A narrative review of primary research endpoints of neoadjuvant therapy for lung cancer: past, present and future

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Objective: This review summarizes the current status of neoadjuvant therapy and discusses the choice of new clinical research endpoints for non-small cell lung cancer.

Background: Neoadjuvant chemotherapy is a recognized practice in patients with resectable and locally advanced lung cancer. With the introduction of molecular targeted drugs and immune checkpoint inhibitors (ICIs), the overall survival (OS) of patients with lung cancer has been significantly improved, and the original traditional clinical research endpoints are no longer suitable for existing clinical research. In order to accelerate the process of clinical trials and the development and approval of drugs, it is necessary to find suitable alternative indicators as the main indicators of clinical research.

Methods: Therefore, this article focuses on clinical trials using disease-free survival (DFS), progression free survival, and pathological evaluation indicators, pathologic complete response and major pathologic response, as surrogate endpoints. We search related literature through PubMed database and clinical trials through clinicaltrials.gov.

Conclusions: Pathologic complete response and major pathologic response are recommended as surrogate endpoints in the era of neoadjuvant immunotherapy, and secondary endpoints are listed for the prediction of pathological results. In addition, the definitions of major pathological response (MPR) and PCR should be standardized, and a new pathological evaluation standard should be developed, which is applicable to all current treatment methods.

Keywords: Neoadjuvant therapy; resectable lung cancer; clinical research endpoint; pathological response

Introduction

Resectable non-small cell lung cancer (NSCLC) refers to completely resectable stage I, stage II, and part of stage IIIA NSCLC. In recent years, the treatment of resectable NSCLC has made rapid progress, but the 5-year survival rate remains only 50%, mainly due to distant recurrence. Even completely resected primary tumors less than 1 cm in size without evidence of nodal spread carry a suboptimal prognosis, with 8% of patients dying from their disease within 5 years and more than 25% of patients with stage I recurring within 5 years (1-4). Systemic therapy given before or after surgery (termed neoadjuvant versus adjuvant therapy, respectively) has therefore been actively explored as a means to increase the eradication of micrometastasis in such patients and thereby increase the cure rate.

The option of neoadjuvant therapy is already considered part of routine practice, specifically neoadjuvant chemotherapy or neoadjuvant chemoradiation. However, neoadjuvant molecular targeted therapy, and neoadjuvant immunotherapy remain exploratory. The treatment-related pathological changes of the primary tumor that can be assessed post-surgical resection provide a reliable method for evaluating the impact of neoadjuvant therapy on the tumor. There has already been considerable evaluation of how chemotherapy- or chemoradiotherapy-induced pathological responses in the neoadjuvant setting across several tumor types correlate with later outcomes, reflecting their value as surrogate endpoints of clinical benefit. However, because the mechanisms of action of immunotherapy and targeted therapy differ from those of conventional cytotoxic therapies, and the specific histopathological characteristics of response to these different approaches may vary, whether the previous validation of pathological responses as predictors of long-term benefit has required additional investigation. Because neoadjuvant trials offer a means to more quickly assess the effectiveness of drugs many studies of novel agents are evaluated in this setting. Therefore, it is necessary to standardize and unify the research design to explore the research endpoints that better predict the survival benefits of patients after neoadjuvant immunotherapy. This review discusses the endpoints of current clinical trials of neoadjuvant therapy for lung cancer. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tlcr-21-259).

Method

To obtain relevant literature, we searched on the PUBMED database and Google website. We search clinical trials through clinicaltrials.gov. The last search date is January 2021. Authors used following combinations of terms: Neoadjuvant therapy, Immune checkpoint inhibitors (ICIs); clinical research endpoint; PFS; DFS; major pathological response (MPR); PCR; positron emission tomography (PET); T-cell response; circulating tumor DNA (ctDNA). Our search was restricted to publications in English language. We retrieved other eligible studies by manual searching of the reference lists of included studies.

Neoadjuvant therapy for lung cancer

Neoadjuvant therapy has many potential advantages. First of all, neoadjuvant therapy can eliminate all micrometastasis to the greatest extent, thereby increasing the chance of survival. Second, the pathological changes after resection provide a reliable method for evaluating the impact of neoadjuvant therapy on tumors. At least in principle, the detection of the residual tumors provides an opportunity to change (when the response is considered suboptimal) or continue (when the treatment has shown a good activity) the induction program after surgery. Third, the tissues obtained before and after treatment can be used for translational research and utilization of alternative endpoints, thereby significantly speeding up the translation of clinical research results into drug approval (5).

Neoadjuvant chemotherapy

A meta-analysis of randomized trials of neoadjuvant chemotherapy (5) showed that compared with surgery alone, the overall survival rate (OS) of preoperative chemotherapy was significantly improved [hazard ratio (HR), 0.87; 95% confidence interval (CI), 0.78–0.96; P=0.007]. This is equivalent to the survival benefit of adjuvant chemotherapy (6). However, after neoadjuvant chemotherapy, 5-year distant recurrence-free survival (DRFS) was found to be 10%; in contrast, adjuvant chemotherapy only provided an absolute improvement of 5%. There is no clear evidence that age, sex, histology (squamous and nonsquamous), and chemotherapy cycle can affect the OS benefit of neoadjuvant chemotherapy.

Neoadjuvant radiotherapy and chemoradiotherapy

Neoadjuvant radiotherapy alone does not improve resectability or survival. For patients with comorbidities or

other inoperable reasons, if the patient has stage I NSCLC, stereotactic radiotherapy can be the first choice, with the 5-year local control rate being about 90% (7). Neoadjuvant chemoradiotherapy is mainly used for patients with locally advanced (stage III) NSCLC, where the treatment can be definitive or followed by surgery in selected cases, based on tumor response. A clinical trial of stage IIIA (N2) NSCLC patients (8) showed that the median event-free survival (EFS) between a neoadjuvant chemoradiation group (12.8 months, 95% CI, 9.7–22.9 months) and a neoadjuvant chemotherapy group was similar (11.6 months, 95% CI, 8.4–15.2 months) (P=0.67). Another meta-analysis showed that (9), neoadjuvant chemoradiation significantly increased the pathological complete response (pCR) in mediastinal lymph nodes. Neoadjuvant chemoradiotherapy is beneficial to patients with superior sulcus non-small cell lung cancer (SS NSCLC) (10), with the 5-year OS rate reaching 44%.

Neoadjuvant molecular therapy

Molecular targeted therapy has greatly improved the treatment of advanced NSCLC. Although a formal demonstration of OS benefit has never been obtained in each single randomized trial versus chemotherapy, Ggefitinib is a first-generation molecular targeted drug directed against epidermal growth factor receptor (EGFR) mutation, which has been shown to double the survival time of NSCLC patients (11). One study evaluated the adjuvant effect of gefitinib combined with chemotherapy in patients with stage II to IIIA NSCLC and EGFR mutation (12). The median disease-free survival (DFS) in the combined treatment group was 28.7 months, while that in the chemotherapy group was 18.0 months (HR, 0.60; 95% CI, 0.42–0.87; P=0.0054). This trial and other series have aroused great interest in the use of targeted therapies in neoadjuvant settings. In an open phase II randomized controlled trial (RCT), patients with stage IIIAN2 NSCLC with EGFR exon 19 or 21 mutations were randomly divided into an erlotinib group and a chemotherapy group (13). The ORR for neoadjuvant erlotinib versus GC chemotherapy was 54.1% versus 34.3% [odds ratio (OR), 2.26; 95% CI, 0.87–5.84; P=0.092]. Median progression-free survival (PFS) was also improved (median values 21.5 vs. 11.9 months; P=0.003). However, whether targeted therapy is a truly curative modality, such that its benefit persist after the therapy stops remains controversial. Similarly, whether response in the neoadjuvant setting will have the same potential for long-term benefit remains equally unknown.

Neoadjuvant immunotherapy

ICIs have shown longer OS and better toxicity profile than chemotherapy in advanced NSCLC (14-16). This has inspired the use of ICIs in early resectable NSCLC. Immune checkpoint blockade may be more effective when used as neoadjuvant therapy, because the immune microenvironment of the primary tumor and surrounding lymph nodes is easily recognizable and activated by immune drugs before surgery, thereby increasing T cell infiltration. At present, a number of clinical trials evaluating programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors as neoadjuvant therapy have been performed. Neoadjuvant nivolumab showed that, of the 20 patients who underwent resection, 9 (45%) achieved major pathological response (MPR) (17). Major pathologic response is defined as a ≤10% portion of surviving tumor cells in different parts of the tumor found during surgery after neoadjuvant therapy. In a phase II clinical trial using atezolizumab, the MPR ratio reached 19.5% (18), with no increase in the perioperative mortality and postoperative complications showing. The combination of immunotherapy with surgery, chemotherapy, radiotherapy, targeted therapy, and other treatment methods can produce a synergistic effect (19). In a clinical trial of neoadjuvant chemotherapy combined with atezolizumab, 17 of 30 patients (57%) achieved MPR. with acceptable toxicity and no new or increased surgical complications (20). One meta-analysis evaluating the efficacy and safety of neoadjuvant immunotherapy in resectable NSCLC showed that, compared with neoadjuvant chemotherapy (MPR <25%, pCR 2–15%), the pathological remission rate with neoadjuvant immunotherapy was higher (MPR: OR, 0.59; 95% CI, 0.36–0.98; pCR: OR, 0.16; 95% CI, 0.09–0.27).

The incidence of treatment-related adverse events (TRAEs), surgical complications, and surgical delay with neoadjuvant immunotherapy have also proven to be significantly better than those of the neoadjuvant chemotherapy (21). To understand the optimal treatment duration of neoadjuvant immunotherapy and timing of surgery after neoadjuvant treatment, new biomarkers, such as ctDNA may facilitate treatment decision making. In addition, Sepesi et al. (22) reported nodal immune flare (NIF) following neoadjuvant anti-PD-1 and anti-CTLA-4 therapy in NSCLC. They defined "the apparent radiographic progression of lymph nodes without pathological evidence of tumor" as NIF and highlighted the importance of judicious restaging of sites of suspected progression after neoadjuvant ICIs prior to definitive

treatment decisions. Therefore future clinical trials are needed to evaluate further the appropriate schedule for immune checkpoint blockade and to find biomarkers to select patients most likely to benefit from this strategy.

Based on the interesting preliminary results reported above, the results of phase III trials testing the efficacy of neoadjuvant immunotherapy are awaited, in order to better discuss the role of this very promising strategy in clinical practice. As of February 2021, immunotherapy is not currently approved for neoadjuvant use in clinical practice.

The primary endpoints of lung cancer trials

Features of OS, PFS, and DFS

In oncology clinical trials, the selection of endpoints needs to consider many factors, such as cancer type, stage, treatment purpose, and expected survival of related diseases. An ideal research endpoint should be clinically relevant, easily measurable, sensitive, specific, low-cost, and reproducible (23). OS is the gold standard for measuring assessing curative effects strategies, and is often used as the primary indicator endpoint of large-scale randomised studies. However, it takes more than 10 years to collect longer follow up and is easily affected by other treatments at progression or patient comorbidities (24). In recent years, in order to accelerate the development of drugs, PFS, DFS, and ORR have become surrogate endpoints for OS.

PFS is one of the most common preferred endpoints in oncology clinical trials. PFS is easy to measure, and compared with death, disease progression occurs earlier and more frequently, which greatly shortens the time period of clinical trials and reduces costs. PFS benefit can predict the benefit of OS, which has been confirmed in colorectal cancer and ovarian cancer. However, surrogacy cannot be extrapolated from one tumor to another, and it should be demonstrated within each specific type of tumor and setting. As a matter of fact, of the phase III RCTs of advanced NSCLC conducted from 1980 to 2010, more trials used PFS as the research endpoint (1980–1990: no progress; 2001–2010 13%; P=0.002) (25).

Similarly to PFS in patients with advanced disease, DFS has been proposed as a surrogate endpoint of OS in patient group undergoing curative treatment, with long-term expected survival. Similar to studies that use PFS, studies using DFS as the end point are less costly and take less time to complete. DFS is most commonly used in the research of adjuvant therapy after radical surgery or radiotherapy.

DFS is currently the main primary endpoint for approval for adjuvant hormone therapy for breast cancer, adjuvant therapy for colon cancer, and adjuvant chemotherapy for breast cancer (23).

Although there is no obvious evidence that surrogate endpoints can predict OS in patients with lung cancer, many meta-analyses have evaluated the correlation between surrogate endpoints and final endpoints, both at the individual and trial level. Fiteni *et al.* summarized and analyzed current lung cancer trials, which evaluate potential surrogate endpoints for OS (26). They found that in lung cancer trials, the current level of evidence supporting the relationship between OS and potential surrogate endpoints is low. A meta-analysis conducted by Mauguen *et al.* in surgically resectable and locally advanced NSCLC found that in adjuvant chemotherapy trials, the correlation between individual-level DFS and OS was 0.83 (95% CI, 0.83), while the correlation between DFS and OS at the test level was 0.92 (95% CI, 0.88–0.95). In the study of locally advanced disease, they were 0.77 to 0.85 and 0.89 to 0.97, respectively (27).

pCR as a predictor of OS

Pathologic complete response, which is defined as the absence of any active tumor cells remaining, is a clinical endpoint, especially for neoadjuvant studies. Because pCR can show clinical benefits in a shorter time, especially in high-risk groups, it is especially used to accelerate drug approval. A number of neoadjuvant trials conducted in breast cancer patients have shown that pCR has a strong prognostic correlation with EFS and OS, so pCR has been approved as a surrogate endpoint for breast cancer neoadjuvant treatment studies (28,29). In terms of immunotherapy, it was found that early detected triple-negative breast cancer patients who received pembrolizumab combined with neoadjuvant chemotherapy had a significantly higher pCR than those treated with neoadjuvant chemotherapy (30). Lung cancer trials can learn lessons from studies on other cancers, meaning that pCR can be studied and proposed as a meaningful research endpoint for NSCLC neoadjuvant therapy (*Table 1*).

More than 20 years ago, Pisters and colleagues published a report after neoadjuvant chemotherapy for patients with stage IIIA N2 NSCLC (31). Of the 73 patients who received preoperative chemotherapy, 9 patients (12%) achieved pCR. The 3-year survival rate was 62%, and the 5-year survival rate was 54%, which is very rare in IIIA N2

Table 1 Pathologic complete response as a clinical endpoint after neoadjuvant chemotherapy in NSCLC

Investigator name	No. of patients	Stages	Treatment	pCR (%)	Long-term survival data
Pisters et al.	73	IIIA (N2)	PCT (mitomycin + vinca alkaloid + cisplatin) + surgery	12%	Survival estimates are 62% at 3 years, and 54% at 5 years
Depierre et al.	179	Resectable stage I (except T1N0), II, and IIIA	PCT (mitomycin + ifosfamide + cisplatin) + surgery	11%	RRs of death: 0.4; 95% CI, 0.26–0.70; P=0.00007
Betticher et al.	75	IIIA (N2)	PCT (docetaxel + cisplatin) +surgery	19%	pCR group vs. non-pCR group (months)
					5-year OS: NR vs. 28.8; P=0.03
					5-year EFS: 62.5 vs. 12.4; P=0.008
Mouillet et al.	492	IB–II	PCT (platinum-based) + surgery	8.3%	pCR group vs. non-pCR group (%)
					5-year OS: 80.0% vs. 55.8% P= 0.0007
					5-year DFS: 80.1% vs. 44.8%; P<0.0001

PCT, preoperative chemotherapy; pCR, pathologic complete response; RR, relative risk; OS, overall survival; EFS, event-free survival; DFS, disease-free survival.

cancer. The report proposed for the first time that pCR can predict excellent survival and functional levels, and should be regarded as the primary endpoint for evaluating preoperative chemotherapy plans. Depierre et al. examined 179 patients with stage IB–IIIA NSCLC patients who received neoadjuvant chemotherapy (32) and found that the pCR rate reached 11%, and the relative risk (RR) of death was 0.42 (P<0.001). In addition, a multicenter phase II trial in 2003 studied the efficacy of neoadjuvant chemotherapy in locally advanced NSCLC. Of the 90 patients with stage IIIA N2 cancer confirmed by mediastinoscopy, 75 patients underwent surgical resection after receiving neoadjuvant chemotherapy. Complete pathological remission occurred in 19% of tumor resection patients, and downgrading to N0–1 during surgery could significantly prolong EFS and OS (P=0.0001) (33). The subsequent 5-year follow-up study indicated that the OS and EFS of 75 patients undergoing surgery were 35 and 15 months, respectively. Local recurrence and distant metastasis occurred in 60% and 65% of patients, respectively. The most common sites of distant metastasis were the lungs (24%) and brain (17%). The OS rate of the patient is significantly correlated with complete mediastinal lymph node response and clinical and pathological responses (34). There are also many studies that prove that patients who achieve pCR after preoperative chemotherapy can improve the prognosis. However, in these studies, too few pCRs were observed for a full analysis.

Mouillet et al. (35) reported combined analysis of two IFCT randomized trials evaluating neoadjuvant chemotherapy for early NSCLC. The results showed that 41 patients (8.3%) achieved pCR and the 5-year OS and DFS rates of pCR patients were 80.0% and 80.1%, respectively, while those of non-pCR patients were 55.8% and 44.8%, respectively. This indicated that pCR after neoadjuvant chemotherapy is a strong and favorable prognostic factor for OS (RR, 0.34; 95% CI, 0.18–0.64) and DFS (RR, 0.29; 95% CI, 0.16–0.56). However, the incidence of pCR in cisplatin-based chemotherapy is usually less than 10%, which greatly limits its application as a surrogate endpoint. Therefore, it is necessary to find new pathological evaluation methods.

MPR as a clinical research endpoint

Major pathologic response is defined as a ≤10% portion of surviving tumor cells in different parts of the tumor found during surgery after neoadjuvant therapy. Many studies have explored MPR is a pathological-related factor suitable for use as a research endpoint in neoadjuvant trials (*Table 2*).

As early as 2001, Junker et al. conducted a thorough pathological analysis on the resection specimens of 40 locally advanced NSCLC samples that were surgically removed after neoadjuvant chemoradiotherapy. The results showed that for patients with residual tumor tissue <10% versus patients with residual tumor tissue >10%, the median survival time

Table 2 Major pathologic response as a clinical endpoint after neoadjuvant therapy

Investigator name	No. of patients	Stages	Treatment	MPR (%)	Long-term survival data MPR group *vs.* non-MPR group
Junker *et al.*	40	IIIA and IIIB	Neoadjuvant chemotherapy (carboplatin, ifosfamide, etoposide, vindesine) + radiotherapy (45 Gy) + surgery	67.5%	Median survival time: 36 *vs.* 14 months; 3-year survival rate: 52% *vs.* 9%; P=0.02
Pataer *et al.*	192	I–IV	Neoadjuvant chemotherapy + surgery	19%	5-year OS: 85% *vs.* 40%; P<0.0001; 5-year DFS: 78% *vs.* 35%; P<0.001
Chaft *et al.*	50	IB–IIIA	Neoadjuvant therapy (bevacizumab + cisplatin + docetaxel) + surgery	27%	3-year OS: 100% *vs.* 49%; P=0.011; 3-year RFS: 91% *vs.* 48%; P=0.024

MPR, major pathological response; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival.

was 36 and 14 months, respectively, while the 3-year OS was 52% and 9%, respectively (P=0.02). Tumor tissue residues of ≤10% caused by treatment are essential to achieve favorable long-term results (36). Later, a retrospective study attempted to determine whether the histopathological remission of NSCLC patients after neoadjuvant chemotherapy was related to OS. The study performed pathological evaluation of tissue specimens from 192 patients with stage I–IV NSCLC after surgical resection (37). The results showed that different tumor cell survival rates and surgical pathological stages were related to OS (P=0.005) and DFS (P=0.01). Compared with patients with surviving tumor cells >10%, patients with surviving tumors ≤10% had significantly prolonged long-term OS (5-year OS: 40% *vs.* 85%; P<0.0001) and DFS (5-year DFS: 35% *vs.* 78%; P<0.001). This suggests that the histopathological evaluation of resected specimens after neoadjuvant chemotherapy can predict survival. They then investigated whether tumor response measured by computed tomography (CT) and evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) correlated OS in patients with NSCLC after neoadjuvant chemotherapy and surgical resection. The results showed that compared with the tumor RECIST remission measured by CT (P=0.03), tumor pathological remission (≤10% *vs.* >10% live tumor; P=0.002) had a stronger predictive effect on OS (38). In a phase II clinical trial of 50 patients with stage IB–IIIA NSCLC who were treated with neoadjuvant chemotherapy and bevacizumab, patients who achieved MPR during surgery had a better 3-year survival rate than patients who did not achieve MPR (100% *vs.* 49%; P=0.01) (39). After that, an editorial signed by several American oncologists, surgeons, and pathologists suggested that the MPR should be included as a surrogate endpoint for future neoadjuvant trials of resectable lung cancer (40). However, the validity of this in relation to novel therapies, just as with pCR, remains under investigation.

MPR is currently the primary endpoint of many ongoing trials of neoadjuvant immunotherapy. This will help determine the effectiveness of this endpoint as a surrogate for survival. In 2018, Bott *et al.* published the preliminary results of the histopathological response characteristics and immune-mediated tumor clearance characteristics of 20 patients with NSCLC who received nivolumab neoadjuvant treatment and obtained complete tumor resection and chest lymph node resection specimens (41). The results showed that the MPR reached 45%, 8 patients (40%) had a decrease in pathological stage, and 2 patients reached pCR. At 18 months after the operation, the patient's recurrence-free survival (RFS) reached an exciting 73%, and no increase in mortality and disease recurrence rate was observed in the perioperative period. The NEOSTAR trial was a randomized controlled study that compared the efficacy of nivolumab monotherapy and nivolumab combined with ipilimumab dual-immune neoadjuvant therapy in patients with resectable NSCLC (42). Recent reports showed that in the single-drug group (23 patients) and the dual-drug group (21 patients), the MPR rates were 22% (5/23) and 38% (8/21), respectively. Compared with nivolumab monotherapy, nivolumab combined with ipilimumab resulted in higher PCR (10% *vs.* 38%), and less viable tumor (median 50% *vs.* 9%). In a phase II clinical trial of atezolizumab combined with chemotherapy (20), after two cycles of treatment, the MPR rate increased to 57% (17/30). The NADIM trial from Spain (43), a total of 46 patients were enrolled and given nivolumab combined with chemotherapy. The results reported that among 41 patients undergoing surgery, 83% (34/41) achieved MPR and 63% (26/41) achieved PCR. Furthermore, combined immunotherapy was found to increase the frequency of tumor-infiltrating lymphocytes; no unacceptable toxicity

was found, nor was an increase in perioperative morbidity/ mortality observed. The results of these trials further increased the need to define the value MPR as a surrogate endpoint for survival in neoadjuvant therapy. Currently, a number of phase III neoadjuvant immunotherapy clinical studies are underway, including CheckMate816 (44), KEYNOTE-671 (45), IMpower030 (46), AEGEAN (47), etc. The main research endpoints include MPR.

Standardization of pathological evaluation

Chemotherapy, oncogene targeted therapy, and immunotherapy have different mechanisms of action, and different treatment-related characteristics can be observed on resected specimens post-neoadjuvant therapy. Originally, Pataer *et al.* (37) proposed to obtain at least 1 section per centimeter of the maximum tumor diameter, and then average the results of all slides. They reviewed a large number of histological criteria, with the main 3 characteristics including necrosis, stromal fibrosis, and live tumor. It was proposed that the percentage of live tumors is the only histological index with predictive significance. Hellmann *et al.* (40) modified this method, and subsequently, Cottrell *et al.* proposed to establish a new immune-related pathological response standard (irPRC) (48), with the area of "return bed" being increased to the area of remaining viable tumor and necrosis. In addition, the terms "stroma", "fibrosis", and "inflammation" were described in greater detail as tissue repair-neovascularization and proliferative fibrosis, dense tumor-infiltrating lymphocytes, and tertiary lymphoid structures. It was concluded that irPRC can be used for pathological evaluation of standardized immunotherapy efficacy. However, long-term follow-up is needed to determine the reliability of irPRC as a surrogate indicator of RFS and OS. Examination of MPR score should perform by two pathologists independently. All pathologists need have some training regarding MPR scoring. There are few data on the repeatability of MPR assessments. In the study of Qu *et al.* (49), they used intraclass correlation (ICC) to quantify the Interobserver agreement and Bland-Altman diagram to show the level of difference. The results showed that in the assessment of adenocarcinoma (ADC) (ICC =0.97; 95% CI, 0.93–0.99) and squamous cell carcinoma (SCC) (ICC =0.99; 95% CI, 0.96–1.00) by two pathologists, there was a high degree of interobserver reproducibility. In addition, in the study of Blaauwgeers *et al.* (50), two experienced lung pathologists independently scored the proportion and distribution of

important tumors. A 10% cutoff for viable tumor was used to evaluate the relationship between histopathological changes and clinical outcomes. The final result found that there was no difference in the scores between the two pathologists.

The International Association for the Study of Lung Cancer (IASLC) has made detailed recommendations on how to handle lung cancer resection specimens and define pathological responses. This method can be used for all systemic therapies (51). A standardized method is recommended to assess the percentage of live tumors, necrosis, and stroma (including inflammation and fibrosis), makes these add up to 100%. In addition, specific recommendations are made for the pathological evaluation of lymph nodes in patients with lung cancer. They pointed out that when assessing lymph node metastasis, the same methods as recommended for primary lung tumors can be used. And it is suggested that if there is a clear scar and, or tumor necrosis area in the absence of discernible viable tumor cells, then PCR in the lymph nodes can be recognized. However, in lymph node metastatic lung cancer, the detailed histological characteristics have not yet been determined.

Other potential secondary endpoints

Metabolic response PET

After neoadjuvant chemotherapy for NSCLC, the standardized uptake value (SUV) (max, corr) obtained by 2 consecutive PET scans can predict the histopathological response of the primary tumor and mediastinal lymph nodes, and has prognostic value (52). Studies have shown that for patients with an SUV (max) reduction in primary tumors after neoadjuvant chemotherapy of more than 60% under PET imaging, the 5-year OS rate is significantly higher (53). Pöttgen *et al.* (54) analyzed PET scans before and after treatment in a neoadjuvant trial, and the results showed that in univariate and multivariate analysis, remaining maintained as a continuous variable that could predict OS, PFS, and presence of extracerebral metastasis (P<0.016). Furthermore, for every 50% increase in SUV%, the HR of these 3 endpoints also increased significantly. They thus reasoned that %SUV remaining is a predictor for survival and other end points after multimodality treatment. PET can be used in the selection and application of neoadjuvant chemotherapy. Chaft *et al.* (55) used 18-F fluorodeoxyglucose (18F-FDG) PET scans on 40 patients

with stage IB–IIIA lung cancer who received 2 cycles of cisplatin chemotherapy. If the SUV in the primary tumor was reduced by at least 35%, the patient continued with initial therapy. Patients with a PET response lower than 35% were switched to vinorelbine plus docetaxel. The endpoint was defined as the response rate of previously unresponsive patients to the new chemotherapy regimen. There were 15 patients whose SUV decreased by less than 35%, and 13 patients received vinorelbine plus docetaxel treatment. 10 of 13 patients reached their primary endpoint (67%). Furthermore, 6 out of 40 patients achieved MPR. Studies have shown that 18F-FDG PET can evaluate the patient's response to different chemotherapy regimens by measuring the decline in SUV before and after medication. This adaptive method can also be used to test new drugs in an attempt to optimize perioperative chemotherapy for better long-term efficacy.

Moreover, 18F-FDG PET can also be used to predict pathological results after neoadjuvant immunotherapy. Previously, Lopci et al. analyzed the relationship between FDG-PET metabolic information and the tissue expression of immune markers in patients with NSCLC after surgical resection (56). It was found that the maximum value of SUV and the average value of SUV were directly related to the expression of PD-1 (rho =0.33; P=0.017 and rho =0.36; P=0.009). Studies have also shown that the high expression level of PD-L1 is closely related to 18 F-FDG uptake, glucose metabolism, and hypoxia. PD-L1 and SUV max are independent prognostic predictors (57). Recently, studies have evaluated the relationship between the tumor metabolism parameters of 18 F-FDG PET and the pathological response of neoadjuvant sintilimab in patients with resectable NSCLC. The results showed that in 13 of the 36 tumors removed (36.1%), MPR was achieved; PET scans showed that 13 patients (36.1%) had partial metabolic response (PMR). All (100.0%) PMR (ΔSUL peak %<–30.0%) tumors showed MPR. This proves that the metabolic response caused by 18F-FDG is significantly related to the pathological response after neoadjuvant immunotherapy and can predict the MPR rate of resectable NSCLC after neoadjuvant therapy (58).

T-cell response

A preclinical study evaluating a triple-negative breast cancer model found that neoadjuvant immunotherapy can increase tumor-specific CD8+ T cells in peripheral blood and organs, thereby suggesting that the increase and continuous maintenance of peripheral tumor-specific immune response can enhance the antitumor efficacy induced by neoadjuvant immunotherapy. Blood sampling of tumor-specific CD8+ T cells immediately before and after surgery could provide a predictive indicator of results (59). In resectable NSCLC, some researchers have used tumor/blood samples from phase II clinical trials to explore whether peripheral T-cell clonal dynamics can predict the pathological response after neoadjuvant PD-1 blockade (60). The results show that the T-cell receptor (TCR) repertoire reaching MPR has a higher clonality and a greater tumor invasion rate. A higher intratumoral TCR clonotype is associated with a decrease in the percentage of residual tumors during surgery. The study suggested that exchange of T-cell clones between tumor and blood represents a key correlate of pathologic response to neoadjuvant immunotherapy and can be used to predict the pathological results of NSCLC patients.

ctDNA analysis

Deep sequencing (CAPP-seq) ctDNA analysis may represent a promising approach for monitoring responses during and after neoadjuvant therapy. Research has suggested that residual ctDNA after curative-intent surgery or radiotherapy of localized lung cancer is a sensitive and specific marker of patients at the highest risk of recurrence. Chaudhuri et al. (61) conducted analysis on 255 samples from 40 cured lung cancer patients and 54 healthy adults. The results showed that 53% of the patients had ctDNA mutation characteristics, which were related to blockade of tyrosine kinase inhibitors or immune checkpoints. This indicates that ctDNA analysis during adjuvant chemotherapy can strongly identify posttreatment molecular residual disease (MRD) in patients with localized lung cancer. Future trials should test its ability to predict treatment response early in neoadjuvant therapy, its correlation with MPR and pCR, and its ability to identify patients who may receive other treatments after surgery.

Summary and prospect

The main goals of neoadjuvant trials are to increase chances of cure, more quickly identify drugs that can improve prognosis after complete resection, and to standardize endpoints and trial design, so that neoadjuvant results can be used to accelerate drug development and approval. Traditional research endpoints in the curative setting such as OS, DFS, etc. consume considerable resources and time. In order to accelerate the development and approval

of neoadjuvant drugs, new biomarkers that can be used as surrogate endpoints should be sought to record the impact on long-term survival.

The pathological response after surgical resection is an important factor in evaluating the efficacy of neoadjuvant therapy. Nowadays, there is an abundance of data that can be used to analyze whether pathological response criteria, such as MPR or pCR, are viable as surrogate endpoints. A significant correlation between MPR or pCR and EFS and OS has been demonstrated. With the development of ICIs, the pathological response to EFS or OS may be different from the pathological response to chemotherapy or targeted therapy. Therefore, the definitions of MPR and pCR should be standardized, and a new standard should be developed that can be used in all ongoing and planned neoadjuvant immunotherapy trials, neoadjuvant targeted therapy trials, and combination therapy. The residual percentage of surviving tumor cells in resected NSCLC patients is also a valuable measure. It can provide more accurate and rapid comparisons between different neoadjuvant treatment options, thereby reducing the time required to evaluate new drugs in clinical trials.

However, there are still many issues to be resolved, such as the balance and unification between imaging evaluation and histopathological evaluation, the selection of other biomarkers for accurate prediction of MPR or pCR, and the need for more prospective trials and meta-analyses to determine if MPR and pCR can predict survival uniformly across treatment modalities or whether different rules will need to be applied for different kinds of treatment. In addition, further study of the association between MPR and longer-term outcomes in various histologies, genetic subgroups, and pharmacologic classes of neoadjuvant therapies should be explored and more suitable clinical alternative endpoints should be sought.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at http://dx.doi.org/10.21037/tlcr-21-259

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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.

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