery with SBRT has been tried in patients with recurrent or persistent lung cancers and associated with lower toxicity in reirradiation situation,<sup>[8]</sup> although our case showed progression on SBRT which was given after third locoregional recurrence. This unusual pattern of recurrent locoregional spread in the absence of distant metastasis is rare and may be attributed to the presence of lymphovascular space invasion.<sup>[9]</sup> Nivolumab, a human IgG4 anti-programmed cell death protein 1 monoclonal antibody, has been associated with superior survival over docetaxel in unselected patients with advanced, previously treated nonsquamous NSCLC.<sup>[10]</sup> In the last resort following SBRT, the patient was started on intravenous nivolumab, but developed hospital-acquired pneumonia after 1 week and expired.

The important finding, in this case, was changing histopathology from squamous cell to adenosquamous lung carcinoma following lobectomy and adjuvant chemotherapy. There are only a few reports available, showing histological transformation following treatment.<sup>[11–14]</sup> This may be due to the tumor heterogeneity, drug-induced selection mechanisms or changing cell behavior on chemotherapy and highlights the importance of re-biopsy when managing a case of locoregional recurrent lung cancer. The remarkable number of molecular changes following systemic therapy and the genetic complexity of some cases underline the value of histological and molecular re-evaluation of lung cancer to tailor the most appropriate therapy during disease progression.

Another rare observation in our case was multiple locoregional recurrences without distant metastasis during illness and this may be due to the peculiar molecular characteristic of the tumor, lesser number of mutations the tumor cell acquired or lack of mutations in tumor cells that predispose for distant metastases. Recent advances have provided provocative insights regarding these cell-biological and molecular changes, which carry implications concerning the pathogenesis of metastatic progression and the steps of the invasion-metastasis cascade that appear amenable to therapeutic targeting.

## CONCLUSION

The therapeutic strategy for recurrent locoregional lung tumor is still a debatable issue. Altered tumor histology with recurrence and multiple locoregional recurrences without distant metastasis despite adequate surgical resection and adjuvant therapy emphasizes on the need for further understanding of tumor behavior and characteristics for optimizing treatment protocols. Although pneumonectomy with SVC resection is technically challenging, if done in experienced centers, it is associated with better prognosis for lung cancer in a patient with N0 status. This case

is unique as it displays an unusual pattern of multiple locoregional recurrences without any systemic metastasis and changing histopathology on treatment that mandated a better understanding of tumor molecular characteristics.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflict of interest

There are no conflicts of interest.

### REFERENCES

1. Yano T, Hara N, Ichinose Y, Asoh H, Yokoyama H, Ohta M, *et al.* Local recurrence after complete resection for non-small-cell carcinoma of the lung. Significance of local control by radiation treatment. *J Thorac Cardiovasc Surg* 1994;107:8-12.
2. Sugimura H, Nichols FC, Yang P, Allen MS, Cassivi SD, Deschamps C, *et al.* Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. *Ann Thorac Surg* 2007;83:409-17.
3. Saisho S, Yasuda K, Maeda A, Yukawa T, Okita R, Hiram Y, *et al.* Post-recurrence survival of patients with non-small-cell lung cancer after curative resection with or without induction/adjuvant chemotherapy. *Interact Cardiovasc Thorac Surg* 2013;16:166-72.
4. Subotic D, Van Schil P, Grigoriu B. Optimising treatment for post-operative lung cancer recurrence. *Eur Respir J* 2016;47:374-8.
5. Spaggiari L, Thomas P, Magdeleinat P, Kondo H, Rollet G, Regnard JF, *et al.* Superior vena cava resection with prosthetic replacement for non-small cell lung cancer: Long-term results of a multicentric study. *Eur J Cardiothorac Surg* 2002;21:1080-6.
6. Yildizeli B, Darteville PG, Fadel E, Mussot S, Chapelier A. Results of primary surgery with T4 non-small cell lung cancer during a 25-year period in a single center: The benefit is worth the risk. *Ann Thorac Surg* 2008;86:1065-75.
7. Bar J, Ng D, Moretto P, Goss GD, Sun A, Macrae R, *et al.* Chemoradiotherapy for locoregional recurrence of non-small-cell lung cancer after surgical resection: A retrospective analysis. *Clin Lung Cancer* 2013;14:200-4.
8. Kelly P, Balter PA, Rebuena N, Sharp HJ, Liao Z, Komaki R, *et al.* Stereotactic body radiation therapy for patients with lung cancer previously treated with thoracic radiation. *Int J Radiat Oncol Biol Phys* 2010;78:1387-93.
9. Kelsey CR, Marks LB, Hollis D, Hubbs JL, Ready NE, D'Amico TA, *et al.* Local recurrence after surgery for early stage lung cancer: An 11-year experience with 975 patients. *Cancer* 2009;115:5218-27.
10. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, *et al.* Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627-39.
11. Jiang SY, Zhao J, Wang MZ, Huo Z, Zhang J, Zhong W, *et al.* Small-cell lung cancer transformation in patients with pulmonary adenocarcinoma: A case report and review of literature. *Medicine (Baltimore)* 2016;95:e2752.
12. Ahn S, Hwang SH, Han J, Choi YL, Lee SH, Ahn JS, *et al.* Transformation to small cell lung cancer of pulmonary adenocarcinoma: Clinicopathologic analysis of six cases. *J Pathol Transl Med* 2016;50:258-63.
13. Vatrano S, Righi L, Vavalá T, Rapa I, Busso M, Izzo S, *et al.* Molecular and histological changes in post-treatment biopsies of non-squamous non-small cell lung cancer: A Retrospective study. *Target Oncol* 2016;11:157-66.
14. Oser MG, Niederst MJ, Sequist LV, Engelman JA. Transformation from non-small-cell lung cancer to small-cell lung cancer: Molecular drivers and cells of origin. *Lancet Oncol* 2015;16:e165-72.