Review Article

Values of circulating tumor DNA for non-small cell lung cancer patients receiving neoadjuvant therapy, progress and challenges: a narrative review

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Background and Objective: The value of circulating tumor DNA (ctDNA) in neoadjuvant therapy (NAT) for lung cancer remains controversial. Therefore, we conducted a review to further investigate the role of ctDNA in non-small cell lung cancer (NSCLC) patients undergoing NAT for individualized management.

Methods: A search of online databases (PubMed, Embase, Web of Science, Science Direct, and Cochrane Library) was conducted to evaluate the value of ctDNA in predicting relapse, risk stratification, and efficacy of NAT in NSCLC. Only articles published in English within the last 25 years, between January 1st, 1998 and November 30th, 2023, were included. Additionally, the application of ctDNA in NSCLC is briefly reviewed.

Key Content and Findings: ctDNA is a non-invasive and dynamic method that plays an important role in future treatment guidance. Additionally, ctDNA successfully predicted the effect of neoadjuvant immunotherapy before surgery, and positive testing was strongly correlated with a lower major pathological response or complete pathological response rate. Sequential testing of ctDNA may serve as a secondary indicator to guide the adjustment of treatment programs. However, the application of this method has been limited by false negative results, a lack of objective indicators, and high costs. These issues must be addressed by researchers.

Conclusions: ctDNA has strong potential in NAT, based on positive preliminary studies. However, its widespread use is limited by the high cost of testing. Further research is needed to explore its value in risk stratification and treatment guidance in the future.

Keywords: Non-small cell lung cancer (NSCLC); neoadjuvant therapy (NAT); circulating tumor DNA (ctDNA); biomarker; individualized treatment

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Introduction

Lung cancer is one of the most lethal malignancies globally and continues to be the leading cause of death from malignancy. Non-small cell lung cancer (NSCLC) accounts for about 85%. Although there has been an increase in the proportion of early-stage NSCLC, approximately 60% of patients still present with locally advanced or advanced NSCLC when diagnosed initially (1). Lung cancer exhibits a suboptimal prognosis and high probability of recurrence. Stage I–II NSCLC with high-risk pathologic subtypes has up to 40–50% recurrence rate within 5 years post-radical resection (2-4). Improving long-term survival of patients is the priority. Neoadjuvant therapy (NAT) is believed to be beneficial in staging down and increasing the R0 resection rate, ultimately improving patients' survival (5). Recent studies have demonstrated that neoadjuvant immunotherapy and targeted therapies can improve overall survival (OS), progression-free survival (PFS), or event-free survival (EFS) in patients with stage IB–IIIA NSCLC (6-8). Developing an individualized treatment plan for patients undergoing composite treatment modality requires additional tools.

Circulating tumor DNA (ctDNA) is a non-invasive assay that has recently emerged with advances *in vitro* assay counting and detection. It is fragment of DNA derived from tumor cells that is actively shed or passively released into the peripheral circulation (9). ctDNA contains numerous tumor-associated characteristics enabling the identification of highly diverse individual features (10,11). Meanwhile, ctDNA detection relies on peripheral blood, with or without tumor information obtained from tissue biopsy. These detection strategies correspond to two application focuses. For tumor-informed approach, individual information is obtained by lung cancer tissue. These idiosyncratic features serve as internal controls, enabling ctDNA to achieve greater accuracy and more comprehensive mutation capture with lower detection limits. CtDNA can also act as complementary for missed variations in tissue detection (12-14). In contrast, tissue-free ctDNA detection focuses more on same variations like driven genes with faster process. It does have relatively reliable specificity, but defect in sensitivity (15,16). Former studies have established its significance in predicting early recurrence of lung cancer and determining the prognosis of advanced stages, in addition to assessing treatment effectiveness and risk stratification (17,18). It is also utilized to monitor patients post-treatment who are undergoing NAT (19). We conducted a literature review to elucidate the research progress and limitations of ctDNA in NAT for NSCLC, specifically in precision treatment. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-265/rc).

Methods

This is a narrative review that focuses on literature published between 1998 and 2023. We reviewed all relevant articles, including case series and clinical outcomes of case reports in retrospective studies, published between January 1, 1998, and November 30, 2023. We conducted a literature search using the following key words: 'circulating tumor DNA', 'lung cancer', 'neoadjuvant', 'perioperative treatment', and 'biomarker'. The PubMed, Embase, Web of Science, Science Direct, and Cochrane Library databases were searched for relevant studies. Additionally, ongoing clinical trials were identified through www.clinicaltrials.gov.

Any type of publication was eligible for inclusion, including randomized controlled trial, observational study, case control study and case series with detailed clinical information. Detection techniques or tools were excluded. Abstracts of eligible literatures were evaluated independently by two investigators. Duplicate references were removed by software Endnote X9. The including criteria: English-language publications describing ctDNA detection in lung cancer, with more than one treatment option. Exclusion criteria: non-English language articles, editorials, commentary, abstracts, letters to the editor and the introduction of platform or other technique of ctDNA detection (*Table 1*).

Application of ctDNA in NSCLC

NSCLC is a highly heterogeneous disease, with differences in prognosis even in same stage (20,21). Imaging and tumor markers were previously used as non-invasive methods to monitor recurrence in NSCLC patients before ctDNA detection available (22-24). However, both imaging and tumor markers have suboptimal specificity and sensitivity (25-27). Identifying recurrent lesions under a specific minimum size proves difficult for radiologists (28). Invasive peripheral percutaneous puncture or endobronchial ultrasound-guided (EBUS) puncture often leads to discomfort, along with risks of complications and false negatives (29-32). Limiting the follow-up strategy can negatively impact long-term survival. Additionally, ctDNA offers advantages in forecasting the

Table 1 The search strategy summary

Items	Specification
Date of search	November 30th 2023
Databases and other sources searched	PubMed, Embase, Web of Science, Science Direct, Cochrane Library
Search terms used	"Circulating Tumor DNA" OR "ctDNA" OR "Biomarker" AND "Neoadjuvant therapy" OR "NAT" OR "Perioperative treatment"
Timeframe	1998–2023
Inclusion and exclusion criteria	Inclusion: randomized controlled trial, observational study, case control study and case series with detailed clinical information
	Exclusion: non-English language articles, editorials, commentary, abstracts, letters to the editor and the introduction of platform or other technique of ctDNA detection
Selection process	Abstracts of eligible literatures were evaluated independently by two investigators

ctDNA, circulating tumor DNA.

recurrence and prognosis of NSCLC patients (33).

Postoperative surveillance

For lung cancer patients undergoing radical or salvage surgery, ctDNA can be used for risk stratification, and positive results often forecast unfavorable results like recurrence, which precedes imaging recurrence (34). Post-operative results offer the strongest predictive ability for patient prognosis (35,36). Xia and Chaudhuri's study highlights ctDNA's significance as an important risk factor for postoperative recurrence of early-stage lung cancer. Patients with negative ctDNA are at a lower risk of early recurrence than those with positive results, while long-term prognosis for both groups remains unknown (37,38). Gale's retrospective study showed that early ctDNA detection has a high clinical specificity (>98.5%) for predicting recurrence. In patients with recurrence, the median duration of positive ctDNA before positive imaging findings was about 212.5 days. Totally 28 patients had a primary tumor relapse, 18 of whom had a positive test after treatment (64.3%), and this correlated with shorter recurrence-free survival and OS (39).

Monitoring ctDNA dynamically during surgery can be beneficial for patients with early-stage lung cancer. However, the significance of the changes in guiding postoperative treatment is uncertain. Similarly, postoperative sequential ctDNA detection has not exhibited superior performance to single ctDNA detection (37,40). Further exploration is necessary to determine its value in early-stage lung cancer.

Driven gene detection and drug resistance monitoring

Targeted therapy and immunotherapy have altered the treatment approach for advanced NSCLC, improved prognosis, and of life (41-44), while ctDNA is a non-invasive means of obtaining tumor genetics information with good accuracy. Obtaining detailed pathological data is vital for antineoplastic therapy (45,46). Lyu's meta-analysis found that the pooled sensitivity of ctDNA was 67.1% (95% CI: 0.647–0.695) for detecting epidermal growth factor receptor (EGFR) mutations. It was 65.1% (95% CI: 0.558–0.736) in detecting Kirsten ratsarcoma viral oncogene homolog (KRAS) mutations, and was also able to detect anaplastic lymphoma kinase (ALK), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), and mesenchymal to epithelial transition factor (MET), but few data from related studies limited further investigation (47). In advanced stages, patients showed concordance in 88.2% clinically (48). Additionally, the rapid turnaround time of ctDNA analysis results enables prompt medication administration and early implementation of interventions compared to conventional tissue analysis (49). Commonly, pathological specimens are obtained through invasive operations. However, they cannot always provide complete pathological specimens and can cause discomfort to patients. In advanced stages, it is very hard to obtain both primary and metastatic tumor samples (50). For elderly patients with poor physical condition, invasive biopsy poses a higher risk, especially for those who developed drug resistance.

CtDNA offers a more convenient way. Several case

reports and retrospective studies suggest that sequential monitoring during therapy with EGFR or ALK mutation can recognize patients resistant to treatment (51-53). However, continuous ctDNA monitoring is controversial for rare mutations and developed rapid metastasis in several case reports while some were effective (54-57). These findings are undoubtedly concerning, and the inclusion criteria in future studies will pose a challenge for researchers.

Predictor of systemic therapy in prognosis

Positive ctDNA results predicted a poor prognosis in patients diagnosed with advanced lung cancer, regardless of their driver gene carrier status (58-60). Patients frequently worry about the side effects of chemotherapy in comparison to the advancement of their disease, and this influences their medical decisions. Patients with advanced lung cancer frequently have varying levels of metastatic disease, the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria commonly used to assess imaging remission are inadequate, requiring WHO assessment criteria instead. Imaging remission correlates with a better prognosis remains uncertain. Hong's study discovered that dual-energy CT imaging can predict the effectiveness of chemotherapy in patients with advanced lung adenocarcinoma (61). Birchard's study, however, discovered no noteworthy discrepancy in survival rates between patients whose tumors initially receded and those whose disease initially advanced (62). In patients receiving targeted therapy compared to immunotherapy, there may be discrepancies between imaging remission and efficacy in practice (63-65). However, the results of ctDNA in the pre-treatment node should not be solely relied upon for aggressive or palliative treatment. Although ctDNA does indicate poor prognosis for advanced NSCLC, the value of prognosis prediction does not seem to be so imperative.

Values in NSCLC NAT

Currently conducted trials related to ctDNA

Numerous clinical trials investigating neoadjuvant immunotherapy and targeted therapies are currently in progress, incorporating ctDNA into monitoring metrics or secondary endpoints. Most of them were designed a single test during or after NAT for grouping (like NCT04965831 and NCT04351555). The observational trials used the ctDNA for evaluating prognosis by dynamic monitor, and they focused more on perioperative or postoperative period in long-term (like NCT06111807 and NCT05778253). They are summarized in *Table 2*.

Current conducted trials mainly use ctDNA as biomarker. The data from the current study indicate that ctDNA is a risk factor for poorer DFS in NAT. Additionally, variant allele frequencies (VAF) or mutant allele frequencies (MAF) have value as a cut-off, as previously demonstrated (66,67). Several high-quality studies have effectively demonstrated the predictive value of the subject (7,68,69). Ongoing studies will reveal its value in long-term survival and risk stratification.

Identify patients benefit from NAT

The NCCN guidelines have expanded the indication for NAT patients to stage IB–IIIA (70). NAT is undeniably effective for cases of locally advanced staging or direct invasion of vital structures by the primary tumor. However, there is a lack of studies exploring whether neoadjuvant or adjuvant therapy is preferable for patients with early-stage lung cancer who can undergo direct R0 resection (71). Similarly, certain patients receiving neoadjuvant immunotherapy have encountered swift disease progression, thus rendering them ineligible for surgery and necessitating exposure to concurrent or sequential radiochemotherapy (72). Although patients who initially receive treatment are typically in good condition, current research and clinical practice suggest that not all individuals will benefit from NAT (73). It is important to identify patients benefit from NAT potentially in order to avoid ineffective or even harmful treatments. Lebow's study demonstrated the significance of baseline ctDNA testing for identifying treatment benefits in patients undergoing radiotherapy. Patients who tested negative at baseline had a better prognosis. However, positive patients had various clinical outcomes that necessitate continuous dynamic monitoring for assessment (74). The current process for NAT is briefly summarized in *Figure 1*.

Isolated baseline testing has limited value as a guide for subsequent treatment. Yang's study demonstrated the difficulty in predicting whether a patient will benefit from receiving ctDNA as a measure of baseline value in patients who are primed for treatment, regardless of stage (75). There may be several reasons for this. Firstly, ctDNA has a short half-life, often only a few hours. Therefore, the point in time at which it is monitored can affect the results to varying degrees (9). Secondly, there are no standards for ctDNA results (76). Gale's study demonstrated a direct correlation between the detection rate of ctDNA and the

Table 2 ctDNA application in ongoing NSCLC neoadjuvant clinical studies

No.	Registration	Researcher	Year	Study type	Country	Patients	Driven gene	Stage	Neoadjuvant theraputic regimen	Detection period	Time frame
1	NCT04302025	Roche	2020	Phase II	United States	85	Positive	IB–IIIB	Alectinib entrectinib vemurafenib cobimetinib pralsetinib	Neoadjuvant	6 weeks before surgery
2	NCT06065813	Wang	2022	Phase II	China	20	Negative	IIB–IIIA	Triprizumab + radiotherapy	Neoadjuvant	Single detection before 42 months postoperation
3	NCT04351555	Chaft	2020	Phase III	United States	328	Positive	IIB–IIIB	Osimertinib ± platinum-based doublet chemotherapy	Neoadjuvant	12 weeks after the first dose
4	NCT04965831	Wang	2021	Phase II	China	40	Positive	IIIA–IIIB	Furmonertinib	Neoadjuvant	8 weeks after the first dose
5	NCT05061550	Cascone	2022	Phase II	United States	350	Negative	IIA–IIIB	Durvalumab + oleclumab/ monalizumab/AZD0171 + platinum doublet chemotherapy	Baseline and long-term	Baseline and up to 24 months after last dose
6	NCT05798845	Fu	2023	Phase II	China	124	Negative	IIA–IIIA	Toripalimab + radiotherapy/platinum-based doublet chemotherapy	Postoperative	1 year after the first dose
7	NCT05778253	Hu	2023	Cohort	China	50	Negative	IIA–IIIB	Immunochemotherapy (no limitations)	Neoadjuvant and postoperative	Perioperation and each cycle before NAT
8	NCT04638582	Chipman	2022	Phase II	Canada	44	Negative	IA3–IIA	Pembrolizumab + platinum-based doublet chemotherapy	Perioperative	Perioperation and several times 24 months after surgery
9	NCT06111807	Hiltermann	2023	Cohort	Netherlands	248	No limitations	IIIA–IIIC	No limitations	Baseline and postoperative	Baseline and 36 months after initial treatment
10	NCT04367311	Hanna	2020	Phase II	United States	100	Negative	IB–IIA	Atezolizumab+ platinum-based doublet chemotherapy	Neoadjuvant and postoperative	Each cycle before NAT and 3.6.9.12 months after surgery
11	NCT05382052	Pereira	2022	Cohort	Spain	100	No limitations	IIIA	No limitations	Postoperative	Several times until 24 months after surgery

All trials were searched on https://www.clinicaltrials.gov, the filter options were: "disease: lung cancer; other terms: neoadjuvant; intervention/treatment: null; study status: all studies". ctDNA, circulating tumor DNA; NSCLC, non-small cell lung cancer; NAT, neoadjuvant therapy.

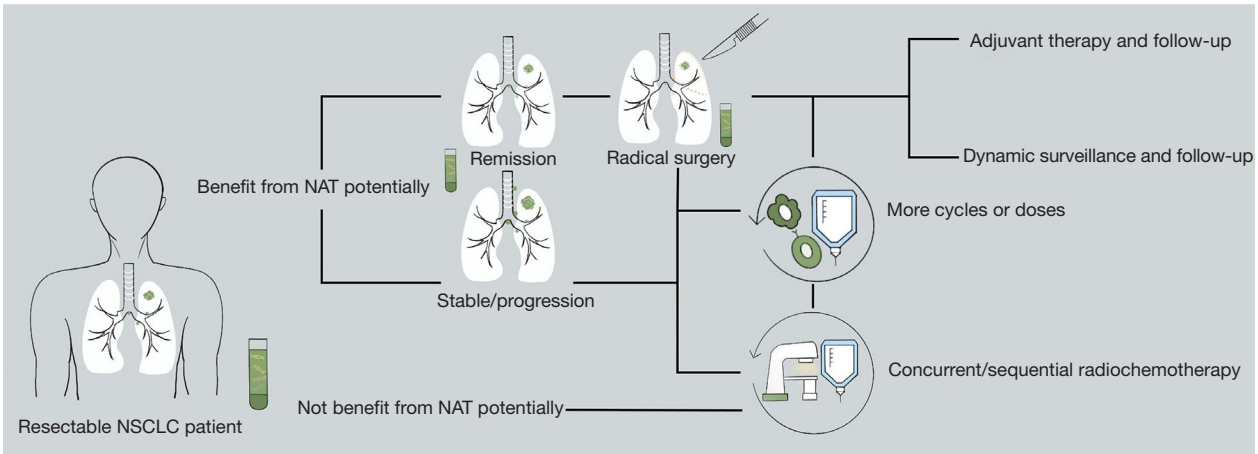

Figure 1 The current process for neoadjuvant therapy. NAT, neoadjuvant therapy; NSCLC, non-small cell lung cancer.

diameter of the primary lesion and stage. Therefore, the clinical significance of ctDNA results varied at different stages, indicating the need for cautious interpretation and the elimination of confounding factors (39). With advances in testing and standardization, we believe that ctDNA can provide a more reliable basis for predicting outcomes at baseline.

Predict efficacy of NAT

Several criteria exist for evaluating radiological response, and RECIST 1.1 stands out as the most economical and intuitive choice in assessment of antitumor therapy efficacy (77). Nevertheless, this criterion appears unsatisfied for predicting NAT efficacy in NSCLC, especially neoadjuvant immune or target therapy (78,79). Currently, postoperative resected pathological specimens are considered the most appropriate for assessing the response to NAT. Major pathological remission (MPR) and pathological complete remission (pCR) are regarded as indicators of good response (80). But without surgery, it is very hard to assess actual efficacy of NAT. Therefore, new imaging tools or other predictors are needed for pre-evaluation. For example, positron emission tomography/computed tomography (PET/CT) has a role in predicting the efficacy of NAT in NSCLC (81). In other types of tumors, clearance of ctDNA could partially reflect the efficacy of NAT, like pCR rate or prognosis (82-85). While no similar researches for NSCLC patients receiving NAT have been published yet. Forde found longer EFS and higher pCR rates in patients with ctDNA clearance present without significant difference, however (7). Reck's research did show clearance of ctDNA was necessary for pCR (100% negative predictive value), but not sufficient (40.5% positive predictive value) (86). Conventional next generation sequencing (NGS)-based assay can partially reflect the trend but have unsatisfactory accuracy. While the ctDNA-based minimal residual disease (MRD) detection showed unique advantages like high sensitivity, which may be more suitable for NAT assessment (87). Current research involving NSCLC is imperfect, although some studies have demonstrated the role of ctDNA in predicting the response to NAT. Yue conducted a retrospective study on ctDNA dynamics during NAT in NSCLC patients. The study found that negative test results were associated with higher MPR rates, with a sensitivity of 100%, a specificity of 83.33%, and an overall accuracy of 91.67%. However, the study's limitation is small sample size, which only included 22 cases (88). Deutsch's study is significant because he demonstrated that residual tumor volume (RVT) can predict the prognosis of patients undergoing NAT. After grouping patients according to RVT, it was found to be highly correlated with 2-year EFS [area under the curve (AUC) =0.74]. Pathologic response may serve as a survival surrogate, simplifying the process of evaluating NAT in NSCLC. Additionally, ctDNA has shown positively, as its clearance is associated with better pathologic response (89). Provencio's study in 2022 analyzed ctDNA in baseline, and found it was not a significant predictor of NAT clinical response, while pathological response was not fully discussed (67). Therefore, the role of ctDNA in predicting response to NAT needs to be validated by additional high-quality prospective studies.

Evaluate perioperative and long-term prognosis

Positive ctDNA test is a marker of a worse prognosis. It has been used as a grouping criterion and predictor in several clinical studies (90,91). Based on the available studies, it appears that ctDNA cannot be used as a perioperative risk factor in patients receiving NAT due to its lack of predictability for drug side effects and surgical risk (92). Several researchers demonstrated that perioperative ctDNA positivity is associated with worse recurrence-free survival and OS in lung cancer, revealing that neoadjuvant and adjuvant therapies did not affect this association (93-95). Two studies from Provencio *et al.* proved baseline ctDNA could be predictor of disease-free survival (DFS) and OS (67,68).

Some investigators argued that in NAT, EFS or DFS can serve as a surrogate for 5-year OS, which is considered the golden standard for long-term prognosis (96). Some considered that prognosis can be predicted by pathological remission, but larger trials are needed to confirm this (89). The long-term prognosis is a crucial factor in determining the effectiveness of a treatment. Therefore, neoadjuvant immune and targeted therapies for NSCLC must demonstrate their superiority in long-term survival compared to surgery with adjuvant therapy or concurrent radiotherapy (97). To reach this conclusion, more real-world studies are necessary, in addition to tightly designed clinical studies. Unfortunately, there are no clinical studies that reveal 5-year OS rates due to the late conduct of relevant clinical trials. Additionally, there is a lack of studies related to long-term postoperative monitoring of ctDNA, which is limited by various factors. However, as more studies are published, we will have more systematic and authoritative evidence to elaborate on the role of ctDNA in long-term prognosis.

Indicating optional perioperative treatment

Studies related to adjuvant therapy in NSCLC patients predate NAT. Previous studies have shown that adjuvant chemotherapy is beneficial in reducing the recurrence rate of stage IB-IIIA lung cancer (98-100). The ADAURA study demonstrated that osimertinib is better option for EGFR-positive patients in adjuvant therapy (101). NAT has been formally incorporated into the treatment regimen for NSCLC like "neoadjuvant + surgery + adjuvant" process. Some researchers are exploring its safety and efficacy. Wakelee's phase III trial demonstrated that this model significantly improved EFS, major pathologic response and pathologic complete response rate. Yan's phase Ib trial showed similar results (102,103). However, there are still some controversies that need clarification. The staging of patients currently recommended for NAT covered that of postoperative adjuvant therapy in the past. However, the safety and necessity of receiving both neoadjuvant and adjuvant therapy are not well understood (104). The incidence of immune-related adverse events (irAEs) tends to increase with the number of cycles in patients receiving long-term immunotherapy (105). Patients receiving adjuvant targeted therapy experience few drug-related side effects. However, prolonging the treatment cycle increases the risk of rapid failure of the first-line therapeutic regimen due to distant drug resistance (106). Therefore, further studies are needed to explore the use of dynamic monitoring during adjuvant therapy as a basis for downstaging and identify high risk of recurrence with standardized adequate adjuvant therapy. Meanwhile, the reappearance of ctDNA positivity during the postoperative period is linked to a high risk of recurrence, which occurs 5–6 months earlier than a positive imaging result. Is it possible to decrease the risk of recurrence by undergoing salvage therapy again during this period (107)? The available research does not provide sufficient evidence.

The criteria for NAT, including the optimal cycle and dose, have not been clearly defined. Deng's retrospective study suggests that longer cycles of neoadjuvant immunotherapy may be beneficial, even when imaging suggests remission, which indicated superior median relapse-free survival rates and MPR rates (108). However, in another study, this advantage appears to be less evident (109). There is no exact standard for the timing of surgery according to relevant publications (110). Therefore, ctDNA may assist in determining the appropriate cycle and dosage of treatment for the patient before surgery, optimizing surgical conditions. In high-risk patients, it is necessary to evaluate the recommended dose and prolong the induction cycle during induction and postoperative adjuvant therapy (111). This can improve the prognosis and quality of life of patients while avoiding unnecessary treatments (112). For patients who experience complications during treatment, ctDNA can assist physicians in determining whether to continue treatment.

Future prospects and challenges

Future prospects

As a representative of liquid biopsy, ctDNA is a non-invasive, dynamic, and rapidly accurate method that determines

its important role in treatment guidance. Neoadjuvant immunotherapy has proven to improve patient prognosis while neoadjuvant targeted therapies require additional phase III clinical studies to authenticate their efficacy (113). Additionally, ctDNA successfully predicted the effect of neoadjuvant immunotherapy before surgery, and testing positively was strongly correlated with lower major pathological response or complete pathological response rate.

The NAT needs collaboration of doctors from different disciplines. For example, some surgeons reported difficulty in pulmonary resection after NAT, with increased rate of thoracotomy, longer duration of surgery and bronchopleural fistula. But some researches showed rate of postoperative complications did not reflect significant difference (114-116). The development of modified risk model is necessary. Meanwhile, there is no consensus on the dose of NAT and best time point of surgery, relying more on the experience of the thoracic surgeon or oncologist (109). Furthermore, neoadjuvant regimens are founded on the principles of advanced lung cancer treatment. ctDNA demonstrated its role in predicting prognosis versus NAT efficacy, although the evidence was not strong (88).

In the future, it may be possible to classify patients earlier using more advanced testing techniques. This would enable each patient to receive appropriate treatment. Measurable, data-driven metrics are needed to capture the specific characteristics that differentiate prognoses and allow us to treat comparable patients (117,118). Recent studies have emphasized the value of ctDNA-based MRD detection (119,120), particularly in cases where tumor samples can be obtained before the start of NAT (86). In the future, more robust evidence may emerge regarding the value of ctDNA-based MRD detection in assessing NAT efficacy, predicting prognosis and facilitating escalation or de-escalation treatment. But the feasibility of this approach requires confirmation of substantial prospective study.

Challenges

We must acknowledge that current ctDNA application in NAT for NSCLC is imperfect and facing more challenges in the future. Despite improved specificity, a limit to the detection ability of ctDNA is evident from the existence of false-negative results in various studies (121). Even continuous negative-testing results may occur in recurrence of early NSCLC incidence, thereby creating challenges in the treatment of patients at stages IB–II undergoing NAT (122). A few studies have also shown recurrence in patients with consistently negative results during surveillance (66,95,123,124). It is unclear whether this recurrence is due to errors in ctDNA testing or heterogeneity between primary and recurrent lung cancer.

Secondly, there is a dearth of standardized evaluation criteria, and most of the present studies are confined to detecting or not detecting ctDNA. Nevertheless, it is undeniable that quantitative metrics are more favorable to analysis. Certain researchers have regarded VAF or MAF as a supplementary indicator or threshold for detection. Consequently, they have proved that such quantitative indicators can indicate the prognosis of tumor patients to some extent (125-127). The standardization level in the detection of these quantitative indicators and the specific data reflections require further investigation by researchers.

Thirdly, the cost of routine ctDNA testing far exceeds traditional imaging monitoring. For example, the recommended enhanced CT scan and related tumor marker screening two cycles after NAT costs about 1,400–1,600 CNY (193.6–221.3 USD), while ctDNA detection for targeted driven gene costs about 5,000–6,000 CNY (691.6–829.9 USD), ctDNA-MRD detection costs about 13,000–16,000 CNY (1,383.1–2,213.0 USD) in our hospital. In Europe, one single NGS-based ctDNA test costs over 1,000 EUR (1,073.20 USD) (128). It imposes a significant financial burden on patients. There is an urgent need to improve ctDNA testing techniques and reduce the associated costs (129,130). Current sequential ctDNA testing falls significantly short of expectations for dynamic monitoring, and repeated monitoring does not demonstrate superior predictive utility (37). This limitation becomes especially notable in early-stage lung cancer patients, further restricting the potential application of ctDNA in NAT (39).

Conclusions

NAT for lung cancer provides additional treatment options for patients. It is important to evaluate its efficacy accurately. The related study included ctDNA early on due to its unique advantages. Several studies have shown that ctDNA can predict the effectiveness of NAT (69,88,89). Positive test results or low clearance rates may be associated with a higher recurrence rate and worse prognosis. At the same time, ctDNA has the potential to assist in the development of current treatment regimens and to assess step-up or step-down therapy. Many studies have used ctDNA as a secondary or primary assessment, and with the completion of appropriate studies, we will be able to explore the value

of ctDNA more fully. Meanwhile, researchers believe that combining ctDNA testing with tissue samples is more appropriate for today's neoadjuvant treatment paradigm. Although value of ctDNA in lung cancer is recognized by clinicians, and it is the most effective biomarker in liquid biopsy, its accuracy, standardization and costs remain to be solved for its wider application in NAT. To better evaluate the validity and cost-effectiveness of this test, large-scale, multicenter clinical trials are necessary, including additional testing and subsequent analysis.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48.
2. Fujikawa R, Muraoka Y, Kashima J, et al. Clinicopathologic and Genotypic Features of Lung Adenocarcinoma Characterized by the International Association for the Study of Lung Cancer Grading System. J Thorac Oncol 2022;17:700-7.
3. Moreira AL, Ocampo PSS, Xia Y, et al. A Grading System for Invasive Pulmonary Adenocarcinoma: A Proposal From the International Association for the Study of Lung Cancer Pathology Committee. J Thorac Oncol 2020;15:1599-610.
4. Wang Y, Song W, Wang X, et al. Does the presence of a micropapillary component predict worse prognosis in pathological stage IA lung adenocarcinoma? Pathol Res Pract 2023;242:154314.
5. Takeda S, Maeda H, Okada T, et al. Results of pulmonary resection following neoadjuvant therapy for locally advanced (IIIA-IIIB) lung cancer. Eur J Cardiothorac Surg 2006;30:184-9.
6. Zhong WZ, Yan HH, Chen KN, et al. Erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 EGFR-mutant non-small-cell lung cancer: final overall survival analysis of the EMERGING-CTONG 1103 randomised phase II trial. Signal Transduct Target Ther 2023;8:76.
7. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386:1973-85.
8. Bian D, Sun L, Hu J, et al. Neoadjuvant Afatinib for stage III EGFR-mutant non-small cell lung cancer: a phase II study. Nat Commun 2023;14:4655.
9. Pessoa LS, Heringer M, Ferrer VP. ctDNA as a cancer biomarker: A broad overview. Crit Rev Oncol Hematol 2020;155:103109.
10. Goldberg SB, Narayan A, Carriero NJ, et al. Detection of sensitizing and resistance EGFR mutations from circulating tumor DNA (ctDNA) in blood using multiplexed next-generation sequencing in patients with advanced EGFR-mutant lung adenocarcinoma. J Clin Oncol 2014;32:8093.
11. Zhou Q, Yang JJ, Chen ZH, et al. Serial cfDNA assessment of response and resistance to EGFR-TKI for patients with EGFR-L858R mutant lung cancer from a prospective trial. Journal of Hematology & Oncology 2016;9:86.
12. Chen K, Yang F, Shen H, et al. Individualized tumor-informed circulating tumor DNA analysis for postoperative monitoring of non-small cell lung cancer. Cancer Cell 2023;41:1749-1762.e6.
13. Iams WT, Mackay M, Ben-Shachar R, et al. Concurrent Tissue and Circulating Tumor DNA Molecular Profiling

to Detect Guideline-Based Targeted Mutations in a Multicancer Cohort. JAMA Netw Open 2024;7:e2351700.
14. Tomasik B, Skrzypski M, Bieńkowski M, et al. Current and future applications of liquid biopsy in non-small-cell lung cancer-a narrative review. Transl Lung Cancer Res 2023;12:594-614.
15. Tan L, Brown C, Mersiades A, et al. A Phase II trial of alternating osimertinib and gefitinib therapy in advanced EGFR-T790M positive non-small cell lung cancer: OSCILLATE. Nat Commun 2024;15:1823.
16. Rolfo C, Mack P, Scagliotti GV, et al. Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer. J Thorac Oncol 2021;16:1647-62.
17. Abbosh C, Frankell AM, Harrison T, et al. Tracking early lung cancer metastatic dissemination in TRACERx using ctDNA. Nature 2023;616:553-62.
18. Rosell R, Karachaliou N. Lung cancer: Using ctDNA to track EGFR and KRAS mutations in advanced-stage disease. Nat Rev Clin Oncol 2016;13:401-2.
19. Chen K, Wang C, Shen H, et al. Individualized tumor-informed circulating tumor DNA (ctDNA) analysis for postoperative monitoring of non-small cell lung cancer (NSCLC) - the MEDAL study. Cancer Res 2023;83:1039.
20. Wang C, Dai J, Qin N, et al. Analyses of rare predisposing variants of lung cancer in 6,004 whole genomes in Chinese. Cancer Cell 2022;40:1223-1239.e6.
21. Wu F, Fan J, He Y, et al. Single-cell profiling of tumor heterogeneity and the microenvironment in advanced non-small cell lung cancer. Nat Commun 2021;12:2540.
22. Grunnet M, Sorensen JB. Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. Lung Cancer 2012;76:138-43.
23. Cho WC. Potentially useful biomarkers for the diagnosis, treatment and prognosis of lung cancer. Biomed Pharmacother 2007;61:515-9.
24. Caulo A, Mirsadraee S, Maggi F, et al. Integrated imaging of non-small cell lung cancer recurrence: CT and PET-CT findings, possible pitfalls and risk of recurrence criteria. Eur Radiol 2012;22:588-606.
25. 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;21:407-14.
26. Schneider BJ, Ismaila N, Aerts J, et al. Lung Cancer Surveillance After Definitive Curative-Intent Therapy: ASCO Guideline. J Clin Oncol 2020;38:753-66.
27. Suster DI, Mino-Kenudson M. Molecular Pathology of Primary Non-small Cell Lung Cancer. Arch Med Res 2020;51:784-98.
28. Reinmuth N, Grohe C, Seese B, et al. Investigating the utility of circulating-free tumor-derived DNA (ctDNA) in plasma for the detection of epidermal growth factor receptor mutation (EGFRM) status in German patients (pts) with advanced non-small-cell lung cancer (aNSCLC)-ASSESS study. Oncology Research and Treatment 2016;39:27.
29. Oh AS, Arnold CW, Vangala S, et al. Imaging-histologic discordance at percutaneous biopsy of the lung. Acad Radiol 2015;22:481-7.
30. Zlevor AM, Mauch SC, Knott EA, et al. Percutaneous Lung Biopsy with Pleural and Parenchymal Blood Patching: Results and Complications from 1,112 Core Biopsies. J Vasc Interv Radiol 2021;32:1319-27.
31. Serra Mitjà P, Gonçalves Dos Santos Carvalho F, Garcia Olivé I, et al. Incidence and Risk Factors for Infectious Complications of EBUS-TBNA: Prospective Multicenter Study. Arch Bronconeumol 2023;59:84-9.
32. Leong TL, Loveland PM, Gorelik A, et al. Preoperative Staging by EBUS in cN0/N1 Lung Cancer: Systematic Review and Meta-Analysis. J Bronchology Interv Pulmonol 2019;26:155-65.
33. Cho JH, Kim IJ, Lee J, et al. Circulating tumor DNA (ctDNA) mutation and epigenomic patterns in early-stage lung cancer patients and its utility in identifying patients at high risk for early recurrence. J Clin Oncol 2019;37:e14557.
34. Li N, Wang BX, Ou W, et al. Dynamic monitoring circulating tumor DNA in plasma samples by PEAC technology for patients with early-stage non-small cell lung cancer after surgery. J Clin Oncol 2022;40:8547.
35. Waldeck S, Mitschke J, Wiesemann S, et al. Early assessment of circulating tumor DNA after curative-intent resection predicts tumor recurrence in early-stage and locally advanced non-small-cell lung cancer. Mol Oncol 2022;16:527-37.
36. Abbosh C, Frankell A, Garnett A, et al. Phylogenetic tracking and minimalresidual disease detection using ctDNA in early-stageNSCLC: A lung TRACERx study. Cancer Res 2020;80:CT023.
37. Xia L, Mei J, Kang R, et al. Perioperative ctDNA-Based Molecular Residual Disease Detection for Non-Small Cell Lung Cancer: A Prospective Multicenter Cohort Study (LUNGCA-1). Clin Cancer Res 2022;28:3308-17.
38. Chaudhuri AA, Chabon JJ, Lovejoy AF, et al. Early Detection of Molecular Residual Disease in Localized

Lung Cancer by Circulating Tumor DNA Profiling. Cancer Discov 2017;7:1394-403.
39. Gale D, Heider K, Ruiz-Valdepenas A, et al. Residual ctDNA after treatment predicts early relapse in patients with early-stage non-small cell lung cancer. Ann Oncol 2022;33:500-10.
40. Guo K, Shao C, Han L, et al. Detection of epidermal growth factor receptor (EGFR) mutations from preoperative circulating tumor DNA (ctDNA) as a prognostic predictor for stage I-III non-small cell lung cancer (NSCLC) patients with baseline tissue EGFR mutations. Transl Lung Cancer Res 2021;10:3213-25.
41. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
42. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.
43. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
44. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
45. Scott JA, Lennerz J, Johnson ML, et al. Compromised Outcomes in Stage IV Non-Small-Cell Lung Cancer With Actionable Mutations Initially Treated Without Tyrosine Kinase Inhibitors: A Retrospective Analysis of Real-World Data. JCO Oncol Pract 2024;20:145-53.
46. Brody R, Zhang Y, Ballas M, et al. PD-L1 expression in advanced NSCLC: Insights into risk stratification and treatment selection from a systematic literature review. Lung Cancer 2017;112:200-15.
47. Lyu M, Zhou J, Ning K, et al. The diagnostic value of circulating tumor cells and ctDNA for gene mutations in lung cancer. Onco Targets Ther 2019;12:2539-52.
48. Qvick A, Stenmark B, Carlsson J, et al. Liquid biopsy as an option for predictive testing and prognosis in patients with lung cancer. Mol Med 2021;27:68.
49. Sacher AG, Paweletz C, Dahlberg SE, et al. Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer. JAMA Oncol 2016;2:1014-22.
50. Kerr KM, Bubendorf L, Edelman MJ, et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. Ann Oncol 2014;25:1681-90.
51. Deng T, Tang J, Zhou L, et al. Effective targeted therapy based on dynamic monitoring of gene mutations in non-small cell lung cancer. Transl Lung Cancer Res 2019;8:532-8.
52. De Carlo E, Schiappacassi M, Urbani M, et al. Therapeutic decision based on molecular detection of resistance mechanism in an ALK-rearranged lung cancer patient: a case report. Onco Targets Ther 2018;11:8945-50.
53. Jenkins S, Yang JC, Ramalingam SS, et al. Plasma ctDNA Analysis for Detection of the EGFR T790M Mutation in Patients with Advanced Non-Small Cell Lung Cancer. J Thorac Oncol 2017;12:1061-70.
54. Wang J, Yao W, Wang W, et al. Complete pathological response and negative postoperative ctDNA were not predictive of discontinuation of adjuvant crizotinib therapy in a patient with locally advanced MET ex14 skipping mutation-positive non-small cell lung cancer: a case report. Front Oncol 2023;13:1164543.
55. Yeung V, Kim C, Kiedrowski LA, et al. Use of on-therapy ctDNA monitoring in a patient with KIF5B-RET fusion positive advanced non-small cell lung cancer: a case report. Transl Lung Cancer Res 2022;11:111-6.
56. Yao B, Han X, Pang L, et al. Acquired ALK Resistance Mutations Identified from Liquid Biopsy in an ALK-Rearranged Squamous Cell Lung Cancer Patient Treated with Sequential ALK TKI Therapy: A Case Report. Onco Targets Ther 2021;14:4329-33.
57. Yang Y, Zhang X, Wang R, et al. Osimertinib Resistance With a Novel EGFR L858R/A859S/Y891D Triple Mutation in a Patient With Non-Small Cell Lung Cancer: A Case Report. Front Oncol 2020;10:542277.
58. Wang J, Yang X, Zhuo M, et al. Quantification of mutant alleles in circulating tumor DNA from advanced non-small cell lung cancer. J Thorac Oncol 2015;10:S205.
59. Ding PN, Becker TM, Bray VJ, et al. The predictive and prognostic significance of liquid biopsy in advanced epidermal growth factor receptor-mutated non-small cell lung cancer: A prospective study. Lung Cancer 2019;134:187-93.
60. Reichert ZR, Morgan TM, Li G, et al. Prognostic value of plasma circulating tumor DNA fraction across four common cancer types: a real-world outcomes study. Ann Oncol 2023;34:111-20.
61. Hong SR, Hur J, Moon YW, et al. Predictive factors for treatment response using dual-energy computed tomography in patients with advanced lung adenocarcinoma. Eur J Radiol 2018;101:118-23.
62. Birchard KR, Hoang JK, Herndon JE Jr, et al. Early changes in tumor size in patients treated for advanced

stage nonsmall cell lung cancer do not correlate with survival. Cancer 2009;115:581-6.
63. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.
64. Katz SI, Hammer M, Bagley SJ, et al. Radiologic Pseudoprogression during Anti-PD-1 Therapy for Advanced Non-Small Cell Lung Cancer. J Thorac Oncol 2018;13:978-86.
65. Igawa S, Ono T, Kasajima M, et al. Real-world assessment of afatinib for patients with EGFR-positive non-small cell lung cancer. Invest New Drugs 2020;38:1906-14.
66. Wang S, Li M, Zhang J, et al. Circulating tumor DNA integrating tissue clonality detects minimal residual disease in resectable non-small-cell lung cancer. J Hematol Oncol 2022;15:137.
67. Provencio M, Serna-Blasco R, Nadal E, et al. Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non-Small-Cell Lung Cancer (NADIM phase II trial). J Clin Oncol 2022;40:2924-33.
68. Provencio M, Nadal E, González-Larriba JL, et al. Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med 2023;389:504-13.
69. Liu SY, Dong S, Yang XN, et al. Neoadjuvant nivolumab with or without platinum-doublet chemotherapy based on PD-L1 expression in resectable NSCLC (CTONG1804): a multicenter open-label phase II study. Signal Transduct Target Ther 2023;8:442.
70. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines® Insights: Non-Small Cell Lung Cancer, Version 2.2023. J Natl Compr Canc Netw 2023;21:340-50.
71. Lococo F, Chiappetta M, Evangelista J, et al. Role of Peripheral Blood Markers for Detecting Response and Predicting Prognosis in Patients with Non-small-cell Lung Cancer Undergoing Neoadjuvant Therapy and Surgery. Lung 2022;200:393-400.
72. Shu CA, Gainor JF, Awad MM, et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2020;21:786-95.
73. Casarrubios M, Provencio M, Nadal E, et al. Tumor microenvironment gene expression profiles associated to complete pathological response and disease progression in resectable NSCLC patients treated with neoadjuvant chemoimmunotherapy. J Immunother Cancer 2022;10:e005320.
74. Lebow ES, Murciano-Goroff YR, Jee J, et al. Minimal residual disease (MRD) detection by ctDNA in relation to radiographic disease progression in patients with stage I-III non-small cell lung cancer (NSCLC) treated with definitive radiation therapy. J Clin Oncol 2022;40:8540.
75. Yang M, Forbes ME, Bitting RL, et al. Incorporating blood-based liquid biopsy information into cancer staging: time for a TNMB system? Ann Oncol 2018;29:311-23.
76. Campos-Carrillo A, Weitzel JN, Sahoo P, et al. Circulating tumor DNA as an early cancer detection tool. Pharmacol Ther 2020;207:107458.
77. Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer 2016;62:132-7.
78. William WN Jr, Pataer A, Kalhor N, et al. Computed tomography RECIST assessment of histopathologic response and prediction of survival in patients with resectable non-small-cell lung cancer after neoadjuvant chemotherapy. J Thorac Oncol 2013;8:222-8.
79. Cheng Y, Chen ZY, Huang JJ, et al. Efficacy evaluation of neoadjuvant immunotherapy plus chemotherapy for non-small-cell lung cancer: comparison of PET/CT with postoperative pathology. Eur Radiol 2023;33:6625-35.
80. Travis WD, Dacic S, Wistuba I, et al. IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy. J Thorac Oncol 2020;15:709-40.
81. Zhuang F, Haoran E, Huang J, et al. Utility of (18) F-FDG PET/CT uptake values in predicting response to neoadjuvant chemoimmunotherapy in resectable non-small cell lung cancer. Lung Cancer 2023;178:20-7.
82. Parikh A, Van Seventer E, Boland G, et al. Serial assessment of cell-free circulating tumor DNA (ctDNA) to assess treatment effect and minimal residual disease during neoadjuvant and adjuvant therapy in colorectal cancer. Ann Oncol 2019;30:IV131.
83. Riva F, Bidard FC, Houy A, et al. Patient-Specific Circulating Tumor DNA Detection during Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer. Clin Chem 2017;63:691-9.
84. Wang Y, Yang L, Bao H, et al. Utility of ctDNA in predicting response to neoadjuvant chemoradiotherapy and prognosis assessment in locally advanced rectal cancer: A prospective cohort study. PLoS Med 2021;18:e1003741.
85. Magbanua MJM, Brown-Swigart L, Hirst GL, et al. Personalized serial circulating tumor DNA (ctDNA) analysis in high-risk early stage breast cancer patients

to monitor and predict response to neoadjuvant therapy and outcome in the I-SPY 2 TRIAL. Cancer Res 2019;79:PD2-01.
86. Reck M, Gale D, Harpole D, et al. LBA59 Associations of ctDNA clearance and pathological response with neoadjuvant treatment in patients with resectable NSCLC from the phase III AEGEAN trial. Ann Oncol 2023;34:S1300.
87. Christopoulos P. The emerging perioperative treatment paradigm for non-small cell lung cancer: a narrative review. Chin Clin Oncol 2024;13:12.
88. Yue D, Liu W, Chen C, et al. Circulating tumor DNA predicts neoadjuvant immunotherapy efficacy and recurrence-free survival in surgical non-small cell lung cancer patients. Transl Lung Cancer Res 2022;11:263-76.
89. Deutsch JS, Cimino-Mathews A, Thompson E, et al. Association between pathologic response and survival after neoadjuvant therapy in lung cancer. Nat Med 2024;30:218-28.
90. McDuff SGR, Hardiman KM, Ulintz PJ, et al. Circulating Tumor DNA Predicts Pathologic and Clinical Outcomes Following Neoadjuvant Chemoradiation and Surgery for Patients With Locally Advanced Rectal Cancer. JCO Precis Oncol 2021;5:PO.20.00220.
91. Shen T, Li SF, Wang JL, et al. TP53 R249S mutation detected in circulating tumour DNA is associated with Prognosis of hepatocellular carcinoma patients with or without hepatectomy. Liver Int 2020;40:2834-47.
92. Chen K, Kang G, Zhao H, et al. Liquid biopsy in newly diagnosed patients with locoregional (I-IIIA) non-small cell lung cancer. Expert Rev Mol Diagn 2019;19:419-27.
93. Vandekerckhove O, Cuppens K, Pat K, et al. Liquid Biopsy in Early-Stage Lung Cancer: Current and Future Clinical Applications. Cancers (Basel) 2023;15:2702.
94. Li N, Wang BX, Li J, et al. Perioperative circulating tumor DNA as a potential prognostic marker for operable stage I to IIIA non-small cell lung cancer. Cancer 2022;128:708-18.
95. Chen K, Zhao H, Shi Y, et al. Perioperative Dynamic Changes in Circulating Tumor DNA in Patients with Lung Cancer (DYNAMIC). Clin Cancer Res 2019;25:7058-67.
96. Cameron RB, Hines JB, Torri V, et al. What is the ideal endpoint in early-stage immunotherapy neoadjuvant trials in lung cancer? Ther Adv Med Oncol 2023;15:17588359231198446.
97. Fu R, Huang J, Tian X, et al. Postoperative circulating tumor DNA can refine risk stratification in resectable lung cancer: results from a multicenter study. Mol Oncol 2023;17:825-38.
98. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719-27. Erratum in: Lancet Oncol 2006;7:797.
99. Booth CM, Shepherd FA, Peng Y, et al. Adoption of adjuvant chemotherapy for non-small-cell lung cancer: a population-based outcomes study. J Clin Oncol 2010;28:3472-8.
100. Rotolo F, Dunant A, Le Chevalier T, et al. Adjuvant cisplatin-based chemotherapy in nonsmall-cell lung cancer: new insights into the effect on failure type via a multistate approach. Ann Oncol 2014;25:2162-6.
101. Herbst RS, Wu YL, John T, et al. Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. J Clin Oncol 2023;41:1830-40.
102. Wakelee H, Liberman M, Kato T, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. N Engl J Med 2023;389:491-503.
103. Yan W, Zhong WZ, Liu YH, et al. Adebrelimab (SHR-1316) in Combination With Chemotherapy as Perioperative Treatment in Patients With Resectable Stage II to III NSCLCs: An Open-Label, Multicenter, Phase 1b Trial. J Thorac Oncol 2023;18:194-203.
104. Chaft JE, Shyr Y, Sepesi B, et al. Preoperative and Postoperative Systemic Therapy for Operable Non-Small-Cell Lung Cancer. J Clin Oncol 2022;40:546-55.
105. Hussaini S, Chehade R, Boldt RG, et al. Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors - A systematic review and meta-analysis. Cancer Treat Rev 2021;92:102134.
106. Patel S, Patel JD. Current and Emerging Treatment Options for Patients with Metastatic EGFR-Mutated Non-small Cell Lung Cancer After Progression on Osimertinib and Platinum-Based Chemotherapy: A Podcast Discussion. Adv Ther 2023;40:5579-90.
107. Verzè M, Pluchino M, Leonetti A, et al. Role of ctDNA for the detection of minimal residual disease in resected non-small cell lung cancer: a systematic review. Transl Lung Cancer Res 2022;11:2588-600.
108. Deng H, Liang H, Chen J, et al. Preoperative immunochemotherapy for locally advanced non-small cell lung cancer: an analysis of the clinical outcomes, optimal number of cycles, and peripheral immune markers. Transl

Lung Cancer Res 2022;11:2364-81.
109. Shao M, Yao J, Wang Y, et al. Two vs three cycles of neoadjuvant sintilimab plus chemotherapy for resectable non-small-cell lung cancer: neoSCORE trial. Signal Transduct Target Ther 2023;8:146.
110. Ulas EB, Bahce I. Neoadjuvant immunochemotherapy in resectable non-small cell lung cancer: the more cycles, the better? Transl Lung Cancer Res 2023;12:1369-71.
111. König D, Schär S, Vuong D, et al. Long-term outcomes of operable stage III NSCLC in the pre-immunotherapy era: results from a pooled analysis of the SAKK 16/96, SAKK 16/00, SAKK 16/01, and SAKK 16/08 trials. ESMO Open 2022;7:100455.
112. Guo K, Lu J, Lou Y, et al. Prognostic value of postoperative ctDNA detection in patients with early non-small cell lung cancer: a systematic review and meta-analysis. Ther Adv Med Oncol 2023;15:17588359231177008.
113. Godoy LA, Chen J, Ma W, et al. Emerging precision neoadjuvant systemic therapy for patients with resectable non-small cell lung cancer: current status and perspectives. Biomark Res 2023;11:7.
114. Tong BC, Gu L, Wang X, et al. Perioperative outcomes of pulmonary resection after neoadjuvant pembrolizumab in patients with non-small cell lung cancer. J Thorac Cardiovasc Surg 2022;163:427-36.
115. Bott MJ, Yang SC, Park BJ, et al. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. J Thorac Cardiovasc Surg 2019;158:269-76.
116. Sun C, Liu Y, Zhang P, et al. Interim analysis of the efficiency and safety of neoadjuvant PD-1 inhibitor (sintilimab) combined with chemotherapy (nab-paclitaxel and carboplatin) in potentially resectable stage IIIA/IIIB non-small cell lung cancer: a single-arm, phase 2 trial. J Cancer Res Clin Oncol 2023;149:819-31.
117. Krug AK, Enderle D, Karlovich C, et al. Improved EGFR mutation detection using combined exosomal RNA and circulating tumor DNA in NSCLC patient plasma. Ann Oncol 2018;29:700-6.
118. Martignano F, Munagala U, Crucitta S, et al. Nanopore sequencing from liquid biopsy: analysis of copy number variations from cell-free DNA of lung cancer patients. Mol Cancer 2021;20:32.
119. Li Y, Jiang G, Wu W, et al. Multi-omics integrated circulating cell-free DNA genomic signatures enhanced the diagnostic performance of early-stage lung cancer and postoperative minimal residual disease. EBioMedicine 2023;91:104553.
120. Chen K, Shields MD, Chauhan PS, et al. Commercial ctDNA Assays for Minimal Residual Disease Detection of Solid Tumors. Mol Diagn Ther 2021;25:757-74.
121. Pascual J, Attard G, Bidard FC, et al. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group. Ann Oncol 2022;33:750-68.
122. Lupini L, Roncarati R, Belluomini L, et al. Monitoring Somatic Genetic Alterations in Circulating Cell-Free DNA/RNA of Patients with "Oncogene-Addicted" Advanced Lung Adenocarcinoma: A Real-World Clinical Study. Int J Mol Sci 2022;23:8546.
123. Qiu B, Guo W, Zhang F, et al. Dynamic recurrence risk and adjuvant chemotherapy benefit prediction by ctDNA in resected NSCLC. Nat Commun 2021;12:6770.
124. Jung HA, Ku BM, Kim YJ, et al. Longitudinal Monitoring of Circulating Tumor DNA From Plasma in Patients With Curative Resected Stages I to IIIA EGFR-Mutant Non-Small Cell Lung Cancer. J Thorac Oncol 2023;18:1199-208.
125. Malapelle U, Buono M, Pisapia P, et al. Circulating tumor DNA in cancer: Predictive molecular pathology meets mathematics. Crit Rev Oncol Hematol 2021;163:103394.
126. Bernard V, Kim DU, San Lucas FA, et al. Circulating Nucleic Acids Are Associated With Outcomes of Patients With Pancreatic Cancer. Gastroenterology 2019;156:108-118.e4.
127. Zhang Q, Luo J, Wu S, et al. Prognostic and Predictive Impact of Circulating Tumor DNA in Patients with Advanced Cancers Treated with Immune Checkpoint Blockade. Cancer Discov 2020;10:1842-53.
128. Christopoulos P. Liquid biopsies come of age in lung cancer. Transl Lung Cancer Res 2022;11:706-10.
129. Wang K, Peng Z, Lin X, et al. Electrochemical Biosensors for Circulating Tumor DNA Detection. Biosensors (Basel) 2022;12:649.
130. Gao M, Callari M, Beddowes E, et al. Next Generation-Targeted Amplicon Sequencing (NG-TAS): an optimised protocol and computational pipeline for cost-effective profiling of circulating tumour DNA. Genome Med 2019;11:1.

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