Characteristics and outcomes of secondary nodules identified on initial computed tomography scan for patients undergoing resection for primary non–small cell lung cancer

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Objective: We sought to define the prevalence, malignancy rate, and outcome of secondary nodules (SNs) detected on computed tomography (CT) scan for patients undergoing resection for primary non–small cell lung cancer (NSCLC).

Methods: In consecutive patients with NSCLC, we reviewed all CT scan reports obtained at diagnosis of the dominant tumor for description of SNs. When resected, pathology was reviewed. Serial CT reports for 2 years postoperatively were evaluated to follow SNs not resected.

Results: Among 155 patients, 88 (57%) were found to have SNs. A total of 137 SNs were evaluated (median size, 0.5 cm). Thirty-two nodules were resected at primary resection. Nineteen (61%) resected nodules were benign, whereas 13 (39%) were malignant (8 synchronous primary tumors and 5 lobar metastases). A total of 105 unresected nodules were followed by CT. Of these, 32 (30%) resolved completely, 20 (19%) shrunk, and 28 (27%) were stable, whereas 11 (11%) were lost to follow-up. Fourteen SNs (13%) grew, of which 5 were found to be malignant, each a new primary. Overall 5-year survival was not different between patients with or without SNs (67% vs 64%; $P = .88$).

Discussion: The prevalence of SNs on CT scan in patients undergoing resection for primary NSCLC is high. Only a low proportion of SNs are ever found to be malignant, predominantly those on the ipsilateral side as the dominant tumor. The presence of SNs has no effect on survival. Patients with SNs, if otherwise appropriately staged, should not be denied surgical therapy. (J Thorac Cardiovasc Surg 2015;149:19-24)

See related commentary on pages 24-5.

Physicians who treat lung cancer are confronted with myriad incidental findings on computed tomography (CT) scans performed to diagnose or characterize dominant lung nodules. It is common to simultaneously discover smaller, secondary nodules (SNs) in the ipsilateral or opposite lung. Although the prevalence of nodules found on CT scans has been well defined in populations of patients undergoing CT screening for lung cancer, it is unclear how many newly diagnosed lung cancer patients have SNs.[1,2] One would perhaps expect the prevalence of nodules found in patients with lung cancer to be higher than that of the general population and expect a higher rate of malignancy of these "incidental" nodules found in patients with lung cancer. Based on that assumption, concern arises that SNs detected on CT scan for primary non–small cell lung cancer may simply be thought to represent locally advanced or metastatic disease by treating or referring physicians. In this situation, patients could be denied potentially curative surgery. Understanding the frequency and the natural history of SNs is critical to provide appropriate surgical care for patients. It is therefore important to define the prevalence of SNs identified on CT scans for patients with primary lung cancer, to determine the rate of malignancy of SNs, and to determine whether SNs affect survival of patients undergoing resection for lung cancer.

METHODS

In a cohort of consecutive patients with non–small cell lung cancer undergoing resection in 2008, we reviewed all CT scan reports obtained at the time of the diagnosis of the dominant tumor (DT). The DT was defined as the nodule for which the primary workup and surgery were being performed. We purposefully chose a remote year to have adequate CT and survival follow-up. We then reviewed all CT reports for the mention of SNs. When available, images were reviewed. SNs were characterized by size, location, and CT characteristics. Nodules were documented to be characterized as either solid, part-solid (or part ground glass), or ground

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Abbreviations and Acronyms
CT = computed tomography
DT = dominant tumor
PET = positron emission tomography
SN = secondary nodule

glass (nonsolid). When resected, pathology of SN was reviewed and compared with the DT. Images and reports for 2 years postoperatively were evaluated to follow those SNs not resected. In particular, all CT scan images on which an SN was reported to grow or in which there was a discrepancy of SN location were evaluated. Surveillance CT reports were obtained at 6, 12, 18, and 24 months, then yearly. Patient information was retrieved from a prospectively maintained thoracic surgery database. The Institutional Review Board of Weill Medical College and the New York-Presbyterian Hospital approved the database and the study design. Patient consent was waived. Demographic, clinical, and pathologic characteristics of patients with and without SNs were compared. Predictors of malignancy in SNs were evaluated by univariate analysis, with significant predictors ($P < .20$) incorporated into a multivariate model. Overall survival was analyzed using the Kaplan-Meier method. Differences in survival were compared using the log-rank test. Follow-up is updated in our clinical database every 6 months.

RESULTS

Among 155 patients undergoing resection for primary lung cancer in 2008, 88 patients (57%) were found to have SNs (Figure 1). Patients with SNs were more likely to have smoked tobacco (81% vs 72%; $P = .044$). Patients with SNs had no significant differences in age, gender, or DT histology compared with patients without SNs (Table 1). There were no differences between groups regarding comorbidities or forced expiratory volume in 1 second. The majority of patients (n = 105; 68%) had a positron emission tomography (PET) scan as part of their clinical workup. Another 53 patients (34%) underwent mediastinoscopy before resection. There was no difference in PET or mediastinoscopy use in patients with and without SNs. The majority of patients in each group underwent anatomic resection of their primary tumors (90% for patients with SNs vs 85% for those without; $P = .396$). The incidence of nodal metastases and the final pathologic stages were also not significantly different between the groups as a whole (Table 1).

Among 88 patients with SNs, 11 were identified as having scattered nodules not distinguished individually on CT reports. These were excluded from follow-up studies due to our inability to explicitly compare them on follow-up CT scans. In the remaining 77 patients with positive CTs, we identified 137 nodules (1.8 nodules per patient) (Table 2). The mean and median size of the SN was 0.62 cm and 0.5 cm, respectively (range, 0.1-2.7 cm). Sixty-seven SNs (49%) were ipsilateral, including 26 (19%) in the same lobe as the DT, whereas 70 (51%) were contralateral. By CT reports, 105 SNs (77%) were characterized as solid, 11 (8%) were part-solid, and 21 (15%) were characterized as ground-glass opacities.

Among patients with additional nodules, 119 of 137 SNs were further evaluated by PET scan. The remaining 18 nodules were present in patients who did not receive PET scans. Of the 119 SNs, 14 were reported as PET positive (any reported maximum standardized uptake value greater than background) with a mean and median maximum standardized uptake value of 3.5 and 1.75, respectively. Of these, 10 SNs were solid, 1 was part-solid, and 3 were ground-glass opacities. The mean and median size of PET-positive SNs was 1.2 cm and 1.1 cm, respectively.

Thirty-one nodules were resected at the time of primary resection, of which most (n = 22; 71%) were in the same lobe as the primary tumor. The majority of the resected nodules (n = 19; 61%) were benign, whereas 12 (39%) were malignant (Table 3). One other contralateral nodule judged to be a synchronous primary tumor was resected 4 months later as a staged resection. Of 13 total malignant nodules, 8 were thought to be distinct primary tumors, whereas 5 were thought to have similar histology to the DT. Eight malignant nodules resected initially were in the same lobe as the primary tumor.

A total of 105 unresected nodules were followed by CT (median CT follow-up was 25 months). The fate of those nodules is demonstrated in Figure 1. Two-thirds did not grow. Of those, 32 SNs resolved completely (30%), 20 SNs shrunk (19%), and 28 SNs were stable (27%) over time. Eleven patients with SNs (11%) were lost to CT follow-up. Fourteen nodules (13%) grew, of which only 5 (4.8% of total) were found to be malignant, each a new primary adenocarcinoma. Three new cancers were ipsilateral, whereas 2 were contralateral. The 9 additional nodules had only minimal growth on CT and were assumed to be benign, although 1 patient died from undocumented causes and was therefore lost to further CT follow-up.

The overall rate of malignant SN was low in our series (n = 18 out of 137; 13%). In particular the rate of SNs found to be metastases from the DT was only 3.6% (5 out of 137). In patients found to have SN in the same pulmonary lobe as the DT, the rate of malignancy was 36%. We analyzed the data to determine predictors of malignancy in the SN, excluding those patients (n = 11) with scattered nodules (Table 3). By multivariate analysis, location of the SN on the ipsilateral side as the DT (odds ratio [OR], 5.77; 95% confidence interval [CI], 1.16-28.72) and SN size (continuous variable OR, 5.16; 95% CI, 1.46-18.21) were the most important predictors of malignancy for SNs. Smoking history, CT characteristics, and node status were not predictors of malignancy in SNs. We performed a second analysis on only ipsilateral SNs (n = 67), because the decision regarding whether or not to remove them at