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REVIEW

Perioperative EGFR-Targeted Therapy in Resectable EGFR-Mutated NSCLC: A Narrative Review from Drug Design to Pain-Informed MRD-Guided Care

Lile Xiong[1], Xiufen Yang[2], Hua Yuan[1], Lan Qin[3], Binghu Lin[1], Fengjiao Chen[1], Yi Wen[1]

[1]Department of Thoracic Surgery, Shenzhen People's Hospital, Shenzhen, Guangdong, People's Republic of China; [2]Department of Emergency, Shenzhen People's Hospital, Shenzhen, Guangdong, People's Republic of China; [3]Department of Nursing, Shenzhen People's Hospital, Shenzhen, Guangdong, People's Republic of China

Correspondence: Yi Wen, Email wenyi70380825@163.com

Abstract: Perioperative EGFR-targeted therapy has transformed the management of resectable EGFR-mutated NSCLC. However, prolonged exposure introduces chronic toxicity and pain that may erode long-term benefit. This narrative review synthesizes evidence from pivotal perioperative EGFR-TKI trials, emerging fourth-generation EGFR-TKIs, and studies on pain, toxicity, adherence, and patient-reported outcomes, with a focus on minimal residual disease (MRD)-guided treatment adaptation. Current data show that adjuvant and neoadjuvant EGFR-TKIs substantially reduce recurrence and may improve survival, yet pain and related functional impairment remain under-recognized, under-measured, and inconsistently managed. Procedure-related and treatment-emergent pain, neuropathy, and musculoskeletal symptoms interact with psychological, comorbid, and social factors to undermine adherence, particularly during prolonged adjuvant therapy. Fourth-generation EGFR-TKIs and MRD-guided strategies create opportunities to optimize exposure and duration but demand structured monitoring of pain, standardized electronic patient-reported outcomes, and integrated oncology–anesthesiology–palliative care pathways. We propose an efficacy–safety–pain–adherence loop in which pain is treated as a core determinant of therapeutic success, aiming to maximise cure potential while preserving quality of life.

Plain Language Summary: Many people with early-stage non–small cell lung cancer (NSCLC) can have surgery to remove the tumour. Even after a "complete" resection, however, the cancer often comes back. For patients whose tumours have changes in a gene called EGFR, tablets known as EGFR tyrosine kinase inhibitors (EGFR-TKIs) are now used before or after surgery to lower the risk of the cancer returning. These targeted drugs can keep the disease under control for longer, but they are taken for many months or years and can cause ongoing side effects such as skin problems, diarrhoea, nail changes, and muscle or nerve pain. Lung surgery itself may also lead to long-lasting pain in the chest and shoulder.

In this review, we explain how EGFR-TKIs are designed, how they are used around the time of surgery, and how they affect pain, daily activities, and patients' ability or willingness to keep taking treatment. We also describe blood tests that can detect tiny amounts of cancer DNA—called minimal residual disease—and electronic tools that let patients report symptoms from home.

Based on these data, we suggest a practical approach in which doctors and nurses monitor pain and other symptoms regularly, combine this information with blood test results, and adjust the dose and duration of EGFR-TKIs when needed. The goal is to give patients the best chance of being cured while protecting their comfort, function, and overall quality of life.

Keywords: EGFR-mutated NSCLC, perioperative targeted therapy, fourth-generation EGFR-TKI, pain management, patient-reported outcomes

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Introduction

Evolving Perioperative Treatment Landscape in Resectable NSCLC and the Rise of Targeted Therapy

Lung cancer—predominantly non-small cell lung cancer (NSCLC)—remains the leading cause of cancer-related mortality worldwide,[1] although a proportion of patients present with early-stage or locally advanced disease that is resectable.[2] For decades, anatomical resection followed by adjuvant platinum-based chemotherapy has been standard, yet the absolute survival benefit is modest (≈5% at 5 years) and 25–70% of patients relapse despite complete resection.[3,4]

The success of targeted agents in advanced oncogene-driven NSCLC has led to their evaluation in the curative-intent setting, with EGFR-mutated disease providing the most mature example. The Phase III ADAURA trial established adjuvant osimertinib as a standard of care, showing marked improvements in disease-free and overall survival for completely resected stage IB–IIIA EGFR-mutated NSCLC.[5] Similar perioperative immunotherapy trials further support the value of systemic therapy around surgery.[6,7] Collectively, these advances are reshaping perioperative management toward biomarker-guided multimodality care. However, most trials prioritise radiologic or pathologic outcomes, while perioperative pain, symptom burden and functional recovery—key determinants of real-world benefit—receive far less attention. Incorporating targeted agents into the perioperative window therefore introduces additional considerations for tolerability and symptom control—particularly postoperative pain—that are not fully addressed in current paradigms.

Perioperative Pain Burden and Chronic Postsurgical Pain in Lung Cancer Surgery

Thoracic surgery is associated with intense acute postoperative pain and a high incidence of chronic postsurgical pain (CPSP), often neuropathic and disabling.[8] CPSP occurs in about 40–60% of patients after thoracotomy and 20–30% after video-assisted thoracoscopic surgery, driven by intercostal nerve injury, peri-incisional inflammation and central sensitisation.[9] Psychological factors and social context further modulate pain experience, supporting multimodal, multidisciplinary management strategies. In patients receiving perioperative systemic therapy, this vulnerability to pain may interact with treatment-related toxicities such as musculoskeletal or neuropathic symptoms. Overlapping burdens influence adherence, dose intensity, rehabilitation, sleep and physical activity, ultimately shaping the effectiveness of perioperative regimens; pain is therefore not merely a postoperative complication but a key modifier of perioperative targeted therapy.

Next-Generation EGFR-TKIs and MRD-Guided Strategies: Opportunities and Challenges in the Perioperative Setting

Next-generation EGFR tyrosine kinase inhibitors (TKIs) have been designed to overcome atypical and acquired resistance and extend benefit beyond common sensitising mutations. Sunvozertinib (DZD9008), for example, selectively targets EGFR exon 20 insertion mutations and has shown durable responses with a manageable safety profile in platinum-pretreated advanced NSCLC, supporting accelerated regulatory approval.[10–12] Although current evidence derives from advanced disease, such "fourth-generation" agents are plausible candidates for perioperative trials in biomarker-selected resectable NSCLC and raise specific questions regarding pharmacokinetics under surgical stress, overlapping toxicities with postoperative symptoms and interactions with acute and chronic pain syndromes.Circulating tumour DNA (ctDNA)–based minimal residual disease (MRD) assays are refining postoperative risk stratification: postoperative ctDNA positivity predicts substantially higher recurrence risk, whereas ctDNA clearance correlates with improved survival.[13–15] Integrating MRD status with functional and symptom endpoints—including pain and patient-reported outcomes—may enable perioperative decision-making that better balances oncologic control against toxicity and pain burden.

Central Role of Pain and Symptom Management in Treatment Adherence, Quality of Life and Long-Term Outcomes

For oral targeted therapies around surgery, adherence and persistence are critical determinants of real-world effectiveness. Observational studies show suboptimal adherence to EGFR- or ALK-directed agents, influenced by dosing schedules, treatment duration and toxicity profiles.[16] Educational and behavioural interventions can improve adherence,[17] while electronic patient-reported outcome (ePRO) monitoring reduces symptom burden and enhances

quality of life.[18] Given the high prevalence of surgical and neuropathic pain, together with TKI-associated musculoskeletal, dermatologic and other adverse events, pain and symptom management are central—not ancillary—to maintaining dose intensity and achieving the intended oncologic benefit. Uncontrolled pain or cumulative symptoms drive dose reductions, interruptions and early discontinuation and contribute to psychological distress and functional decline. Across studies of oral anticancer agents, higher symptom burden—particularly pain and fatigue—has been consistently associated with missed doses and early discontinuation, highlighting pain control as a modifiable determinant of adherence.

Multidisciplinary Clinical and Nursing Collaboration in Perioperative Targeted Therapy and Pain Management

Perioperative care for resectable NSCLC spans surgery, systemic therapy, pain control, rehabilitation and survivorship, and requires coordination among thoracic surgeons, medical oncologists, anaesthesiologists, pain specialists, rehabilitation teams and oncology nurses. Multidisciplinary pathways that align treatment scheduling with multimodal analgesia, early mobilisation and psychosocial support are key to optimising oncologic and pain-related outcomes. Oncology nurses play pivotal roles in serial pain assessment, implementation of ePRO or symptom diaries, patient education and identification of individuals with psychological vulnerability or pre-existing chronic pain.

Objectives of This Narrative Review

This narrative review focuses on perioperative targeted therapy in resectable NSCLC, with an emphasis on EGFR-directed TKIs. Its objectives are to integrate evidence from drug design and clinical development relevant to perioperative EGFR-TKI use; evaluate pain-related tolerability, analgesic strategies and patient experience—including CPSP and ePRO-based monitoring; and propose an integrated "efficacy–safety–pain–adherence" framework to guide future research and clinical practice (Figure 1). To our knowledge, this is the first review to bring together perioperative targeted therapy, pain-related tolerability and multidisciplinary pain-management strategies within a single framework for resectable NSCLC.

This narrative review was informed by literature identified through searches of major biomedical databases (eg, PubMed/Medline and Embase) and relevant conference abstracts, focusing on perioperative EGFR-TKI trials, ctDNA/

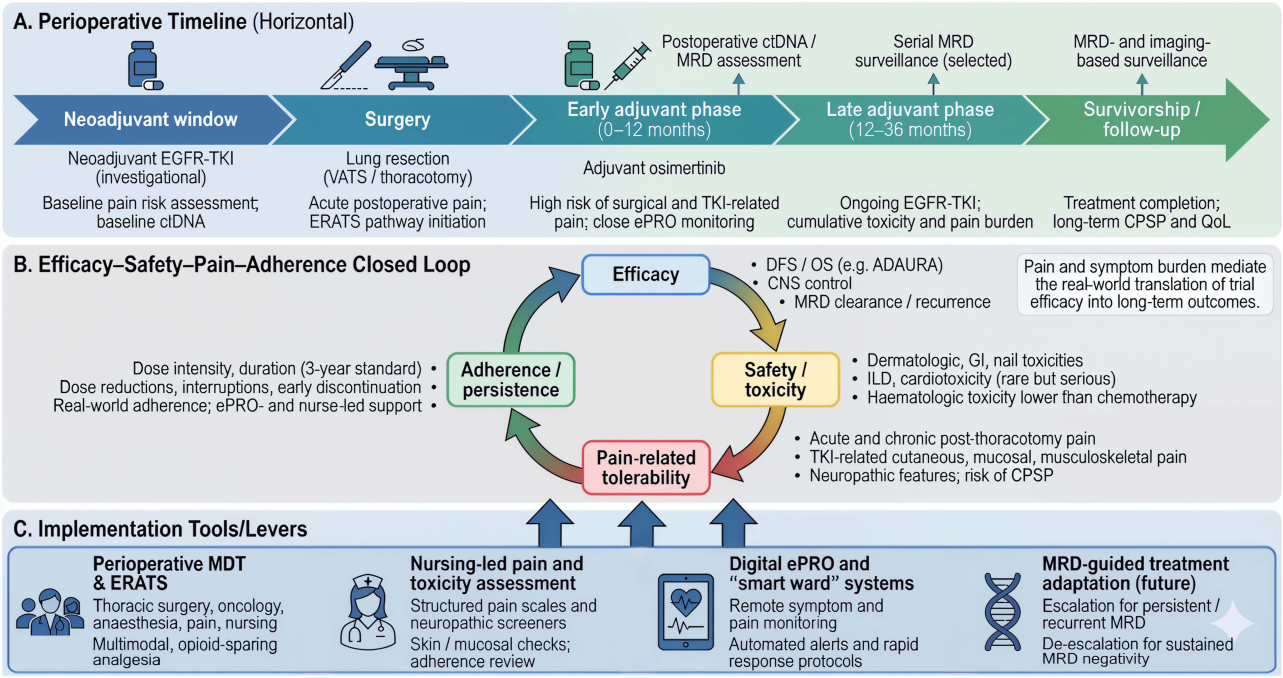

Figure 1 Conceptual efficacy–safety–pain–adherence framework for perioperative EGFR-targeted therapy in resectable EGFR-mutated NSCLC. (**A**) Perioperative Timeline (Horizontal). (**B**) Efficacy-Safety-Pain-Adherence Closed Loop. (**C**) Implementation Tools/Levers.

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MRD studies, postoperative and chronic pain after lung resection, and patient-reported outcomes/adherence interventions. Priority was given to pivotal randomised trials, large prospective cohorts, and consensus guidelines; mechanistic and implementation studies were included to support the proposed framework. Given the narrative scope, formal risk-of-bias assessment and meta-analysis were not performed.

Molecular Mechanisms and Fundamentals of Drug Design

Oncogenic Drivers in Resectable NSCLC and Their Therapeutic Relevance

Early-stage NSCLC is genetically diverse even when potentially curable by surgery. Prospective cohorts such as EARLY-EGFR have shown that sensitizing EGFR mutations—including exon 19 deletions and L858R—are highly prevalent in resected stage I–III adenocarcinoma, particularly in Asian populations.[19] In Western cohorts, KRAS mutations (notably G12C) are more common, whereas ALK rearrangements, MET exon 14 skipping and RET fusions define smaller but clinically relevant subgroups.[20]

Driver alterations also shape recurrence patterns. EGFR-mutant and ALK-rearranged tumours exhibit an early relapse peak within two to three years after surgery, suggesting persistent MRD and ongoing oncogenic signalling.[21] These observations support perioperative systemic therapy aimed at suppressing MRD and preventing micrometastatic outgrowth and justify broad next-generation sequencing (NGS) for stage I–III disease to identify actionable drivers and anticipate resistance and toxicity profiles relevant to perioperative decision-making.[22]

Structural Evolution of EGFR-TKIs Toward Fourth-Generation Agents

The development of EGFR TKIs exemplifies progressive refinement in mutant selectivity and resistance avoidance. First-generation reversible TKIs (gefitinib, erlotinib) occupy the ATP-binding pocket via hinge-region hydrogen bonds but lack strong selectivity for mutant EGFR; acquisition of the T790M gatekeeper mutation restores ATP affinity and confers resistance.[23] Second-generation agents (afatinib, dacomitinib) introduce irreversible covalent binding to Cys797 but maintain broader ErbB-family inhibition, leading to dermatologic and gastrointestinal toxicities that can limit tolerability in the perioperative setting.[24]

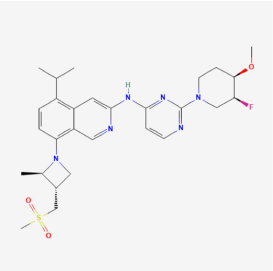
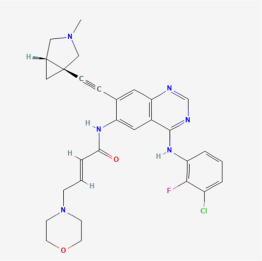
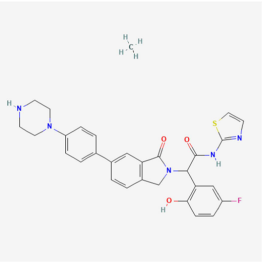
Third-generation inhibitors such as osimertinib combine irreversible Cys797 binding with enhanced mutant selectivity and improved safety; nonetheless, C797S remains a major on-target resistance mechanism.[25] Fourth-generation compounds, including sunvozertinib (DZD9008), employ compact scaffolds and alternative binding modes to retain potency against C797S and exon 20 insertions while relatively sparing wild-type EGFR.[26,27] These design features translate into durable responses and more manageable toxicity profiles—attributes that are particularly important in perioperative contexts where adverse events, pain and adherence directly influence recovery and long-term outcomes. Representative fourth-generation EGFR-TKIs and their potential perioperative relevance are summarised in Table 1.

Perioperative Pharmacokinetics, Surgical Stress Physiology and Drug Safety

The perioperative period is characterised by dynamic physiological changes that can alter the pharmacokinetics of oral targeted therapies. Osimertinib exposure, for example, varies widely among patients and may be further modified after thoracic surgery by transient hepatic dysfunction, changes in CYP3A activity and altered gastrointestinal motility.[28] Surgical stress and concurrent physiological changes can also affect plasma protein binding and tissue distribution, altering the pharmacologically active fraction of TKIs.[29] Concomitant use of antibiotics, corticosteroids, proton-pump inhibitors or analgesics adds complexity through drug–drug interactions.[30]

Toxicities such as diarrhoea, anorexia and rash can compromise nutrition, wound healing and participation in rehabilitation programmes. Understanding the interplay between pharmacokinetics, postoperative physiology and pain control is therefore critical to maintaining adequate therapeutic exposure while supporting safe recovery in the perioperative phase.

Table 1 Representative Fourth-Generation EGFR-TKIs and Their Potential Perioperative Relevance

Agent	2D Structure	Key Target Mutations (Examples)	Key Structural/ Pharmacologic Features	Development Stage and Potential Perioperative Role
BLU-945		Exon 19 deletion/ L858R plus on-target resistance (eg T790M, T790M/C797S)	Oral, mutant-selective, ATP-competitive 4th-generation EGFR-TKI with wild-type EGFR sparing; designed for combination with osimertinib	Phase 1/2 in advanced EGFR-mutant NSCLC; potential post-osimertinib option for C797S-positive relapse after perioperative therapy and for MRD-positive high-risk patients
BDTX-1535 (silevertinib)		Classical and uncommon EGFR mutations (exons 18–21), including some C797S and rare variants	Irreversible, "MasterKey" 4th-generation EGFR-TKI; mutation-selective, CNS-penetrant and wild-type sparing	Phase 1/2 in relapsed/refractory EGFR-mutant NSCLC; candidate salvage for complex resistance patterns and CNS relapse following perioperative osimertinib
JIN-A02	Not shown (structure not publicly available)	C797S-mediated resistance (eg ex19del/T790M/ C797S) after 3rd-generation EGFR-TKIs	Oral, reversible 4th-generation EGFR-TKI selectively targeting C797S/T790M with encouraging preclinical and early clinical activity	Ongoing phase 1/2 study in C797S-positive disease; potential targeted option for C797S-driven recurrence after adjuvant osimertinib within a resistance-profile–guided strategy
BLU-701	Not shown (structure not publicly available)	Exon 19 deletion/ L858R plus C797S double mutants	Oral, brain-penetrant, mutant-selective 4th-generation EGFR-TKI; designed for single-agent or combination use	Early phase 1/2 experience; development subsequently deprioritised, but illustrates design principles for future brain-directed 4th-generation perioperative TKIs
JBJ-04-125-02		L858R/T790M/C797S triple mutants and related on-target resistance profiles (preclinical)	Mutant-selective allosteric EGFR inhibitor, synergistic with ATP-site TKIs such as osimertinib in preclinical models	Preclinical proof-of-concept; supports future combination strategies to suppress triple-mutant clones and delay on-target resistance after perioperative EGFR-TKIs

Note: 2D structures for BLU-945, BDTX-1535 and JBJ-04-125-02 were redrawn in ChemDraw based on publicly available sources. For BLU-701 and JIN-A02, detailed chemical structures are not yet available in public small-molecule databases and are therefore not shown.

Targeted Therapies and Pain-Related Neurobiology: Mechanistic Cross-Talk

Perioperative EGFR-targeted therapy intersects with nociceptive and neuropathic pain mechanisms that are central to thoracic surgery. Surgical trauma induces intercostal nerve injury, local inflammation and central sensitisation; CPSP can persist for years in 15–20% of patients.[31]

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EGFR signalling modulates neuronal excitability through PI3K–AKT, MAPK and TRPV1-related pathways. Activation of EGFR in dorsal root ganglia and spinal microglia enhances glutamate release and synaptic sensitisation, amplifying nociceptive transmission.[32] Conversely, chronic EGFR inhibition may interfere with neural repair and Schwann-cell function, contributing to neuropathic-like symptoms such as paraesthesia or myalgia. The net effect depends on drug selectivity, dose intensity and timing of exposure relative to tissue injury. Because the intensity of acute postoperative pain strongly predicts CPSP risk,[33] strategic coordination of EGFR-TKI initiation with optimised multimodal analgesia is essential.

Inflammatory cytokines released after surgery (eg IL-6, TNF-α) can modify TKI pharmacodynamics and pain thresholds, creating bidirectional feedback between inflammation, analgesic response and toxicity. Emerging preclinical models suggest that EGFR–MAPK interference can modulate TRPV1 and NaV1.8 channels, potentially influencing neuronal plasticity and pain chronification. Clinically, selecting TKIs with low neurotoxicity potential, employing regional analgesia where feasible and involving pain specialists early may improve pain outcomes and support adherence to perioperative targeted therapy.

Translational Continuum from Molecular Design to Perioperative Clinical Application

Perioperative EGFR-targeted therapy exemplifies a translational continuum that links medicinal chemistry, molecular diagnostics, and clinical implementation.[34] Fourth-generation EGFR-TKIs were rationally designed through iterative structure–activity optimisation and, in some cases, allosteric modulation to overcome resistance mediated by C797S substitution and exon 20 insertions.[35,36] Within this continuum, plasma ctDNA-based MRD assays provide real-time estimation of recurrence risk and treatment response and form the basis for risk-adapted perioperative strategies, which are discussed in detail in MRD-Guided Adaptation of Perioperative EGFR-TKI Therapy.

Clinical Evidence for Perioperative EGFR-Targeted Therapy

From Platinum-Based Chemotherapy to Genotype-Directed Perioperative Therapy

Meta-analytic data from the Lung Adjuvant Cisplatin Evaluation (LACE) confirmed that postoperative cisplatin-based chemotherapy confers only a modest survival benefit (HR 0.89) and that this benefit is stage dependent—clear in stage II–III but minimal in stage I disease.[37,38] With routine molecular profiling, EGFR-mutated NSCLC has emerged as a biologically distinct subset characterised by oncogene addiction, stereotyped recurrence patterns and profound TKI sensitivity in advanced disease.[39] Retrospective cohorts suggest that the benefit of platinum chemotherapy is attenuated in early-stage EGFR-mutant tumours, with several analyses showing no significant improvement in recurrence-free survival.[40,41] These observations support genotype-directed perioperative therapy that targets underlying oncogenic drivers rather than non-specific cytotoxic pathways.

Large perioperative chemo-immunotherapy trials have established event-free survival benefits in unselected populations;[42] however, evidence in EGFR-mutated subgroups remains limited and is often based on small numbers and exploratory analyses.[43] Given the established efficacy of EGFR-TKIs in oncogene-driven disease and the potential for overlapping pulmonary toxicities, the optimal role and sequencing of immunotherapy in resectable EGFR-mutated NSCLC remains uncertain and should be individualised and preferably addressed in prospective biomarker-stratified studies.[44]

Adjuvant EGFR-TKIs After Complete Resection of EGFR-Mutated NSCLC

First-Generation Adjuvant EGFR-TKIs

Evidence supporting adjuvant EGFR-TKIs has expanded rapidly, encompassing phase III trials, pooled analyses and real-world cohorts.[45] Across stage IB–IIIA disease, adjuvant TKIs consistently improve DFS, although the magnitude of overall-survival (OS) benefit varies by stage, TKI generation and treatment duration.[46] Toxicity profile and treatment burden relative to platinum chemotherapy are crucial in the perioperative context, where postoperative recovery, pain and adherence strongly influence long-term outcomes.

ADJUVANT/CTONG1104 remains the most mature first-generation trial. Twenty-four months of gefitinib improved DFS versus vinorelbine–cisplatin in resected stage II–IIIA EGFR-mutant NSCLC, with markedly fewer haematologic

toxicities.[47] Long-term follow-up confirmed a persistent DFS advantage, whereas OS was similar (HR 0.92), likely reflecting access to TKIs at recurrence in the chemotherapy arm.[48,49] In higher-risk disease, EVAN showed that two years of erlotinib yielded a clinically meaningful OS benefit in stage IIIA patients (5-year OS ≈85% vs 51%).[50]

Meta-analytic synthesis reinforces these findings: pooled analyses of randomised trials, including third-generation TKIs, show substantial DFS improvement (HR ≈0.46),[45] but only a modest overall-survival advantage (HR ≈0.7), mainly in stage III disease and with higher-potency agents.[46] A Bayesian network meta-analysis comparing TKI monotherapy, TKI plus chemotherapy and chemotherapy alone suggested no inferiority for TKI monotherapy and higher rates of grade ≥3 toxicity with combination regimens.[51] Real-world data similarly indicate that prolonged TKI exposure (≥2 years) improves DFS and OS, whereas adding platinum chemotherapy confers little incremental benefit.[52]

In lower-stage disease, the CORIN (GASTO1003) Phase II trial showed that 12 months of icotinib significantly improved 5-year DFS (88.5% vs 67.7%) in resected stage IB EGFR-mutant NSCLC.[53,54] These results support adjuvant targeted therapy for high-risk stage IB patients, particularly in settings where third-generation TKIs are unavailable. Overall, first-generation agents (gefitinib, erlotinib, icotinib) consistently improve DFS and can enhance OS in selected cohorts.[55] However, limited CNS penetration, cutaneous and gastrointestinal toxicity and inconsistent OS benefit have prevented them from becoming the preferred adjuvant option in contemporary practice.

Third-Generation Osimertinib and the ADAURA Paradigm

In ADAURA, three years of adjuvant osimertinib significantly improved disease-free survival and reduced CNS relapse versus placebo in resected stage IB–IIIA EGFR-mutated NSCLC, with a confirmed overall-survival benefit on mature follow-up.[56] The safety profile was predominantly low-grade and manageable, supporting prolonged postoperative exposure with proactive toxicity and symptom monitoring.[57]

Three-year safety data showed predominantly low-grade, manageable adverse events concentrated in the first treatment year.[58] Health-related quality of life remained stable compared with placebo, supporting sustained post-operative exposure with limited symptomatic burden—an important consideration for patients already dealing with surgical pain and functional recovery. Comparative analyses highlight a clear hierarchy: osimertinib delivers the largest and most consistent DFS and OS benefits, superior CNS protection and a more favourable tolerability profile than earlier-generation TKIs.[56] Where osimertinib is inaccessible, first-generation TKIs remain pragmatic alternatives but should be viewed as context-dependent options rather than preferred perioperative therapy. Targeted therapy provides greater DFS benefit than chemo-immunotherapy in completely resected EGFR-mutant disease, reinforcing its role as the backbone of adjuvant systemic therapy.[59]

Collectively, the evolving evidence base establishes osimertinib as the reference standard for adjuvant treatment of resected stage II–IIIA and selected IB EGFR-mutant NSCLC. Key perioperative trials of adjuvant EGFR-TKIs in resected EGFR-mutant NSCLC are summarised in Table 2. This "ADAURA paradigm" underpins ongoing efforts to integrate EGFR-TKIs with neoadjuvant strategies, MRD-guided personalisation and structured perioperative symptom—including pain—management discussed in subsequent sections.

Neoadjuvant EGFR-TKIs in Resectable EGFR-Mutant NSCLC

Applying EGFR-TKIs preoperatively is conceptually attractive: early systemic therapy may eradicate micrometastases, shrink tumours to facilitate resection and provide an in vivo assessment of drug sensitivity.[60] However, neoadjuvant TKIs must preserve surgical feasibility and downstream adjuvant options, particularly given the established ADAURA standard.

Early-phase studies with first- and second-generation TKIs have shown consistent radiographic activity but modest pathological responses. Single-arm trials of gefitinib or erlotinib in stage II–IIIA EGFR-mutant NSCLC reported objective response rates of 50–70%, R0 resection rates around 90%, but low major pathological response (MPR ≈10%) and complete response (pCR ≈3%).[61] These data confirm surgical feasibility and antitumour activity yet indicate that short-course TKIs mainly induce cytoreduction rather than true eradication.

The randomised EMERGING-CTONG1103 trial provides the strongest comparison to date. In stage IIIA-N2 EGFR-mutant NSCLC, perioperative erlotinib improved progression-free survival (≈21.5 vs 11.4 months) and objective response (54% vs 34%) versus cisplatin–gemcitabine.[62] R0 resection and surgical complication rates were similar, but

Table 2 Key Perioperative Adjuvant EGFR-TKI Trials in Resected EGFR-Mutated NSCLC

Trial (Phase)	Population (Stage/ Setting)	Intervention (Duration)	Comparator	Primary Endpoint	Key Efficacy Results	Key Tolerability Signals/ Perioperative Notes
ADJUVANT/ CTONG1104 (III)	Completely resected stage II–IIIA EGFR-mutant NSCLC	Gefitinib 250 mg daily for 24 months	Vinorelbine–cisplatin (up to 4 cycles)	DFS	Improved DFS with gefitinib vs chemotherapy; no clear OS difference at long-term follow-up (HR for OS ~0.9)	Fewer haematologic toxicities and better QoL with gefitinib; demonstrates feasibility of prolonged oral TKI after surgery
EVAN (II)	Completely resected stage IIIA EGFR-mutant NSCLC	Erlotinib 150 mg daily for 24 months	Cisplatin-based chemotherapy	2-year DFS	Higher 2-year DFS and numerically superior OS (5-year OS ≈85% vs 51%) with erlotinib	Better tolerability than chemotherapy; supports genotype-directed adjuvant therapy in high-risk disease
CORIN/GASTO1003 (II)	Completely resected stage IB EGFR-mutant NSCLC	Icotinib 125 mg three times daily for 12 months	Observation	DFS	Improved 5-year DFS (~88.5% vs 67.7%) with icotinib	Supports adjuvant TKIs for high-risk stage IB where third-generation agents are unavailable
Pooled first-generation TKI trials (meta-analyses)	Stage IB–IIIA EGFR-mutant NSCLC	Gefitinib/erlotinib/ icotinib (1–2 years)	Platinum-based chemotherapy or observation	DFS, OS	Consistent DFS benefit (pooled HR ~0.45–0.50); OS benefit inconsistent, greater in stage III and longer exposure	Limited CNS protection; dermatologic and GI toxicity; not preferred where osimertinib is accessible
ADAURA (III)	Completely resected stage IB–IIIA EGFR-mutant NSCLC	Osimertinib 80 mg daily for 3 years	Placebo	DFS (stage II–IIIA); DFS (IB–IIIA); OS (key secondary)	Marked DFS benefit (HR ~0.17 for stage II–IIIA; ~0.20 for IB–IIIA) and significant OS improvement (5-year OS ~85% vs 73% in stage II–IIIA; ~88% vs 78% in IB–IIIA)	Predominantly low-grade toxicities, rare serious events; stable HRQoL; now global adjuvant standard and perioperative backbone

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MPR rates remained ≈10% and pCR was not achieved; OS was comparable at follow-up. These results highlight feasibility and cytoreductive potential but underscore the limited depth of pathological response and the absence of a proven survival advantage.

Third-generation osimertinib has shown greater promise. In the multicentre NEOS phase IIb trial, six weeks of neoadjuvant osimertinib in stage IIA–IIIB disease achieved an ORR of 71% and an R0 resection rate of 94%, with predominantly low-grade adverse events.[63] Retrospective and real-world series corroborate safety: surgery after appropriate TKI interruption does not appear to increase perioperative morbidity or mortality.[64,65]

The phase III NeoADAURA trial is now directly comparing neoadjuvant osimertinib ± chemotherapy with chemotherapy alone. Early 2025 results reported MPR rates of ≈25–26% versus 2%, greater nodal downstaging, high surgical completion (≈94%) and improved 12-month event-free survival (≈93–95% vs 83%).[66,67] Although mature OS and recurrence data are pending, these findings suggest that neoadjuvant osimertinib, alone or combined with chemotherapy, can meaningfully deepen pathological responses while maintaining surgical feasibility. Current guidelines therefore classify neoadjuvant EGFR-TKIs as promising yet investigational.[68] Adjuvant osimertinib remains the only targeted agent with proven survival benefit, and questions around optimal sequencing with MRD-guided strategies and perioperative symptom management remain central research priorities.

MRD-Guided Adaptation of Perioperative EGFR-TKI Therapy

ctDNA–based MRD assays provide a biologically informed framework for refining perioperative EGFR-TKI strategies beyond fixed-duration therapy. A 2023 meta-analysis of 16 lung-cancer cohorts showed that postoperative ctDNA positivity has high specificity (≈0.90–0.95) for recurrence but only moderate sensitivity at a single time point; longitudinal surveillance increases sensitivity to ≈75–80% while maintaining high specificity[13] Thus, MRD positivity reliably identifies high-risk patients, whereas MRD negativity—although favourable—remains insufficient to justify omission of adjuvant therapy in current practice.

Prospective perioperative cohorts validate the prognostic importance of ctDNA. In LUNGCA-1, postoperative ctDNA positivity predicted markedly higher recurrence rates and shorter relapse-free survival, often preceding radiologic relapse by several months.[69] Longitudinal analyses demonstrate that persistently positive or recurrent ctDNA identifies a subgroup with inferior long-term outcomes, whereas durable ctDNA clearance correlates with favourable prognosis.[70] Even in early-stage tumours—particularly stage I—where ctDNA shedding is limited, postoperative positivity marks a small but clinically meaningful high-risk subset.[71]

Technological advances have improved MRD detection. Tumour-informed, ultra-sensitive assays such as PROPHET use whole-exome sequencing of the resected tumour to track dozens of patient-specific clonal variants, lowering detection limits to 10^{-3}–10^{-5} and extending lead time to recurrence compared with tumour-naïve fixed panels.[72] TRACERx modelling indicates that many early-stage tumours shed ctDNA near assay thresholds, highlighting that sampling schedules and analytical sensitivity critically determine MRD performance.[73] Current reviews emphasise that MRD should complement—not replace—clinicopathologic risk factors when designing perioperative algorithms.[74,75]

In EGFR-mutant NSCLC, emerging data suggest that MRD can guide both intensification and de-escalation of adjuvant TKIs. A 2024 observational study in JTO Clinical and Research Reports followed 71 patients with resected stage I–III EGFR-mutant NSCLC receiving adjuvant TKIs plus tumour-informed MRD testing.[76] Longitudinal sensitivity reached ≈86%, and negative predictive value ≈90%. Among patients who discontinued TKIs after sustained MRD negativity, 2-year DFS remained ≈80%, and most recurrences were salvageable with TKI re-initiation—providing hypothesis-generating support for MRD-guided de-escalation within prospective protocols, while recognising the absence of phase III validation. Conversely, persistent or recurrent MRD despite adjuvant therapy identified a high-risk subgroup, supporting MRD positivity as a trigger for escalation or clinical-trial enrolment.

Exploratory analyses from ADAURA (2025) showed that MRD positivity preceded DFS events by ≈4–5 months, and combined DFS/MRD event-free rates were higher with adjuvant osimertinib than with placebo.[77] Many DFS or MRD events in the osimertinib arm occurred within 12 months of planned cessation, suggesting that re-emergent MRD may identify patients who could benefit from extended-duration therapy. Conceptually, MRD may serve as a bidirectional signal for future

trial designs (eg, exploring earlier discontinuation in sustained MRD-negative patients and extension/intensification in persistent MRD-positive patients); however, routine clinical adoption remains premature in the absence of phase III validation.

Randomised MRD-guided perioperative trials in EGFR-mutant NSCLC are still scarce, but analogous designs in other malignancies demonstrate feasibility. The DYNAMIC trial in stage II colon cancer showed that ctDNA-guided adjuvant chemotherapy reduced treatment intensity without compromising relapse-free survival.[78] In advanced EGFR- or ALK-positive NSCLC, ctDNA-guided TKI de-escalation after local consolidation permitted treatment breaks, with retreatment at MRD recurrence yielding high response rates.[79] These models highlight operational principles—pre-specified MRD thresholds, structured surveillance intervals and retreatment criteria—that are directly applicable to future EGFR-mutant NSCLC trials. Selected studies informing ctDNA/MRD-guided perioperative strategies in NSCLC and related settings are summarised in Table 3.

Important challenges persist. Assay heterogeneity in design, sensitivity and error suppression limits comparability. Even state-of-the-art assays may miss biologically relevant MRD in low-shedding tumours, whereas clonal haematopoiesis can generate false positives, requiring careful bioinformatic filtering.[80] Clinically, overreliance on MRD negativity risks undertreatment. These caveats underscore the need for cautious, trial-based adoption in which MRD informs—but does not solely determine—perioperative decision-making.

A conceptual MRD-integrated framework for resectable EGFR-mutant NSCLC may comprise three strata: MRD-positive early postoperative or persistent MRD: candidates for treatment escalation (extended osimertinib, combinations or next-generation EGFR inhibitors); High-risk but MRD-negative patients (eg N2 disease): continuation of standard 3-year osimertinib with MRD monitoring rather than early de-escalation; Low-risk, sustained MRD-negative patients: potential de-escalation, particularly when toxicity, pain burden or adherence issues arise. This MRD-integrated, pain-informed stratification approach is illustrated in Figure 2.

Overall, MRD-guided adaptation of EGFR-TKI therapy is promising yet remains investigational. ctDNA MRD is a powerful prognostic marker and early relapse detector, but assay heterogeneity, imperfect sensitivity and lack of phase III validation mean that three years of adjuvant osimertinib is still the standard of care. As MRD technologies mature and are embedded into perioperative trial design, MRD-guided personalisation of EGFR-TKI therapy is likely to become central to curative-intent management of resectable EGFR-mutant NSCLC.

Perioperative Targeted Therapy in Other Oncogene-Driven Subsets (ALK, MET, RET and KRAS)

Although EGFR-mutated NSCLC provides the most mature perioperative model, parallel strategies are emerging across other oncogene-defined subsets. Alterations in ALK, RET, MET and KRAS account for a meaningful minority of early-stage NSCLC, and highly active TKIs developed for metastatic disease are now being tested before and after surgery.[81] These translational efforts mirror the EGFR experience but must address smaller populations, existing chemo-immunotherapy standards and the need to balance prolonged targeted therapy with perioperative tolerability and symptom burden.

ALK-rearranged NSCLC has advanced the furthest. The phase III ALINA trial randomised patients with completely resected stage IB (≥4 cm)–IIIA ALK-positive NSCLC to 24 months of alectinib or platinum-based chemotherapy.[82] Alectinib produced a striking DFS benefit (3-year DFS ≈88% vs 53% in stage II–IIIA; HR ≈0.24) and markedly reduced CNS relapse, with toxicity consistent with prior experience. Based on these results, adjuvant alectinib is now approved for resected ALK-positive NSCLC, establishing a second genotype-directed perioperative standard alongside osimertinib.[83]

In RET fusion–positive NSCLC, the highly selective inhibitor selpercatinib has shown robust efficacy in advanced disease. The global phase III LIBRETTO-432 trial mirrors ADAURA and ALINA by evaluating three years of adjuvant selpercatinib versus placebo in stage IB–IIIA disease.[84] Its outcomes will determine whether RET-directed adjuvant therapy can extend targeted approaches into early-stage disease.

For MET exon 14 skipping (METex14) or high-level MET amplification, perioperative data remain limited but conceptually aligned with the EGFR paradigm. Capmatinib and tepotinib induce durable responses in advanced METex14-mutant NSCLC.[85] The GEOMETRY-N phase II trial is evaluating neoadjuvant and adjuvant capmatinib in resectable MET-driven

Table 3 Selected Studies Informing ctDNA/MRD-Guided Perioperative Strategies

Study/Cohort	Tumour Type and Setting	Design/ Population	MRD Assay Type	Key MRD Findings	Implications for Perioperative EGFR-TKI
2023 lung cancer MRD meta-analysis (16 cohorts)	Localised NSCLC after curative-intent therapy	Meta-analysis of prospective and retrospective cohorts	Mixed tumour-informed and tumour-naïve assays	Postoperative ctDNA positivity shows high specificity (~0.90–0.95) for recurrence; single time-point sensitivity moderate, improved with serial sampling	MRD positivity reliably identifies high-risk patients; MRD negativity favourable but insufficient to omit adjuvant therapy
LUNGCA-1	Resected NSCLC (mixed genotypes)	Prospective perioperative cohort with serial ctDNA	Tumour-informed assay	Postoperative ctDNA positivity predicts markedly higher recurrence rates and shorter relapse-free survival; ctDNA often precedes imaging relapse by months	Supports MRD as early relapse detector and risk stratifier to refine duration and intensity of adjuvant therapy
EGFR-mutant adjuvant TKI + MRD cohort (JTO Clinical and Research Reports 2024)	Resected stage I–III EGFR-mutant NSCLC on adjuvant TKIs	Observational cohort with longitudinal MRD testing	Tumour-informed assay	Longitudinal sensitivity ≈80–90%; sustained MRD negativity associated with ~80% 2-year DFS; most MRD-negative relapses salvageable with TKI re-initiation	Suggests MRD-guided de-escalation may be feasible in selected low-risk patients; persistent MRD may trigger escalation or trial enrolment
ADAURA exploratory MRD analysis (2025)	Resected EGFR-mutant NSCLC treated with adjuvant osimertinib vs placebo	Post-hoc analysis with serial ctDNA	Tumour-informed assay	MRD positivity precedes DFS events by ~4–5 months; MRD/DFS event-free rates higher with osimertinib; many events occur within 12 months after treatment cessation	MRD could identify patients requiring extended adjuvant osimertinib beyond 3 years and those suitable for de-escalation after sustained MRD negativity
DYNAMIC (stage II colon cancer)	Resected colon cancer	Randomised trial: ctDNA-guided vs standard adjuvant chemotherapy	Tumour-informed assay	ctDNA-guided strategy reduced chemotherapy use without compromising relapse-free survival	Provides proof-of-concept that MRD can safely guide adjuvant escalation/de-escalation in solid tumours; design principles applicable to future EGFR-mutant NSCLC trials
ctDNA-guided TKI de-escalation in advanced EGFR/ALK-positive NSCLC	Stage IV EGFR- or ALK-positive NSCLC after local consolidation	Prospective studies allowing TKI breaks guided by MRD	Tumour-informed ctDNA	TKI interruption after MRD clearance with retreatment at MRD recurrence yielded high response rates	Demonstrates feasibility of MRD-guided TKI interruption/re-initiation; relevant to designing perioperative MRD-guided duration studies

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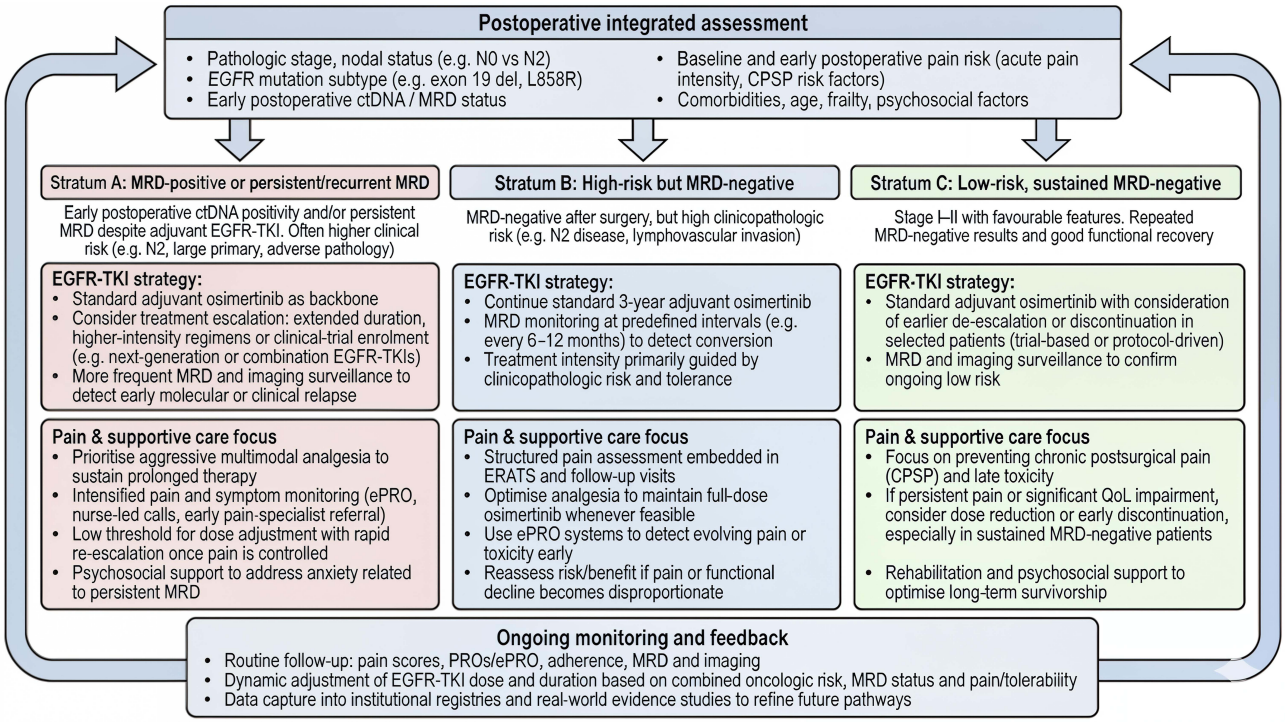

Figure 2 MRD-integrated, pain-informed perioperative stratification model for EGFR-mutated NSCLC.

NSCLC, focusing on pathological response and surgical feasibility.[86] Older age, comorbidities and MET inhibitor–specific toxicities (oedema, hepatotoxicity) are likely to influence clinical integration and perioperative tolerability.

By contrast, KRAS-mutant NSCLC—particularly KRAS G12C—remains at an earlier stage of perioperative development. Sotorasib and adagrasib have demonstrated superiority to docetaxel in previously treated stage IV disease,[87,88] but phase III perioperative data are lacking. Ongoing phase II trials include neoadjuvant sotorasib plus platinum–pemetrexed (NCT05118854) and adagrasib ± nivolumab (NCT2024-09121), which are assessing MPR, surgical feasibility and short-term recurrence.[89,90] Interpretation will require careful consideration of existing chemo-immunotherapy standards, and the optimal perioperative duration—short-course neoadjuvant versus extended adjuvant—remains undefined.

Taken together, perioperative targeted therapy beyond EGFR is rapidly evolving but heterogeneous in maturity. Alectinib for ALK-positive disease now constitutes an established adjuvant standard, whereas RET-, MET- and KRAS-directed approaches remain investigational. Across all molecular subsets, successful integration depends on timely molecular testing, proactive management of overlapping toxicities and inclusion of patient-centred endpoints—pain, functional recovery and quality of life—alongside traditional survival outcomes.[91] These principles directly connect to the following section on safety, pain-related tolerability and multidisciplinary supportive care in perioperative targeted therapy.

These efficacy data define the "efficacy" axis of the loop; subsequent sections address how chronic toxicities and pain can erode adherence and thereby attenuate real-world benefit.

Safety, Pain-Related Tolerability and Supportive Care in Perioperative Targeted Therapy

Overall Safety and Tolerability of Perioperative EGFR-TKIs

Because perioperative EGFR-TKIs are often administered for months or years after major thoracic surgery, long-term safety and tolerability are central determinants of real-world benefit. In ADAURA, three years of adjuvant osimertinib was mainly associated with low-grade, class-specific toxicities—diarrhoea, rash, paronychia and stomatitis—while grade ≥3 events were uncommon. Health-related quality-of-life scores remained similar to placebo, indicating that most adverse events can be managed by structured dose interruptions or reductions rather than permanent discontinuation.

Neoadjuvant trials provide complementary information on short-term perioperative risk. In NEOS (phase IIb), six weeks of preoperative osimertinib yielded an objective response rate >70%, with treatment-related events in roughly three-quarters of patients but grade 3 toxicity in only 7–8%; more than 90% achieved R0 resection without excess perioperative morbidity.[63] A 2025 systematic review of neoadjuvant targeted-therapy trials reported grade ≥3 toxicity rates generally below 10% and no signal for impaired operability or postoperative recovery.[92]

Taken together, consensus reviews conclude that perioperative EGFR-TKIs are better tolerated than platinum-based chemotherapy or chemo-immunotherapy, especially with respect to haematologic toxicity, nausea, vomiting and neuropathy. Instead, toxicity is dominated by chronic low-grade dermatologic, gastrointestinal and nail-related effects, punctuated by rare pulmonary or cardiac events—patterns that directly shape adherence, pain burden and functional recovery. Accordingly, early-stage guidelines emphasise pretreatment counselling, regular toxicity monitoring, early intervention for rash and diarrhoea, baseline and periodic cardiac evaluation to preserve dose intensity while minimising harm.[93]

Targeted Therapy–Specific Adverse Events and Their Impact on Pain and Recovery

Perioperative EGFR-TKIs produce a characteristic spectrum of mechanism-based, predominantly non-haematologic toxicities that interact directly with pain and function.

Dermatologic reactions are among the most common. Acneiform rash, xerosis, pruritus and paronychia occur frequently even with third-generation agents and are particularly prevalent in Asian populations.[94] These cutaneous events are often painful or intensely pruritic; nail-fold inflammation, fissures and fingertip tenderness interfere with fine motor tasks and daily activities.[95] In the absence of proactive skin care—emollients, topical corticosteroids, oral antibiotics and low-threshold dermatology referral—rash and nail changes become major drivers of treatment interruptions and quality-of-life decline.[96]

Gastrointestinal events, especially diarrhoea and stomatitis, form a second major toxicity cluster. Across trials, diarrhoea affects 20–80% of patients, with a smaller subset experiencing grade ≥3 episodes that cause dehydration, electrolyte imbalance and cramping abdominal pain.[97] Mechanisms include altered epithelial transport, dysbiosis and mucosal inflammation. Early management with diet modification, loperamide-based regimens and structured patient education can substantially mitigate severity.[98] In perioperative patients, reduced oral intake, fluid shifts and vulnerability to malnutrition magnify the impact of even moderate diarrhoea or mucositis, delaying mobilisation and prolonging hospital stay.

Less common but clinically significant toxicities include ILD, hepatotoxicity and cardiotoxicity. Pharmacovigilance data suggest that EGFR-TKI–associated ILD, though rare, remains a leading cause of treatment-related mortality and is more frequent in some ethnic groups.[99,100] ILD typically presents with acute dyspnoea, hypoxaemia and pleuritic pain, and may mimic postoperative pneumonia or pulmonary embolism; prompt recognition, immediate drug discontinuation and early corticosteroids are critical. Regulatory reviews of osimertinib identify ILD, cardiomyopathy and QTc prolongation as uncommon (<1%) but serious adverse reactions that can trigger rehospitalisation and abrupt cessation of adjuvant therapy.[101] Although infrequent, these events exert a disproportionate psychological and functional impact, reinforcing the need for vigilant, multidisciplinary monitoring.

Pain-Related Adverse Events: Mechanisms and Clinical Phenotypes

Pain in the perioperative EGFR-TKI setting arises from converging sources: thoracic surgery, tumour biology and prolonged targeted therapy. After lung resection, up to one-third of patients develop chronic postsurgical pain, frequently with neuropathic features such as burning, allodynia or electric shocks along the chest wall or shoulder, which can persist for years and substantially impair quality of life.[102,103] EGFR-TKI–related pain syndromes may overlay or amplify this background, complicating attribution and influencing decisions on dose modification or discontinuation.

As outlined in Targeted Therapy–Specific Adverse Events and Their Impact on Pain and Recovery, painful cutaneous and mucosal toxicities are hallmark EGFR-TKI effects that frequently limit daily function and medication adherence.[104] At a mechanistic level, EGFR signalling regulates keratinocyte proliferation, epidermal integrity and barrier repair; inhibition promotes differentiation, thins the epidermis and favours inflammation and peripheral sensitisation.[105] EGFR-driven pathways intersect with PI3K and MAPK nociceptive cascades, enhancing neuronal excitability and contributing to pain hypersensitivity.[106]

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Musculoskeletal and neuropathic symptoms—including arthralgia, myalgia, tendon discomfort and distal paraesthesia—are also reported. Distinguishing these from post-thoracotomy, drain-related or tumour-related pain requires systematic assessment using numeric rating scales and neuropathic screening tools (eg DN4, S-LANSS, painDETECT), together with temporal correlation to surgery and treatment exposure.[107] Rare but serious complications such as drug-induced ILD or cardiac ischaemia may present with chest pain, highlighting the importance of differentiating benign TKI-related discomfort from emergencies requiring urgent evaluation.[108] Comprehensive, structured pain assessment is therefore fundamental to balanced decisions on dose adjustment, multimodal analgesia and continuation of perioperative EGFR-TKI therapy. Common EGFR-TKI toxicities that influence perioperative pain and recovery, together with practical management recommendations, are summarised in Table 4.

Multidisciplinary Perioperative Pain Management and ERAS-Based Care Pathways

Optimising pain control and tolerability during perioperative EGFR-TKI therapy requires coordinated input from thoracic surgeons, anaesthesiologists, pain specialists, medical oncologists, nurses and rehabilitation teams. Enhanced Recovery After

Table 4 Common EGFR-TKI Toxicities Relevant to Perioperative Pain and Recovery, and Suggested Management

Toxicity Cluster	Typical Features with EGFR-TKIs	Pain-related Impact in Perioperative Setting	Suggested Management Strategies
Cutaneous toxicity (rash, xerosis, pruritus)	Acneiform papulopustular rash on face, scalp, trunk; dry, itchy skin; often more frequent/severe in Asian patients	Local pain, burning and pruritus; sleep disruption; cosmetic distress; risk of fissures/infection; may reduce activity and adherence	Proactive emollients and gentle skin care; early use of topical steroids ± oral antibiotics; antihistamines for pruritus; dermatology referral for moderate–severe cases; dose interruption/reduction if refractory
Nail and periungual changes (paronychia, fissures)	Tender periungual inflammation, granulation tissue, nail-fold fissures, ingrown nails	Pain on walking, grasping or fine motor tasks; substantial functional limitation; major reason for treatment interruption	Warm soaks, topical antiseptics and steroids; protective footwear/gloves; podiatry or dermatology input; consider short TKI breaks or dose reduction when pain interferes with daily activities
Gastrointestinal toxicity (diarrhoea, stomatitis)	Loose stools ranging from mild to severe; cramping; oral sores and mucosal sensitivity	Abdominal pain, dehydration, reduced oral intake; impaired nutrition and wound healing; difficulty swallowing tablets, limiting adherence	Early dietary counselling; loperamide-based protocols for diarrhoea; oral care and topical agents for mucositis; fluid/electrolyte replacement; hospitalisation for severe dehydration; short interruptions for grade ≥3 events
Musculoskeletal and neuropathic symptoms	Arthralgia, myalgia, tendon discomfort; distal paraesthesia or burning; sometimes overlapping with post-thoracotomy pain	Amplification of baseline chest wall/shoulder pain; reduced mobility and participation in rehabilitation; sleep disturbance	Routine pain scoring and neuropathic screening tools (DN4, S-LANSS, painDETECT); stepwise multimodal analgesia (paracetamol/NSAIDs if appropriate, gabapentinoids, duloxetine); early pain-specialist referral for refractory symptoms
Interstitial lung disease (ILD)	New or worsening dyspnoea, cough; hypoxaemia; diffuse infiltrates on imaging	Pleuritic chest pain and breathlessness; may be misattributed to pneumonia or postoperative complications; high morbidity and mortality	Immediate TKI discontinuation; urgent imaging and respiratory review; systemic corticosteroids; supportive oxygen therapy; avoid rechallenge in severe cases
Cardiotoxicity and QTc prolongation	Asymptomatic LVEF decline; palpitations, syncope; QTc prolongation on ECG	May present with chest discomfort, fatigue, dyspnoea; anxiety about cardiac risk can undermine adherence	Baseline and periodic ECG and echocardiography in at-risk patients; correction of electrolytes; review of QT-prolonging co-medications; cardiology referral; dose interruption/reduction for clinically significant events

Surgery (ERAS) programmes emphasise preoperative optimisation, minimally invasive techniques, early mobilisation and multimodal, opioid-sparing analgesia to reduce complications and facilitate timely resumption of systemic therapy after lung resection.[109] Embedding EGFR-TKI–specific considerations into ERAS pathways—systematic review of drug–drug interactions, planned TKI interruption and restart around surgery, and early recognition of cutaneous, mucosal or respiratory symptoms—helps avoid unnecessary discontinuation and supports safe reinstitution of targeted therapy.[110]

Oncology nursing frameworks add an essential longitudinal perspective, with nurse-led pain assessment, skin and mucosal surveillance, and patient education integrated into ERAS pathways and oral targeted-therapy programmes, as detailed in Nursing Roles in Pain Assessment, Symptom Surveillance and Adherence Support.[111]

Early integration of supportive and palliative care—extended to high-risk surgical candidates rather than confined to advanced disease—can further improve pain control, quality of life and care coordination.[112] Within resectable EGFR-mutant NSCLC, such multidisciplinary models ensure that decisions to continue, interrupt or adjust perioperative TKIs explicitly weigh tumour control against postoperative pain, functional recovery and patient preference.

Dose Modification, Treatment Interruption and Supportive-Care Decision Frameworks

Dose modification is a key tool in sustaining the efficacy–safety–pain–adherence loop. Decisions to reduce, interrupt or discontinue perioperative EGFR-TKIs should incorporate not only CTCAE grade but also patient-reported pain, functional interference and quality of life. Real-world studies show that a substantial proportion of patients receiving osimertinib require dose adjustment, yet moderate down-titration often preserves antitumour efficacy while improving tolerability.[113] Therapeutic drug monitoring, where available, may allow pre-emptive adjustment in high-exposure patients, limiting severe toxicity without compromising outcomes.[114]

From a pain-centred perspective, persistent grade 2 toxicities that cause clinically meaningful pain—numeric rating ≥4, sleep disruption or limitation of daily activities—should prompt early intervention with topical therapy, adjuvant analgesics and, if needed, temporary interruption or stepwise dose reduction, rather than waiting for grade 3 escalation.[115] Recent consensus recommendations advocate embedding patient-reported outcomes into dose-optimisation frameworks, recognising that clinician-graded adverse events frequently underestimate symptom burden.[116]

Patients at heightened risk of chronic postsurgical pain—those with severe acute postoperative pain, pre-existing chronic pain or psychological comorbidity—warrant tailored strategies linking perioperative pain pathways with EGFR-TKI management. These include structured preoperative risk screening, aggressive multimodal analgesia, early pain-specialist referral and predefined thresholds for reassessing dose or duration when pain worsens or function declines.[117]

This section populates the "safety" and "pain" axes and defines actionable thresholds that should feed back into adherence-preserving dose optimisation.

Real-World Tolerability, Adherence and Pain Burden with Perioperative EGFR-TKIs

Real-World Safety and Tolerability of Perioperative EGFR-TKIs

Outside clinical trials, the tolerability of perioperative EGFR-TKIs is increasingly described in national and multicentre cohorts. Real-world studies of adjuvant osimertinib in resected EGFR-mutant NSCLC confirm broadly ADAURA-like safety, with mostly low-grade adverse events and few treatment-related deaths.[118] However, UK and European datasets show that up to one-third of patients discontinue adjuvant osimertinib before the planned three years, most often because of cumulative toxicity, comorbidities or patient preference rather than disease progression, and with higher rates of dose reduction and early interruption than reported in trials.[119,120]

Although most registries lack granular pain data, several observations are directly relevant to pain and functional recovery. First, as outlined in Perioperative Pain Burden and Chronic Postsurgical Pain in Lung Cancer Surgery, chronic chest wall and shoulder pain are common long after lung resection and frequently have neuropathic features. This pre-existing pain may amplify perceived toxicity and contribute to non-completion of adjuvant perioperative EGFR-TKI therapy. Second, registry and ERAS-linked datasets indicate that failure to initiate or complete prescribed adjuvant

treatment is common and correlates with postoperative complications, poor recovery and high symptom burden, even in the absence of CTCAE grade ≥3 toxicity.[110] These findings suggest that real-world tolerability of perioperative EGFR-TKIs reflects not only intrinsic drug toxicity but also the background of post-thoracotomy pain, fatigue and psychosocial stress that shapes recovery from lung cancer surgery.

Pain, Analgesic Burden and Adherence to Perioperative EGFR-TKIs

Building on the adherence patterns described in Section 1.4, large claims and review data for EGFR-TKIs and other oral anticancer agents show that symptom burden—including pain, fatigue and nausea—is a key driver of missed doses and early discontinuation, with older age, female sex and polypharmacy identifying more vulnerable subgroups.[121]

A meta-analysis of healthcare professional–led adherence interventions showed that programmes integrating structured toxicity education, proactive symptom management and regular follow-up improved adherence compared with usual care, underscoring that symptom control—not reminders alone—is key to sustaining long-term oral therapy.[17] Qualitative studies in patients receiving EGFR-TKIs for advanced NSCLC report that chronic discomfort, skin and mucosal irritation and fear of cumulative toxicity often lead patients to "negotiate" treatment by skipping doses or shortening duration when pain and fatigue interfere with everyday life.[122]

Extrapolated to the perioperative context, these data imply that post-thoracotomy chest and shoulder pain, compounded by TKI-related cutaneous or oral pain, are likely important—and potentially modifiable—drivers of dose reduction, interruption and early discontinuation. Systematic assessment of pain intensity and functional interference, embedded within adherence monitoring, is therefore a core component of perioperative EGFR-TKI management and directly motivates the PRO- and nursing-based strategies discussed in Patient-Reported Outcome Tools and Digital Monitoring of Pain–5.4.

In the perioperative setting, post-thoracotomy pain and EGFR-TKI–related painful toxicities (paronychia, mucositis, myalgia/neuropathy) can jointly drive dose interruptions and non-persistence. Because adjuvant benefit depends on sustained exposure, pain interference with function should be treated as an early warning signal prompting protocolised supportive care and dose optimisation rather than a secondary comfort issue.

Patient-Reported Outcome Tools and Digital Monitoring of Pain

In routine care, patient-reported outcome (PRO) instruments provide practical tools to track perioperative pain and TKI-related symptoms. Generic oncology measures such as the EORTC QLQ-C30 and lung cancer–specific modules (QLQ-LC13/LC29) capture pain intensity, analgesic use and functional limitation, and have been widely used to characterise postoperative chest and shoulder pain trajectories.[123] The PRO-CTCAE library offers complementary coverage of treatment-related toxicities, including TKI-associated dermatologic and mucosal events, although certain symptom domains remain underrepresented.

Electronic PRO (ePRO) systems extend this approach beyond clinic visits. Randomised and quasi-experimental trials in lung cancer–surgery populations show that ePRO-based symptom monitoring—with or without integration of wearable-derived data—can improve pain control, reduce unplanned healthcare utilisation and enhance activity levels and patient satisfaction.[124]

For perioperative EGFR-TKIs, embedding brief pain assessments—such as daily or weekly numeric rating scales coupled with simple neuropathic screeners—into ePRO pathways offers a realistic means of linking dose adjustments and supportive care directly to evolving pain profiles, rather than relying solely on intermittent clinician-graded CTCAE evaluations. These data provide a rationale for integrating brief, pain-focused ePRO modules into perioperative EGFR-TKI pathways, as further detailed in the implementation framework in Multidisciplinary Collaboration and Key Perioperative Touchpoints.

For future perioperative EGFR-TKI trials, a pragmatic minimum set could include: (i) pain intensity and interference (numeric rating scale plus brief interference items), (ii) neuropathic pain screening when relevant, (iii) PRO-CTCAE items capturing painful dermatologic/mucosal toxicities, (iv) functional recovery metrics (return to baseline activity/work), and (v) adherence/persistence measures (dose interruptions, relative dose intensity, and time-to-discontinuation). Pre-specified thresholds should trigger protocolised supportive care and dose optimisation.

Nursing Roles in Pain Assessment, Symptom Surveillance and Adherence Support

Evidence from thoracoscopic lung-surgery cohorts shows that nurse-led pain assessment using validated scales and structured documentation improves recognition of undertreated pain and facilitates timely escalation of multimodal analgesia within ERAS pathways.[125] Postoperative protocols that combine early mobilisation, respiratory exercises and routine pain scoring enhance functional recovery and are associated with higher rates of initiation and completion of adjuvant systemic therapy.[126,127]

For oral targeted agents, including EGFR-TKIs, professional nursing guidelines recommend early (within 1–2 weeks) and ongoing monitoring of symptoms and adherence, with nurses leading education, toxicity counselling and refill checks.[128,129] In the perioperative EGFR-TKI setting, these principles translate into nurse-led workflows that link routine pain scores, skin and mucosal assessments and reports of fatigue or sleep disruption to predefined clinical algorithms—specifying when to intensify multimodal analgesia, when to trigger medical review and when to consider dose modification. These nurse-driven processes form a practical bridge between the pain- and adherence-focused evidence summarised in Safety, Pain-Related Tolerability and Supportive Care in Perioperative Targeted Therapy and Real-World Tolerability, Adherence and Pain Burden with Perioperative EGFR-TKIs and the multidisciplinary implementation strategies outlined in Clinical and Nursing Implementation of an Efficacy–Safety–Pain–Adherence Framework.

Integrative Strategies and Practical Implications

Taken together, emerging real-world data, PRO-based symptom monitoring and nurse-led adherence programmes indicate that tolerability, pain control and treatment continuity must be managed as a single, integrated domain in perioperative EGFR-TKI therapy. These insights provide the practical foundation for the efficacy–safety–pain–adherence framework and multidisciplinary implementation models developed in Clinical and Nursing Implementation of an Efficacy–Safety–Pain–Adherence Framework.

Real-world discontinuation and symptom burden illustrate the "adherence" axis, supporting the need for ePRO-driven monitoring to close the loop.

Clinical and Nursing Implementation of an Efficacy–Safety–Pain–Adherence Framework

From Drug Development to Bedside: A Closed-Loop Model

As summarised in Adjuvant EGFR-TKIs After Complete Resection of EGFR-Mutated NSCLC–3.4, perioperative use of third-generation EGFR-TKIs such as osimertinib has become a standard component of curative-intent care in resected EGFR-mutated NSCLC, and ctDNA-based MRD studies together with perioperative trials like NeoADAURA are reshaping expectations around duration, sequencing and risk-adapted use.[130]

Within this evolving landscape, an efficacy-focused paradigm is no longer sufficient. We therefore propose an efficacy–safety–pain–adherence framework (Figure 1) that explicitly links four domains—oncologic efficacy, toxicity, pain-related tolerability and long-term adherence—with bidirectional feedback between drug development, clinical trials and bedside practice. In this closed-loop model, perioperative treatment decisions are informed not only by stage, mutation subtype and MRD status, but also by baseline pain risk, prior pain history and patient-reported symptom trajectories.

Trial data indicate that long-term adjuvant osimertinib can maintain health-related quality of life despite chronic exposure, provided that toxicities are recognised early and managed proactively.[131] In this context, structured pain assessments and digital PRO tools embedded in routine care act as the monitoring backbone of the framework, enabling timely corrective actions rather than waiting until uncontrolled symptoms force irreversible treatment discontinuation (see Multidisciplinary Collaboration and Key Perioperative Touchpoints).

Practical Operationalisation of the Efficacy–Safety–Pain–Adherence Loop

To translate the proposed framework into clinical and trial workflows, perioperative care can be structured around four linked elements: baseline risk assessment, longitudinal monitoring, pre-specified intervention thresholds, and protocolised response pathways. Before treatment, teams should document pre-existing pain (including neuropathic features),

psychosocial vulnerability, and functional status, counsel expected EGFR-TKI toxicities, and agree on an adherence plan and contact pathway. During treatment initiation and early postoperative recovery, symptom capture should be more frequent (eg, weekly to biweekly), transitioning to at least monthly assessments during adjuvant therapy; monitoring should include pain intensity and interference, key EGFR-TKI toxicities, and missed doses. Clinically meaningful pain that interferes with sleep or daily activities, persistent low-grade toxicities with functional impact, recurrent missed doses, or red-flag cardiopulmonary symptoms should trigger early escalation of supportive care, including dermatologic and gastrointestinal management, neuropathic analgesics when appropriate, and timely referral to pain or regional-anaesthesia services, with MDT review for complex cases. Within this structure, ctDNA/MRD results may inform risk discussions and trial enrolment; however, MRD-guided de-escalation or intensification should be regarded as investigational and ideally implemented only within prospective protocols or clinical trials.

Multidisciplinary Collaboration and Key Perioperative Touchpoints

Enhanced Recovery After Thoracic Surgery (ERATS) programmes, summarised in Multidisciplinary Perioperative Pain Management and ERAS-Based Care Pathways, provide a natural backbone on which to integrate perioperative EGFR-TKI management and pain-focused interventions. However, current ERATS pathways rarely incorporate targeted therapy–specific toxicities or long-term pain trajectories.[132]

A dedicated perioperative multidisciplinary team (MDT) for resectable, EGFR-mutated NSCLC should therefore define explicit decision nodes along four key touchpoints—pre-treatment planning, the neoadjuvant window, the perioperative inpatient stay and the adjuvant follow-up phase—at which oncologists, thoracic surgeons, anaesthesiologists, pain specialists, pharmacists and nurses coordinate around both systemic therapy and pain management.

At the pre-treatment planning stage, MDT meetings can align on neoadjuvant versus adjuvant strategies, anticipated EGFR-TKI choice and timing of interruption and resumption around surgery, while concurrently documenting baseline pain, psychosocial factors and patient expectations.[133] During the neoadjuvant window, nurses and advanced practitioners can use standardised tools to track cutaneous, musculoskeletal and neuropathic symptoms, flagging patterns that may predict postoperative pain amplification or adherence challenges.

Examples of ERATS-aligned additions for patients receiving perioperative EGFR-TKIs include: standardised restart checklists (wound healing, oral intake, cardiopulmonary symptoms), drug–drug interaction screening with analgesics and perioperative medications, early dermatology/oral-care pathways for painful rash/mucositis, and discharge-to-home ePRO monitoring with pre-defined escalation rules.

During the perioperative inpatient stay, ERATS elements (regional anaesthesia, scheduled non-opioid analgesia, early mobilisation, respiratory physiotherapy) should be tailored to the presence of concurrent or recent EGFR-TKI exposure—for example, considering drug–drug interactions with non-steroidal anti-inflammatory drugs, steroids or neuropathic agents, and ensuring wound-healing assessment before restarting TKIs.[134] In the adjuvant phase, MDT visits can synchronise ctDNA/MRD results with structured review of pain and functional recovery; patients with MRD positivity and high pain burden may require intensified supportive care and closer analgesic follow-up to sustain adherence to prolonged TKI therapy. Implementation of such MDT-based pathways is demanding, but nursing and allied-health leadership, together with institutional guidelines such as the AORN-enhanced recovery recommendations, can translate high-level ERATS principles into daily bedside practice.[135]

Nursing Data, Digital Tools and the "Smart Ward"

Meta-analyses and lung cancer–specific studies, summarised in Sections 1.4 and 5.3, show that ePRO-based symptom-monitoring programmes can improve health-related quality of life, reduce hospitalisations and, in some settings, prolong survival when used to trigger timely clinical responses. As outlined in From Drug Development to Bedside: A Closed-Loop Model, combining structured pain assessments with ePRO-based symptom monitoring provides the core clinical signals within the efficacy–safety–pain–adherence framework. These findings align with expert guidance from oncology societies, which now regard remote ePRO monitoring as a component of high-quality cancer care.[136] Within this landscape, nurses are central to operationalising a pain-centred, adherence-sensitive perioperative pathway.

In a "smart ward" model for perioperative EGFR-mutated NSCLC, nursing teams can use ePRO platforms integrated into the electronic health record to capture pain scores, neuropathic symptoms, functional status and TKI-specific adverse events during neoadjuvant or adjuvant therapy and after discharge. Large multi-centre implementation projects such as the SIMPRO consortium emphasise that successful deployment depends on workflow redesign, shared response protocols and institutional support rather than technology alone.[137] Within this framework, nurses often act as first-line responders to red-flag alerts—such as rapidly escalating chest wall pain, uncontrolled neuropathic symptoms or skin/mucosal pain that interferes with function—initiating protocolised dose modifications, arranging earlier MDT review or activating specialised pain services.

At the same time, smart ward infrastructure enables structured data capture at scale. Routine aggregation of pain scores, rescue-analgesic use, unscheduled contacts and missed or delayed EGFR-TKI doses can be used to refine institutional thresholds for intervention, identify high-risk phenotypes (eg patients with persistently high pain despite good oncologic response) and contribute anonymised data to registries and pragmatic real-world evidence studies. In this way, nursing-led digital monitoring functions both as a clinical tool and as a research engine, reinforcing the efficacy–safety–pain–adherence loop between bedside experience and future trial and guideline development.

Implementation barriers include variable access to tumour-informed ctDNA assays, cost and turnaround time, infrastructure for longitudinal blood draws and data integration, and the workforce burden of responding to ePRO alerts. Digital literacy and language barriers may also affect engagement. These constraints support stepwise deployment with clear response protocols, prioritisation of high-risk patients, and prospective evaluation of feasibility and cost-effectiveness.

Conclusion

Perioperative EGFR-targeted therapy is transforming curative-intent care for resectable EGFR-mutated NSCLC, but prolonged treatment introduces chronic toxicity and pain that can erode adherence and real-world benefit. ADAURA demonstrates that adjuvant osimertinib can deliver substantial survival gains with manageable toxicity when symptoms are proactively monitored. Elevating pain from a secondary "comfort" issue to a core determinant of treatment success—and embedding it within an efficacy–safety–pain–adherence framework (the proposed loop)—may help translate trial efficacy into better lived survivorship; MRD-guided tailoring of duration should remain limited to prospective protocols/trials. As a narrative review, selection bias cannot be fully excluded, and evidence strength varies across domains.

Abbreviations

ALK, Anaplastic lymphoma kinase; CNS, Central nervous system; CPSP, Chronic postsurgical pain; ctDNA, Circulating tumour DNA; DFS, Disease-free survival; EGFR, Epidermal growth factor receptor; EGFR-TKI, Epidermal growth factor receptor tyrosine kinase inhibitor; EFS, Event-free survival; ERAS, Enhanced Recovery After Surgery; ERATS, Enhanced Recovery After Thoracic Surgery; ePRO, Electronic patient-reported outcome; HR, Hazard ratio; HRQoL, Health-related quality of life; ILD, Interstitial lung disease; KRAS, KRAS proto-oncogene, GTPase; MDT, Multidisciplinary team; MET, MET proto-oncogene, receptor tyrosine kinase; MPR, Major pathological response; MRD, Minimal residual disease; NSCLC, Non-small cell lung cancer; ORR, Objective response rate; OS, Overall survival; pCR, Pathological complete response; PRO, Patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; R0, Complete microscopic resection; RET, REarranged during transfection proto-oncogene; RWE, Real-world evidence; TKI, Tyrosine kinase inhibitor.

Data Sharing Statement

Data sharing is not applicable to this article as no new datasets were generated or analyzed. All data discussed are from previously published studies cited in the references.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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