Management of Pulmonary Nodules in Oncologic Patients: *AJR* Expert Panel Narrative Review

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Cancer survivors are at higher risk than the general population for development of a new primary malignancy, most commonly lung cancer. Current lung cancer screening guidelines recommend low-dose chest CT for high-risk individuals, including patients with a history of cancer and a qualifying smoking history. However, major lung cancer screening trials have inconsistently included cancer survivors, and few studies have assessed management of lung nodules in this population. This narrative review highlights relevant literature and provides expert opinion for management of pulmonary nodules detected incidentally or by screening in oncologic patients. In patients with previously treated lung cancer, a new nodule most likely represents distant metastasis from the initial lung cancer or a second primary lung cancer; CT features such as nodule size and composition should guide decisions regarding biopsy, PET/CT, and CT surveillance. In patients with extrapulmonary cancers, nodule management requires individualized risk assessment; smoking is associated with increased odds of primary lung cancer, whereas specific primary cancer types are associated with increased odds of pulmonary metastasis. Nonneoplastic causes, such as infection, medication toxicity, and postradiation or postsurgical change, should also be considered. Future prospective studies are warranted to provide evidence-based data to assist clinical decision-making in this context.

Cancer survival has increased over time. In the United States, almost 17 million people with a history of cancer were alive on January 1, 2019, and this number is projected to reach 22 million by 2030 [1]. Cancer survivors have a 14% higher risk of developing a new primary malignancy compared with the general population, with lung cancer being the most common diagnosis [2, 3]. Genetic and behavioral risk factors, long-term sequelae of chemotherapy and radiotherapy, and the passage of time potentially account for this increased risk of a new cancer among cancer survivors [4].

Second primary lung cancer (SPLC) represents 8–14% of all lung cancer cases [5–7] and is considered the primary driver of future life expectancy among cancer survivors [8, 9]. Cancer survivors are at higher risk of SPLC than the general population; however, important lung cancer screening (LCS) randomized trials, such as the National Lung Screening Trial and the Dutch-Belgian LCS trial, have not included patients with a current or past diagnosis of cancer [10, 11]. Although sufficient evidence that LCS screening reduces mortality outside the setting of these clinical trials is lacking, other studies have suggested that cancer survivors may benefit from inclusion in LCS trials [3, 12–14].

Previously published guidelines recommend low-dose CT for LCS in high-risk individuals for whom the benefit of screening is believed to outweigh the risks [15]. The role of CT as a screening or surveillance tool in lung cancer survivors remains debatable, and whether CT surveillance represents the best model for managing pulmonary nodules detected in these patients is unknown. The Fleischner Society guidelines for management of pulmonary nodules apply to nodules detected incidentally on CT in the nononcologic population [16]. The most recent version of the American College of Radiology Lung-RADS focuses on the management of nodules detected by low-dose CT screening programs

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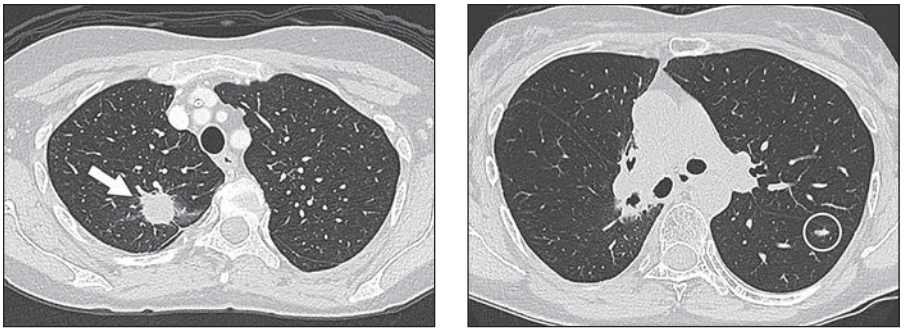

Fig. 1—66-year-old woman with lung adenocarcinoma characterized by predominant acinar pattern.
A, Axial CT image shows mass (*arrow*) in right upper lobe (RUL). Patient underwent surgical resection via RUL lobectomy.
B, Axial CT image obtained 18 months after RUL lobectomy shows new small nodule (*circle*) in contralateral lung (left lower lobe). Pathologic assessment and genomic profiling after wedge resection confirmed metastatic disease from primary adenocarcinoma in RUL.

but does not provide specific recommendations for patients with previously treated and presumably cured lung cancer or those with a history of extrathoracic malignancy [17]. In clinical practice, most radiologists rely on experience and common sense in managing pulmonary nodules in cancer survivors, and standardized guidelines tailored to this population are still needed [18, 19].

This article provides expert opinion by applying a comprehensive and critical approach to the current literature regarding the management of pulmonary nodules, detected either incidentally or by screening, in oncologic patients.

Pulmonary Nodules in Patients With a History of Lung Cancer

Historical Data and Review of Prior Studies

For patients with a history of lung cancer, a major and common clinical dilemma is whether additional lung nodules represent recurrence of the primary disease, including locally recurrent and distant metastatic disease, or an SPLC.

During the first 5 years after a lung cancer diagnosis, patients with surgically resected stage I–IIIA lung cancer remain at an elevated risk of local recurrence and distant metastatic disease. The rate of recurrence is influenced by the histology of the primary malignancy and stage at diagnosis. Among patients with surgically resected non–small cell lung cancer (NSCLC), rates of 5–12.3% for local recurrence and even higher rates of 14.5–21.5% for distant metastases after a median follow-up of 3–5 years have been reported [20, 21]. The rate of recurrence is lowest in stage I disease. The median time to recurrence is 15.9 months. The rate of local or distant recurrence is elevated in the first 4 years after surgery: 7% in the first 12 months, 10% in year 2, 7% in year 3, and 6% in year 4 [20]. The rate of recurrence decreases to 2% in year 5. In the patient's fifth year after surgical resection, the incidence of SPLC (1% in year 1, 3% in year 2, 3% in year 3, 4% in year 4, and 6% in year 5) exceeds the rate of recurrent disease.

A study of patients who underwent lobectomy for stage IA NSCLC reported rates of 5% for local recurrence and 12% for distant metastases [22]. Conversely, SPLC occurred in 15% of these patients. The timing of detection of the two entities after lobectomy was a distinguishing feature in this study, whereby recurrent disease was found at a mean of 22 ± 19 (SD) months, and SPLC was found at a mean of 52 ± 31 months ($p < .01$) [22].

Although recurrent disease is found more commonly than SPLC during the first 2 years of surveillance, it seldom presents as a solitary pulmonary nodule (Fig. 1). Thus, the observation of a new solitary pulmonary nodule may be more likely to represent SPLC than recurrent disease at any point after surgical resection of the initial primary lung cancer.

Confirmation that SPLC is an independent malignancy requires confirmation that either the initial tumor and new tumor have different histologies or, when the tumors share the same histology, the new (second) malignancy has occurred at least 2 years after the initial malignancy (Fig. 2); has originated from carcinoma in situ; or is located in a different lung, lobe, or segment without common lymphatics and without distant metastases [23, 24]. Tumors that are determined to be independent may be further categorized as synchronous if discovered 2 years or less after diagnosis of the first primary lung cancer or metachronous if occurring after 2 years. This time interval has been variably defined and may be increasingly influenced by the ability to identify lung cancers at an earlier time point on chest CT.

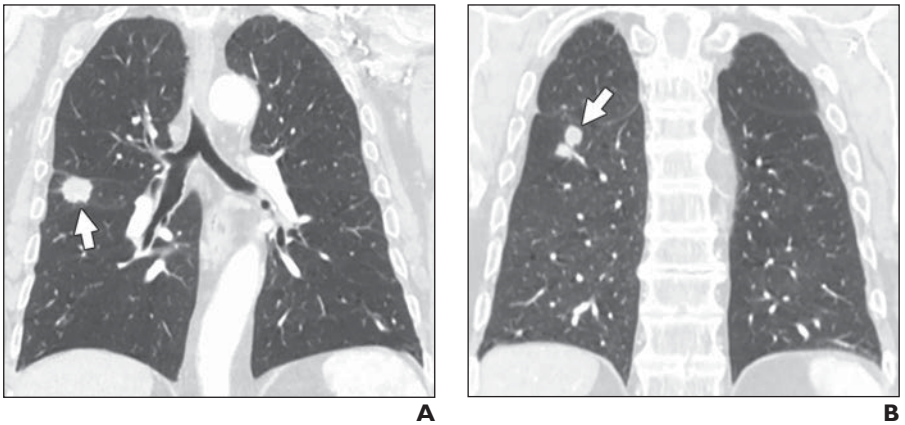

Fig. 2—87-year-old man with squamous cell lung cancer.
A, Coronal reconstructed CT image shows spiculated mass (*arrow*) in right middle lobe. Patient underwent surgical resection via robotic-assisted right middle lobectomy.
B, Coronal reconstructed CT image obtained 3 years after lobectomy shows new nodule (*arrow*) in superior segment of right lower lobe. Bronchoscopic biopsy of hilar nodes revealed small cell lung cancer, confirming second primary (metachronous) lung cancer.

A large retrospective analysis estimated the incidence of SPLC to be 0.7–1.1% per patient per year [25, 26]. The risk is cumulative over time with no plateau. This incidence rate makes lung cancer survivors more likely to develop a new lung cancer compared with the general population. Another study found that the cumulative incidence of SPLC is similar in patients who have never smoked and have undergone resection for stage I NSCLC compared with patients who have smoked, with 10-year cumulative incidences of 20.3% and 18.2%, respectively [27].

Current Guidelines for Surveillance of Patients With Lung Cancer

Recent guidelines for surveillance of recurrent disease or SPLC in patients treated with curative intent include diagnostic chest CT every 6 months for 2 years followed by low-dose CT annually for SPLC surveillance [28]. At 2 years, chest CT is the equivalent of screening CT, and Lung-RADS version 1.1 recommendations for evaluating new or enlarging nodules may be followed [17]. If a new lung nodule is solid and at least 8 mm in diameter or part solid with a solid component at least 8 mm in diameter, tissue sampling or PET/CT is recommended. A new solid nodule 6 to less than 8 mm in diameter or a part-solid nodule with a new or growing solid component less than 4 mm in diameter should be considered suspicious and further evaluated with repeat chest CT in 3 months (Fig. 3). A new nonsolid nodule should be followed with repeat chest CT in 6–12 months and observed for the development of a solid component. These management recommendations are in agreement with the American College of Chest Physicians, which also recommends that referring clinicians discuss with their patients the alternative management strategies for indeterminate solid nodules that measure less than 8 mm in diameter [29].

Overview and Recommendations

In patients with previously treated lung cancer, a new lung nodule most likely represents either distant metastasis from the initial lung cancer or SPLC, although benign disease or metastasis from an unknown malignancy should be considered in the differential diagnosis. A new or enlarging nodule in a patient with a history of lung cancer should be considered to have a high pretest probability of malignancy. Tissue sampling, PET/CT, or both may be used for indeterminate solid nodules that measure at least 8 mm in diameter (Fig. 3). Solid nodules smaller than 8 mm in diameter, part-solid nodules with a solid component less than 8 mm in diameter, and nonsolid (ground-glass) nodules may require continued CT surveillance before tissue sampling or PET/CT is feasible.

Pulmonary Nodules in Patients With Extrapulmonary Cancers

Historical Data and Review of Prior Studies

In patients with known extrapulmonary cancers, both identifying whether nodules are malignant and determining whether suspected malignant nodules represent metastasis or primary lung cancer are diagnostic challenges. The history of investigating the management of pulmonary nodules in this clinical context dates back to the 1970s, before the widespread implementation

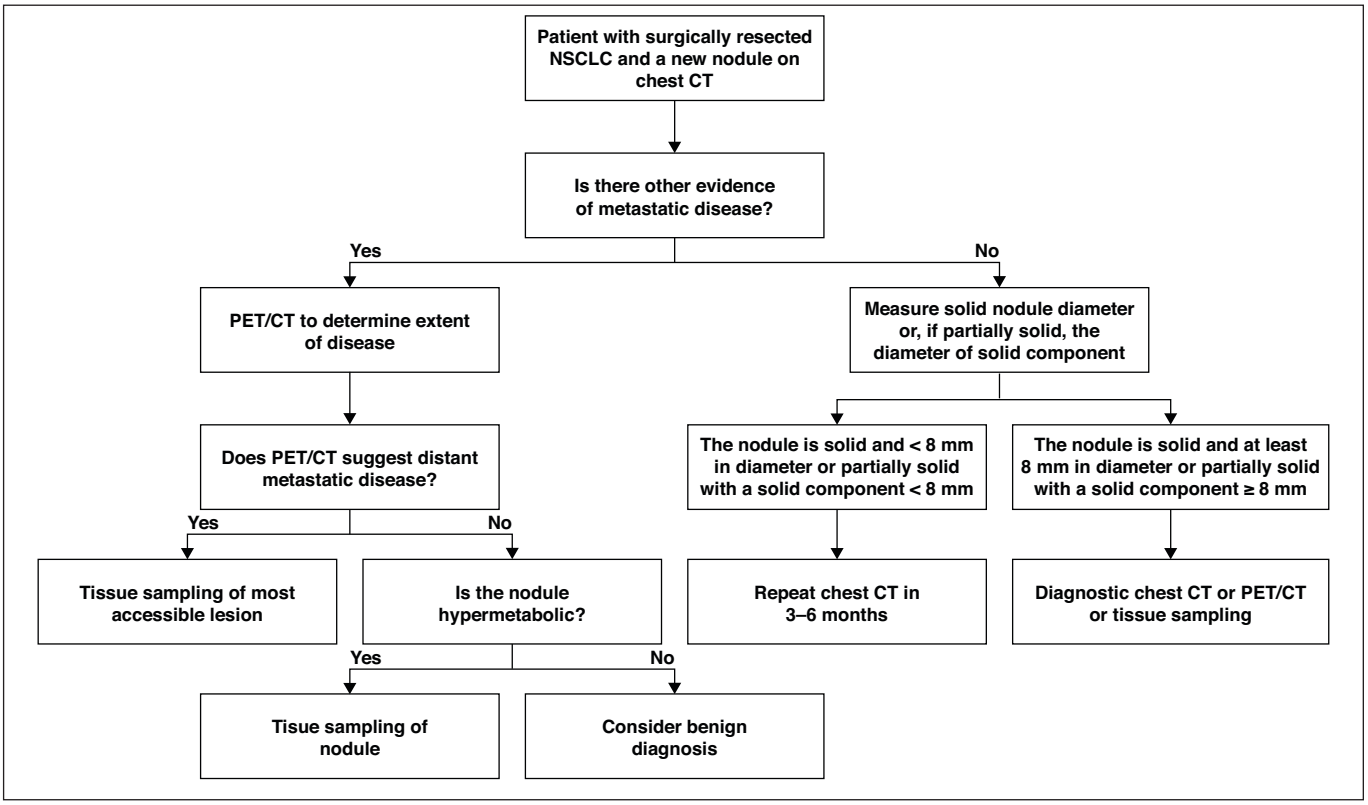

Fig. 3—Flowchart illustrates suggested algorithm for management of new nodule on chest CT in patients with surgically resected non–small cell lung cancer (NSCLC).

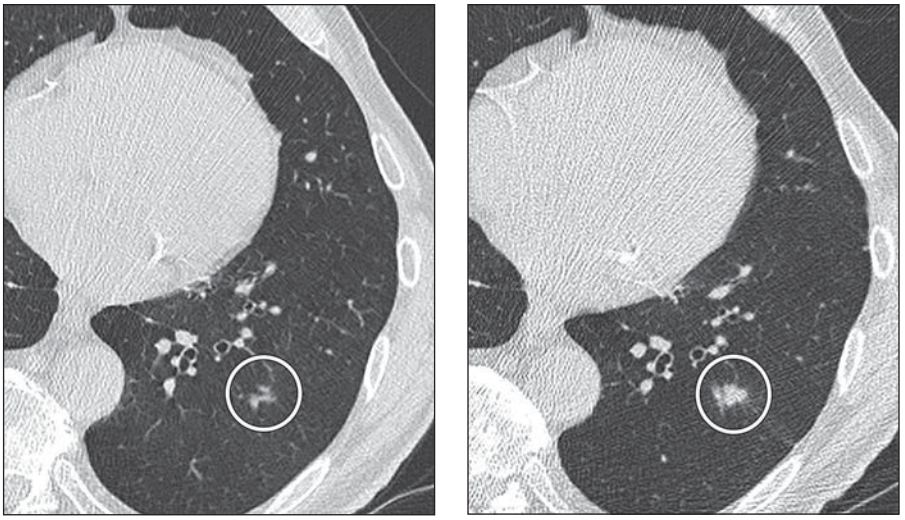

Fig. 4—69-year-old man with history of head and neck cancer (squamous cell carcinoma) who was enrolled in lung cancer screening program.
A, Low-dose CT image shows 6-mm solid nodule (*circle*) in left lower lobe. Nodule had slowly increased in size from prior imaging studies (not shown).
B, Low-dose CT image obtained 1 year later shows growth of nodule (*circle*), now measuring 11 mm. Lesion was subsequently resected and confirmed as large cell neuroendocrine carcinoma.

of CT. Cahan et al. [30] studied over 800 patients with known cancer who underwent thoracotomy for pulmonary nodules between 1940 and 1975 and found that nodules represented primary lung cancer in approximately 500 patients and metastatic disease in 196 patients. Patients with known malignancy of the head and neck (Fig. 4), bladder, breast, and prostate were more likely to have primary lung cancer, whereas patients with melanoma, bone and soft-tissue sarcomas, and testicular cancers were more likely to have metastatic nodules [30].

Four decades after the study by Cahan et al. [30], stratification by the histology of the primary extrapulmonary cancer remains a key component when evaluating lung nodules in patients with extrapulmonary cancers. Quint et al. [31] developed a histologic grouping of extrapulmonary cancers (Table 1) based on the earlier data of Cahan et al. This grouping has been used in subsequent investigations [32, 33]. Table 2 summarizes studies of pulmonary nodules in patients with extrapulmonary cancers. In a study of 161 patients with extrapulmonary malignant neoplasms and solitary pulmonary nodules [31], patients with group 1 and group 2 histology were more likely to have primary lung cancer than metastasis, whereas patients with group 4 histology were more likely to have metastasis than primary lung cancer. Smokers had 3.5-fold higher odds of developing lung cancer compared with nonsmokers [31]. In another study of 151 patients with extrapulmonary cancers and noncalcified pulmonary nodules, pack-years of smoking and nodule size were significant predictors of malignancy [32]. Mery et al. [34] evaluated 1104 patients who underwent solitary pulmonary nodule resection, including 288 patients with a history of extrapulmonary malignancies. They found that older age, smoking history, and larger nodule size were associated with NSCLC, and patients with a history of breast or prostate cancer more commonly had NSCLC than metastasis. Other studies based on thoracoscopic resection [35] and thin-section CT [33] have reported similar findings.

Ground-glass nodules (GGNs) are another important issue for patients with extrapulmonary cancer. In a report of 59 pathologically proven GGNs in 34 patients with a history of extrapulmonary cancers, 40 GGNs (67.8%) were diagnosed as malignancies (24 adenocarcinoma, 16 bronchioloalveolar carcinoma), whereas the others were benign [36]. None of the GGNs resulted from metastasis. Clinical characteristics did not differ between malignant and benign GGNs. Larger lesion size; the presence, larger size, and proportion of the internal solid portion; lobulated margin; and the presence of bubble lucency, air bronchogram, or pleural retraction were associated with malignant GGNs, indicating the importance of radiologic feature characterization of these nodules.

Studies have also investigated pulmonary nodules in individual cancer types. Smyth et al. [37] found that among 229 patients with melanoma undergoing biopsy of a suspicious new lung lesion, 202 (88%) biopsies were positive for malignancy, including 159 (69%) metastatic melanomas, 31 (14%) primary NSCLCs, and 12 (5%) recurrent nonmelanoma metastases. Melanoma stage II or higher, negative smoking history, multiple lung nodules, and lack of prior nonmelanoma cancer were predictive of lesions being metastatic melanoma. In a subset of 113 patients who underwent PET, FDG avidity did not differentiate benign from malignant lesions. In another study of 40 patients with colorectal cancer who underwent lung resection for indeterminate nodules, 30 patients had metastasis and 10 had benign pathology [38]. The rectum as the primary site, advanced tumor stage, and lymphatic invasion of the primary tumor were associated with metastasis.

Limitations of the available data include the retrospective nature of the studies and relatively small sample sizes recruited over long time periods. Additionally, the inclusion criteria of the studies had a major impact on their results. Studies requiring

TABLE 1: Example of Histologic Groupings of Extrapulmonary Primary Cancers

Group	Site of Extrapulmonary Primary Cancers
1	Head and neck
2	Urinary bladder, breast, uterine cervix, biliary tree, esophagus, ovary, prostate, or stomach
3	Colon, rectum, liver, adrenal, kidney, uterus, or carcinoid
4	Melanoma, sarcoma, or testicular

Note—Based in part on previously reported data [31–33].

TABLE 2: Summary of Studies of Pulmonary Nodules in Patients With Extrapulmonary Cancers

First Author [Reference]	Population: No. of Patients	Population: Cancer Type	Final Diagnosis of Nodule[a]	Major Findings
Quint [31]	161	Extrapulmonary cancers and SPN	Lung cancer, 81 (50) Metastasis, 50 (31) Benign, 30 (19)	Tumors associated with lung cancer over metastasis: group 1 (ratio, 25:3) and group 2 (ratio, 26:8) histology[b] Tumors associated with metastasis over lung cancer: group 4 histology[b] (ratio, 23:9) Risk factor for developing lung cancer: smokers (3.5-fold-higher odds than nonsmokers)
Khokhar [32]	151	Extrapulmonary cancers and noncalcified nodules	Malignant nodules, 64 (42) · New lung cancers, 32 · Metastasis, 28 · Undetermined cause, 4 Nonmalignant nodules, 87 (58)	Predictors of malignancy: pack-years of smoking (OR, 1.21; $p = .007$) and nodule size (OR, 1.07; $p = .001$)
Hanamiya [33]	137	Extrapulmonary cancers and noncalcified nodules[c]	Malignant nodules, 28 (20) Benign nodules, 109 (80)	Factors associated with malignant nodules: group 4 histology,[b] larger nodule size (≥ 10 mm), and increased distance from pleural surface (≥ 10 mm)
Mery [34]	288	Extrapulmonary cancers and SPN resection[d]	Malignant nodules, 227 (79) · NSCLC, 118 (41) · Metastasis, 109 (38) Benign, 61 (21)	Factors associated with nodule being NSCLC: older age, smoking history and pack-years of smoking, larger mean nodule size, and history of breast or prostate cancer
Bellier [35]	140	Thoracoscopic resection of SPN	Benign nodules, 34 (24) Malignant nodules, 106 (76) · Metastasis, 70 · Primary lung cancer, 36	Factors associated with malignancy: upper lobe localization and $SUV_{max} > 2.5$ Smoking history associated with new primary lung cancer

Note—SPN = solitary pulmonary nodule, OR = odds ratio, NSCLC = non–small cell lung cancer.
[a]Values are the number of patients with the percentage in parentheses.
[b]Tumor histology groups are described in Table 1.
[c]Of 308 patients with extrapulmonary cancers who underwent thin-section chest CT for staging, 233 had one more noncalcified nodules. Of these, 137 patients had nodules that met the criteria for either benign or malignant nodules and were included in the predisposing factor analyses.
[d]Of 1104 patients who underwent SPN resection, 767 had with no history of cancer, 49 had a history of lung cancer, and 288 had a history of extrapulmonary malignancy.

pathologic evaluation of nodules provided a definitive diagnosis. However, the rate of malignancy of nodules in such studies is likely much higher than that of all nodules noted on staging or surveillance CT because a higher number of suspicious nodules will undergo resection or biopsy, thus introducing selection bias. Future studies based on histologic sampling of these nodules may yield different results given that tissue sampling is increasingly unnecessary for diagnosing malignancy because genomic and molecular characterization of obviously malignant nodules can better guide precision therapy decisions.

Overview and Recommendations

The malignancy rate of nodules in patients with known extrapulmonary cancers who have undergone histologic sampling is high, ranging from approximately 40% to 80%. Certain tumor types are more likely to have metastatic nodules, whereas others are more likely to be primary lung cancers. Smoking is associated with increased odds of these nodules being primary lung cancer rather than metastasis. GGNs have a similarly high rate of malignancy and are much more likely to be primary lung cancer than metastasis.

When evaluating nodules in patients with extrapulmonary cancers, knowing the histology of their primary cancers is particularly important. Not all malignant nodules result from metastasis given that they can be primary lung cancer. GGNs represent a subset of nodules that require special attention because they have high malignancy rates and are often primary lung cancers. Though further research is needed, it is important to recognize that each cancer is different and to prioritize individualized risk assessment [39].

Nonneoplastic Pulmonary Nodules in Oncologic Patients

Historical Data and Review of Previous Studies

Most pulmonary nodules detected on staging or surveillance CT are benign [32, 40, 41] and relate to clinical conditions such as infection, sequalae of medication toxicity, or changes resulting from radiation treatment or surgery. A recent retrospective study found a higher rate of false-positive chest CT findings in cancer survivors compared with control patients without a cancer history, likely because of complex posttherapy findings in that patient cohort [12].

In studies of cancer survivors, the likelihood of nonmetastatic lesions varied from 20% to 81% [33, 34, 42]. When patients undergo biopsy in this setting, prebiopsy factors that predict the presence of malignancy include larger nodule size, the presence of multiple nodules over 5 mm in diameter, and the presence of cavitation or necrosis [42]. The histology of the primary tumor is also important. Patients with a history of testicular cancer, sarcoma, or melanoma are more likely to have metastatic disease [33].

Patients who undergo biopsy represent a highly select group of patients with large pulmonary nodules who are presumably deemed not suitable for surveillance imaging given an implied higher risk for neoplastic disease [33, 34, 42]. A more common clinical scenario is that of small pulmonary nodules, which may not

meet the size or other criteria for biopsy. Radiologists may face challenges in issuing definitive guidance for small pulmonary nodules in oncologic patients without the aid of guidelines comparable to the Fleischner guidelines, which address assessment of nodules in the nononcologic population. Size is a vital discriminating factor in determining the likelihood of malignancy. In one large retrospective cohort of patients with extrapulmonary cancer, 85% of nodules 10 mm or more in diameter detected on staging CT were malignant [32]. In another cohort of patients with cancer and nodules of 4 mm or less, 72% of nodules were benign [41]. Of nodules that grew, the majority did so within 1 year of follow-up.

Another study found that the mean time to growth in patients with extrapulmonary cancer was 65 days and that nodule morphology and primary tumor stage were also important [43]. The study concluded that patients with a higher-stage primary tumor are more likely to have lung metastases. Although metastases presenting as ground-glass or subsolid lesions may be seen occasionally in a variety of cancer subtypes [44, 45], GGNs overall are unlikely to represent metastases [36]. Close imaging follow-up of oncologic patients with GGNs is required, typically at a higher frequency and sooner than would be required for nononcologic patients. Larger nodules and nodules in patients with high-stage primary tumors or with testicular cancer, sarcoma, or melanoma should be treated with a higher degree of suspicion.

Several imaging features have been used in nononcologic populations to infer benignancy in lung nodules. For example, perifissural nodules are typically considered benign, particularly when smooth, solid, ovoid, or triangular [46]. One study assessing the natural history of perifissural nodules in oncologic patients found that the majority (97%) remained stable after 3 years of follow-up, suggesting that these nodules are likely to be benign, though follow-up in a cancer setting is still needed [47]. Calcification is another feature that is typically considered to be benign when seen in pulmonary nodules, particularly when the calcification shows a diffuse, laminated, central, or "popcorn" pattern [48]. In an oncologic population, most calcified nodules may also be considered benign. However, the histology of the primary tumor must be taken into account when assessing such lesions. Lung metastases from certain sarcoma subtypes, particularly osteosarcoma, and from thyroid cancer may be calcified or ossified, and calcified lung lesions in these patients cannot be assumed to be benign. Calcified lung metastases may also be seen in patients with mucinous primary neoplasms [45].

Inflammatory lung nodules may pose a diagnostic dilemma in patients with cancer, many of whom are immunocompromised and thus at increased risk of infection. Fungal, tuberculous, and viral pneumonias in particular may present with a nodular pattern on chest CT and are well-documented mimics of both primary and metastatic lung lesions [49]. If new lung nodules are seen in a patient who has undergone bone marrow transplant, particularly a patient in the neutropenic or early posttransplant phase, fungal or viral pneumonia should be strongly considered [50]. Ancillary imaging findings may be useful in these cases. For example, patients with viral pneumonia may also show consolidation and ground glass in addition to lung nodules, whereas nodularity surrounded by a halo of ground glass is a typical finding in angioinvasive fungal infection, with a differential diagnosis of pulmonary hemorrhage and hemorrhagic metastases [50].

Noninfectious complications of anticancer therapy may also present with a nodular pattern on CT. Lung toxicity is a frequently encountered side effect of anticancer medical therapies, and pulmonary nodularity is a well-described feature of some forms of drug-induced lung toxicity [51]. For example, organizing pneumonia has been described as a side effect of many anticancer medical therapies, including checkpoint inhibitor immunotherapy and vascular endothelial growth factor inhibitors, among others [52, 53]. Although foci of subpleural consolidation represent the most common presentation of organizing pneumonia, a nodular pattern is well described and may mimic metastases [53] (Fig. 5). In our experience, drug toxicity should be considered in

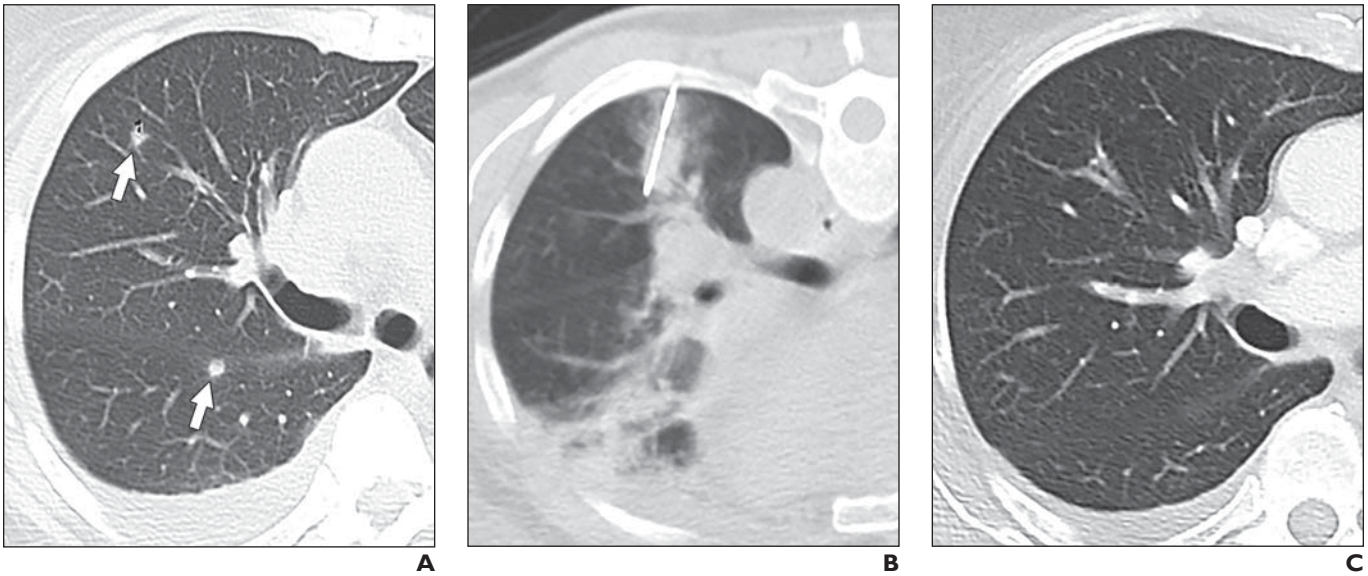

Fig. 5—59-year-old woman undergoing immune checkpoint inhibitor therapy for primary lung cancer.
A, Follow-up chest CT image shows new small solid nodules (*arrows*) suspicious for metastases.
B, Chest CT image shows biopsy of one lesion detected in **A**. Biopsy results showed organizing pneumonia.
C, Follow-up CT image obtained 3 months later shows resolution of lung nodules after corticosteroid therapy.

patients who present with new lung nodularity in the context of stable or improving cancer observed elsewhere on imaging and if no infection is clinically evident.

Overview and Recommendations

In the absence of formal guidelines, the follow-up of oncologic patients who have indeterminate pulmonary nodules detected on staging CT should be decided on a case-by-case basis. Factors to consider include the stage of primary cancer, likelihood of pulmonary metastases from that cancer subtype, morphology and pattern of pulmonary nodules, and clinical presentation (e.g., signs or symptoms of infection). If the clinical and radiologic patterns suggest infection, then a reasonable follow-up for a patient who is clinically stable is a CT examination in 4–6 weeks. Considering that nodules discovered on staging CT that ultimately prove to be neoplastic grow after a mean of 65 days [43], a follow-up interval of 2–3 months is reasonable for small pulmonary nodules without overtly suspicious imaging features. If nodules are documented as stable at that time point, then subsequent follow-up will typically be determined by guidelines for surveillance of that particular cancer subtype.

Is It Worth Screening for (Smoking-Related) Lung Cancer in Cancer Survivors?

Though few studies have assessed the utility of LCS in cancer survivors, some retrospective studies have found that SPLCs are detected at a greater rate than previously reported in large lung cancer trials and that the majority of these lesions are prevalent cancers [12]. It is not clear whether the survival benefit seen in lung screening trials will be borne out in patients with a history of malignancy who undergo screening.

Maintaining low false-positive rates is vital for any screening program. Chest CT interpretation in cancer survivors can be challenging, often because of the presence of posttreatment changes. This could lead to an unacceptably high rate of invasive procedures with higher rates of false-positive biopsy and resection findings [54]. As with all radiation exposure, the benefit of CT exposure must outweigh any potential risk. Despite the use of a low-dose CT technique for LCS, consideration of radiation exposure is particularly important in cancer survivors undergoing screening because they may have already accrued a large cumulative radiation dose from both diagnostic and therapeutic sources over the course of their past treatments.

The cost-effectiveness of LCS in the general population has long been debated. Ultimately, the cost-effectiveness of screening is likely strongly predicated on correctly identifying an appropriate high-risk group to screen. To date, however, limited data describe the cost-effectiveness of LCS in a population of cancer survivors. Previous studies of Hodgkin lymphoma survivors found LCS to be considerably more cost-effective in smokers when compared with nonsmokers in terms of quality-adjusted life-years [55, 56]. Finally, it is unclear whether cancer survivors have the same life expectancy as individuals without a cancer history or whether quality of life metrics are comparable between these two groups. Both of these factors potentially impact the calculation of quality-adjusted life-years as part of a cost-effectiveness analysis.

Future Perspectives

The high costs and substantial false-positive rates of the current LCS strategies are main issues that demand new approaches. New techniques have been evaluated for earlier detection of lung cancer, including transcriptomics, proteomics, and circulating tumor cells, and are currently undergoing clinical trials [57].

Studies conducted in the last few years have focused on analyzing tumor genetic material released into the bloodstream, a biopsy-free technique known as circulating tumor DNA (ctDNA) [57, 58]. However, ctDNA is not detectable in all patients with lung cancer [59] and is currently limited to early diagnosis in asymptomatic patients. Nevertheless, ctDNA testing after a positive CT finding could improve screening accuracy and reduce the number of unnecessary invasive procedures [60]. Whereas ctDNA is collected by venipuncture, volatile organic compounds are metabolites actively expelled through the breath, saliva, skin, urine, and feces. Despite encouraging initial results, the utility of volatile organic compounds for LCS has been hampered by the lack of large multicenter clinical trials including external validation [57].

In recent years, artificial intelligence tools have been extensively studied for detection, diagnosis, and prognostication of different types of cancer. New approaches to computer-aided detection or diagnosis of pulmonary lesions on chest radiograph or CT are based on the automatic identification of suspicious nodules and their categorization as benign or malignant [61]. Recent studies show the potential for deep learning models to increase the accuracy, consistency, and adoption of LCS worldwide [62]. These new techniques are promising for improved CT screening as a more efficient and cost-effective strategy.

Consensus Statements

- Cancer survival is increasing in prevalence. The management of pulmonary nodules among cancer survivors and the role of CT as a screening or surveillance tool in this population are not addressed by current guidelines and remain controversial.
- In patients with previously treated lung cancer, a new lung nodule is most likely to represent either distant metastasis from the initial lung cancer or an SPLC. This differentiation is challenging and requires a multidisciplinary integration of all available clinical, radiologic, pathologic, and molecular information. CT features such as nodule size and composition should be used to guide decisions regarding surveillance with biopsy, PET/CT, and further CT.
- In patients with extrapulmonary cancers, the management of lung nodules requires an individualized risk assessment. Smoking is associated with increased odds of these nodules being primary lung cancer rather than metastasis, whereas specific primary cancer types (particularly melanoma, sarcoma, and testicular carcinoma) are associated with increased odds of these nodules representing pulmonary metastatic disease.
- Nonneoplastic causes, such as superimposed infection, sequelae of medication toxicity, and postradiation or postsurgical change, should also be considered in the differential diagnosis of pulmonary nodules in oncologic patients.
- Future prospective and multiinstitutional LCS studies that incorporate molecular and genomic correlation and multimodality approaches are warranted to provide evidence-based data to assist clinical decision-making in this growing population.

References

1. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin* 2019; 69:363–385
2. Curtis REFD, Ron E, Ries LAG, et al. *New malignancies among cancer survivors: SEER cancer registries, 1973-2000*. Washington, DC: National Cancer Institute, 2006
3. Donin N, Filson C, Drakaki A, et al. Risk of second primary malignancies among cancer survivors in the United States, 1992 through 2008. *Cancer* 2016; 122:3075–3086
4. Preyer O, Concin N, Obermair A, Concin H, Ulmer H, Oberaigner W. The relative risk of second primary cancers in Austria's western states: a retrospective cohort study. *BMC Cancer* 2017; 17:699
5. Reinmuth N, Stumpf P, Stumpf A, et al. Characteristics of lung cancer after a previous malignancy. *Respir Med* 2014; 108:910–917
6. Quadrelli S, Lyons G, Colt H, Chimondeguy D, Silva C. Lung cancer as a second primary malignancy: increasing prevalence and its influence on survival. *Ann Surg Oncol* 2009; 16:1033–1038
7. Hofmann HS, Neef H, Schmidt P. Primary lung cancer and extrapulmonary malignancy. *Eur J Cardiothorac Surg* 2007; 32:653–658
8. del Rey J, Placer J, Vallmanya F, et al. Are patients with non-muscle-invasive bladder cancer a suitable population for a lung cancer screening trial? *BJU Int* 2010; 106:49–52
9. Milano MT, Peterson CR 3rd, Zhang H, Singh DP, Chen Y. Second primary lung cancer after head and neck squamous cell cancer: population-based study of risk factors. *Head Neck* 2012; 34:1782–1788
10. Aberle DR, Adams AM, Berg CD, et al.; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; 365:395–409
11. van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). *Int J Cancer* 2007; 120:868–874
12. O'Dwyer E, Halpenny DF, Ginsberg MS. Lung cancer screening in patients with previous malignancy: is this cohort at increased risk for malignancy? *Eur Radiol* 2021; 31:458–467
13. Halpenny DF, Cunningham JD, Long NM, Sosa RE, Ginsberg MS. Patients with a previous history of malignancy undergoing lung cancer screening: clinical characteristics and radiologic findings. *J Thorac Oncol* 2016; 11:1447–1452
14. Donin NM, Kwan L, Lenis AT, Drakaki A, Chamie K. Second primary lung cancer in United States cancer survivors, 1992–2008. *Cancer Causes Control* 2019; 30:465–475
15. Roberts H, Walker-Dilks C, Sivjee K, et al.; Lung Cancer Screening Guideline Development Group. Screening high-risk populations for lung cancer: guideline recommendations. *J Thorac Oncol* 2013; 8:1232–1237
16. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology* 2017; 284:228–243
17. American College of Radiology. *Lung CT Screening Reporting & Data System (Lung-RADS) version 1.1*. American College of Radiology, 2019
18. Occhipinti M, Heidinger BH, Pfannenberg C, Munden RF, Eisenberg RL, Bankier AA. Managing incidental lung nodules in patients with a history of oncologic disease: a survey of thoracic radiologists. *J Thorac Imaging* 2017; 32:115–120
19. Shapiro CL. Cancer survivorship. *N Engl J Med* 2018; 379:2438–2450
20. Lou F, Huang J, Sima CS, Dycoco J, Rusch V, Bach PB. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. *J Thorac Cardiovasc Surg* 2013; 145:75–81; discussion, 81–82
21. Wong ML, McMurry TL, Stukenborg GJ, et al. Impact of age and comorbidity on treatment of non-small cell lung cancer recurrence following complete resection: a nationally representative cohort study. *Lung Cancer* 2016; 102:108–117
22. Mayne NR, Mallipeddi MK, Darling AJ, et al. Impact of surveillance after lobectomy for lung cancer on disease detection and survival. *Clin Lung Cancer* 2020; 21:407–414
23. Martini N, Melamed MR. Multiple primary lung cancers. *J Thorac Cardiovasc Surg* 1975; 70:606–612
24. Antakli T, Schaefer RF, Rutherford JE, Read RC. Second primary lung cancer. *Ann Thorac Surg* 1995; 59:863–866; discussion, 867
25. Reinmuth N, Stumpf A, Stumpf P, et al. Characteristics and outcome of patients with second primary lung cancer. *Eur Respir J* 2013; 42:1668–1676
26. Thakur MK, Ruterbusch JJ, Schwartz AG, Gadgeel SM, Beebe-Dimmer JL, Wozniak AJ. Risk of second lung cancer in patients with previously treated lung cancer: analysis of surveillance, epidemiology, and end results (SEER) data. *J Thorac Oncol* 2018; 13:46–53
27. Ripley RT, McMillan RR, Sima CS, et al. Second primary lung cancers: smokers versus nonsmokers after resection of stage I lung adenocarcinoma. *Ann Thorac Surg* 2014; 98:968–974
28. Schneider BJ, Ismaila N, Aerts J, et al. Lung cancer surveillance after definitive curative-intent therapy: ASCO guideline. *J Clin Oncol* 2020; 38:753–766
29. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed—American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143(suppl):e93S–e120S
30. Cahan WG, Shah JP, Castro EB. Benign solitary lung lesions in patients with cancer. *Ann Surg* 1978; 187:241–244
31. Quint LE, Park CH, Iannettoni MD. Solitary pulmonary nodules in patients with extrapulmonary neoplasms. *Radiology* 2000; 217:257–261
32. Khokhar S, Vickers A, Moore MS, Mironov S, Stover DE, Feinstein MB. Significance of non-calcified pulmonary nodules in patients with extrapulmonary cancers. *Thorax* 2006; 61:331–336
33. Hanamiya M, Aoki T, Yamashita Y, Kawanami S, Korogi Y. Frequency and significance of pulmonary nodules on thin-section CT in patients with extrapulmonary malignant neoplasms. *Eur J Radiol* 2012; 81:152–157
34. Mery CM, Pappas AN, Bueno R, et al. Relationship between a history of antecedent cancer and the probability of malignancy for a solitary pulmonary nodule. *Chest* 2004; 125:2175–2181
35. Bellier J, Perentes JY, Abdelnour-Berchtold E, et al. A plea for thoracoscopic resection of solitary pulmonary nodule in cancer patients. *Surg Endosc* 2017; 31:4705–4710
36. Park CM, Goo JM, Kim TJ, et al. Pulmonary nodular ground-glass opacities in patients with extrapulmonary cancers: what is their clinical significance and how can we determine whether they are malignant or benign lesions? *Chest* 2008; 133:1402–1409
37. Smyth EC, Hsu M, Panageas KS, Chapman PB. Histology and outcomes of newly detected lung lesions in melanoma patients. *Ann Oncol* 2012; 23:577–582
38. Jung EJ, Kim SR, Ryu CG, Paik JH, Yi JG, Hwang DY. Indeterminate pulmonary nodules in colorectal cancer. *World J Gastroenterol* 2015; 21:2967–2972
39. Nishino M, Jagannathan JP, Krajewski KM, et al. Personalized tumor response assessment in the era of molecular medicine: cancer-specific and therapy-specific response criteria to complement pitfalls of RECIST. *AJR* 2012; 198:737–745
40. Chalmers N, Best JJ. The significance of pulmonary nodules detected by CT but not by chest radiography in tumour staging. *Clin Radiol* 1991; 44:410–412
41. Munden RF, Erasmus JJ, Wahba H, Fineberg NS. Follow-up of small (4 mm

or less) incidentally detected nodules by computed tomography in oncology patients: a retrospective review. *J Thorac Oncol* 2010; 5:1958–1962
42. Caparica R, Mak MP, Rocha CH, et al. Pulmonary nodules in patients with nonpulmonary cancer: not always metastases. *J Glob Oncol* 2016; 2:138–144
43. Yang Q, Wang Y, Ban X, et al. Prediction of pulmonary metastasis in pulmonary nodules (≤10 mm) detected in patients with primary extrapulmonary malignancy at thin-section staging CT. *Radiol Med (Torino)* 2017; 122:837–849
44. Haro A, Wakasu S, Takada K, et al. Pulmonary metastasis presenting as a ground glass opacity-like lesion with a thin-walled cavity: a case report. *Int J Surg Case Rep* 2019; 60:287–290
45. Seo JB, Im JG, Goo JM, Chung MJ, Kim MY. Atypical pulmonary metastases: spectrum of radiologic findings. *RadioGraphics* 2001; 21:403–417
46. Mets OM, Chung K, Scholten ET, et al. Incidental perifissural nodules on routine chest computed tomography: lung cancer or not? *Eur Radiol* 2018; 28:1095–1101
47. Golia Pernicka JS, Hayes SA, Schor-Bardach R, et al. Clinical significance of perifissural nodules in the oncologic population. *Clin Imaging* 2019; 57:110–114
48. Chai JL, Patz EF Jr. CT of the lung: patterns of calcification and other high-attenuation abnormalities. *AJR* 1994; 162:1063–1066
49. Furuya K, Yasumori K, Takeo S, et al. Lung CT. Part 1. Mimickers of lung cancer: spectrum of CT findings with pathologic correlation. *AJR* 2012; 199:[web]W454–W463
50. Worthy SA, Flint JD, Müller NL. Pulmonary complications after bone marrow transplantation: high-resolution CT and pathologic findings. *RadioGraphics* 1997; 17:1359–1371
51. Rossi SE, Erasmus JJ, McAdams HP, Sporn TA, Goodman PC. Pulmonary drug toxicity: radiologic and pathologic manifestations. *RadioGraphics* 2000; 20:1245–1259
52. Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: radiographic patterns and clinical course. *Clin Cancer Res* 2016; 22:6051–6060
53. Dettmer S, Grünwald V, Fuehner T, et al. CT patterns of organizing pneumonia in patients treated with VEGF/mTOR inhibitors for metastatic renal cell cancer: an observational study. *Acta Radiol Open* 2017; 6:2058460117694216
54. Kaminetzky M, Milch HS, Shmukler A, et al. Effectiveness of Lung-RADS in reducing false-positive results in a diverse, underserved, urban lung cancer screening cohort. *J Am Coll Radiol* 2019; 16(4 pt A):419–426
55. Das P, Ng AK, Earle CC, Mauch PM, Kuntz KM. Computed tomography screening for lung cancer in Hodgkin's lymphoma survivors: decision analysis and cost-effectiveness analysis. *Ann Oncol* 2006; 17:785–793
56. Wattson DA, Hunink MG, DiPiro PJ, et al. Low-dose chest computed tomography for lung cancer screening among Hodgkin lymphoma survivors: a cost-effectiveness analysis. *Int J Radiat Oncol Biol Phys* 2014; 90:344–353
57. Succony L, Rosenfeld N, Rintoul RC. Multimodality approaches to screening for lung cancer. *Clin Oncol (R Coll Radiol)* 2019; 31:702–705
58. Fiala C, Diamandis EP. Utility of circulating tumor DNA in cancer diagnostics with emphasis on early detection. *BMC Med* 2018; 16:166
59. Villaflor V, Won B, Nagy R, et al. Biopsy-free circulating tumor DNA assay identifies actionable mutations in lung cancer. *Oncotarget* 2016; 7:66880–66891
60. Cescon DW, Bratman SV, Chan SM, Siu LL. Circulating tumor DNA and liquid biopsy in oncology. *Nat Cancer* 2020; 1:276–290
61. Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts HJWL. Artificial intelligence in radiology. *Nat Rev Cancer* 2018; 18:500–510
62. Ardila D, Kiraly AP, Bharadwaj S, et al. End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. *Nat Med* 2019; 25:954–961