REVIEW ARTICLE

The Overlooked Cornerstone in Precise Medicine: Personalized Postoperative Surveillance Plan for NSCLC

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ABSTRACT

Non-small cell lung cancer recurrence after curative-intent surgery remains a challenge despite advancements in treatment. We review postoperative surveillance strategies and their impact on overall survival, highlighting recommendations from clinical guidelines and controversies. Studies suggest no clear benefit from more intensive imaging, whereas computed tomography scans reveal promise in detecting recurrence. For early-stage disease, including ground-glass opacities and adenocarcinoma in situ or minimally invasive adenocarcinoma, less frequent surveillance may suffice owing to favorable prognosis. Liquid biopsy, especially circulating tumor deoxyribonucleic acid, holds potential for detecting minimal residual disease. Clinicopathologic factors and genomic profiles can also provide information about site-specific metastases. Machine learning may enable personalized surveillance plans on the basis of multiomics data. Although precision medicine transforms non-small cell lung cancer treatment, optimizing surveillance strategies remains essential. Tailored surveillance strategies and emerging technologies may enhance early detection and improve patients' survival, necessitating further research for evidence-based protocols.

Keywords: NSCLC; Postoperative surveillance; Tumor recurrence

Introduction

In 1973, Matthews et al.[1] reported a study on autopsy results of patients who died within 1 month after curative-intent surgical resection for lung cancer. The authors found 35% of the patients possessed either residual local disease or systemic metastases, raising concerns regarding the postoperative recurrence in patients with lung cancer.[1] Patients with non-small cell lung cancer (NSCLC) face the remarkable risk of recurrence even after curative-intention therapy. Even in cases of early-stage lung cancer, recurrence or the development of a second primary lung cancer (SPLC) has been identified in 27% of cases.[2] Despite notable advancements in targeted therapies targeting mutant oncoproteins and immune checkpoint blockades in recent decades, lung cancer persists as the foremost cause of cancer-related mortality globally.[3]

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Surveillance plays a crucial role in managing lung cancer after curative-intent resection. It involves monitoring treatment outcomes, identifying relapse and complications early, managing symptoms, providing information, and offering supportive care. With advancements in lung cancer screening, more patients are diagnosed at early stages with favorable prognoses after curative therapy.[4] Nevertheless, despite evolving treatments for NSCLC over the past two decades, including targeted therapies and immunotherapy, postoperative surveillance strategies remain relatively simplistic. Studies have yielded conflicting results regarding the effectiveness of frequent imaging in improving outcomes.[5–7] The optimal surveillance approach for NSCLC, particularly early-stage disease, remains poorly defined. In this review, we aim to address key questions surrounding postoperative surveillance and contribute to the development of more refined and effective surveillance strategies.

What Surveillance Strategies Are Recommended in Guidelines?

Clinical practice guidelines serve the pivotal role of optimizing patient care and providing essential guidance to clinicians in NSCLC management. Nevertheless, it was not until the early 2000s that recommendations for surveillance methods for patients with NSCLC after curative-intent therapy were incorporated.[6] Regarding follow-up and surveillance modalities for NSCLC after surgery, we reviewed the recommendations in clinical practice guidelines[8–11] (Table 1).

All the reviewed guidelines illustrate the importance of early surveillance after curative-intent surgery, advocating for frequent follow-up visits during the initial 2 to 3 years and subsequently on an annual basis, aiming at the prompt detection of recurrence or the emergence of a metachronous primary. The American Society of Clinical Oncology recommends that patients undergo surveillance imaging for recurrence every 6 months for 2 years and then annually for the detection of new primary lung cancers. Chest computed tomography imaging is the optimal imaging modality for surveillance. Along with other guidelines, the recommended surveillance protocols contain a detailed patient history, physical examination, and chest computed tomography (CT) scan. Importantly, these procedures are advised to be conducted under specialist supervision. Despite this consensus, there exists a divergence of perspectives regarding the use of positron emission tomography (PET) during this surveillance period. Notably, only the European Society of Medical Oncology recommends PET-CT as an optional assessment if deemed necessary. Both European Society of Medical Oncology and the National Comprehensive Cancer Network guidelines place important emphasis on smoking cessation for all patients with lung cancer, recommending the initiation of smoking cessation interventions after treatment. The American College of Chest Physicians guidelines, in particular, introduce the use of validated health-related quality of life instruments at baseline and during follow-up as part of their recommended practices.[8–11]

Does a Postoperative Surveillance Improve Overall Survival After Curative-Intent Resection?

Although improving, the 5-year overall survival (OS) of all patients diagnosed with lung cancer is still only approximately 23%; fewer than 50% of the patients with curative-intent surgery for NSCLC survive 5 years.[12] Nevertheless, studies have failed to reveal the theoretical advantages of surveillance. Backhus et al.[13] studied a large cohort of 4421 patients who underwent resection for stage I or II NSCLC and found no survival benefit, whether CT scan or no imaging occurred at the initial episode of surveillance. In subgroup analysis in patients with stage I, the authors describe a 15% reduced risk of death (hazard ratio [HR] = 0.85, 95% confidence interval: 0.74–0.98) compared with no imaging; nevertheless, there was no difference in lung cancer-specific survival (HR = 1.03, 95% confidence interval: 0.85–1.26).[13] Crabtree et al.[5] revealed that among patients with a subsequent malignancy, time to diagnosis was shorter for those who received CT surveillance than for those who received plain chest radiography (CXR) (1.93 y versus 2.56 y; $p = 0.046$), whereas 5-year cancer-specific survival did not significantly differ (39.1% for CT versus 50.7% for CXR; mean 4.47 y versus 6.51 y; $p = 0.353$), and there is no difference between CT and CXR in whether subsequent malignancies were treated with curative or palliative intent (41% versus 40%; $p = 0.639$).

Does Postoperative Surveillance Improve Recurrence or SPLC Detection?

Undoubtedly, with the emerging innovative imaging technologies, our ability to detect extrapulmonary metastases has greatly improved over the past 50 years. Nevertheless, occult micrometastases and SPLC are still threatening patients' health; recurrence seems far too often after curative-intent therapy.[14–16] A prior study indicated that there were no significant differences in 5-year survival rates between secondary primary NSCLCs and initial primary cancers.[2]

Brain metastases after lung cancer resection are observed in 6.3% to 15.6% of cases,[17–20] and recurrence of brain metastases directly leads to a decrease in

Table 1. Summary of Recommendations for Surveillance After Curative-Intent Therapy of NSCLC[8-11]

	Surveillance						
	≈2000			≈2010		Now	
Source	First 2 Y	Y 3-5	After	First 2 Y	After	First 2 Y	After
ASCO	Not included					➢ CT Q 6 mo **The recommendation did not address the frequency of the clinical evaluation (history and physical examination)*	➢ CT annually
ESMO	Not included			➢ PC surveillance for 3-6 moafter therapy ➢ Hx, PE, CXR or chest CT Q 6 mo	➢ Hx, PE, CXR or CCT annually	➢ Hx, PE and contrast-enhanced chest and abdominal CT Q 6 mo ➢ PET-CT optional	➢ Hx, PE, and chest and upper abdominal CT annually
ACCP	➢ PC surveillance for 3-6 mo after therapy ➢ Hx, PE, CXR or chest CT Q 6 mo	➢ Hx, PE CXR or chest CT annually	➢ Hx, PE CXR or chest CT annually	➢ Chest CT, HRQOL Q 6 mo	➢ CCT, HRQOL annually	Not updated	
NCCN	➢ Chest CT at 3 moafter therapy ➢ Hx, PE, CXR Q 3-4 mo; spiral CT Q12 mo	➢ Hx, PE, CXR Q 6 mo; spiral CT Q12 mo	➢ Hx, PE, CXR Q 12 mo; spiral CT Q12 mo	➢ Hx, PE, contrast-enhanced chest CT Q 4-6 mo	➢ Hx, PE, chest CT annually	Stage I and II: ➢ Hx, PE, (contrast enhanced) chest CT Q 6 mo FOR 2-3 YRs Stage III and IV: ➢ Hx, PE, (contrast enhanced) chest CT Q 3-6 mo for 3 y	➢ Hx, PE, chest LDCT annually Y 3-5: ➢ Hx, PE, (contrast enhanced) chest CT Q 6 mo After: ➢ Hx, PE, chest LDCT annually

ACCP, American College of Chest Physicians; ASCO, American Society of Clinical Oncology; CT, computed tomography; CXR, chest radiograph; ESMO, European Society of Medical Oncology; HRQOL, health-related quality of life; Hx, history; NCCN, National Comprehensive Cancer Network; PC, postoperative complications; PE, physical examination; PET-CT, [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography computed tomography; Q, every.

patients' quality of life, making early detection desirable. Nevertheless, there are no randomized trials concerning brain magnetic resonance imaging in surveillance; American Society of Clinical Oncology guidelines do not recommend screening for brain metastases during surveillance.[11] Multiple studies have concluded that CT scan was a superior tool to diagnose asymptomatic or locoregional disease recurrence. In a retrospective study by Lou et al.,[2] covering nearly 1300 patients with resected stage I or II NSCLC, regular CT surveillance (every 6 months for the first 2 years, followed by annual surveillance) indicated efficacy in identifying 82% of locoregional-only recurrences and 93% of SPLCs. Most SPLCs were in stage I or II at diagnosis, and more than half received curative surgical resection, but the study did not involve survival outcomes. Crabtree et al.[5] also revealed that CT scan was superior to CXR in detecting asymptomatic recurrence, 81% versus 51% ($p = 0.001$). In a novel study comparing CT with CXR, Hanna et al.[21] prospectively analyzed a cohort of 271 patients with stages I to III who underwent definitive resection and had surveillance with both low-dose CT and CXR at 3 months for the first 2 years and 6 months until 5 years. In their cohort, locoregional disease recurrence or SPLC developed in 23.2%. Pairs of CXR and minimal-dose CT were analyzed, and CT was significantly more sensitive than CXR for diagnosing new or recurrent cancer (94% versus 21.2%). This allowed 77.8% of cases to be detected while the patient was asymptomatic—75% of these were candidates for curative treatment.

Would a More Frequent Surveillance Strategy Improve Survival?

Theoretically, a more frequent detection of incurable recurrence might facilitate the earlier initiation of additional treatment. Nevertheless, current evidence does not substantiate this hypothesis. A meta-analysis incorporating nine studies (comprising seven retrospective studies, one prospective cohort study, and one randomized controlled trial) revealed a not significant trend toward improved survival with intensive follow-up strategies that included routine surveillance imaging.[7] McMurry et al.[22] used the robust Surveillance, Epidemiology, and End Results Program database to compare survival in patients who were obse21rved every 3 months versus 6 months versus 12 months and found no difference in survival among any groups (6 mo relative to 3 mo HR = 1.12, CI: 0.98–1.29 $p = 0.09$; 12 mo relative to 3 mo HR = 1.06 CI: 0.86–1.31). Other studies also revealed there was no harm introduced by more intensive imaging but also no benefit on survival, either in early-stage or advanced-stage NSCLC.[22,23]

Can a More Lenient Follow-up Strategy Be Adopted in Early-Stage Lung Cancer?

Recurrence patterns in NSCLC exhibit variability among different types. For instance, tumors characterized by pure ground-glass opacities (GGOs) or adenocarcinoma in situ (AIS) or minimal invasive adenocarcinoma (MIA) rarely exhibit recurrence within 5 or even 10 years after complete resection. For patients with the earliest-stage disease (pT1aN0M0R0), the estimated 5-year survival is more than 75% and may even be as high as 91% in screen-detected early-stage cancers.[24] Given annual CT has been recommended for lung cancer screening, there has been a notable increase in the proportion of early-stage lung cancer.[25] The next step is to determine whether a less frequent surveillance strategy is applicable in these patients, with more emphasis on detection of SPLC rather than recurrence. Nevertheless, more data are awaited as a more evidence-informed surveillance strategy is sought.

Ground-Glass Opacities

In 1992, Remy-Jardin et al.[26] systematically defined GGO. Subsequently, in 2002, Henschke et al.[27] further categorized GGO into part-solid nodules (nodules with both GGO and solid components) and nonsolid nodules, typically referred to as pure GGO. The consolidation-to-tumor ratio (CTR), defined as the ratio of the solid portion size to the total size in the lung window, serves as a prevalent index for measuring the solid proportion of GGO and is closely associated with prognosis.

For pure GGO, Li et al.[28] reviewed 308 patients with lung adenocarcinoma who underwent surgery and found a 10-year recurrence-free survival (RFS) of 100%, and a 10-year OS rate of 96.9%. Both 5-year and 10-year lung cancer-specific survival were 100%, indicating negligible recurrence or metastasis over a decade. In contrast, the 5-year RFS of mixed GGO ranges from 63.6% to 99.7%, depending on CTR, tumor size, and surgical procedure.[29–32] Fu et al.[33] reported that for patients with invasive stage I NSCLC, the 5-year RFS for pure GGO, part-solid, and solid nodules was 100%, 87.6%, and 73.2%, respectively. Hattori et al.[34] revealed that the 5-year OS for clinical stage IA lung adenocarcinoma was 91.2% for GGO and 68.9% for solid nodules. These findings suggest that a smaller CTR is indicative of a better prognosis, with lower recurrence and metastasis rates. Consequently, different follow-up strategies should be considered for GGO with varying CTR. Nevertheless, there is a lack of specific follow-up strategies for GGO with different CTR based on their distinct prognoses.

Notably, the recurrence patterns of GGO may change with the range of resection. Suzuki et al.[35] defined

radiological lung adenocarcinoma with a maximum tumor diameter of 2.0 cm or less and CTR of 0.25 or less as early adenocarcinoma of the lung, indicating specificity for no lymph node metastasis and no vascular invasion at 98.7%. Furthermore, the 5-year OS and 5-year RFS for lobectomy were 97.1% and 92.4%, respectively.[29] Moreover, Suzuki et al.[30] prospectively examined 333 patients who underwent subsegmentectomy with radiological early adenocarcinoma and concluded 5-year RFS was 99.7%,and no local relapse for any patient. Nevertheless, the situation is more complicated when the tumor contains more solid part. Among 1106 patients with tumor diameter of 2 cm or less and CTR greater than 0.5 of NSCLC, the 5-year RFS was 88.0% for segmentectomy and 87.9% for lobectomy. The proportions of local relapse were 10.5% for segmentectomy and 5.4% for lobectomy.[31] Aokage et al.[32] analyzed 357 patients who underwent segmentectomy with a tumor diameter of 3 cm or less and CTR of 0.5 or less and revealed the 5-year RFS was 98.0%.

In cases when the tumor is solid (CTR = 1), indicating the worst prognosis and the highest likelihood of recurrence and metastasis, even in small tumors, Park et al.[36] reported a higher frequency (16.5%) of brain metastasis in patients with clinical stage I solid adenocarcinoma than that in GGO.

Adenocarcinoma In Situ or Minimal Invasive Adenocarcinoma

AIS and MIA were officially defined with the release of the fourth edition of the WHO classification of lung tumors. Essentially, tumors previously categorized as bronchioloalveolar carcinoma with a size of 3 cm or less and devoid of invasion were redesignated as AIS. Similarly, tumors previously identified as mixed adenocarcinoma with bronchioloalveolar carcinoma components and invasion of 0.5 cm or less were newly termed MIA.[37] AIS and MIA are both characterized by a favorable prognosis, owing to their predominantly preinvasive or limited invasive components. Numerous reports have consistently highlighted the positive RFS outcomes associated with AIS or MIA after curative-intent resection.[38–40] Zhang et al.[41] conducted a retrospective study enrolling 1644 patients with resected AIS or MIA and found that the 5-year RFS remains 100%, even with a more conservative sublobar resection. Furthermore, they revealed similar 5-year RFS in AIS or MIA diagnosed with intraoperative frozen section.[42]

Meanwhile, owing to the limited time scale, only a few studies have reported long-term (>5 y) recurrence patterns of AIS or MIA. Li et al.[24] reported 10-year recurrence survival results in 125 patients with AIS or MIA. Most of the patients (62.4%) received wedge resection, and the 10-year RFS of AIS or MIA were all 100%. A retrospective study in 3170 patients with lung adenocarcinoma (LUAD) revealed no recurrence in 524 patients with AIS or MIA. Nevertheless, SPLC developed in 27 patients (5.2%).[25] In most studies, most of the patients underwent lobectomy owing to the lack of the validity of sublobar resection for small preinvasive lesions. Nakao et al.[43] reported long-term survival results of 50 patients with Noguchi-type A or B or C tumors. The RFS remained 100% in patients who underwent lobectomy, whereas four patients revealed possibly cut-end recurrences in a limited resection group.[43] Because of the increasing prevalence of screening using low-dose CT, it is considered that early-stage tumors, including AIS and MIA, will be detected more frequently. To achieve better management of AIS and MIA, it is important to evaluate the follow-up strategies after surgery for these types of tumors. On lobectomy, the risk of recurrence is quite low at even longer than 5 years for AIS or MIA. Nevertheless, the development of SPLC should be noted. In addition, the recurrence pattern for AIS or MIA with limited resection may need further validation from clinical trials such as JCOG0802,[44] 0804,[45] and 1211.[45]

Other Factors May Influence the Surveillance Strategies of NSCLC

Despite the features of the resected tumors, other characteristics of patients may also influence the recurrence patterns and surveillance strategies of patients with NSCLC. Schmidt-Hansen et al.[46] conducted a meta-analysis that revealed a potential link among patient satisfaction, quality of life, median survival, and follow-up leader. Smoking cessation after diagnosis may reduce the risk of SPLC, given Aredo et al.[47] revealed that smoking pack-years (HR 1.18 per 10 pack-years; $p < 0.001$) and smoking intensity (HR 1.30 per 10 cigarettes per d; $p < 0.001$) were significantly associated with increased SPLC risk. Moreover, in LUAD, micropapillary or solid predominant pattern group (versus acinar or papillary) was a significant poor prognostic factor for survival.[48] Other relevant factors include postcurrence therapy, sex, histologic diagnosis, initial recurrence sites, communications with doctors, surgeon quality and so on.[48–50]

Can We Predict the Metastatic Pattern of NSCLC Through Clinicopathologic Factors?

Unveiling timing and site-specific failure pattern and developing risk prediction models that widely incorporate clinicopathologic factors and genetic features are critical for stratifying patients and guiding better surveillance strategies. The most frequent metastatic site of

NSCLC is bone, followed by the lung, brain, liver, and adrenal glands.[51] A study based on the Swedish Family Cancer Database revealed that approximately 38% of all patients with lung cancer who died had one metastatic site, and 19% had two or more reported metastases.[52] Nevertheless, another study revealed approximately 63.8% of all metastatic cohorts exhibited metastasis to one site, and the most common two-site metastatic combination was bone and lung.[51] Early in the past century, the value of accurately predicting metastases to specific organs was not recognized.[53,54] Later, Finkelstein et al.[55] reported that bone and liver metastases were identified as independent prognostic factors in 893 patients with metastatic NSCLC. Sorensen et al.[56] also revealed that patients with NSCLC with brain metastasis exhibited a shorter survival than did those without brain metastasis. Furthermore, accurate prediction of site-specific metastasis in NSCLC and the targeted development of follow-up strategies would considerably reduce the types and frequency of examinations required for patients, and enable timely appropriate treatment strategies.

There have been studies analyzing the recurrence patterns stratified by isolated organs and regions. Shimada et al.[57] revealed that vascular invasion and tumor differentiation significantly affect the prediction of cancer recurrence in patients with stage IA NSCLC. Other studies also identified smoking history, tumor histologic diagnosis, lymphovascular invasion (LVI), visceral pleural invasion, tumor size, lymph node status, and *p*-stage as independent predictors for overall or site-specific recurrence.[58–65] These results laid foundations for developing a model to predict metastatic patterns of NSCLC. Zhang et al.[66] developed a clinicopathologic prediction model for postoperative recurrence in stage IA NSCLC on the basis of five variables (central tumor location, stage T1B, high histologic diagnosis grade, poor differentiation, and LVI), which were revealed by Cox multivariate survival analysis. Furthermore, Zhang et al.[58] investigated the pattern of recurrence in a series in 2017 patients with NSCLC and established nomograms to predict overall recurrence and site-specific recurrence with considerable accuracy. Similarly, Bains et al.[67] developed a clinical tool to predict recurrence in patients with resected small LUAD, involving all clinical, radiological, surgical, and pathologic variables known to contribute to patient lung cancer and noncancer survival.

Would Genomic Profile (eg, Driver Mutations) Help With the Prediction of the Metastatic Pattern of NSCLC?

Although numerous clinicopathologic predictors have been incorporated to optimize the risk prediction models, such models may have hit the ceiling given they still lack patient genetic signatures. Multiple previous studies revealed conflicting results on the prognostic value of *EGFR* mutations in patients with surgically resected lung cancer. Kim et al.[68] revealed that *EGFR* mutation was not a significant prognostic factor for disease-free survival or freedom from recurrence after surgical resection of lung adenocarcinomas, which coincided with the result of another matched-pair and multi-institutional analysis.[68,69] A retrospective study including only patients with stage I NSCLC indicated that *EGFR* mutation was associated with a lower recurrence rate ($p = 0.03$) and greater disease-free survival ($p = 0.008$).[70] After excluding patients with AIS or MIA or lepidic adenocarcinoma and pure GGO component, *EGFR* mutation was not an independent prognostic factor for RFS.[71–73] Deng et al.[73] also reported that exon 19 deletions and exon 21 L858R revealed almost no difference in RFS regardless of stratification in the subtype analysis, which was similar to other studies.[73–75] Moreover, *EGFR* mutation was reported to be associated with risk of brain metastases.[76,77] Suda et al.[78] reported that in patients with lung cancer with *EGFR* mutations, initial recurrence sites identified significantly higher frequencies of brain and adrenal gland metastases. In addition, exon 19 Del has a more aggressive phenotype, and patients have a poorer prognosis than with L858R in early-stage lung cancers.[78] Several reports have confirmed that *KRAS* mutation was related to poor survival and *EGFR* with organ-specific tropism in patients with resected LUAD, which was consistent with findings in this study.[67,73,77,79,80] LUAD with *KRAS* G12C mutation also exhibited a potentially aggressive phenotype associated with early and locoregional recurrence.[81] Nevertheless, *KRAS* G12D may not be prognostic in resected LUAD.[82] A study enrolled 209 consecutive patients with stage IV nonsquamous NSCLC with common mutations including *EGFR*, *KRAS*, *ALK,* and wild-type for all three, which revealed that there was a higher incidence of pericardial, pleural, and liver metastasis in patients with *ALK*+ than in patients without an *EGFR*, *KRAS*, or *ALK* oncogene abnormality. Patients with an *EGFR* mutation also had a higher rate of liver metastases than that of the triple negative cohort.[80] A retrospective study concerning nine common oncogenic driver mutations from 1531 patients with resected LUAD revealed that bone and brain recurrence tended to occur early (median 11.7 and 17.0 months, respectively) whereas thorax recurrence occurred later (median 22.2 months), which was validated across different tumor stages. In addition, *EGFR* mutation was an independent predictor for brain and bone recurrence and *KRAS* mutation for early recurrence.[83]

Apart from driver mutation, other metastases-associated genes in the primary tumor may also help to predict risk of recurrent disease, including *BRCA1,*

YAP1, GATA2, and so on.[84,85] Models based on these gene sets have been developed and revealed promising predicting efficacy.[84] Moreover, epigenetic changes in specific genes such as cyclin-dependent kinase inhibitor 2A gene p16, the H-cadherin gene *CDH13,* etc, could also predict the recurrence pattern.[86] Yang et al.[87] developed a methylome-based malignancy density scoring system to predict recurrence risk in early-stage LUAD.

Would PET-CT be a More Effective Technique for Postoperative Surveillance?

It is known that CT imaging is more sensitive than conventional CXR for detecting tumor recurrence, with a greater resolution and improved evaluation of the hilum and mediastinum.[88] The promotion of low-dose screening chest CT allows reconstruction imaging obtained at reduced radiation doses.[89]

The most contentious issue revolves around whether 18F-labeled fluorodeoxyglucose PET (18F-FDG PET)-CT imaging should be recommended for surveillance. A study involving 92 patients resected compared 18F-FDG PET-CT and standard CT, bone scintigraphy, and brain magnetic resonance imaging at 6-month intervals after resection.[90]

In this study, no enhancements in sensitivity or specificity for the detection of recurrence were observed with 18F-FDG PET-CT. Another comparable study involving 358 participants revealed that 18F-FDG PET-CT did identify recurrences not detected by CT. Nevertheless, it was noted that ground-glass lesions and small adenocarcinomas were frequently overlooked by FDG PET-CT.[91] The radiation exposure of FDG PET-CT may be five times higher than that of CT imaging (32 mSv versus 3–7 mSv). Comparatively, a low-dose screening CT is typically less than 2 mSv.

Lastly, considering the cost perspective, the typical cost for PET-CT is approximately $3000, whereas a CT scan costs $190 and with contrast, $230.[92–94] In summary, although 18F-FDG PET-CT may exhibit comparable sensitivity and specificity to those of CT alone in detecting recurrence, the heightened cost and radiation exposure associated with PET-CT outweigh the perceived benefits of this imaging modality, especially given its lack of proved superiority as a surveillance tool.

Would Liquid Biopsy Help With the Detection of Recurrence or SPLC for NSCLC?

Liquid biopsy refers to different biofluid-derived analytes analyses (urine, cerebral spinal fluid, ascites, and pleural fluid), mostly obtained through blood sampling. At present, circulating biomarkers of liquid biopsy typically are circulating tumor cells, circulating cell-free deoxyribonucleic acid (DNA), circulating tumor DNA (ctDNA), exosomes, microRNAs, peripheral blood circulating RNA, tumor-educated blood platelets, and circulating tumor vascular endothelial cells,[95] among which ctDNA, circulating tumor cells, and exosomes are the most typically detected biomarkers. Therefore, ctDNA may be a powerful biomarker with the potential to identify minimal residual disease (MRD) and monitor recurrence that has been shown in many cancers.[96–99] Chen et al.[100] examined 25 patients with lung cancer and revealed patients with detectable ctDNA MRD 3 days after surgery had shorter RFS than did their counterparts with undetectable ctDNA. Abbosh et al.[101] prospectively included 24 patients with NSCLC who underwent surgical treatment and revealed that disease relapse developed in 14 patients during a median follow-up of 775 days, and 13 of 14 patients (93%) had detectable ctDNA before or at the time of clinical relapse. Nevertheless, 36% of patients with disease relapse had detectable ctDNA at the first time point after surgery; by contrast, disease relapse did not develop in 90% of patients with undetectable ctDNA at the first time point after surgery. Significantly, among the 10 patients without relapse, ctDNA was detected in three individuals in at least one time point. On the basis of the above studies, Abbosh et al.[102] further used ArcherDx technology to carry out further research and indicated that 51 of 108 patients with NSCLC who underwent surgical treatment had a relapse. Moreover, 27 of 108 patients (25%) exhibited one or more positive ctDNA calls, and 25 of 27 of these patients had a relapse, which concluded the positive predictive value of landmark for relapse was 93%; the negative predictive value was 68%, and sensitivity of landmark for relapse was 49%. It is remarkable that 11 of 12 patients with landmark positive before adjuvant therapy had eventual clinical relapse despite five of 11 patients exhibiting undetectable ctDNA after adjuvant therapy, which indicated that ctDNA clearance in adjuvant therapy did not always predict less relapse. Besides, Zviran et al.[103] used the whole-genome sequencing of cell-free DNA named MRDetect to analyze 22 patients with LUAD who underwent surgery. With a median follow-up of 18 months, 12 of 22 patients had negative ctDNA after surgery, and none had relapse. Among the 10 patients with detectable ctDNA, disease recurrence developed in 50%. In addition, patients with detectable ctDNA MRD after surgery had significantly worse RFS than did their counterparts with ctDNA MRD-negative results. In brief, ctDNA MRD detection is the most promising potential liquid biopsy technique for follow-up of lung cancer. Although it represents many advantages such as being noninvasive, radiation-free, and convenient, and having earlier detection time than do other methods, its sensitivity and

specificity are currently insufficient for clinical practice, for which technical improvement and further clinical trials are needed.

Potential Application of Multi-Omics and Machine Learning to Personalized Surveillance Plan

Given that various factors including patient characteristics, tumor pathology, and post-currence therapy will influence the recurrence pattern and surveillance strategies of patients with NSCLC, machine learning analyses of multi-omics data may be a promising area in the artificial intelligence era. In 2018, Zhang et al.[58] developed web-based clinicopathologic prediction models for conditional risk of site-specific recurrence on the basis of Cox regression. The variables used in the analysis included sex, age, smoking history, tumor size, tumor histologic diagnosis, LVI, visceral pleural invasion, and pathologic TNM stage.[58] More recently, Yang et al.[104] have integrated the genomic, clinical, and demographic data of patients with LUAD and squamous cell carcinoma from The Cancer Genome Atlas and introduced copy number variation and mutation information of 15 selected genes to generate predictive models for recurrence and survivability. Several other studies also established recurrence prediction models with various algorithms and parameters, and revealed superior performance to TNM stage in predicting recurrence and OS.[105–107] These robust and ready-to-use machine learning methods, validated and externally tested, set the stage for future clinical trials entailing quantitative personalized risk stratification and surveillance after curative-intent radiotherapy for NSCLC.

Discussion

Precision therapy has now become an essential component of the standard practices for diagnosing and treating multiple types of cancer, particularly lung cancer.[108] The genomics-driven comprehension of cancer pathogenesis has propelled clinical treatment for NSCLC into the era of precision medicine. Particularly in advanced-stage NSCLC, the transition from molecularly targeted therapy to immune checkpoint inhibitors has remarkably enhanced patient prognosis. Individualized follow-up strategies refer to accurately predicting the time and site of recurrence on the basis of a patient's imaging, clinical, and pathologic characteristics, and then devising rational follow-up methods and intervals to improve patient well-being and enhance the utilization of medical resources. Considering the advancements in precision medicine, tailoring postoperative surveillance plans on the basis of the individual genomic profile of patients could potentially optimize the detection of recurrence or metastasis, ensuring timely intervention and personalized care for better outcomes.

The optimal surveillance of patients with NSCLC for recurrence and SPLC after curative-intent surgery is controversial. Many studies have revealed the distinct recurrence patterns of early-stage lung cancer, such as GGOs or AIS or MIA. It has been shown that more frequent surveillance with CT will not benefit patients with advanced NSCLC, nor was PET-CT recommended. Nevertheless, it is not clear whether extending the interval of surveillance of early-stage lung cancer with excellent prognosis is applicable. A personalized surveillance plan with lower frequency of follow-up will obviously benefit patients both economically and mentally. Furthermore, it will definitely benefit populations with NSCLC in under-resourced countries with imbalanced medical care.

In the absence of high-quality prospective data, IFCT-0302 trial (The Intergroupe Francophone de Cancerologie Thoracique-0302, ClinicalTrials.gov identifier: NCT00198341) is the first randomized trial of follow-up in resected NSCLC. Data from the trial suggested CT detected more recurrence and SPLCs but did not improve survival compared with CXR.[109] Moreover, another randomized trial for follow-up in resected NSCLC, named JCOG2012 (Japan Clinical Oncology Group-2021, or PHOENIX), has just started. This trial is expected to provide more insights into the best practices for postoperative surveillance in these patients.[110] As new therapies to treat recurrent disease develop, earlier recognition of recurrence has the potential to cause survival improvement. More studies will need to be performed to inform optimal surveillance strategies. Recent multi-omics studies and spatial omics research have further elucidated the more complex genetic alterations and molecular mechanisms involved in lung cancer and its metastasis.[111,112] Simultaneously, with the advancement of liquid biopsies, we need to consider a more comprehensive range of clinical and biological information to achieve more accurate predictions. It is worth noting that owing to issues such as cost, equipment, and technology, the tools of multi-omics are still difficult to apply routinely in clinical practice. Therefore, the way to simplify their ultimate clinical implementation is also a very important issue. In addition, as artificial intelligence and the deep learning model develop, a more precise postoperative surveillance strategy on the basis of sufficient clinical evidence will be available. Nevertheless, it is noted that there is an ongoing debate regarding the potential benefits of early detection in lung cancer recurrence, metastasis, or the emergence of SPLC on patient prognosis. As systematic treatments evolve, incorporating personalized strategies for addressing metastases at distinct anatomical locations, there remains a rationale to anticipate improvements in patient outcomes.

CRediT Authorship Contribution Statement

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Yang Zhang: Conceptualization; Data curation; Writing - original draft.

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Disclosure

The authors declare no conflict of interest.

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