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Activation of Prodrugs Depend on the Metabolism of These Prodrugs

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Abstract

Prodrugs depend on enzymatic processes, essentially in the liver, but can also occur in other tissues to release the active metabolite. These metabolic biotransformations are often enzymatically controlled, ensuring the drug becomes pharmacologically active at its site of action. Metabolism may occur at the target site (e.g., in viruses, where drugs are phosphorylated) or in the liver or other tissues. For example, codeine is activated by demethylation to morphine, which is a more active analgesic than codeine. Clopidogrel oxidized to 2-oxoclopidogrel which is active and 2-oxoclopidogrel which is metabolized in two active thiol metabolite. Enalapril is a prodrug that is metabolized to enalaprilat, the active form. L-Dopa is a prodrug that is converted into dopamine in the brain by decarboxylation. Azathioprine is metabolized to mercaptopurine, which is immunosuppressive. Sulfasalazine is a prodrug metabolized by azoreductase and converted to 5-aminosalicylic acid and sulfapyridine, which are more active than sulfasalazine. Prontosil is a prodrug converted into sulfanilamide, which is more active than prontosil. Salicin is a glycoside that is metabolized into salicylic acid, which is active as an analgesic. Valacyclovir is metabolized into acyclovir, which is an active antiviral.

Keywords: prodrugs, active drugs, metabolism, oxidation, hydrolysis, dealkylation

1. Introduction

Codeine is a narcotic drug when metabolized by dealkylation (demethylation), of codeine, which is used as antitussive more than analgesic when metabolized by oxidative dealkylation convert into morphine which used a narcotic analgesic more than codeine. This process activates the codeine by changing it into morphine and makes it more active than codeine.

Clopidogrel is a prodrug, meaning it is inactive needs to be metabolized into an active form to be effective, this process occur in the liver, where is

the clopidogrel oxidized in clopidogrel which further metabolized to the active thiol metabolite, this metabolite (thiol metabolite) binds to receptor on platelets which inhibit ADP from binding and preventing platelet aggregation.

Enalapril is a prodrug metabolized in the liver by its active form, enalaprilat, which is an ACE inhibitor that is currently available in USA. The metabolism occurs via cleavage of its ester group by the esterase enzyme and converts enalapril to enalaprilat, which is active as an ACE inhibitor.

Levodopa is a prodrug which is able to cross blood-brain barrier due to resemble amino acid; so penetrate to the brain, hence L-Dopa metabolized through several pathways, the decarboxylation it is the main process where L-Dopa convert to dopamine which is unable to cross the blood-brain barrier; so that L-Dopa which is prodrug is preferable to used in treatment of parkinsonism.

Azathioprine is an immunosuppressant that undergoes metabolism in the body through multiple pathways, primarily converting to 6-mercaptopurine, further metabolized by various enzymes into an active metabolite via the hypoxanthine phosphoribosyl transferase pathway, where 6-mercaptopurine is converted into its metabolite form 6-thioguanine nucleotide, which is incorporated into DNA and RNA, disrupting cellular processes and causing immunosuppression.

Sulfasalazine is a prodrug which used orally and inactive compound which is metabolized (hydrolyzed) in the intestine and convert into two active compounds (sulfapyridine) which is antibacterial and 5-amino salicylic acid which is anti-inflammatory, the 5-amino salicylic acid not absorbed from intestine and remain in the colon to treat the ulcerative colitis, in addition to antibacterial agent sulfapyridine.

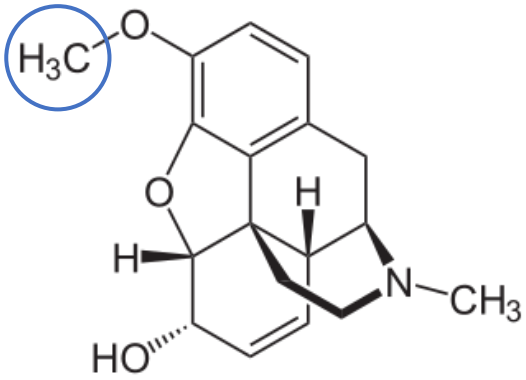
Prontosil is the compound which is revolute the sulfa drugs era where it is a red dye act as a prodrug i.e. inactive invitro but in vivo metabolized where it reduced by reductase enzyme which result from intestinal flora and cleavage the prontosil into sulfanilamide which is active antibacterial and the first sulfa drug detected and try amino benzene, the other compound resulted from prontosil.

Salicin found in willow park is metabolized into salicylic acid and sugar part where the salicin is a glycoside (sugar part and non-sugar part), the salicylic acid is non-sugar part which has anti-inflammatory and analgesic properties, the cleavage of salicin in gastrointestinal tract and the salicylic acid is metabolized via bind with glycine and form salicyluric acid which is easily excreted, which easily detected in the urine.

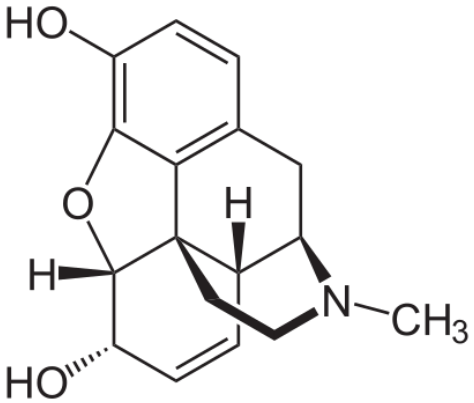
Valacyclovir is a prodrug which converted to acyclovir and L-Valine through first pass intestinal and/or hepatic metabolism, acyclovir is the active drug which is also activated by phosphorylation to act as antiviral drug, and β-Lactamase inhibitors e.g., penicillins and cephalosporins, many of them are considered as prodrugs, e.g., ampicillin and amoxicillin, where the amino group of ampicillin may be metabolized via oxidative deamination and converted to benzylpenicillin (penicillin G). Also, amoxicillin, which has a phenolic OH and an amino group, may be converted to benzylpenicillin (penicillin G); hence, the metabolism of many drug derivatives may result in the lead drug of the class, e.g., penicillins and cephalosporins.

2. Pharmacology and Chemistry

(1) Codeine:



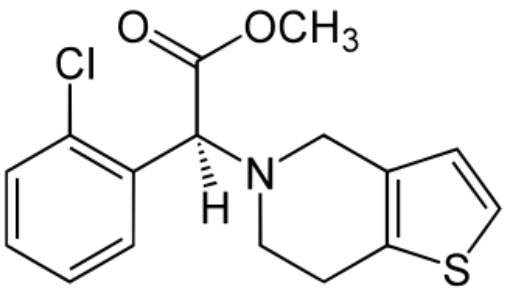
Codeine



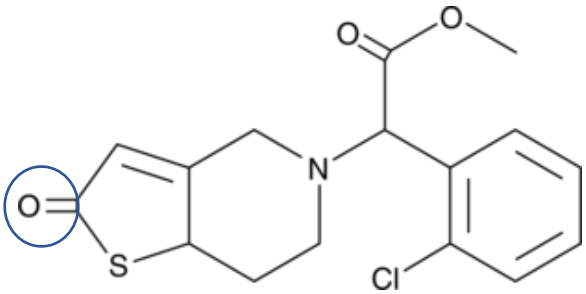
Morphine

Codeine is an opioid compound used to relieve mild and moderate pain in people who suffer from moderate pain and know respond to non-steroidal anti-inflammatory drugs (NSAIDs). Codeine is used to relieve cough and has a moderate analgesic compared to morphine; so codeine is metabolized by oxidative dealkylation and converted to morphine, which has more analgesic activity than codeine.

(2) Clopidogrel:



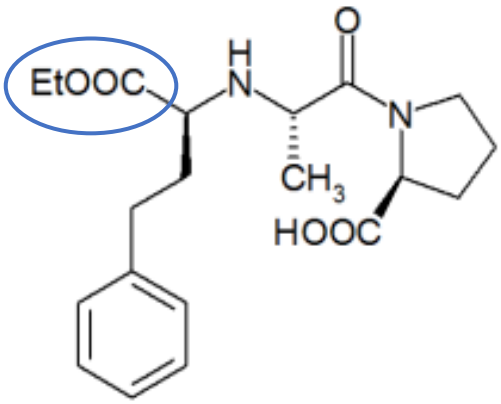
Clopidogrel



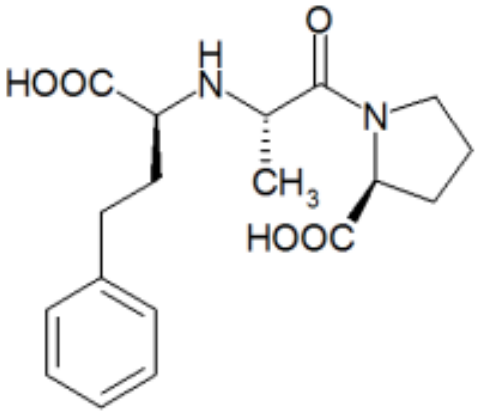
Oxoclopidogrel

Clopidogrel is metabolized into oxoclopidogrel, which is active as an antiplatelet clopidogrel approved for managing unstable angina which may cause myocardial infarction (MI), where the oxoclopidogrel prevents platelet aggregation and inhibits clot formation. In addition, into the fibrinolytic of the oxoclopidogrel which is more active than clopidogrel.

(3) Enalapril:



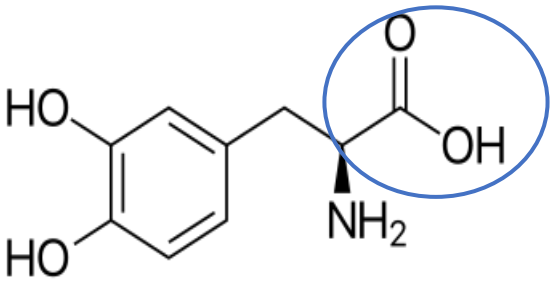
Enalapril



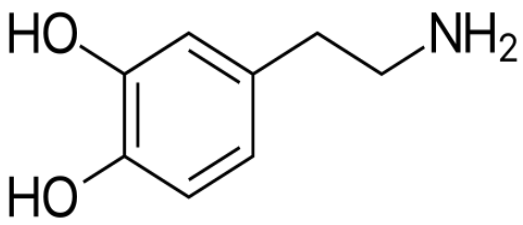
Enalaprilat

Enalapril is an angiotensin-converting enzyme inhibitor (ACE I) which converts into enalaprilat, the active metabolite, which treat the hypertension via inhibit the vasoconstriction of blood vessels; hence increases the blood supply and oxygen to the heart.

(4) L-Dopa:



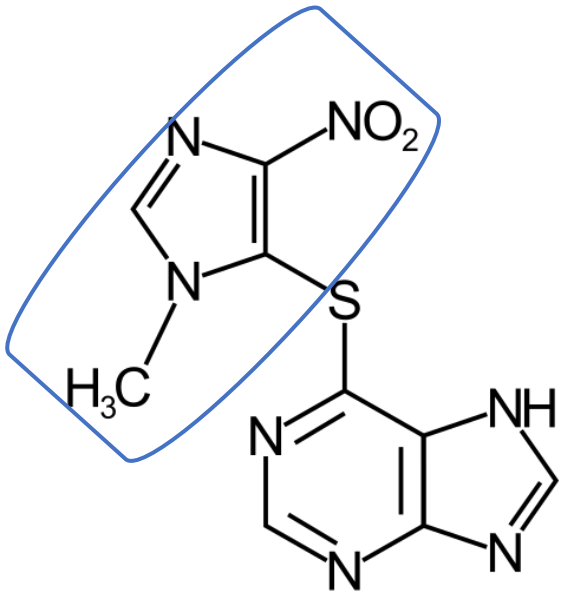
L-Dopa



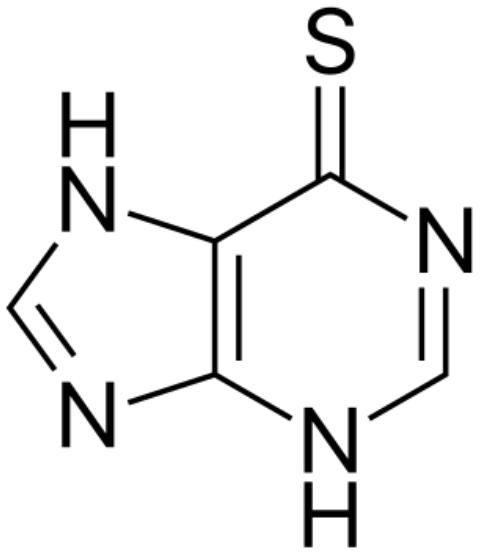
Dopamine

L-Dopa used to treat the motor symptoms of Parkinson's disease, L-Dopa is similar to amino acids; hence carried by amino acid carrier and cross blood-brain barrier, dopamine is lipophilic more than L-Dopa and not cross the blood-brain barrier; so the L-Dopa metabolized in the brain by decarboxylase enzyme and converted to dopamine which treated the parkinsonism where helps to alleviate symptoms like tremor, stiffness, and slow movements and may treat encephalitis or brain injury which maybe cause parkinsonism.

(5) Azathioprine:



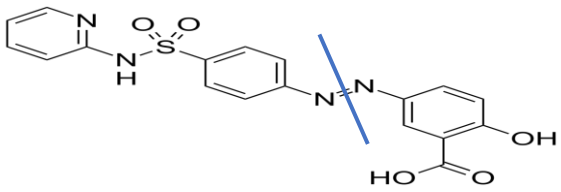
Azathioprine



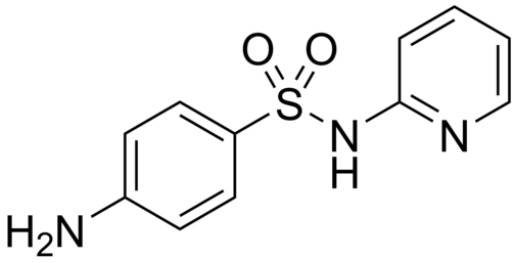
6-Mercaptopurine

Azathioprine is an immunosuppressive after metabolized into 6-mercaptopurine. It is used to treat rheumatoid arthritis, and granulomatosis with polyangiitis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus (SLE) and in kidney transplant to prevent rejection; hence, as azathioprine is considered a prodrug needs to be metabolized to active 6-mercaptopurine.

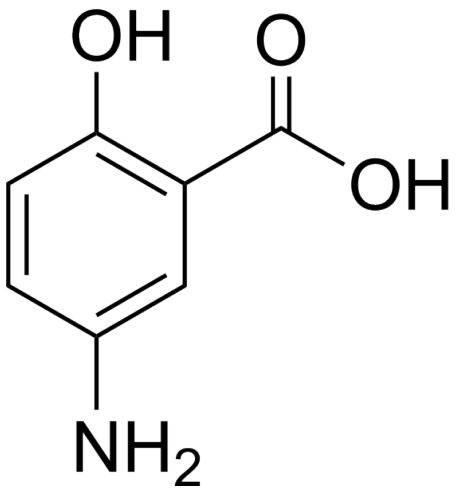
(6) Sulfasalazine:



Sulfasalazine



Sulfapyridine

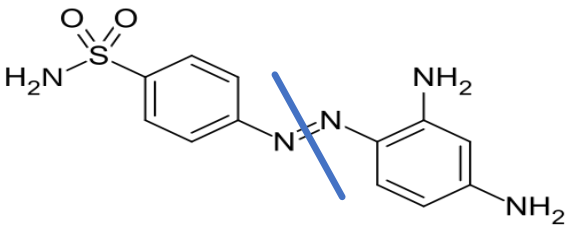


5-aminosalicylic acid

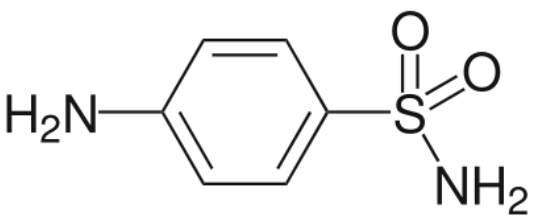
Sulfasalazine is a prodrug that needs to be cleaved between the two nitrogen to result in 5-aminosalicylic acid, which is anti-inflammatory and analgesic, and sulfapyridine, which is antibacterial.

Sulfasalazine is used in the treatment of inflammatory bowel disease, including ulcerative colitis and Crohn's disease. It is also indicated for use in rheumatoid arthritis and used in other types of inflammatory arthritis, e.g., psoriatic arthritis and reactive arthritis; so the sulfasalazine inactive prodrug needs to be activated by metabolism to become active compounds.

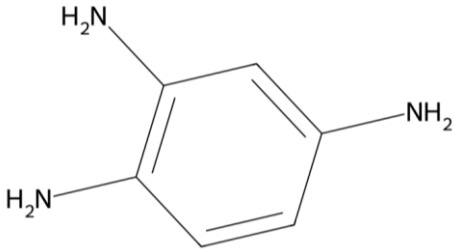
(7) Prontosil:



Prontosil



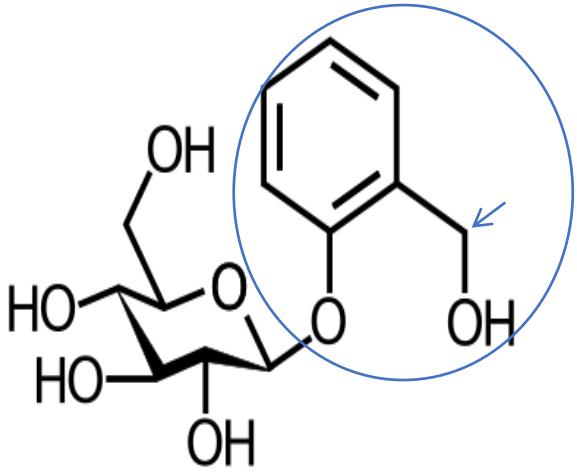
Sulfanilamide



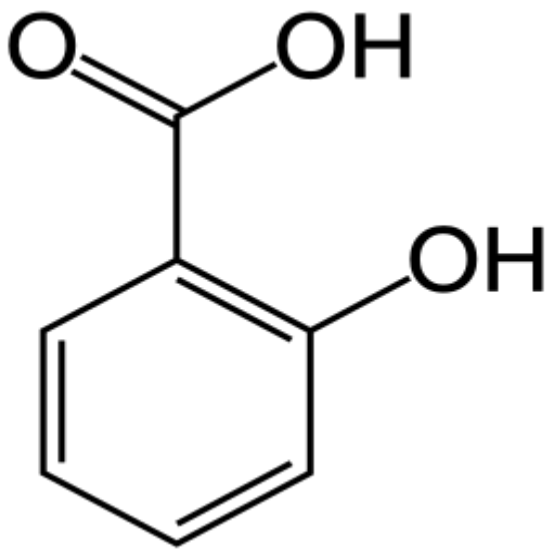
1,2,4-Triaminabenzene

Prontosil is sulfonamide antibacterial was one of the first effective drugs for treating bacterial infections caused by streptococci, it works by being converted in the body to sulfanilamide through metabolism by azoreductase enzyme; hence, sulfanilamide which resulted from prontosil inhibit the folic acid synthesize required for the growth and division of bacteria. Sulfanilamide was initially effective in puerperal fever and meningitis caused by meningococcus.

(8) Salicin:



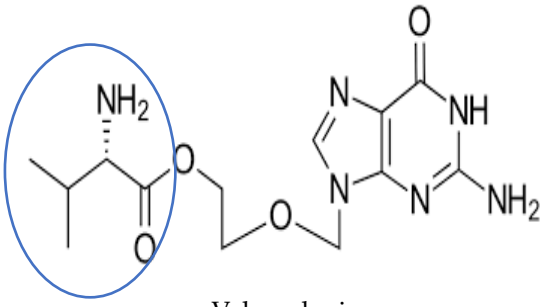
Salicin



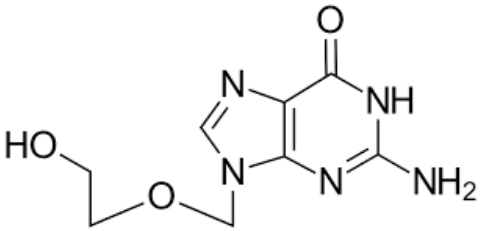
Salicylic acid

Salicin is a glycoside obtained from Salix, which is used in medicine for the relief of pain and inflammation, where it is precursor to salicylic acid, which is used in the treatment. Salicin is a prodrug that needs activation through cleavage of the glycosidic linkage between the glycone part and aglycon part, which is active, but salicin as is inactive. Salicin is used to reduce cartilage degeneration in osteoarthritis, potentially slowing disease progression the Salicylic acid also has a role in reducing the risk of cardiovascular diseases. Salicin has neuroprotective properties.

(9) Valacyclovir:



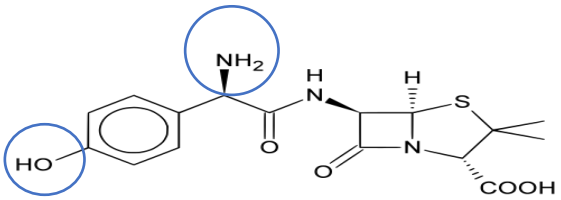
Valacyclovir



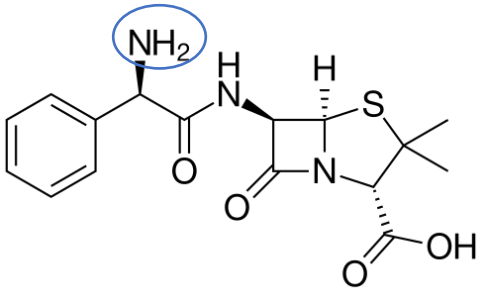
Acyclovir

Valacyclovir is a prodrug need to activate into an acyclovir through break valacyclovir into valine amino acid and acyclovir, which used in treatment of herpes virus infections including herpes labialis, also known as cold sores, herpes zoster also known as shingles, and herpes simplex also known as genital herpes in adults, it is also used to treat chicken pox and cold sores in children; hence valacyclovir is inactive when metabolized into acyclovir become active, further activated through phosphorylation.

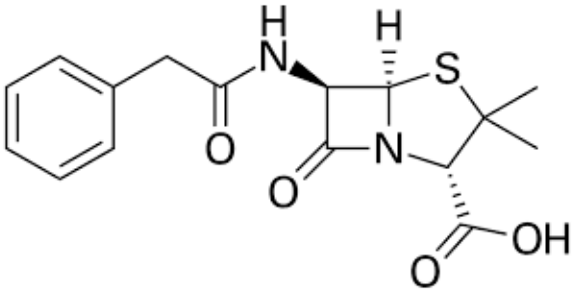
(10) Ampicillin and amoxicillin:



Amoxicillin



Ampicillin



Benzylpenicillin

Ampicillin and amoxicillin are active prodrugs which are metabolized into benzylpenicillin become has longer duration (Ampicillin and Amoxicillin) more than benzylpenicillin, in this case the ampicillin and amoxicillin when metabolized retained with antibacterial properties, the penicillin used in treatment of a wide range of bacterial infection including those of the skin, throat, lungs and urinary tract maybe

used in treatment of pneumonia, air infections, dental abscesses and some sexually transmitted diseases (STD) in some cases penicillin can be uses to prevent rheumatic fever following streptococcal infection, the penicillins inhibit the cell wall of bacteria via inhibits the formation of peptidoglycan cross linkage; hence weakening the cell wall and cause bacterial rupture.

3. Conclusion

The pharmacological and biochemical significance of prodrugs, demonstrating how inactive or less active compounds are metabolically transformed into therapeutically active agents. Prodrugs such as codeine, clopidogrel, enalapril, levodopa, azathioprine, sulfasalazine, prontosil, salicin, valacyclovir, and certain β-lactam derivatives undergo specific metabolic pathways—oxidative dealkylation, enzymatic cleavage, reduction, phosphorylation, or ester hydrolysis—that enhance their bioavailability, selectivity, and therapeutic efficacy.

This metabolic activation allows for improved pharmacokinetics, targeted drug delivery, reduced adverse effects, and expanded clinical applications. Examples include levodopa's ability to cross the blood–brain barrier before conversion to dopamine for Parkinson's disease management, sulfasalazine's site-specific release of anti-inflammatory and antibacterial components in the colon, and clopidogrel's conversion to an active thiol metabolite for antiplatelet activity.

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Structural and Functional Neuroimaging in Major Depressive Disorder with Suicidal Ideation: A Review

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Abstract

Major depressive disorder with suicidal ideation (MDD-SI) represents a clinically high-risk subtype of depressive disorders characterized by marked neurobiological heterogeneity and has become a major focus of suicide prevention and precision intervention research. In recent years, neuroimaging studies have increasingly demonstrated that patients with MDD-SI exhibit distinct structural and functional brain alterations compared with depressed patients without suicidal ideation. These abnormalities primarily involve the prefrontal–cingulate–limbic system, the default mode network (DMN), and reward-related circuits. With the growing number of longitudinal neuroimaging studies, accumulating evidence suggests that biological treatments—particularly electroconvulsive therapy (ECT)—not only lead to significant reductions in depressive symptoms and suicidal ideation but also induce measurable structural and functional plasticity in these key brain regions and networks.

Structural MRI studies indicate that, at baseline, patients with MDD-SI commonly show gray matter abnormalities in regions such as the anterior cingulate cortex, prefrontal cortex, and hippocampus. Following ECT treatment, regionally selective structural changes have been observed, most notably hippocampal volume increases and structural recovery in the anterior cingulate cortex and ventromedial prefrontal cortex. Functional neuroimaging studies further demonstrate that treatment-related reductions in suicidal ideation are accompanied by enhanced prefrontal–limbic regulatory control, normalization of anterior cingulate cortex function, and suppression of excessive self-referential processing within the DMN. Collectively, these findings suggest that treatment-related neuroimaging changes may constitute an important neural substrate underlying the improvement of suicidal ideation.

This review summarizes current structural and functional neuroimaging findings in patients with MDD-SI before and after treatment, with particular emphasis on treatment-related plasticity in key brain regions and networks. Furthermore, an integrative conceptual framework—linking baseline structural abnormalities, treatment-induced neuroplasticity, and the alleviation of suicidal ideation—is proposed to provide insights for future research on imaging-based predictive biomarkers and the neurobiological mechanisms underlying treatment response.

Keywords: major depressive disorder, suicidal ideation, neuroimaging, functional magnetic resonance imaging, therapy

1. Introduction

Major depressive disorder (MDD) is a mood disorder characterized by persistent depressed mood and/or a marked loss of interest or pleasure. It is one of the most representative and disabling conditions within the spectrum of depressive disorders (Association, 2013; Malhi & Mann, 2018).

Major depressive disorder (MDD) shows considerable clinical heterogeneity (Kessler et al., 2003). According to symptom severity, MDD can be classified as mild, moderate, or severe; based on clinical features, it may also present with psychotic features, anxious distress, mixed features, or somatic symptoms (Association, 2013). Major depressive disorder (MDD) is strongly associated with an increased risk of suicide, with approximately 60% of suicide deaths linked to depressive disorders (Turecki & Brent, 2016). Suicidal ideation and a history of suicide attempts are important indicators of disease severity and poor prognosis (Mann et al., 2005).

Major depressive disorder with suicidal ideation (MDD-SI) refers to a clinical condition in which individuals meeting the diagnostic criteria for major depressive disorder experience persistent or recurrent suicidal thoughts during depressive episodes (Association, 2013; Turecki & Brent, 2016). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Association, 2013), suicidal ideation is one of the core symptoms of a major depressive episode and includes both passive wishes for death and active suicidal thoughts, such as recurrent thinking about suicide methods or plans.

Accumulating evidence indicates that suicidal ideation not only reflects the severity of depression but also represents a key clinical indicator for predicting suicidal behavior and adverse outcomes (Ribeiro, Huang, Fox, & Franklin, 2018). Compared with depressed patients without suicidal ideation (MDD-nSI), individuals with MDD-SI generally show more severe depressive symptoms, particularly depressed mood, hopelessness (Ribeiro et al., 2018) and anhedonia (Ballard et al., 2017), and are often accompanied by pronounced negative cognitive biases, such as rumination, feelings of worthlessness, and excessive guilt. Epidemiological studies indicate that approximately 40%–70% of patients with major depressive disorder experience suicidal ideation at some point during their lifetime (Cai et al., 2021). Persistent or recurrent suicidal ideation is widely regarded as one of the most robust risk factors for suicide attempts and suicide deaths (Turecki & Brent, 2016). Depressive disorders are also among the psychiatric conditions most strongly associated with suicide, and more than half of individuals who die by suicide have a history of depressive disorders (Turecki & Brent, 2016).

The assessment of suicidal ideation varies across studies, and commonly used instruments include the Beck Scale for Suicide Ideation (BSSI) (Beck, Kovacs, & Weissman, 1979), the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011) and suicide-related items from depression rating scales(Guo et al., 2024), such measurement heterogeneity may affect the comparability of findings across studies.

Increasing evidence suggests that suicidal ideation is not merely an epiphenomenon of depression severity but may represent a depressive subtype with relatively distinct psychological and neurobiological underpinnings (Schmaal et al., 2020). Neuroimaging studies have shown that patients with MDD accompanied by suicidal ideation exhibit distinct structural and functional abnormalities in the prefrontal–limbic system, emotion regulation networks, and reward-related brain regions (Schmaal et al., 2020). These alterations may be closely associated with impaired impulse control, dysregulation of negative emotions (Turecki & Brent, 2016), and pessimistic expectations about the future (Ribeiro et al., 2018). Therefore, investigating major depressive disorder with suicidal ideation as a distinct research focus may help to better understand the heterogeneity of depressive disorders and provide important insights into the neural mechanisms underlying suicide risk.

The treatment of major depressive disorder should follow a stratified, individualized, and sequential framework of comprehensive interventions (Lam et al., 2024). Treatment decisions should take into account multiple factors, including symptom severity, the presence of psychotic features or suicide risk, previous treatment response, medical and psychiatric comorbidities, and patient preferences (Health & Excellence, 2022). Overall, pharmacotherapy constitutes the first-line intervention for patients with moderate-to-severe and severe major depressive disorder. In cases

where symptoms are severe, rapid treatment response is required, or pharmacological treatment is ineffective, intensified biological treatments such as electroconvulsive therapy (ECT) may be considered (Lam et al., 2024). Throughout the treatment process, continuous management across the acute, continuation, and maintenance phases is emphasized to achieve symptom remission and reduce the risk of relapse (Bauer et al., 2015).

With the development of longitudinal neuroimaging studies, accumulating evidence suggests that biological treatments not only significantly alleviate depressive symptoms and suicidal ideation but also induce structural and functional plasticity in key brain regions. Therefore, systematically summarizing the structural and functional neuroimaging findings in patients with major depressive disorder with suicidal ideation before and after treatment is of great importance for understanding the neural mechanisms underlying suicidal ideation. This review aims to summarize the neuroimaging abnormalities observed in patients with MDD-SI and to highlight treatment-related imaging changes and their potential neural mechanisms, with the goal of providing insights for future research on imaging-based predictive biomarkers and precision interventions.

2. Neuroimaging Characteristics of MDD-SI

2.1 Structural Neuroimaging Alterations

Structural abnormalities are primarily distributed within the prefrontal–limbic system, which plays a crucial role in key psychological processes such as emotion regulation, impulse control, and value evaluation (Schmaal et al., 2020).

The prefrontal cortex is one of the most consistently reported abnormal regions in studies of MDD-SI (Schmaal et al., 2020). Several voxel-based morphometry (VBM) and cortical thickness studies have demonstrated reduced gray matter volume or cortical thickness in the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), and ventromedial prefrontal cortex (vmPFC), with these alterations being particularly pronounced in patients with MDD who have suicidal ideation or a history of suicidal behavior (Ding et al., 2015). These regions play a critical role in emotion regulation, impulse control, and future value evaluation (Haber & Knutson, 2010), and structural impairments in these areas may reduce individuals' cognitive control over negative emotions and suicidal impulses (Turecki & Brent, 2016).

The anterior cingulate cortex (ACC) (Xia, Wu, Wang, Zhou, & Zhang, 2025), particularly the rostral and dorsal ACC, is widely considered a key neural hub integrating emotional processing and cognitive control (Shackman et al., 2011). Structural MRI studies have reported a higher prevalence of ACC gray matter reduction or cortical thinning in patients with MDD-SI compared with depressed patients without suicidal ideation (H. Li et al., 2021; Wagner et al., 2011). Structural abnormalities of the ACC may be associated with increased feelings of hopelessness, impaired regulation of emotional conflict, and suicide-related rumination (Mann, 2003).

Within the limbic system, structural alterations of the amygdala (Cong et al., 2022) and hippocampus (Xu et al., 2023) have been repeatedly reported in patients with MDD-SI. Some studies have found that depressed patients with suicidal ideation or a history of suicide attempts exhibit reduced amygdala volume (Cong et al., 2022), suggesting abnormalities in emotional reactivity and threat processing. Meanwhile, hippocampal volume reduction is also commonly observed (Gosnell et al., 2016), which may be associated with chronic stress (Sapolsky, 2000), dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (Pariante & Lightman, 2008), and negative biases in emotional memory (Gotlib & Joormann, 2010).

In addition to cortical and limbic structures, several studies have also reported volumetric alterations in subcortical regions such as the striatum (Ho et al., 2021), thalamus (Kang et al., 2020), and insula (Schmaal et al., 2020). These regions are involved in reward processing, interoception, and the perception of distress. Overall, structural abnormalities in patients with MDD-SI are unlikely to occur in isolation but rather reflect a broader imbalance between emotion regulation and cognitive control networks (Marchand et al., 2012).

2.2 Functional Neuroimaging Alterations

Functional neuroimaging studies indicate that patients with MDD-SI exhibit significant functional abnormalities in neural networks involved in emotion regulation (V. C. Chen et al., 2021), cognitive control (Ouyang et al., 2022), self-referential processing (Ouyang et al., 2022), and

reward processing (Qiao et al., 2020).

In both task-based and resting-state functional magnetic resonance imaging (fMRI) studies, patients with MDD-SI commonly exhibit reduced regulatory control of the prefrontal cortex over the limbic system (Pu et al., 2015). Specifically, decreased activity has been observed in the dorsolateral prefrontal cortex (DLPFC) and the ventromedial/orbitofrontal prefrontal cortex (vmPFC/OFC) (Kim et al., 2017), whereas the amygdala shows hyperactivation in response to negative emotional stimuli (Victor, Furey, Fromm, Ohman, & Drevets, 2010). Compared with depressed patients without suicidal ideation (MDD-nSI), individuals with MDD-SI more frequently exhibit weakened or dysregulated functional connectivity between the prefrontal cortex and the amygdala (Li et al., 2022), which may contribute to heightened negative emotional responses and reduced impulse control.

The anterior cingulate cortex (ACC) is one of the most frequently reported abnormal regions in functional neuroimaging studies of MDD-SI (M. Zhang et al., 2025). Studies have shown that patients with MDD-SI exhibit abnormalities in resting-state activity of the ACC (M. Zhang et al., 2025) as well as in its functional connectivity with the prefrontal cortex and limbic system (Du et al., 2017). Network abnormalities involving the dorsal ACC (dACC), which have been associated with suicidal behavior, may be related to dysfunction in conflict monitoring and error detection processes (Minzenberg, Lesh, Niendam, Cheng, & Carter, 2016).

Resting-state fMRI studies have demonstrated significant abnormalities in the default mode network (DMN) in patients with MDD-SI, particularly increased functional connectivity among the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and precuneus (M. Zhang et al., 2025). Compared with depressed patients without suicidal ideation (MDD-nSI), individuals with MDD-SI show more pronounced DMN hyperactivity or enhanced internal connectivity (Wei et al., 2018). These abnormalities are thought to be closely associated with excessive self-focus, rumination, and negative self-evaluation (Hamilton, Farmer, Fogelman, & Gotlib, 2015), and may represent an important neural basis underlying the persistence of suicidal ideation.

In task-based fMRI studies involving reward processing and decision-making, suicide-related depressive populations (including individuals with suicidal ideation and suicide-related subgroups) commonly exhibit reduced responsiveness in the ventral striatum, orbitofrontal cortex (Jollant, Lawrence, Olié, Guillaume, & Courtet, 2011), and other prefrontal regions. Compared with depressed patients without suicidal ideation (MDD-nSI), individuals with MDD-SI show blunted neural responses to positive stimuli and reward feedback. These findings suggest that anhedonia and impaired future value evaluation may play a key role in the development of suicidal ideation (Schmaal et al., 2020).

3. Treatment-Related Neuroimaging Changes in MDD-SI

3.1 Treatment-Related Structural Brain Changes

In recent years, longitudinal structural MRI studies have indicated that some depression- and suicide-related structural abnormalities in patients with MDD-SI may be reversible following effective treatment (Tendolkar et al., 2013), suggesting that structural brain plasticity may represent an important neural basis underlying clinical improvement, particularly the alleviation of suicidal ideation. Current evidence is mainly derived from studies of electroconvulsive therapy (ECT), whereas structural neuroimaging studies examining pharmacological treatments with suicidal ideation as an outcome remain relatively limited (Vieira, Faria, Ribeiro, Picó-Pérez, & Bessa, 2023).

The hippocampus represents one of the most consistently reported regions exhibiting treatment-related structural changes (Wilkinson, Sanacora, & Bloch, 2017). Multiple longitudinal MRI studies have demonstrated that hippocampal volume significantly increases following ECT in patients with MDD, including those with suicidal ideation (Nordanskog et al., 2010; Tendolkar et al., 2013), and the magnitude of this increase has been associated with improvements in certain clinical symptoms, including reductions in suicidal ideation (Nordanskog, Larsson, Larsson, & Johanson, 2014). Given that patients with MDD-SI often exhibit more pronounced hippocampal atrophy(Xu et al., 2023), this “reverse plasticity” has been suggested to reflect the restorative effects of ECT on stress-related neurotoxicity and impaired neurogenesis (Duman & Aghajanian, 2012).

In the anterior cingulate cortex (ACC) (Pirnia et

al., 2016) and certain prefrontal regions, such as the orbitofrontal cortex (OFC) (Gbyl et al., 2019), increases in gray matter volume or cortical thickness have also been observed following ECT. These regions represent key structural nodes that show the most pronounced differences between patients with MDD-SI and those without suicidal ideation (MDD-nSI) (Yi et al., 2025). The treatment-related structural changes in these areas suggest that ECT may reduce the persistence of suicide-related thoughts by reshaping critical hubs involved in emotion regulation and cognitive control (Pirnia et al., 2016; Yi et al., 2025).

Notably, ECT-related structural changes are not diffusely distributed across the entire brain but rather exhibit regional specificity (Mulders et al., 2020), primarily involving the prefrontal–cingulate–limbic system (Pirnia et al., 2016). Some studies have suggested that patients with more pronounced baseline structural abnormalities (e.g., smaller hippocampal volume (Joshi et al., 2016) tend to show greater structural recovery and clinical improvement following ECT. This finding may have potential value in predicting treatment response in patients with MDD-SI (Cao et al., 2018).

Compared with ECT, structural MRI evidence related to pharmacological treatment (antidepressants) remains relatively limited and inconsistent (Schmaal et al., 2016). A small number of longitudinal MRI studies suggest that sustained antidepressant treatment may be associated with stabilization or even modest increases in hippocampal volume. For example, in a 3-year follow-up study, patients who maintained antidepressant treatment exhibited increased left hippocampal volume (Frodl et al., 2008), whereas a longer duration of untreated depressive episodes was associated with hippocampal volume reduction (Sheline, Gado, & Kraemer, 2003). However, high-quality studies specifically focusing on patients with MDD-SI and using changes in suicidal ideation as the primary outcome are still lacking (Schmaal et al., 2020). Therefore, from the perspective of structural neuroimaging, ECT remains the intervention with the most consistent supporting evidence (Gryglewski et al., 2021).

Current structural MRI evidence indicates that, following effective treatment—particularly ECT—patients with MDD-SI may exhibit reversible structural changes in key brain regions such as the hippocampus, anterior cingulate cortex, and prefrontal cortex (Pirnia et al., 2016; Wilkinson et al., 2017). These treatment-related structural plasticity changes may constitute an important neural basis underlying the alleviation of suicidal ideation and provide support for the use of structural imaging markers as tools for predicting treatment response and investigating underlying mechanisms (Joshi et al., 2016; Pirnia et al., 2016).

3.2 Treatment-Related Functional Brain Changes

Existing longitudinal fMRI studies indicate that, following effective treatment, the alleviation of suicidal ideation in patients with MDD-SI is accompanied by functional reorganization in specific brain networks (Su et al., 2025; Wang et al., 2023). These changes are not uniformly distributed across the whole brain (X. Li et al., 2021) but are selectively concentrated in the prefrontal–cingulate–limbic system (Wang et al., 2023), the default mode network (DMN) (Verdijk et al., 2024), and reward- and emotion regulation–related networks. These findings suggest that treatment may exert its effects through two major mechanisms: restoring top-down regulatory control and suppressing excessive self-referential processing.

Following ECT, patients with MDD-SI commonly exhibit increased activity in prefrontal regions, including the dorsolateral prefrontal cortex (DLPFC) and the ventromedial/orbitofrontal prefrontal cortex (vmPFC/OFC) (Wang et al., 2023), along with a reduction in the amygdala's hyperreactivity to negative stimuli (Redlich et al., 2017). More importantly, enhanced functional connectivity between the prefrontal cortex and the amygdala has been observed, suggesting a restoration of top-down cognitive control over emotional responses (Redlich et al., 2017).

The anterior cingulate cortex (ACC) is one of the key nodes with the most consistent evidence of treatment-related functional changes (Pirnia et al., 2016). Longitudinal studies have indicated that, following ECT, patients with depression accompanied by suicidal ideation exhibit significant treatment-related reorganization in both resting-state ACC activity (Wang et al., 2023) and its functional connectivity with the prefrontal–limbic system (Cano et al., 2016). Given the central role of the ACC in processes such as rumination, self-monitoring, and conflict monitoring (Hamilton et al., 2012), this functional reorganization is thought to contribute to the rapid alleviation of suicidal ideation (Schmaal et

al., 2020).

Following ECT, abnormal internal connectivity within the default mode network (DMN) shows partial normalization or reorganization (Verdijk et al., 2024), with some studies reporting increased connectivity (Pang et al., 2022) and others showing reduced connectivity in specific pathways (Denier et al., 2023). These changes particularly involve the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and their coupling with memory-related structures such as the hippocampus. In addition, the anticorrelation between the DMN and task-positive networks, such as the prefrontal control network, is enhanced (Moreno-Ortega et al., 2019). Given that patients with MDD-SI commonly exhibit DMN hyperactivity (S. Zhang et al., 2016) and increased rumination (Hamilton et al., 2015), these changes are thought to correspond to a reduction in repetitive self-referential thoughts related to suicide.

In task-based fMRI studies examining rapid-acting treatments, increased responses in reward-related brain regions, including the striatum, have been observed during reward feedback processing (Kotoula et al., 2022). In contrast, evidence related to ECT has been derived primarily from resting-state studies, which indicate increased intrinsic activity or connectivity within orbitofrontal/prefrontal reward-related circuits, and these changes have been associated with improvements in anhedonia (T. Zhang et al., 2021).

Studies on rapid-acting treatments targeting suicidal ideation, such as ketamine, have shown that increased connectivity within the prefrontal–limbic system (M. H. Chen et al., 2019) and reduced activity in the default mode network (DMN) (Scheidegger et al., 2012) can emerge within a short time frame. These patterns are highly consistent with the network-level changes observed following ECT in terms of "network directionality" (Wang et al., 2023), although they occur on a shorter timescale (Stapper et al., 2025), suggesting that different treatments may alleviate suicidal ideation through similar functional pathways. However, it should be noted that neuroimaging studies of rapid-acting treatments in patients with MDD-SI are currently limited by small sample sizes and short follow-up periods. Larger longitudinal studies with suicidal ideation as the primary outcome are still needed to validate the specificity of the underlying network mechanisms (Sajid, Mann, & Grunebaum, 2025).

Functional neuroimaging evidence suggests that, following effective treatment—particularly ECT—patients with MDD-SI exhibit enhanced prefrontal–limbic regulatory control, normalization of ACC function, and suppression of excessive self-referential processing within the default mode network (DMN). These network-level functional reorganizations may provide an important neural basis for the rapid alleviation of suicidal ideation.

3.3 Potential Mechanisms Underlying Treatment-Related Neuroimaging Changes

Existing neuroimaging studies suggest that the structural and functional changes observed in patients with MDD-SI following effective treatment are unlikely to represent isolated effects in specific brain regions but rather reflect functional reorganization across multiple key brain networks. Based on current structural and functional imaging evidence, the potential mechanisms underlying treatment-related neuroimaging changes may primarily involve the restoration of prefrontal–limbic regulatory control, suppression of excessive self-referential processing within the default mode network (DMN), and improvement in the functioning of reward-processing networks (Verdijk et al., 2024; Wang et al., 2023).

Restoration of prefrontal–limbic regulatory control is considered one of the key neural mechanisms underlying the therapeutic alleviation of suicidal ideation. Numerous studies have shown that patients with MDD-SI commonly exhibit reduced regulatory control of the prefrontal cortex over the limbic system at baseline, manifested by decreased activity in the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (vmPFC) (Kim et al., 2017), along with exaggerated amygdala responses to negative emotional stimuli (Victor et al., 2010). Following ECT and other biological treatments, increased prefrontal activity accompanied by enhanced functional connectivity between the prefrontal cortex and the amygdala has been observed, suggesting a restoration of top-down emotional regulation (Redlich et al., 2017). The enhancement of this regulatory control may help suppress negative emotional responses and impulsive behaviors, thereby reducing the persistence of suicide-related thoughts at the neural level.

Suppression of excessive self-referential

processing within the default mode network (DMN) may represent another important mechanism underlying the alleviation of suicidal ideation. The DMN is primarily involved in self-referential processing and internally oriented cognition, and in patients with MDD-SI it often exhibits hyperactivity and increased internal connectivity, which have been closely associated with rumination, negative self-evaluation, and pessimistic expectations about the future (Hamilton et al., 2015). Longitudinal neuroimaging studies have shown that, following ECT or rapid-acting treatments, patterns of internal DMN connectivity undergo partial normalization (Verdijk et al., 2024), accompanied by enhanced functional anticorrelation between the DMN and the prefrontal control network (Moreno-Ortega et al., 2019). Such network-level functional reorganization may help reduce excessive self-focus and repetitive negative thinking, thereby attenuating the persistent cognitive activation of suicidal ideation.

Improvement in reward-processing network function may also contribute to treatment-related neuroimaging changes. Patients with MDD-SI often exhibit reduced responsiveness to reward-related stimuli in the ventral striatum and orbitofrontal cortex, indicating impairments in hedonic processing and value evaluation (Jollant et al., 2011). Following effective treatment, some studies have observed increased responsiveness in reward-related brain regions as well as improved functional connectivity within prefrontal–striatal circuits (T. Zhang et al., 2021). These changes may reflect the restoration of positive emotional processing, thereby alleviating feelings of hopelessness and negative expectations about the future to some extent.

Overall, treatment-related neuroimaging changes may reflect coordinated reorganization among the emotion regulation network, the default mode network (DMN), and reward-processing networks. In particular, enhanced prefrontal–limbic regulatory control, suppression of excessive self-referential processing within the DMN, and restoration of reward-processing function may jointly constitute key neural mechanisms underlying the alleviation of suicidal ideation. These findings further suggest that different biological treatments may exert their therapeutic effects by modulating common core brain network pathways, thereby facilitating the reduction of suicidal ideation at the neural level.

4. Limitations and Future Directions

Although neuroimaging studies have made important progress in elucidating the neural mechanisms underlying major depressive disorder with suicidal ideation in recent years, several limitations remain in the existing literature. First, many studies are characterized by relatively small sample sizes and predominantly cross-sectional designs, which to some extent limit causal interpretations of neuroimaging findings. Although some longitudinal studies have begun to examine treatment-related structural and functional changes, research specifically focusing on changes in suicidal ideation as the primary outcome remains relatively limited.

In addition, substantial heterogeneity exists across studies in terms of suicidal ideation assessment methods, imaging acquisition parameters, and analytical strategies. For example, some studies employ dedicated suicidal ideation scales, such as the Beck Scale for Suicide Ideation (BSSI) (Beck et al., 1979) or the Columbia–Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011), whereas others rely on suicide-related items embedded within depression rating scales (Guo et al., 2024). Such methodological differences may affect the comparability of findings across studies. Furthermore, different imaging analysis approaches—such as voxel-based morphometry (VBM), cortical thickness analysis, or functional connectivity analysis—may also contribute to variability in the interpretation of results.

At present, most studies focus on a single imaging modality, while multimodal neuroimaging integration remains relatively limited. Combining multiple imaging techniques, including structural MRI, functional MRI, and diffusion tensor imaging (DTI), may provide a more comprehensive understanding of abnormal brain network patterns in MDD-SI and their treatment-related changes.

Future studies should further conduct large-sample, multicenter longitudinal investigations and integrate multimodal neuroimaging with machine learning approaches to identify imaging biomarkers capable of predicting treatment response in suicidal ideation. In addition, comparative studies examining the network-level regulatory mechanisms underlying different treatment modalities, such as

electroconvulsive therapy (ECT) and rapid-acting antidepressant interventions, may further deepen our understanding of the neural mechanisms of suicidal ideation and provide a basis for the development of personalized intervention strategies.

5. Conclusion and Future Perspectives

In summary, major depressive disorder with suicidal ideation (MDD-SI) exhibits relatively consistent and clinically meaningful abnormalities at both structural and functional brain levels. Increasing longitudinal neuroimaging evidence indicates that biological treatments—particularly electroconvulsive therapy (ECT)—not only rapidly alleviate suicidal ideation but also induce structural and functional plasticity within the prefrontal–cingulate–limbic system and related brain networks. These treatment-related neuroimaging findings provide important insights into the neural mechanisms underlying suicidal ideation and further suggest that brain network–level plasticity may represent a critical link between biological treatments and clinical symptom improvement. Moreover, these findings highlight the potential value of neuroimaging markers in predicting treatment response, guiding personalized interventions, and validating underlying neurobiological mechanisms in future research. Based on the current evidence, this review proposes an integrative conceptual framework of "baseline structural abnormalities—treatment-induced neuroplasticity—alleviation of suicidal ideation," which can be summarized in the following three aspects:

Structural Vulnerability Network Hypothesis

Patients with MDD-SI exhibit baseline structural abnormalities centered on the prefrontal–cingulate–limbic system, primarily manifested as reduced gray matter in regions such as the anterior cingulate cortex (ACC), ventromedial/orbitofrontal prefrontal cortex (vmPFC/OFC), and hippocampus. This "structural vulnerability" may provide a neuroanatomical basis for enhanced negative self-referential processing, impaired impulse control, and the development of hopelessness.

Biological Treatment–Induced Plasticity Hypothesis

Biological treatments may act on these vulnerability-related networks and induce regionally selective structural recovery—such as increased hippocampal volume and improvements in gray matter in the ACC and prefrontal cortex—while simultaneously promoting network-level functional reorganization. These changes may be characterized by enhanced top-down regulatory control within the prefrontal–limbic system and suppression of excessive self-referential processing within the default mode network (DMN).

Neuroimaging Mediation Hypothesis

The structural and functional imaging changes observed after treatment may not simply represent accompanying phenomena but may instead serve as mediators linking ECT to improvements in suicidal ideation, thereby constituting a critical bridge between neural modulation and clinical benefit.

Overall, these conclusions and hypotheses provide a testable theoretical framework for future studies focusing on suicidal ideation as a primary outcome, particularly those integrating longitudinal multimodal neuroimaging approaches to investigate underlying mechanisms and identify predictive biomarkers.

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Research Progress on the Safety of Oliceridine in Perioperative Application

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Abstract

Oliceridine is the first approved biased μ-opioid receptor agonist. It produces analgesia by selectively activating the G protein pathway while minimizing β-arrestin recruitment, a mechanism that theoretically uncouples analgesia from adverse effects. This article systematically reviews the pharmacological basis for the perioperative use of oliceridine, the clinical evidence for its safety, and its value in special patient populations. Studies indicate that at equianalgesic doses, oliceridine is associated with a significantly lower incidence of respiratory depression and better gastrointestinal tolerability compared to conventional opioids. In elderly patients and those with renal or hepatic impairment, no or only mild dose adjustment is required. Cardiovascular and central nervous system adverse effects are manageable, with no risk signals identified beyond those of conventional opioids. Within the framework of multimodal analgesia, oliceridine demonstrates good synergy with other analgesic agents. However, critical questions remain insufficiently addressed, including the risks of long-term tolerance and dependence, as well as its impact on hard endpoints such as postoperative ileus. Future research should focus on long-term follow-up studies and clinical trials centered on bowel function recovery to refine its positioning within Enhanced Recovery After Surgery (ERAS) pathways.

Keywords: oliceridine, perioperative period, opioids, safety, analgesia

1. Introduction

Perioperative pain management is a key component affecting the quality of postoperative recovery in patients. Opioid analgesics, due to their potent analgesic effects, have long served as the cornerstone for the treatment of moderate to severe acute pain. However, while traditional opioids activate the μ-receptor G protein signaling pathway to produce analgesia, they simultaneously activate the β-arrestin pathway to a similar extent, which is closely associated with adverse reactions such as respiratory depression, nausea and vomiting, gastrointestinal dysfunction, and tolerance and dependence (N. Daksla et al., 2023; K. M. Raehal et al., 2005; J. Zhao, 2024). These adverse reactions not only affect patient comfort but may also delay the recovery process and prolong the length of hospital stay, thereby conflicting with the

concept of Enhanced Recovery After Surgery (ERAS) (M. R. Shen & J. F. Waljee, 2019; J. C. Simpson et al., 2019).

How to ensure analgesic efficacy while minimizing the risk of adverse reactions has always been a central challenge in perioperative pain management. In recent years, the development of biased μ-receptor agonists has provided a new approach to addressing this dilemma. Oliceridine, as the first approved biased μ-receptor agonist worldwide, theoretically achieves the decoupling of analgesia and adverse reactions by selectively activating the G protein pathway while attenuating β-arrestin recruitment (J. Piekielna-Ciesielska et al., 2023). Since 2017, multiple phase III clinical trials and real-world studies have been published, providing substantial evidence for its perioperative application.

This article aims to systematically review the pharmacological characteristics of oliceridine, the evidence regarding its perioperative safety, and its application value in special populations, in order to provide a reference for rational clinical use and subsequent research.

2. Pharmacological Characteristics of Oliceridine and the Basis for Its Clinical Application

2.1 Pharmacological Characteristics of Oliceridine

Oliceridine, as the first biased μ-opioid receptor agonist approved for clinical application worldwide, has opened a new pathway for perioperative pain management through its unique mechanism of action (Zhu, C. et al., 2024). At the molecular level, this drug achieves selective regulation of downstream signal transduction of the μ receptor: on the one hand, it efficiently activates the G protein signaling pathway, thereby producing potent analgesic effects; on the other hand, it significantly reduces the recruitment of β-arrestin, thereby minimizing adverse reactions mediated by this pathway (Y. Ni et al., 2024). This selective activation strategy constitutes the pharmacological basis for its differentiated clinical effects. Previous studies have confirmed that classic opioid-related adverse reactions, such as respiratory depression, postoperative nausea and vomiting, and gastrointestinal dysfunction, are mainly closely associated with excessive activation of the β-arrestin pathway (N. Daksla et al., 2023). Therefore, oliceridine theoretically achieves the decoupling of analgesia and adverse reactions.

2.2 Pharmacokinetic and Pharmacodynamic Characteristics of Oliceridine

Oliceridine is a short-acting drug administered intravenously, and its pharmacokinetic characteristics meet the requirements of acute pain management. After intravenous injection, its plasma concentration rapidly reaches peak levels, with a rapid onset of action (approximately 2–5 minutes), enabling rapid relief of moderate to severe pain (E. R. Viscusi et al., 2016). Its elimination half-life is approximately 1.3 to 3 hours. A phase I study conducted in Chinese patients with chronic pain also confirmed that its half-life is approximately 1.85–2.08 hours, showing linear kinetic characteristics (Y. Ni et al., 2024). This indicates that its analgesic effect is predictable and controllable, facilitating titration during the perioperative period according to the intensity of pain stimuli and patient responses.

The most notable feature of its pharmacodynamics is the possibility of a wider therapeutic window. A pharmacodynamic study conducted in elderly volunteers found that, compared with morphine at an equivalent analgesic dose, oliceridine caused a lower degree of respiratory depression and its effect resolved more rapidly (A. Dahan et al., 2018). Utility function-based analysis further showed that, when achieving the same probability of analgesia, the probability of respiratory depression with oliceridine was significantly lower than that with morphine (A. Dahan et al., 2018). This characteristic of "potent analgesia with a low risk of respiratory depression" is one of its most important clinical advantages, which was also verified in a phase IIb study after abdominoplasty (N. Singla et al., 2017).

2.3 Comparison Between Oliceridine and Traditional Opioids

Multiple phase III clinical trials represented by the APOLLO series have systematically evaluated the differences in efficacy and safety between oliceridine and classical opioids in postoperative acute analgesia. A study involving patients undergoing abdominoplasty showed that, compared with morphine, oliceridine met the prespecified non-inferiority standard in analgesic efficacy, confirming its reliable analgesic effectiveness (E. R. Viscusi et al., 2019). However, the core difference between the two is mainly reflected in safety. Compared with the morphine group, the "respiratory safety event"

composite endpoint (such as decreased oxygen saturation) occurred with a significantly lower burden in the oliceridine treatment group, and the proportion of patients forced to discontinue medication due to respiratory function suppression was also significantly reduced (S. D. Bergese et al., 2019). It is worth noting that the safety advantages demonstrated by oliceridine are not limited to the respiratory system. In the large open-label ATHENA study involving a broad surgical population, its adverse event profile showed lower incidences of respiratory depression and gastrointestinal adverse reactions (such as nausea and vomiting) (S. D. Bergese et al., 2019). In addition, a pooled analysis of multiple clinical studies further indicated that while ensuring effective analgesia, oliceridine was associated with a lower incidence of typical opioid-related adverse reactions such as nausea and vomiting compared with traditional drugs (C. Huang et al., 2025).

2.4 Theoretical Basis for the Perioperative Use of Oliceridine

The clinical application of oliceridine is highly consistent with the core concept of Enhanced Recovery After Surgery (ERAS), which aims to promote rapid recovery of postoperative physiological function by reducing complications. In the multimodal analgesia strategy of ERAS, limiting opioid-related adverse effects is a key component of successful implementation, whereas respiratory depression and gastrointestinal dysfunction caused by traditional opioids often become major obstacles to early mobilization and oral intake in patients (A. Beverly et al., 2017). Oliceridine, with its unique biased activation mechanism, retains potent analgesic activity while significantly reducing the risk of respiratory depression and having the potential to alleviate gastrointestinal adverse reactions, which provides a solid pharmacological basis for optimizing perioperative analgesic regimens (L. A. Colvin et al., 2019; H. Yu et al., 2026). The use of this drug enables clinicians managing acute moderate to severe pain to potentially overcome the safety limitations of traditional opioids and achieve effective separation between analgesic efficacy and core adverse reactions. Therefore, the theoretical foundation of its perioperative application lies in selectively regulating signaling pathways at the target level to precisely correct the inherent deficiencies of traditional opioids in the ERAS pathway, thereby creating favorable conditions for stable postoperative transition and accelerated recovery in patients (X. Meng et al., 2025).

3. Clinical Evidence on the Perioperative Safety of Oliceridine

As the first biased μ-opioid receptor agonist applied in clinical practice, the core value of oliceridine lies in its potential safety advantages (E. E. Prommer, 2025). Its unique mechanism of preferentially activating the G protein pathway while minimizing the β-arrestin pathway provides new possibilities for reducing the two major risks of traditional opioids—respiratory depression and addiction dependence—and related clinical research is continuously advancing (Y. Liu et al., 2021).

3.1 Studies on the Role of Oliceridine in Reducing the Risk of Perioperative Respiratory Depression

Respiratory depression induced by opioids is one of the most serious complications during the perioperative period. Oliceridine, due to its biased agonist property, was designed to provide potent analgesia while minimizing this risk to the greatest extent possible.

3.1.1 Mechanism of Respiratory Depression and Risk Assessment

Traditional opioids represented by morphine exert pharmacological effects by binding to μ receptors and non-selectively activating both the downstream G protein signaling pathway and the β-arrestin pathway simultaneously (J. Piekielna-Ciesielska et al., 2020; A. Mafi et al., 2020; A. Manglik et al., 2016). Recent studies indicate that excessive activation of the β-arrestin pathway is closely associated with the mechanisms underlying common clinical adverse reactions such as respiratory depression and gastrointestinal motility disorders (Y. Ni et al., 2024). Based on this pathophysiological basis, the risk assessment of opioid-related respiratory depression in the perioperative period has multidimensional characteristics. In addition to drug dosage as the core variable, individual patient factors also play a crucial role. Advanced age, obesity, a history of obstructive sleep apnea, and concomitant use of other central nervous system depressant drugs can all significantly increase the risk of respiratory depression. However, commonly used clinical monitoring methods, such as respiratory rate, pulse oxygen saturation (SpO_2), and end-tidal carbon dioxide partial pressure ($EtCO_2$), although providing important reference information, still lack a

single early warning indicator with both high sensitivity and specificity, which poses challenges for early identification and timely intervention.

3.1.2 Studies on the Effects of Oliceridine on Respiratory Function

Both basic research and clinical studies suggest that the effect of oliceridine on respiratory function is milder and more transient than that of traditional opioids (D. G. Soergel et al., 2014; P. Simons et al., 2023). A pharmacokinetic-pharmacodynamic study conducted in healthy elderly volunteers showed that, compared with morphine at an equivalent analgesic dose, oliceridine caused less ventilatory depression and a faster recovery from suppression (P. Simons et al., 2023). This more favorable respiratory safety profile has been further verified in clinical studies.

A retrospective analysis based on data from three phase III clinical trials (APOLLO-1, APOLLO-2, and ATHENA) showed that the incidence of opioid-induced respiratory depression (OIRD, defined as decreased respiratory rate or hypoxemia requiring clinical intervention) in patients treated with oliceridine was significantly lower than that in patients treated with traditional intravenous opioids (mainly morphine) (8.0% vs. 30.7%) (S. Bergese et al., 2020). Further subgroup analysis of high-risk populations (including elderly patients, obese patients, and those with obstructive sleep apnea) indicated that oliceridine maintained a significantly lower incidence of adverse events in these patients, suggesting potential advantages in high-risk populations (S. Bergese et al., 2020). This finding was further supported by an independent exploratory analysis of the ATHENA trial. Regardless of whether patients were older than 65 years or had a body mass index (BMI) of ≥30 kg/m², the incidence of OIRD in the oliceridine treatment group remained at a low level, and these traditional risk factors were not observed to significantly increase the risk of respiratory depression (M. Brzezinski et al., 2021). These data provide real-world evidence supporting the clinical value of oliceridine in improving perioperative respiratory safety.

3.1.3 Safety Monitoring Indicators in Clinical Application

To more objectively quantify the respiratory safety risks of opioids, some studies have attempted to evaluate "interruption of patient-controlled analgesia administration due to respiratory safety concerns" as a clinical surrogate endpoint for OIRD. Exploratory analyses of two phase III clinical trials showed that among different dose groups receiving patient-controlled analgesia with oliceridine, the proportion of patients whose administration was interrupted due to respiratory depression (0.1 mg group: 3.2%; 0.35 mg group: 13.9%; 0.5 mg group: 15.1%) was significantly lower than that in the morphine control group (22%), and the mean cumulative interruption time in each dose group also showed a decreasing trend (S. Ayad et al., 2020). This finding provides quantitative reference for indirectly monitoring respiratory function in clinical practice through the administration status of analgesia pumps. In addition, a recent dose-exploration study in outpatient hysteroscopic surgery further expanded its application scenarios. Under conditions of preserved spontaneous respiration, the combination of oliceridine and propofol provided satisfactory anesthetic effects, and no respiratory depression events were observed in any of the participants during the procedure (J. He et al., 2025). This result, from the perspective of a surgical model with low-intensity stimulation, supports the potential of oliceridine to maintain respiratory safety while providing sedation and analgesia.

4. Application Value of Oliceridine in the Safety of Perioperative Medication in Special Populations

Due to significant differences in the metabolism, pharmacological effects, and risk of adverse reactions to opioids in special patients such as the elderly and those with hepatic or renal insufficiency, the use of traditional opioids often faces many limitations (D. L. Chau et al., 2008). The unique pharmacological characteristics of oliceridine provide new possibilities for its application in these special populations.

4.1 Studies on Its Application in Elderly Patients

Elderly patients are significantly more susceptible to adverse reactions caused by opioids, such as respiratory depression and excessive sedation, due to factors such as reduced physiological reserve, altered pharmacokinetic characteristics, and multimorbidity. Existing studies indicate that oliceridine may demonstrate a more favorable safety profile in this high-risk population (Li, Y. et al., 2025).

A prospective randomized controlled study in

elderly patients after colorectal cancer surgery showed that, in a patient-controlled intravenous analgesia regimen, oliceridine combined with sufentanil not only provided better analgesic effects than sufentanil alone, but also significantly reduced the incidence of postoperative nausea and vomiting and respiratory depression (Y. Tian et al., 2025). This result suggests that oliceridine has potential value in multimodal analgesic strategies for elderly patients by enhancing efficacy while reducing adverse reactions. From a pharmacodynamic perspective, a sequential dose study on suppressing hemodynamic responses to tracheal intubation found that the effective dose of oliceridine in elderly patients (≥65 years) (ED95 approximately 50 μg/kg) was slightly lower than that in younger patients (55 μg/kg), and there was no significant difference in hemodynamic fluctuations or incidence of adverse events between the two groups, indicating that its dose-response relationship in the elderly population is predictable and controllable (A. N. Nafziger et al., 2020). Of particular concern is the dimension of respiratory safety. An exploratory analysis of a phase III open-label trial in patients with moderate to severe postoperative pain pointed out that, compared with younger patients, elderly patients (≥65 years) did not show an increased risk of opioid-induced respiratory depression after receiving oliceridine (S. Ayad et al., 2020). This finding was further confirmed in subsequent review literature, providing evidence-based support for the maintenance of respiratory safety of oliceridine in the elderly, a traditionally high-risk population (N. Daksla et al., 2023; D. I. Sessler et al., 2025). Overall, current evidence suggests that in the perioperative use of elderly patients, oliceridine is expected to reduce the burden of common adverse reactions associated with traditional opioids while ensuring analgesic efficacy.

4.2 Application Value in Patients with Hepatic and Renal Insufficiency

Hepatic and renal insufficiency can significantly affect the clearance rate of most opioids and their active metabolites, thereby increasing the risk of drug accumulation and toxicity. Oliceridine, due to its unique metabolic and excretory characteristics, may demonstrate better medication safety in this special population. A phase I pharmacokinetic study in patients with end-stage renal disease (ESRD) and varying degrees of hepatic impairment systematically evaluated the in vivo process of oliceridine after a single intravenous administration. The results showed that, compared with individuals with normal renal function, the clearance rate of oliceridine in patients with ESRD did not change significantly, indicating that its pharmacokinetic characteristics are basically unaffected by renal function, and therefore no dose adjustment is required in clinical use (A. N. Nafziger et al., 2020). In patients with hepatic insufficiency, mild to moderate hepatic impairment also did not significantly affect the clearance rate of oliceridine. Although patients with severe hepatic impairment showed prolonged half-life and increased volume of distribution, their overall clearance rate did not decrease significantly (A. N. Nafziger et al., 2020). Based on the above evidence, relevant reviews and clinical study protocols have pointed out that for patients with mild to moderate hepatic insufficiency, oliceridine can be used at the conventional dose without adjustment; for patients with severe hepatic insufficiency, a strategy of reducing the initial dose and strengthening clinical monitoring is recommended, rather than listing it as an absolute contraindication (B. Goudra & P. M. Singh, 2020; J. C. Luo et al., 2024). This pharmacokinetic characteristic simplifies the clinical medication process to a certain extent and reduces the risk of medication caused by fluctuations in hepatic and renal function.

4.3 Evaluation of the Synergistic Application of Oliceridine in Perioperative Multimodal Analgesia

Multimodal analgesia, as a core strategy for optimizing perioperative pain management and reducing the dose of a single drug and its adverse reactions, has become an important component of the ERAS pathway. Oliceridine, by virtue of its unique safety profile, demonstrates potential value as an opioid component in this strategy. Real-world clinical data have confirmed its good compatibility with other analgesic drugs. In the large phase III ATHENA study, as many as 84% of the subjects received non-opioid analgesics concomitantly while receiving oliceridine analgesia, fully reflecting its high compatibility with multimodal analgesic regimens in clinical practice (S. D. Bergese et al., 2019).

Further exploration of drug synergy has further enriched the above findings. The aforementioned randomized controlled trial in elderly patients showed that when oliceridine was combined

with sufentanil in patient-controlled intravenous analgesia (PCIA), it not only significantly reduced postoperative pain scores, but also reduced the number of analgesia pump presses and the need for rescue analgesia, achieving a synergistic analgesic effect between opioids and effectively controlling the burden of adverse reactions (J. Niu et al., 2023). This study provides new evidence-based support for constructing an "opioid-sparing" analgesic regimen centered on low-dose and multi-target approaches.

Based on existing evidence, the academic community generally believes that future studies should further clarify the optimal positioning and dosing regimen of oliceridine in specific ERAS protocols and multimodal analgesic combinations, in order to maximize its clinical benefits while ensuring analgesic efficacy (B. Hong et al., 2025).

5. Conclusion and Prospects

As a biased μ-opioid receptor agonist, oliceridine, with its unique mechanism of selectively activating the G protein pathway while attenuating β-arrestin recruitment, provides a new approach for perioperative analgesia. Existing evidence shows that, at equianalgesic doses, the incidence of core adverse reactions of traditional opioids, such as respiratory depression, nausea, and vomiting, is significantly reduced, gastrointestinal tolerability is improved, and it has good safety characteristics in elderly patients and patients with hepatic and renal insufficiency. These advantages are highly consistent with the concept of Enhanced Recovery After Surgery, making it a valuable supplementary option in multimodal analgesia.

However, there are still obvious gaps in current research. Most clinical trials have short observation periods, making it difficult to evaluate the risks of tolerance and dependence with long-term use. There is still a lack of prospective data supporting the effect of oliceridine on hard endpoints such as postoperative ileus. Evidence for its application in specific surgical procedures and special pathological conditions is also insufficient. In addition, the lack of pharmacoeconomic evaluation limits the decision-making basis for its clinical promotion.

Future research should focus on the following: conducting long-term follow-up studies to clarify the risk of dependence; designing randomized controlled trials centered on the recovery of intestinal function; exploring its optimal combinations and dosing strategies in different ERAS protocols; accumulating real-world data and completing health economic evaluations. With the improvement of the evidence system, oliceridine is expected to play a more precise clinical role in the dual goals of individualized analgesia and rapid recovery.

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Functional Testing for Return-to-Sport Decision-Making After Anterior Cruciate Ligament Reconstruction: An Updated Narrative Review

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Abstract

Return-to-sport (RTS) decision-making after anterior cruciate ligament reconstruction (ACLR) has moved away from time alone toward criterion-based models, yet the optimal composition of a functional testing battery remains debated. Functional tests are still essential because they quantify residual deficits in strength, power, neuromuscular control, balance, and confidence; however, contemporary evidence shows that no single test has adequate validity to clear an athlete independently. This updated narrative review synthesizes landmark cohort studies together with recent reviews, guidelines, and meta-analyses on functional RTS assessment after primary ACLR. The current literature indicates that hop tests remain clinically valuable, especially the single-leg hop for distance, crossover hop, 6-m timed hop, and single-leg vertical hop, but isolated pass/fail thresholds show inconsistent ability to predict second injury or successful RTS. Quadriceps strength remains indispensable, although limb symmetry index (LSI) should not be interpreted without consideration of absolute strength, time since surgery, graft type, sex, and possible deconditioning of the contralateral limb. Movement-quality assessments during landing, single-leg squat, or change-of-direction tasks may reveal high-risk patterns that distance-based tests miss. Psychological readiness, most commonly assessed with the ACL-Return to Sport after Injury scale, is another core domain because fear of reinjury and low confidence often persist despite acceptable physical scores. Importantly, recent evidence shows that RTS testing is commonly administered around 7 months post-operatively, which is earlier than timelines associated with lower reinjury risk in pivoting sports. A contemporary RTS strategy should therefore rely on a domain-based battery combining clinical status, strength testing, at least two hop or jump tasks, movement-quality assessment, patient-reported outcomes, and psychological readiness. For unrestricted return to level I pivoting sports, final clearance is best delayed until at least 9 months after surgery and only after satisfactory performance is demonstrated across domains.

Keywords: anterior cruciate ligament reconstruction, return to sport, functional testing, hop tests, quadriceps strength, psychological readiness

1. Introduction

Anterior cruciate ligament (ACL) injury is one of the most consequential injuries in sport because it affects short-term performance, long-term knee

health, and the athlete's confidence in the injured limb. Although ACL reconstruction (ACLR) restores passive restraint and often allows a return to sport, the period after surgery remains clinically challenging. Young and highly active athletes continue to face a substantial risk of secondary ACL injury after returning to pivoting sports, which makes the quality of the return-to-sport (RTS) decision at least as important as the operation itself (Wiggins AJ, Grandhi RK, Schneider DK, Stanfield D, Webster KE & Myer GD., 2016).

Earlier rehabilitation models often used time from surgery as the dominant criterion for sport clearance. That approach is now widely regarded as insufficient. In the Delaware-Oslo ACL cohort, athletes who returned to level I sport had a more than fourfold higher reinjury rate than those who did not, and the risk of reinjury fell by approximately 51% for each month RTS was delayed until 9 months after surgery (Grindem H, Snyder-Mackler L, Moksnes H, Engebretsen L & Risberg MA., 2016). These data do not mean that time is irrelevant; rather, they indicate that time should be treated as a protective boundary condition rather than a stand-alone decision rule.

Functional testing emerged as an attractive complement to time-based decisions because it is relatively inexpensive, repeatable, and clinically intuitive. Historically, hop tests became the most frequently reported field measures, and early cohort studies suggested that the crossover hop and the 6-m timed hop could help predict self-reported knee function one year after reconstruction (Logerstedt D, Grindem H, Lynch A, Eitzen I, Engebretsen L, Risberg MA, et al., 2012). More recent evidence, however, has complicated this picture by showing that the most commonly used strength and hop tests have limited and inconsistent value when they are used in isolation to predict second injury or successful return to the preinjury level of sport (Gill VS, Tummala SV, Sullivan G, Han W, Haglin JM, Marks L & Tokish JM., 2024).

The purpose of this revised manuscript is to update the original review with a contemporary interpretation of the literature. Rather than ranking tests solely by frequency or convenience, the present paper organizes the evidence by domain—strength, hop and jump performance, movement quality, balance and proprioception, patient-reported outcomes, and psychological readiness—and then proposes a pragmatic, clinically feasible battery for RTS decision-making after primary ACLR.

2. Functional Testing as Part of a Broader RTS Framework

Modern rehabilitation frameworks describe RTS as a continuum rather than a single event. Athletes first progress to running, then to controlled change of direction, then to sport-specific practice, and only later to unrestricted competition and return to performance (Brinlee AW, Dickenson SB, Hunter-Giordano A, Snyder-Mackler L., 2022; Simonsson R, Piussi R, Högberg J, Sundberg A & Hamrin Senorski E., 2024). Functional testing is therefore most useful when it is repeated across phases and interpreted within a broader clinical context that includes symptoms, swelling, range of motion, training exposure, psychological readiness, and the demands of the target sport.

Recent reviews consistently emphasize that no single test can capture the multiple constructs relevant to RTS after ACLR (Brinlee AW, Dickenson SB, Hunter-Giordano A & Snyder-Mackler L., 2022; Turk R, Shah S, Chilton M, Thomas TL, Anene C, Mousad A, et al., 2023; Golberg E, Sommerfeldt M, Pinkoski A, Dennett L & Beaupre L., 2024; Simonsson R, Piussi R, Högberg J, Sundberg A & Hamrin Senorski E., 2024; Kodama E, Tartibi S, Brophy RH, Smith MV, Matava MJ & Knapik DM., 2025; Mengis N, Höher J, Ellermann A, Eberle C, Hartner C, Keller M, et al., 2025). A useful test battery should sample at least five domains: (1) knee status and load tolerance, (2) muscle strength, (3) hop or jump performance, (4) movement quality and sensorimotor control, and (5) self-reported and psychological readiness. This domain-based perspective is more defensible than searching for one universally superior field test because athletes may compensate in one task while still displaying meaningful deficits in another.

Table 1. Contemporary domains that should be represented in RTS assessment after ACL reconstruction

Domain	Examples of common tools	Primary purpose	Important limitation
Clinical	Effusion assessment, pain	Establishes whether	An athlete may feel

Domain	Examples of common tools	Primary purpose	Important limitation
status and load tolerance	response, range of motion, tolerance of running and practice loads	the knee is currently able to tolerate progression	symptomatically well while still showing major performance deficits
Strength	Isokinetic testing, handheld dynamometry, portable dynamometry, 8-repetition maximum testing	Quantifies quadriceps and hamstring recovery and residual asymmetry	Limb symmetry can be misleading if the contralateral limb is also deconditioned
Hop and jump performance	Single hop, triple hop, crossover hop, 6-m timed hop, single-leg vertical hop	Captures explosive function, confidence, and task-specific asymmetry	Distance or time alone can hide compensatory movement strategies
Movement quality and agility	Single-leg squat, drop jump, cutting or change-of-direction tasks, Y-Balance or Star Excursion tests	Detects frontal-plane collapse, trunk compensation, landing asymmetry, and sensorimotor deficits	Observational scoring can be subjective if the task is not standardized or video recorded
Self-reported and psychological readiness	ACL-RSI, IKDC, KOOS Sport/Rec	Captures fear of reinjury, confidence, symptoms, and perceived function	Good questionnaire scores do not guarantee adequate physical capacity

3. Strength Testing

Quadriceps strength remains the anchor of postoperative performance testing. Persistent quadriceps weakness after ACLR is associated with poorer function, altered mechanics, and delayed progression through rehabilitation (Brinlee AW, Dickenson SB, Hunter-Giordano A & Snyder-Mackler L., 2022; Thomeé R, Kaplan Y, Kvist J, Myklebust G, Risberg MA, Theisen D, et al., 2011). In the Delaware-Oslo cohort, more symmetrical quadriceps strength before RTS was associated with a lower reinjury rate (Grindem H, Snyder-Mackler L, Moksnes H, Engebretsen L & Risberg MA., 2016). For that reason, recent reviews still place quadriceps and hamstring testing at the center of RTS evaluation (Turk R, Shah S, Chilton M, Thomas TL, Anene C, Mousad A, et al., 2023; Simonsson R, Piussi R, Högberg J, Sundberg A & Hamrin Senorski E., 2024; Kodama E, Tartibi S, Brophy RH, Smith MV, Matava MJ & Knapik DM., 2025; Mengis N, Höher J, Ellermann A, Eberle C, Hartner C, Keller M, et al., 2025).

At the same time, contemporary evidence warns against simplistic interpretation of limb symmetry index (LSI) thresholds. An LSI of 90% or greater is the most commonly reported criterion in the literature (Kodama E, Tartibi S, Brophy RH, Smith MV, Matava MJ & Knapik DM., 2025), yet a 2025 critical analysis concluded that LSI from muscle-function tests could not distinguish athletes who returned safely from those who sustained a second ACL injury within two years (Simonsson R, Sundberg A, Piussi R, Högberg J, Senorski C, Thomeé R, et al., 2025). The fundamental issue is that symmetry alone is not sufficient to indicate adequacy. An athlete can reach an apparently acceptable LSI because the uninvolved limb is also weak, because the test favors compensation, or because the strength deficit is small in percentage terms but still meaningful in sport-specific contexts.

The practical consequence is that clinicians should interpret symmetry together with absolute performance and the context of recovery. Hazzard and colleagues showed that quadriceps symmetry follows a time-dependent trajectory after surgery and varies by sex, age, and graft type; many athletes are only reaching approximately 80% symmetry around the time they begin running (Hazzard S, Connolly S, Wiater A, Sprague I, Doolan-Roy E, Lampros R & Asnis PD., 2024). Thus, an athlete assessed at 5 to 7 months may appear to be progressing appropriately, while still not meeting the physical demands of competitive pivoting sports. When laboratory isokinetic dynamometry is unavailable, practical alternatives such as portable dynamometry or 8-repetition maximum testing appear reasonable for everyday use

(Mengis N, Höher J, Ellermann A, Eberle C, Hartner C, Keller M, et al., 2025).

4. Hop and Jump Performance Testing

Hop testing remains widely used owing to its practicality and clinical relevance. Single-leg hop tasks are inexpensive, straightforward to administer, and familiar to both clinicians and athletes. The traditional battery typically includes the single hop for distance, triple hop, crossover hop, and 6-m timed hop. In an influential cohort study, the crossover hop and 6-m timed hop measured six months after ACLR were the strongest individual predictors of self-reported knee function at one year (Logerstedt D, Grindem H, Lynch A, Eitzen I, Engebretsen L, Risberg MA, et al., 2012). These tasks therefore still deserve a place in rehabilitation and late-stage progression.

However, the current literature no longer supports the view that horizontal hop tests alone can serve as a dependable surrogate for safe RTS. In a 2024 systematic review, Gill and colleagues found that single-leg hop for distance had no association with retear risk in any included study and no relationship with RTS rates in most studies; quadriceps strength also showed conflicting associations with reinjury, and combined hop-plus-strength batteries demonstrated low sensitivity and negative predictive value (Gill VS, Tummala SV, Sullivan G, Han W, Haglin JM, Marks L & Tokish JM., 2024). In other words, passing a conventional battery does not guarantee safe RTS, and failing a battery does not always identify the athlete who will later experience reinjury.

Recent work suggests that vertical tasks may expose residual deficits more effectively than hop-for-distance alone. In a systematic review and meta-analysis, Wang and colleagues reported that the single-leg vertical jump produced lower LSI values than the single-leg hop for distance between 7 and 18 months after ACLR, indicating that the vertical task may be more sensitive during the period when many athletes are preparing for sport clearance (Wang L, Xia Q, Li T, Wang Z & Li J., 2024). The key implication is not that vertical hopping should replace traditional hop tests, but that horizontal distance, timed hopping, and vertical jumping should be treated as complementary, not interchangeable, measures.

For clinical practice, hop and jump tests are most useful when clinicians record more than one outcome: the score itself, the quality of landing, the consistency across trials, and the athlete's confidence in the task. A horizontal hop performed with a stiff landing, trunk shift, contralateral arm overuse, or obvious valgus collapse should not be treated as a clean pass merely because the distance was acceptable.

5. Movement Quality, Agility, and Sensorimotor Control

One of the clearest developments in the recent literature is the growing emphasis on movement quality. Athletes can often achieve acceptable hop distance by using compensatory strategies that increase joint loading or conceal deficits in eccentric control. In a prospective cohort, Paterno and colleagues showed that landing biomechanics and postural stability deficits predicted second ACL injury after return to sport Paterno MV, Schmitt LC, Ford KR, Rauh MJ, Myer GD, Huang B & Hewett TE., 2010). More recently, Gill et al. reported that asymmetrical knee extension and hip moments, together with increased knee valgus and altered knee flexion patterns, were among the variables associated with retear risk (Gill VS, Tummala SV, Sullivan G, Han W, Haglin JM, Marks L & Tokish JM., 2024). These observations help explain why distance-based tests frequently underperform as standalone predictors.

The single-leg squat remains one of the most useful office-based movement-quality assessments because it is accessible and reveals deficits in trunk control, pelvic control, hip strategy, and dynamic knee valgus. Hall et al. found that 45% of patients still demonstrated poor single-leg squat performance at approximately six months after ACLR, and poor performers also had weaker hip abductors, shorter hop distance, and lower IKDC scores (Hall MP, Paik RS, Ware AJ, Mohr KJ & Limpisvasti O., 2015). Although the single-leg squat is not a complete RTS test by itself, it is a valuable adjunct because it highlights how the athlete produces movement rather than only how far or how fast the athlete can move.

Balance and proprioceptive tests are best viewed as secondary contributors to a broader battery. The Star Excursion Balance Test and related reach tests can detect persistent postural-control deficits, particularly when the involved limb is challenged dynamically (Herrington L, Hatcher J, Hatcher A & McNicholas M., 2009). Nevertheless, contemporary evidence does not support

clearing an athlete for RTS on the basis of balance testing alone. The strongest clinical role of these tests is to complement strength and hop testing and to help guide targeted neuromuscular retraining.

In high-resource settings, three-dimensional motion analysis and force-plate metrics may improve sensitivity, but the absence of laboratory equipment should not prevent clinicians from addressing movement quality. Video-assisted observation of single-leg squats, drop jumps, and change-of-direction tasks can meaningfully strengthen RTS decision-making when the task is standardized and the scoring criteria are explicit.

6. Psychological Readiness and Patient-Reported Outcomes

Functional recovery after ACLR is never purely physical. Fear of reinjury, hesitancy during cutting and landing, and loss of trust in the knee frequently persist even when strength and hop scores improve. For that reason, recent reviews consistently include patient-reported outcome measures (PROMs) and psychological readiness as core components of RTS evaluation (Turk R, Shah S, Chilton M, Thomas TL, Anene C, Mousad A, et al., 2023; Simonsson R, Piussi R, Högberg J, Sundberg A & Hamrin Senorski E., 2024; Kodama E, Tartibi S, Brophy RH, Smith MV, Matava MJ & Knapik DM., 2025; Mengis N, Höher J, Ellermann A, Eberle C, Hartner C, Keller M, et al., 2025).

The ACL-Return to Sport after Injury scale (ACL-RSI) is the most commonly used measure of psychological readiness. In a 2024 systematic review and meta-analysis, Sell and colleagues found that ACL-RSI scores improved early after injury and reconstruction but then remained relatively stable during much of the conventional rehabilitation window, suggesting that fear and confidence deficits may persist despite ongoing physical recovery (Sell TC, Zerega R, King V, Reiter CR, Wrona H, Bullock GS, et al., 2024). The review also noted that the overall certainty of evidence was weak, which further supports repeated monitoring rather than one-time interpretation.

PROMs such as the IKDC or the KOOS Sport and Recreation subscale provide another clinically important perspective. They capture symptoms, perceived function, and sport-related limitations that objective tests may miss. A practical RTS decision is therefore strengthened when PROMs and psychological measures move in the same direction as physical performance. By contrast, low ACL-RSI or IKDC scores despite satisfactory physical performance may indicate the need for continued rehabilitation before return to sport.

7. Timing of RTS Testing and Repeated Interpretation

A central weakness of many existing RTS protocols is not merely what they test, but when they test it. A 2025 systematic review found that RTS testing is administered, on average, at 7.30 months after ACLR, with 6 and 12 months being the most common testing points (Pales Taylor ML, Ihn H, Cushman DM & Bodkin SG., 2025). This timing is problematic because it places much of the literature's RTS assessment earlier than the time frame associated with lower reinjury risk in pivoting sports (Grindem H, Snyder-Mackler L, Moksnes H, Engebretsen L &, Risberg MA., 2016; Pales Taylor ML, Ihn H, Cushman DM & Bodkin SG., 2025).

The solution is not to avoid early testing, but to reinterpret its purpose. Testing at 4 to 6 months is useful for progression decisions such as return to running, more advanced strength work, and early plyometrics. Testing at 7 to 9 months can support late-stage reconditioning and identify residual barriers. Final unrestricted RTS for level I pivoting sports, however, is better conceptualized as a later decision that integrates repeated testing, sport-specific exposure, and an adequate postoperative timeline, ideally 9 months or later (Grindem H, Snyder-Mackler L, Moksnes H, Engebretsen L &, Risberg MA., 2016; Simonsson R, Piussi R, Högberg J, Sundberg A & Hamrin Senorski E., 2024; Pales Taylor ML, Ihn H, Cushman DM &, Bodkin SG., 2025).

This staged approach also helps explain an important clinical tension. Athletes may achieve acceptable results on simplified field-based tests even when graft healing, the physical demands of sport, and the risk of reinjury still suggest that caution is needed. Repeated assessment across recovery phases is therefore more informative than relying on a single pass-or-fail decision near the anticipated return-to-sport date.

8. Proposed Clinically Feasible Battery

Based on the current evidence, an appropriate RTS battery after primary ACLR should prioritize breadth across domains, repeated assessment, and feasibility in real-world practice. The proposed battery in Table 2 is not intended as a universal law or a substitute for clinical judgment. Instead, it offers a pragmatic framework for outpatient clinics, sports medicine

practices, and rehabilitation settings that do not have access to full laboratory biomechanics.

Table 2. Pragmatic domain-based RTS battery for everyday clinical practice

Domain	Suggested assessment	How to interpret it	Minimum progression consideration
Clinical knee status	Pain, effusion, full extension, near-full flexion, tolerance of current training load	Screen for irritability before performance testing	No significant swelling or pain flare after training or testing
Time and exposure	Document months since surgery and recent progression through running, plyometrics, change of direction, and practice	Time is not sufficient alone, but it sets the context for risk	Avoid final clearance for unrestricted pivoting sport before ~9 months after surgery
Strength	Quadriceps and hamstring testing using isokinetic dynamometry, portable dynamometer, or validated field alternative	Interpret LSI together with absolute performance, limb dominance, and contralateral deconditioning	Prefer symmetry of at least 90% plus acceptable sport-relevant strength capacity
Hop and jump performance	At least two tasks, ideally one horizontal (single or crossover hop / 6-m timed hop) and one vertical (single-leg vertical hop)	Record both the score and landing strategy	Do not rely on a single hop task as the decisive clearance criterion
Movement quality	Video-assisted single-leg squat, drop jump, and/or change-of-direction task	Look for valgus collapse, trunk shift, poor eccentric control, asymmetrical loading, and loss of balance	No obvious high-risk compensations on repeated trials
Patient-reported and psychological readiness	ACL-RSI plus IKDC or KOOS Sport/Rec	Use trends and discordance across domains to guide counseling and further intervention	Scores should support—not contradict—the physical testing profile
Sport-specific progression	Controlled practice, reactive drills, fatigue exposure, and gradual return to team training	Final decision should reflect real sporting demands, not only laboratory or clinic tasks	Progress from participation to performance in stages rather than immediate unrestricted competition

Two principles deserve emphasis. First, thresholds should be treated as decision aids rather than guarantees of safety. An athlete may meet every visible criterion and still remain at risk if exposure is advanced too quickly, if task quality deteriorates under fatigue, or if the athlete lacks confidence when competition becomes chaotic. Second, failing one domain should not automatically delay all progress, but it should direct treatment toward the residual problem. For example, an athlete with adequate strength but poor ACL-RSI may need targeted psychological and graded exposure work, whereas an athlete with reassuring questionnaires but marked movement asymmetry requires further neuromuscular

retraining.

9. Limitations of the Current Evidence

The evidence base for RTS testing after ACLR remains heterogeneous. Reviews differ in inclusion criteria, athlete level, surgical techniques, graft types, rehabilitation models, test protocols, and outcome definitions (Golberg E, Sommerfeldt M, Pinkoski A, Dennett L & Beaupre L., 2024; Gill VS, Tummala SV, Sullivan G, Han W, Haglin JM, Marks L & Tokish JM., 2024; Kodama E, Tartibi S, Brophy RH, Smith MV, Matava MJ & Knapik DM., 2025; Pales Taylor ML, Ihn H, Cushman DM & Bodkin SG., 2025). Some studies define success as return to participation, others as return to the same competitive level, and others as absence of reinjury. This heterogeneity makes it difficult to validate one universal battery.

Another limitation is the continued overreliance on LSI. Symmetry is easy to understand and simple to communicate, but it is not equivalent to full recovery (Wang L, Xia Q, Li T, Wang Z & Li J., 2024; Simonsson R, Sundberg A, Piussi R, Högberg J, Senorski C, Thomeé R, et al., 2025). The contralateral limb may also weaken during rehabilitation, and many functional tasks permit compensation patterns that inflate symmetry scores. In addition, much of the literature focuses on young athletes in pivoting sports, so the applicability of the same criteria to older recreational populations is uncertain.

Finally, many promising biomechanics variables are derived from laboratory studies and are not yet standardized for everyday practice. The field therefore needs more validation of portable, low-cost alternatives that preserve as much clinical meaning as possible without demanding specialized motion-analysis infrastructure.

10. Future Directions

Future research should move beyond one-time clearance models and evaluate repeated, phase-specific testing strategies. Portable technology offers a promising route. Recent focused guidance suggests that smartphone-based or sensor-based jump testing, portable dynamometry, and other lower-cost alternatives may allow more clinics to monitor meaningful RTS domains with acceptable validity and feasibility (Mengis N, Höher J, Ellermann A, Eberle C, Hartner C, Keller M, et al., 2025).

Research also needs to determine which combinations of domains—not merely which single tests—best predict safe return to sport. The most clinically relevant outcome is not whether the athlete can pass one battery on one day, but whether the athlete can tolerate progressive exposure to sport without recurrent instability, marked fear, or a second ACL injury. Longitudinal studies that combine strength, movement quality, psychological readiness, and sport-exposure data are likely to be more informative than studies focused on isolated test cutoffs.

11. Conclusion

Functional testing remains indispensable for RTS decision-making after ACLR, but the role of testing has matured. The most useful question is no longer which single test is best, but how a clinician can assemble a battery that samples the domains most relevant to safe and effective return. Contemporary evidence indicates that quadriceps strength, multiple hop or jump tasks, movement-quality assessment, PROMs, and psychological readiness should all contribute to the final decision (Turk R, Shah S, Chilton M, Thomas TL, Anene C, Mousad A, et al., 2023; Gill VS, Tummala SV, Sullivan G, Han W, Haglin JM, Marks L & Tokish JM., 2024; Simonsson R, Piussi R, Högberg J, Sundberg A & Hamrin Senorski E., 2024; Kodama E, Tartibi S, Brophy RH, Smith MV, Matava MJ & Knapik DM., 2025; Mengis N, Höher J, Ellermann A, Eberle C, Hartner C, Keller M, et al., 2025).

Traditional tasks such as the single-leg hop for distance, crossover hop, 6-m timed hop, single-leg squat, and dynamic balance tests remain clinically useful, yet they should be treated as components of a domain-based algorithm rather than as individually decisive clearance tools. For athletes planning to return to pivoting sports, a more cautious return-to-sport timeline, usually no earlier than 9 months after surgery, is better aligned with the documented risk of reinjury. (Grindem H, Snyder-Mackler L, Moksnes H, Engebretsen L & Risberg MA., 2016; Pales Taylor ML, Ihn H, Cushman DM, Bodkin SG., 2025). In practical terms, the strongest RTS decision is the one supported by converging evidence across time, function, movement quality, symptoms, and confidence.

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The Policy-Driven Evolution of Non-Public Hemodialysis Centers in China: A Retrospective Analysis from 2009 to 2025

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Abstract

Background: The number of patients with end-stage renal disease (ESRD) in China continues to rise, while hemodialysis services have long been concentrated in large public hospitals, creating a significant service gap in rural and grassroots areas. Non-public hemodialysis centers, as a crucial supplement to the national healthcare system, have seen their developmental trajectory profoundly shaped by phased adjustments in health policy. ***Methods:*** This study employs a qualitative policy analysis combined with a historical case study approach to examine the evolution of non-public hemodialysis centers in China from 2009 to 2025. We conducted a systematic review of publicly available primary sources, including official policy documents issued by the National Health Commission (NHC), the National Healthcare Security Administration (NHSA), and provincial-level health and medical insurance authorities. Complementary data were drawn from authoritative industry reports, peer-reviewed academic literature, and publicly disclosed corporate information from leading non-public dialysis providers. The analytical framework is structured around a three-phase historical periodization: (1) the Pilot Exploration Phase (2009–2015), (2) the Regulated Expansion Phase (2016–2020), and (3) the Quality-Driven Deepening Phase (2021–2025). Within each phase, we analyzed the interplay between key policy interventions and the strategic responses of the non-public dialysis sector, focusing on how these dynamics shaped operational models and market structures. The authors confirm that large language models (LLMs) or other artificial intelligence (AI)-based tools were used during the preparation of this manuscript solely for language polishing, grammatical refinement, and translation assistance. Specifically, AI tools (including Deepseek) were employed to improve the clarity and fluency of certain English-language passages in the Introduction, Methods, and Discussion sections. All intellectual content, conceptualization, data interpretation, analytical framework, and final editorial decisions were

made exclusively by the human authors. No AI tool was used to generate original scientific content, analyze data, or draft core arguments. In accordance with journal policy, no AI system is listed as an author, nor did it fulfill any authorship role. ***Results:*** The industry's evolution exhibits three distinct phases: Pilot Exploration Phase (2009–2015): Policy shifted from strict control to cautious deregulation, primarily through local pilots, fostering the initial forms of industry-driven and service-driven models. Regulated Expansion Phase (2016–2020): The policy system, centered on the "Basic Standards and Management Regulations for Hemodialysis Centers (for Trial Implementation)" (National Health Commission Document No. [2016] 67), was established, leading to explosive industry growth. The three dominant operational models—industry-driven, service-driven, and capital-driven—were formally established and rapidly expanded. Quality Deepening Phase (2021–2025): Policy focus shifted towards resource decentralization, quality homogenization, and value-based payment, driving the industry from scale-based competition to quality-based competition. The three operational models are now exhibiting trends of deep convergence and upgrading. ***Conclusion:*** The development of non-public hemodialysis centers in China exemplifies a typical path of "state-guided market creation." Through staged interventions characterized by "pilot breakthroughs—regulatory guidance—quality and efficiency enhancement," policy has effectively mobilized social capital to fill public service gaps. This "policy-driven evolution" framework offers a systematic reference for other emerging economies facing similar shortages in specialized medical services. In the future, the industry will continue to evolve towards greater quality, digitalization, and value orientation, becoming deeply integrated into the national chronic kidney disease prevention and treatment system.

Keywords: non-public hemodialysis centers, policy-driven evolution, healthcare reform in China, operational models

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1. Introduction

The global burden of end-stage kidney disease (ESKD) continues to rise, with maintenance hemodialysis (MHD) remaining the predominant form of renal replacement therapy worldwide. In China, the number of MHD patients has grown exponentially over the past decade, driven by an aging population, a high prevalence of diabetes and hypertension, and improved access to healthcare. Meeting this surging demand has posed a formidable challenge to the nation's healthcare system.

The rapid expansion of MHD services in China has been significantly driven by the growth of non-public hemodialysis centers. In the Chinese context, "non-public medical institutions" refer to healthcare facilities established and operated by social capital (including private enterprises and individuals), as distinct from government-run public hospitals. This development trajectory is deeply rooted in the national healthcare reform initiated in 2009, one of whose core objectives was to encourage social capital to enter the medical sector to alleviate the severe shortage of healthcare resources and expand service accessibility. Against this backdrop, non-public dialysis centers have emerged as a crucial force in meeting the surging demand for renal replacement therapy.

Unlike the market-driven models prevalent in the United States or the publicly dominated systems in many European countries, China's non-public dialysis sector has evolved under a unique "policy-driven" paradigm. National and provincial health authorities have not only permitted but actively shaped the entry, operation, and strategic direction of these private entities through a series of targeted regulatory and reimbursement policies. This top-down guidance has led to a dynamic co-evolution between government policy and industry response, resulting in distinct operational models that are now converging toward a more integrated and quality-focused paradigm.

This paper aims to trace and analyze this policy-driven evolution from 2009 to 2025. By delineating three distinct developmental phases—Pilot Exploration (2009–2015), Regulated Expansion (2016–2020), and Quality-Driven Deepening (2021–2025)—we elucidate how successive waves of policy interventions have steered the non-public dialysis market. Finally, we discuss the implications of China's experience for other low- and middle-income

countries seeking to leverage private investment to address critical gaps in specialized care delivery.

2. Policy Thaw and Industry Incubation (2009-2015): From Strict Control to Local Pilots

2.1 Policy Context: Institutional Deregulation Driven by Demand

Prior to 2009, China's hemodialysis sector was trapped in a "triple dilemma" of high demand, low supply, and stringent market access (Ming Minxin & Li Weiping, 2018). The "Detailed Rules for the Implementation of the Administrative Regulations on Medical Institutions" did not classify "hemodialysis center" as an independent category of medical institution, making it impossible for social capital to independently establish such facilities. Nearly one-third of China's county-level administrative regions lacked any dialysis service capacity, making it extremely difficult for grassroots patients to access care (Ma Dandan, 2011).

In November 2009, a widely reported incident in Tongzhou, Beijing, where uremic patients spontaneously organized a "self-help dialysis room," sparked nationwide attention on dialysis accessibility and became a direct catalyst for policy deregulation (Liu Zichen, 2015; Zhou Xiaomei, 2009). The central government began to reassess the supplementary role of non-public capital in specialized medical fields, shifting its policy stance from "strict prohibition" to "tacit exploration."

In 2011, the former Ministry of Health officially approved Weigao Group and Dakang Medical to pilot non-public hemodialysis centers in Shandong Province. This marked the first time the central government formally supported social forces in independently operating dialysis institutions via an official document, representing a milestone event. In 2012, six ministries, including the National Development and Reform Commission, included ESRD in the coverage of the Urban and Rural Residents' Critical Illness Insurance, with a reimbursement rate of no less than 50%. This significantly unleashed patient treatment demand and created a potential market space for non-public medical providers (National Development and Reform Commission, Ministry of Health, Ministry of Finance et al., 2012).

In 2014, the former National Health and Family Planning Commission issued a notice soliciting opinions on the "Basic Standards and Management Regulations for Hemodialysis Centers," explicitly stating for the first time that "independently set up hemodialysis centers" would be permitted, thereby removing the core institutional barrier to their independent establishment (Bureau of Medical Administration, 2016).

During this phase, policy was characterized by "central tacit approval and local leadership," lacking a unified national standard. For instance, Shanxi Province issued its own local trial standards in 2015 (Shanxi Provincial Health and Family Planning Commission, 2015), which differed from explorations in other regions. Although this created regional barriers in the short term, it also accumulated diverse local experiences that informed the subsequent formulation of national unified regulations (Guangdong Provincial Health and Family Planning Commission, 2017).

2.2 Industry Response: From Grassroots Self-Help to the Emergence of Operational Models

Partial policy deregulation stimulated the earliest market explorations. Industry players evolved from emotionally charged grassroots self-help initiatives towards standardized, corporate operations. In November 2009, Shenyang SanSheng Company established the "SanSheng Kidney Friends Home" in Jinzhou, Liaoning, widely regarded as the nation's first independently operated hemodialysis center, marking a critical transition from "self-help" to "institutionalized care."

Under the Shandong pilot framework, enterprises with different resource endowments embarked on differentiated paths: Weigao Group, leveraging its industrial advantage in blood purification equipment and consumables, experimented with an "equipment + service" vertical integration strategy, laying the early groundwork for an "industry-driven" model. Dakang Medical, on the other hand, focused on the operation and management of dialysis services in underserved grassroots markets, exploring a viable model to enhance accessibility and establishing the foundation for a "service-driven" approach.

Despite early challenges such as insufficient patient trust and high operating costs, these explorations validated the commercial feasibility of non-public dialysis services. Between 2012 and 2015, encouraged by the Shandong pilot, social capital began to penetrate into county-level

markets across more provinces. During this period, Dakang Medical established nearly 30 centers in counties in Jiangxi and Shandong, forming a grassroots service model characterized by "small scale, low cost, high turnover, and strong referral networks" (Zhou Li & Fu Ping, 2017). However, due to the absence of national standards, the industry as a whole exhibited a "sporadic expansion with deficient regulation," calling for the introduction of unified national guidelines.

Table 1. Policy and Industrial Development Timeline of China's Non-Public Hemodialysis Centers (2009–2025)

Developmental Phase	Time Point	Key Policy Events	Core Industrial Responses & Quantitative Data
Pilot Exploration (2009–2015) Strict Control → Tacit Deregulation	2009	Tongzhou self-help dialysis room incident sparks national attention on ESRD care accessibility	Shenyang SanSheng establishes China's first non-public hemodialysis center ("SanSheng Kidney Friends Home") in Jinzhou
	2011	Former Ministry of Health approves Weigao & Dakang to launch Shandong provincial pilots	Industry-driven (Weigao) and service-driven (Dakang) models take initial shape
	2012	Six ministries include ESRD in Urban and Rural Residents' Critical Illness Insurance (**reimbursement rate ≥50%**)	Latent ESRD treatment demand released; social capital begins to enter county-level markets
	2014	Former NHFPC solicits opinions on hemodialysis center standards (first official approval for independent establishment)	Core institutional barriers for non-public centers are removed
	2015	Shanxi releases local trial standards for independent hemodialysis centers	Regional pilot experiences accumulated for national unified regulations
Regulated Expansion (2016–2020) National Standardization → Explosive Growth	2016	NHC issues **Document No. [2016] 67** (core national regulation for hemodialysis centers); *Healthy China 2030* outlines socialization/specialization of dialysis services	67 Document grants non-public centers independent legal status; **<50 non-public centers nationwide by late 2016**
	2017	Medical institution regulations revised to list "hemodialysis center" as an independent category	Local governments (Hebei/Guangdong) streamline approval processes to boost market vitality
	2019	NHC issues policies to support chain operation of socially operated medical institutions	Capital-driven model (Changsheng Medical) formally emerges; three dominant models take shape
Quality Deepening	2021	National Kidney Disease Medical Quality Control Center releases *2021 Standard Operating Procedures*	Industry shifts focus to core quality indicators (Kt/V attainment, infection control);

Developmental Phase	Time Point	Key Policy Events	Core Industrial Responses & Quantitative Data
(2021–2025) Scale Competition → Quality-Oriented Development		*for Blood Purification*	digital quality control platforms built by leading enterprises
	2022	NHC issues graded diagnosis guidelines for county-level CKD; medical institution planning principles encourage grassroots layout	Non-public centers transform into CKD management nodes; expansion strategy shifts to "regional deep cultivation"
	2024	Sichuan/Hunan issue grassroots dialysis support policies; Hunan launches "Shen Xiao Bao" AI-IoT intelligent supervision platform	Service network extends to townships; industry models begin convergence (industry + service dual-drive)
	2025	NHC lists "hemodialysis service for all counties with permanent population >60,000" as a key livelihood initiative	Guangdong has the highest number of non-public centers nationwide; non-public centers account for a significantly increased proportion in county-level markets (Hunan/Sichuan); three models realize deep convergence and upgrading

Abbreviations: NHC, National Health Commission; ESRD, end-stage renal disease.

3. Policy Standardization and Industry Expansion (2016–2020): From Local Pilots to National Uniformity

3.1 Core Policy: A Full-Chain Institutional Framework Built on Document No. 67

The year 2016 was the "policy founding year" for the industry. The issuance of the "Basic Standards and Management Regulations for Hemodialysis Centers (for Trial Implementation)" (National Health Commission Document No. [2016] 67) marked the beginning of a new era of nationally unified regulation (National Health and Family Planning Commission, 2016). During this phase, a full-chain policy support system was formed:

Strategic Anchoring at the Top Level: The "Healthy China 2030" Planning Outline, for the first time at the national strategic level, proposed guiding the development of specialized hemodialysis centers, clarifying their direction towards socialization and specialization (State Council, 2016).

Establishment of Core Regulations: Document No. 67 granted non-public hemodialysis centers an independent legal status as medical institutions, fundamentally resolving the institutional barriers to their practice, inclusion in the medical insurance network, and scaled development. The document set reasonable entry thresholds (at least 10 dialysis machines), scientific staffing ratios (specifying qualifications and numbers for physicians and nurses), and explicitly "encouraged chain and group operations," charting a course for the industry's intensive development (National Health and Family Planning Commission, 2016).

Refinement of Supporting Policies: In 2017, the "Detailed Rules for the Implementation of the Administrative Regulations on Medical Institutions" were revised to formally include "hemodialysis center" as a category of medical institution (National Health and Family Planning Commission of the People's Republic of China, 2017). In 2019, the "Opinions on Promoting the Continuous, Healthy, and Regulated Development of Socially Operated Medical Institutions" further emphasized support for chain operations and optimized the approval and regulatory environment (National Health Commission, National Development and Reform Commission, Ministry of Science and Technology et al., 2019). Local governments also issued implementation rules; for example, Hebei and

Guangdong provinces actively streamlined approval processes to stimulate market vitality (Office of the Hebei Provincial Health and Family Planning Commission, 2017; General Office of the People's Government of Guangdong Province, 2016).

3.2 Industry Response: Explosive Growth and the Formation of Three Dominant Models

Propelled by unified policies and stable medical insurance payments, the industry entered a period of high-speed expansion and solidified three distinct mainstream operational models.

Rapid Institutional Growth: At the end of 2016, there were fewer than 50 non-public hemodialysis centers nationwide; by the end of 2018, this number had surged to 559, an increase of over tenfold in just two years (Mei Changlin, Lou Jing & Wang Jiusheng, 2023). Although their share of the total national dialysis service units remained below 10%, the foundation for networked and branded development was firmly laid.

Establishment and Differentiation of the Three Models:

Industry-Driven Model (represented by Weigao Healthcare): Leveraging its parent company's absolute dominance in the dialysis equipment and consumables market (e.g., domestic market share of dialyzers and tubing exceeding 30%), it built an integrated industrial closed loop of "R&D and manufacturing of equipment/consumables + chain operation of centers + patient services." It achieved rapid, standardized replication in grassroots markets through supply chain cost advantages and technological feedback.

Service-Driven Model (represented by Dakang Medical): Precisely targeting county-level markets underserved by public hospitals, its core strategy involved constructing a multi-party payment mechanism combining "medical insurance reimbursement + charitable assistance + center subsidies" to address patients' financial burdens. Simultaneously, it provided holistic "whole-person" care services, including nutritional guidance, psychological support, and social reintegration, building deep patient loyalty and a strong reputation barrier at the grassroots level.

Capital-Driven Model (represented by Changsheng Medical): Backed by financial capital such as Xingjun Industrial Investment, it pursued rapid nationwide expansion through leveraged acquisitions. Its core competitiveness lay in developing a replicable "standardized operating system," exporting unified SOPs, centralized procurement platforms, and information management systems to acquired institutions. This approach reduced costs through economies of scale and explored value-added services.

During this phase, the main theme of industry competition was "staking out territory." However, the regulatory role of policy had already steered the market from "disorder" towards "order," and the competitive landscape among leading enterprises began to take shape (Mei Changlin, Lou Jing & Wang Jiusheng, 2023).

Table 2. Core Characteristics of the Three Dominant Operational Models of China's Non-Public Hemodialysis Centers

Comparative Dimension	**Industry-Driven Model**	**Service-Driven Model**	**Capital-Driven Model**
Representative Enterprise	Weigao Medical Holdings Co., Ltd.	Dakang Medical Management Co., Ltd.	Beijing Changsheng Zhongkang Hospital Management Co., Ltd.
Core Development Logic	Vertical integration of **dialysis equipment/consumables R&D/manufacturing + chain center operation + patient services** (industrial chain synergy)	Grassroots ESRD care accessibility improvement + holistic "whole-person" patient services + multi-party payment mechanism	Leveraged acquisitions + standardized operational system output + economies of scale for cost reduction
Key Competitive	Strong supply chain cost control; technological	Deep grassroots patient loyalty; multi-	Replicable unified SOPs/centralized

Advantages	feedback from equipment R&D to clinical services; high standardization of replication	party payment to alleviate patients' financial burden; strong regional referral networks	procurement/information systems; rapid nationwide expansion capacity
Target Market	County-level grassroots markets nationwide; areas with basic medical resource coverage	Underserved county/township-level grassroots markets; low-to-middle income ESRD patient groups	National multi-level markets (urban + county); potential high-quality local dialysis institutions for acquisition
Core Operational Features	Builds an integrated industrial closed loop; relies on equipment/consumables market dominance (**≥30%** domestic share for dialyzers/tubing)	Provides one-stop services (dialysis + nutrition guidance + psychological support + social reintegration); small-scale, high-efficiency grassroots layout	Exports standardized management systems to acquired institutions; explores value-added medical services; balances scale expansion and quality control
Development Trend (2021–2025)	Strengthens industrial chain advantages + builds professional service brand for patient loyalty	Seeks upstream industrial integration/strategic partnerships for supply chain safety	Establishes benchmark hospitals + unified national quality control system for homogeneous medical quality

Abbreviations: SOPs, standard operating procedures.

4. Policy Enhancement and Industry Convergence (2021–2025): From Scale Growth to Quality Deepening

4.1 Core Policy: Systemic Optimization Oriented Towards Quality and Efficiency

After 2021, the policy focus shifted from "encouraging establishment" to "optimizing and upgrading," aiming to build a policy system that guides high-quality development.

Guiding Resource Decentralization and Optimizing Layout: The "Technical Guidelines for Graded Diagnosis and Treatment of Chronic Diseases, including Chronic Kidney Disease, in County Areas" promoted the transformation of dialysis centers from simple treatment points into nodes for chronic disease management (General Office of the National Health Commission, General Office of the National Administration of Traditional Chinese Medicine, 2022). The "Guiding Principles for the Planning of Medical Institution Establishment (2021–2025)" explicitly encouraged non-public hemodialysis centers to locate in areas with weak medical resources (National Health Commission, 2022). In 2025, the National Health Commission listed "ensuring that every county with a permanent population exceeding 60,000 can provide hemodialysis services" as a key livelihood initiative, directly targeting "county-township collaboration and accessible care" (National Health Commission, 2026). Provinces like Sichuan and Hunan have also introduced corresponding policies to extend the service network to townships (General Office of the CPC Sichuan Provincial Committee, General Office of the Sichuan Provincial People's Government, 2024; General Office of the Hunan Provincial People's Government, 2018).

Unifying Technical Standards and Strengthening the Quality Foundation: The 2021 edition of the "Standard Operating Procedures for Blood Purification" was released, becoming the "technical constitution" that the entire industry must follow (National Kidney Disease Medical Quality Control Center, 2021).

Strengthening Regulation and Innovating Payment to Drive Quality Improvement: Non-public centers were fully integrated into the same medical quality control system as public hospitals. Medical insurance payment methods began to shift from "fee-for-service" towards "value-based payment." For example, Sichuan

Province has linked a portion of its payments to the completion rates of key monitoring indicators in the treatment process (Sichuan Provincial Healthcare Security Administration, 2025), while Hunan Province has provided incentives for grassroots services by consolidating price items (Hunan Provincial Healthcare Security Administration, 2025).

Local Innovative Practices: Guangdong Province has continuously optimized its "streamlining administration, delegating power, and improving regulation and services" (Fangguanfu) reforms, resulting in the highest number of non-public centers nationwide by the end of 2025 (General Office of the People's Government of Guangdong Province, 2016). Hunan Province's "Shen Xiao Bao" intelligent supervision platform, which integrates AI and IoT technologies, has formed a closed-loop policy ecosystem of "price standardization + intelligent supervision + decentralization metrics" (Hunan Provincial Healthcare Security Administration, 2025).

4.2 Industry Response: Quality Competition and the Upgraded Convergence of Models

Guided by policy, the fundamental logic of industry development has undergone a transformative shift, entering a new phase where quality is paramount.

Industry Reshuffling, with Quality as the Lifeline: Stricter regulation and payment reforms have squeezed the survival space of small, medium-sized, and non-compliant institutions, leading to increased industry concentration. The focus of competition has shifted to core quality indicators such as Kt/V attainment rate, infection control, and complication management (National Kidney Disease Medical Quality Control Center, 2021). Leading enterprises are all building digital quality control platforms to enable real-time monitoring and continuous improvement of the treatment process.

Operational Strategies Evolving Towards Intensification and Convergence: The expansion strategy has shifted from "nationwide site deployment" to "regional deep cultivation," with efforts to expand the scale of individual centers to amortize costs. There is active penetration into townships and deep integration with county-level medical consortia, becoming a key force in filling grassroots gaps. By the end of 2025, the proportion of non-public centers in county-level and lower markets in provinces like Hunan and Sichuan has significantly increased.

Strategic Convergence of the Three Models: Industry + Service Dual-Drive: Weigao, while strengthening its industrial chain advantages, is vigorously building its service brand to enhance patient loyalty. Service-oriented enterprises like Dakang are seeking upstream integration or strategic partnerships to secure supply chain safety and cost advantages.

Balancing Scale and Quality: Capital-driven enterprises like Changsheng Medical, during their expansion, are establishing benchmark hospitals and unified quality control systems to ensure homogeneous medical quality at scale.

Digital Transformation as a Consensus: Regardless of the model, building data platforms to connect devices, services, patients, and payers has become the "new infrastructure" for enhancing both operational efficiency and medical quality.

Moving Jointly Towards Value-Based Healthcare: Driven by medical insurance payment reforms, all models are committed to shifting from "providing dialysis treatment" to "managing patient health," aiming to achieve a unity of social and economic benefits by improving patients' long-term health outcomes (General Office of the National Health Commission, General Office of the National Administration of Traditional Chinese Medicine, 2022).

5. Discussion and Conclusion

5.1 Core Findings

This study systematically analyzes the development and model evolution of China's non-public hemodialysis centers from 2009 to 2025, revealing the intrinsic mechanism of the "policy-driven evolution" framework:

Policy-Driven Mechanism: Policy has evolved from breaking the ice under strict control, to enabling scale expansion under comprehensive regulation, and finally to driving quality deepening with a focus on quality and efficiency. This clear evolutionary thread has directly shaped the industry's developmental stages and market structure.

Model Evolution Pathway: During the Policy Thaw Phase (2009–2015), local pilots broke through institutional barriers, incubating the initial forms of industry-driven and service-driven models.

During the Comprehensive Regulation Phase

(2016-2020), core policies like Document No. 67 removed institutional obstacles, triggering explosive growth in the number of institutions. The capital-driven model emerged, and the three mainstream models were formally established.

During the Quality and Efficiency Enhancement Phase (2021-2025), the synergistic effects of resource decentralization, standard unification, strengthened regulation, and payment innovation have forced the industry to shift from scale competition to quality competition, with the three models now showing characteristics of convergence and upgrading.

5.2 Policy Implications

The development of China's non-public hemodialysis centers demonstrates that the healthy development of non-public medical services in specialized fields requires a full-cycle policy system of "guidance—regulation—quality enhancement":

Initial Stage: Break down entry barriers through pilot exploration and institutional deregulation to create space for social capital participation. It is recommended to further simplify approval procedures and implement a "filing + commitment" system to lower entry thresholds.

Expansion Stage: Use unified standards and supporting policies to regulate market order and guide orderly industry development. It is recommended to establish nationally unified construction and operational standards for hemodialysis centers to avoid regional barriers caused by differing local standards.

Mature Stage: Promote high-quality industry transformation through quality control and payment innovation. It is recommended to deepen reforms in medical insurance payment methods, linking payments to quality indicators such as dialysis adequacy and patient satisfaction, and establishing an incentive mechanism for "pay-for-value."

5.3 International Comparison

Placing the development of China's non-public hemodialysis centers in a global context reveals that it differs from both the dominant models of mature Western markets and the innovative practices of other emerging economies.

The pure service-operation model represented by DaVita in the United States achieves maximum efficiency through highly standardized and scaled management (BELLO A K, MCISAAC M, OKPECHI I G, et al., 2021). In contrast, the vertically integrated model represented by Fresenius in Germany builds a "product-to-service" closed loop by leveraging its advantages in equipment and consumable manufacturing (HUG N, NEYENHUY S A & NIENABER A., 2024). Both are built upon a sound medical insurance payment system and a mature healthcare market, but the former is prone to industrial monopolies, while the latter demands extremely high levels of capital and operational capability.

By comparison, India's NephroPlus adopts a frugal, light-asset approach, focusing on low-income populations and rapidly improving dialysis accessibility through management output, digital tools, and local partnerships, embodying typical "frugal innovation" (ALEXANDER S, JASUJA S, GALLIENI M, et al., 2021).

China's non-public hemodialysis centers, however, have followed a unique path of "state-guided market creation." The government did not allow the market to evolve spontaneously but instead used phased policy interventions—from early local pilots, to mid-term unified standards for regulated entry, to late-stage promotion of quality homogenization and value-based payment—to systematically mobilize social capital into this highly regulated, specialized field.

In this process, three indigenous models—industry-driven (e.g., Weigao), service-driven (e.g., Dakang), and capital-driven (e.g., Changsheng)—have gradually taken shape and are converging. They have absorbed Fresenius's ideas on industrial chain synergy, borrowed DaVita's concepts of standardized operations, and simultaneously addressed the grassroots accessibility challenges similar to those faced by NephroPlus. However, their core driver is not the market or technology, but the sustained guidance of national strategy and public policy.

This path has effectively avoided the accessibility inequities caused by excessive commercialization in the U.S. market and overcome the limitations of insufficient social capital participation in the German model. It has also secured more systematic institutional support and broader scaling opportunities than India's NephroPlus.

5.4 Study Limitations

This study has several limitations. First, our analysis is based primarily on publicly available secondary data, including policy texts, industry

reports, and corporate disclosures. Crucially, this study lacks access to granular, quantitative operational and clinical datasets from individual dialysis centers. Consequently, we are unable to empirically compare the three dominant operational models (hospital-affiliated, chain-operated, and PPP-based) in terms of their efficiency, cost-effectiveness, or direct impact on patient-centered outcomes such as survival rates, hospitalization frequency, or quality of life. Second, the dynamic nature of the healthcare policy environment means that emerging regulations post-2025 may alter the trajectories described herein. Third, our focus on the national level may overlook significant regional variations in policy implementation and market development.

Future research should prioritize the collection and analysis of comprehensive center-level databases encompassing financial, operational, and clinical metrics. Such data would enable rigorous econometric modeling to test the "convergence hypothesis" proposed in this paper and to quantify the real-world impact of different operational models on patient value and system sustainability.

Data Availability

Data are available on request to the corresponding author Dr. Jiusheng Wang (e-mail: wangjiusheng009@163.com).

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Current Status and Future Perspectives of Endocrine Therapy for Breast Cancer: From Classical Approaches to the Evolution of Precision Systemic Medicine

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Abstract

Hormone receptor-positive breast cancer is the most prevalent molecular subtype of breast cancer. Its therapeutic strategy has progressively evolved from simple endocrine deprivation toward a systematic management model centered on endocrine therapy and integrated with molecularly targeted treatment and dynamic monitoring. This review summarizes the developmental trajectory of endocrine therapy for breast cancer, outlines the classical therapeutic agents and combination strategies used after endocrine resistance, and discusses future directions driven by liquid biopsy, artificial intelligence, and emerging estrogen receptor degradation technologies.

Keywords: breast cancer, endocrine therapy, CDK4/6 inhibitors, resistance, liquid biopsy, precision medicine

1. Introduction: From Empirical Observation to the Era of Precision Medicine

Breast cancer remains one of the most common malignancies among women worldwide. According to the World Health Organization, approximately 2.3 million new cases and 670,000 deaths were recorded globally in 2022. (World Health Organization, 2025) In China, the burden of breast cancer continues to increase, with an overall upward trend in incidence over recent decades, making it a major challenge in cancer prevention and control among women. (Lei S, Zheng R, Zhang S, et al., 2021) Within the current molecular classification framework, hormone receptor-positive/HER2-negative breast cancer accounts for approximately 70% of all breast cancers. Because its biological behavior is closely associated with persistent activation of estrogen signaling, endocrine therapy has long served as the therapeutic cornerstone for this subtype. (Lim E, Metzger-Filho O & Winer EP., 2012)

The history of endocrine therapy for breast cancer dates back to the late nineteenth century. In 1896, Beatson first reported clinical remission in advanced breast cancer following oophorectomy, thereby establishing the

fundamental concept that estrogen-dependent tumors could be treated through hormonal manipulation. (Beatson GT., 1896) In the second half of the twentieth century, the clinical introduction of tamoxifen shifted endocrine treatment from invasive endocrine ablation to long-term pharmacologic intervention and marked a major milestone in modern anti-estrogen therapy. (Jordan VC., 2014)

2. Mechanisms of Action and Clinical Applications of Endocrine Therapeutic Agents

2.1 Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators act by competitively binding to the estrogen receptor and exert mainly antagonistic effects in breast tissue. Representative agents include tamoxifen and toremifene. (Robert NJ., 1996) A patient-level meta-analysis by the Early Breast Cancer Trialists' Collaborative Group demonstrated that approximately 5 years of adjuvant tamoxifen significantly reduced the long-term risks of recurrence and breast cancer-specific mortality in patients with estrogen receptor-positive early breast cancer. (Early Breast Cancer Trialists' Collaborative Group, 2011) Regarding extended therapy, the ATLAS trial showed that prolonging tamoxifen treatment from 5 to 10 years further reduced the risks of late recurrence and breast cancer-related death. (Davies C, Pan H, Godwin J, et al., 2013)

2.2 Aromatase Inhibitors

In postmenopausal women, estrogen is derived predominantly from the peripheral conversion of androgens by aromatase. Aromatase inhibitors markedly reduce circulating estrogen levels by blocking this key enzymatic step. (Geisler J., 2011) The ATAC trial established that anastrozole was superior to tamoxifen as initial adjuvant therapy, providing further improvements in disease-free survival and lowering the risk of recurrence. (Cuzick J, Sestak I, Baum M, et al., 2010) The BIG 1-98 trial further supported the important role of letrozole in the adjuvant treatment of postmenopausal patients with hormone receptor-positive early breast cancer. (Ruhstaller T, Giobbie-Hurder A, Colleoni M, et al., 2019) For patients at higher risk of recurrence, prolonged aromatase inhibitor therapy may confer additional benefit. The MA.17R trial showed that extending adjuvant endocrine therapy to 10 years improved disease-free survival and reduced the incidence of contralateral breast cancer. (Goss PE, Ingle JN, Pritchard KI, et al., 2016)

2.3 Selective Estrogen Receptor Downregulators

Fulvestrant binds to the estrogen receptor and promotes receptor degradation, thereby achieving more complete suppression of ER signaling. (Wardley AM., 2005) The FALCON trial demonstrated that, in endocrine therapy-naïve patients with hormone receptor-positive advanced breast cancer, fulvestrant significantly prolonged progression-free survival compared with anastrozole, with a more pronounced effect observed in patients without visceral metastases. (Robertson JFR, Bondarenko IM, Trishkina E, et al., 2016)

2.4 Ovarian Function Suppression

In premenopausal patients, adequate endocrine efficacy depends on effective suppression of ovarian estrogen production. (Klijn JGM, Blamey RW, Boccardo F, et al., 2001) The SOFT and TEXT trials demonstrated that, in premenopausal patients with hormone receptor-positive early breast cancer at higher risk of recurrence, ovarian function suppression combined with exemestane further improved disease-free survival compared with ovarian function suppression combined with tamoxifen. (Pagani O, Francis PA, Fleming GF, et al., 2020)

2.5 Emerging Endocrine Therapeutic Agents

To overcome the limitations associated with intramuscular administration and pharmacokinetics of fulvestrant, oral selective estrogen receptor degraders have become a major focus of recent drug development. (Bardia A, Kaklamani VG, Neven P, et al., 2024) The phase III EMERALD trial demonstrated that, in patients with ER-positive/HER2-negative advanced breast cancer previously treated with endocrine therapy and largely exposed to CDK4/6 inhibitors, elacestrant significantly improved progression-free survival compared with standard endocrine therapy, with more clearly defined benefit in the ESR1-mutant population. (Bidard FC, Kaklamani VG, Neven P, et al., 2022) Based on these findings, the U.S. Food and Drug Administration approved elacestrant in 2023 for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer. (U.S. Food and Drug Administration, 2023) In addition, next-generation oral ER-targeting agents such as camizestrant and giredestrant remain under phase III clinical investigation, indicating that oral ER-directed treatment is still undergoing rapid development. (Hamilton EP, Jhaveri K, Kuemmel S, et al., 2025) PROTAC-based estrogen

receptor degraders provide a novel technological platform for ER-targeted therapy. Reported in 2025, the VERITAC-2 trial showed that vepdegestrant outperformed fulvestrant in the ESR1-mutant subgroup, supporting the translational potential of ER protein degradation strategies. (Campone M, Neven P, Oliveira M, et al., 2025)

3. Combination Strategies and Novel Agents for Endocrine Resistance

3.1 CDK4/6 Inhibitors

CDK4/6 inhibitors represent one of the most important therapeutic advances in hormone receptor-positive advanced breast cancer over the past decade. (de Melo Gagliato D, Cortes J, Curigliano G, et al., 2020) The MONALEESA-7 trial demonstrated that, in premenopausal or perimenopausal patients with HR-positive/HER2-negative advanced breast cancer, ribociclib combined with endocrine therapy not only significantly prolonged progression-free survival but also yielded a clear overall survival benefit. (Im SA, Lu YS, Bardia A, et al., 2019) In high-risk early-stage disease, the monarchE trial showed that abemaciclib combined with standard adjuvant endocrine therapy improved invasive disease-free survival, thereby establishing its role in the adjuvant treatment of high-risk early HR-positive/HER2-negative breast cancer. (Johnston SRD, Harbeck N, Hegg R, et al., 2023) In addition, studies of abemaciclib in patients with brain metastases demonstrated central nervous system penetration and modest intracranial activity, providing a rationale for systemic treatment exploration in patients with metastases at special anatomical sites. (Tolaney SM, Sahebjam S, Le Rhun E, et al., 2020)

3.2 Inhibitors of the PI3K/AKT/mTOR Pathway

Aberrant activation of the PI3K/AKT/mTOR signaling pathway is one of the major molecular drivers of endocrine resistance. (Razavi P, Dickler MN & Shah PD., 2023) The BOLERO-2 trial showed that everolimus combined with exemestane significantly improved progression-free survival in patients whose disease had progressed after treatment with nonsteroidal aromatase inhibitors. (Piccart M, Hortobagyi GN, Campone M, et al., 2014) In the context of molecularly stratified treatment, the SOLAR-1 trial demonstrated that alpelisib combined with fulvestrant significantly improved progression-free survival in patients with PIK3CA-mutant HR-positive/HER2-negative advanced breast cancer, although toxicities such as hyperglycemia and rash require careful management. (André F, Ciruelos E, Rubovszky G, et al., 2019) The CAPItello-291 trial further showed that capivasertib plus fulvestrant improved progression-free survival in HR-positive/HER2-negative advanced breast cancer, with more pronounced benefit observed in tumors harboring PIK3CA, AKT1, or PTEN alterations. (Turner NC, Oliveira M, Howell SJ, et al., 2023) This regimen received FDA approval in 2023, marking an important step toward routine clinical implementation of AKT pathway-targeted therapy. (U.S. Food and Drug Administration, 2023)

3.3 Epigenetic Therapy

Epigenetic abnormalities are closely linked to ER signaling reprogramming and endocrine resistance. (Garcia-Martinez L, Zhang Y, Nakata Y, et al., 2021) The ACE trial showed that tucidinostat combined with exemestane improved progression-free survival in postmenopausal patients with HR-positive advanced breast cancer, providing clinical support for the use of HDAC inhibitors after endocrine resistance. (Jiang Z, Li W, Hu X, et al., 2019)

3.4 Antibody-Drug Conjugates

With the changing landscape of later-line treatment, antibody-drug conjugates are entering the therapeutic sequence for HR-positive breast cancer. (Bardia A, Hurvitz SA, Tolaney SM, et al., 2021) The DESTINY-Breast04 trial demonstrated that trastuzumab deruxtecan significantly improved progression-free survival and overall survival in patients with HER2-low metastatic breast cancer, the majority of whom had hormone receptor-positive disease. (Modi S, Jacot W, Yamashita T, et al., 2022) The TROPiCS-02 trial showed that sacituzumab govitecan improved progression-free survival and overall survival compared with physician's choice chemotherapy in patients with heavily pretreated HR-positive/HER2-negative metastatic breast cancer. (Rugo HS, Bardia A, Marmé F, et al., 2023)

4. Future Perspectives: Toward Dynamic Monitoring and Precision Decision-Making

ESR1 mutation is one of the key mechanisms underlying acquired endocrine resistance in advanced HR-positive breast cancer, and circulating tumor DNA testing offers a practical, noninvasive tool for its dynamic detection. (Venetis K, Crimini E, Sajjadi E, et al., 2023) The

integration of multi-omic data is reshaping the research paradigm for treatment response prediction in breast cancer. Machine learning models can combine genomic, transcriptomic, tumor microenvironmental, and clinical data to build predictive frameworks for therapeutic response and recurrence risk. (Sammut SJ, Crispin-Ortuzar M, Chin SF, et al., 2022) Beyond ER itself, epigenetic regulation, metabolic reprogramming, and the immune microenvironment are emerging as additional directions for resistance intervention. Strategies involving epigenetic targets such as EZH2 and BET, as well as engineered T-cell therapies and personalized vaccines, remain largely in early-stage development. (Chamorro DF, Parihar A, Fain K, et al., 2023)

5. Conclusion

Endocrine therapy for breast cancer has progressed from early empirical oophorectomy to a systematic and precision-based therapeutic framework encompassing adjuvant treatment for early disease as well as first-line and later-line treatment for advanced disease. Tamoxifen, aromatase inhibitors, fulvestrant, and ovarian function suppression form the classical foundation of endocrine treatment, whereas CDK4/6 inhibitors and PI3K/AKT/mTOR pathway inhibitors have reshaped the therapeutic landscape after endocrine resistance. At the same time, oral SERDs, PROTAC degraders, liquid biopsy, and artificial intelligence-based multi-omic integration are driving the management of HR-positive breast cancer away from fixed sequential treatment patterns and toward dynamic monitoring, molecular stratification, and individualized decision-making. Future research should focus on clarifying the optimal treatment sequence for different molecular subgroups, defining key nodes in resistance evolution, and characterizing long-term real-world benefit, with the goal of prolonging survival while better preserving quality of life.

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Local Treatment Strategies in Renal Cell Carcinoma: Current Evidence and Future Directions

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Abstract

The role of local treatment in renal cell carcinoma has been substantially refined in recent years. In localized disease, partial nephrectomy remains the standard treatment because it offers durable oncologic control, complete pathological assessment, and nephron preservation. With the development of cryoablation, radiofrequency ablation, microwave ablation, and stereotactic body radiotherapy, non-surgical local therapies have become important options for selected patients. Percutaneous ablation is best supported in small and technically accessible tumors, whereas stereotactic body radiotherapy provides a noninvasive alternative for patients unsuitable for surgery or invasive procedures. In metastatic renal cell carcinoma, cytoreductive nephrectomy has shifted from a routine upfront strategy to a selective intervention determined by patient selection and treatment sequencing. In oligometastatic and oligoprogressive disease, metastasis-directed local therapy may delay systemic treatment initiation, maintain the benefit of ongoing systemic therapy, and prolong disease control. Overall, local treatment for renal cell carcinoma has moved from isolated technical application toward stage-specific and precision-based integration. Future studies should further clarify indication boundaries, patient selection, treatment timing, long-term renal outcomes, and prospective comparative evidence.

Keywords: renal cell carcinoma, local treatment, partial nephrectomy, stereotactic body radiotherapy, cytoreductive nephrectomy

1. Introduction

The scope of local treatment in renal cell carcinoma has expanded in recent years. In localized disease, partial nephrectomy remains the core treatment, while non-surgical modalities such as thermal ablation and stereotactic body radiotherapy have broadened treatment options beyond surgically fit patients. The 2025 European Association of Urology guideline recommends partial nephrectomy for T1 tumors and considers tumor ablation or stereotactic body radiotherapy for cT1 tumors requiring treatment but unsuitable for surgery. (Bex A, Ghanem YA, Albiges L, et al., 2025) In metastatic renal cell carcinoma, local treatment is also being redefined. The 2024 ESMO guideline states that upfront cytoreductive nephrectomy is no longer the standard initial strategy for advanced clear-cell renal cell carcinoma, and that local treatment

should be considered within the broader therapeutic pathway. (Powles T, Albiges L, Bex A, et al., 2024)

Accordingly, the key clinical question is no longer simply whether local treatment should be used, but which patients should receive which modality, in what setting, and for what purpose. This review summarizes recent advances in nephron-sparing surgery for localized disease, non-surgical local treatment for localized disease, the changing role of cytoreductive nephrectomy in metastatic disease, and metastasis-directed local therapy in oligometastatic and oligoprogressive settings.

2. Advances in Nephron-Sparing Surgery for Localized Renal Cell Carcinoma

Despite the diversification of local treatment, partial nephrectomy remains the most mature and best-supported standard strategy for localized renal cell carcinoma. Its value lies in achieving tumor control, pathological assessment, and nephron preservation simultaneously. Current research has therefore extended beyond perioperative safety to long-term survival, competing mortality, and postoperative renal function.

Recent comparative studies continue to support the oncologic and functional advantages of partial nephrectomy in appropriately selected patients. Kohada et al. showed that overall survival was worse after radical nephrectomy than after partial nephrectomy, and that this difference was driven mainly by non-cancer mortality rather than renal cancer-specific death. (Kohada Y, Shikuma H, Goto K, et al., 2025) In a SEER-based study of T1b renal cell carcinoma, Liu et al. likewise found that partial nephrectomy maintained stable long-term oncologic control and was associated with better overall survival than radical nephrectomy. (Liu H, Wang J, Tao L, et al., 2025) These findings indicate that procedure selection should take into account not only tumor removal, but also renal reserve, competing mortality, and comorbidity burden.

Evidence on postoperative renal function further supports the standard role of partial nephrectomy. Cao et al. found that partial nephrectomy was oncologically safe and associated with a persistently higher postoperative estimated glomerular filtration rate than radical nephrectomy, with a more pronounced difference in patients with diabetes. (Cao Y, Cui Y, Li R, et al., 2025) At the same time, advances in minimally invasive surgery have expanded the applicability of nephron-sparing procedures. Liu et al. reported that in highly complex tumors, robotic-assisted partial nephrectomy was associated with improved perioperative outcomes and less warm ischemia-related injury than laparoscopic partial nephrectomy. (Liu S, Zhang B, Weng B, et al., 2024) This suggests that some tumors previously treated with radical nephrectomy on the basis of anatomical complexity may still be candidates for nephron-sparing surgery.

Overall, partial nephrectomy remains the preferred treatment for localized renal cell carcinoma because it provides the most established balance among oncologic control, pathological information, and renal preservation. Radical nephrectomy remains appropriate when nephron-sparing surgery cannot be performed safely or is unlikely to offer meaningful overall benefit.

3. Non-Surgical Local Treatment for Localized Renal Cell Carcinoma

Evidence supporting non-surgical local treatment for localized renal cell carcinoma has increased substantially. Its role has evolved from an alternative for elderly or frail patients to a stratified strategy defined by tumor size, anatomical location, baseline renal function, and feasibility of invasive intervention. The main approaches are percutaneous ablation and stereotactic body radiotherapy. Percutaneous ablation, including cryoablation, radiofrequency ablation, and microwave ablation, is characterized by minimal invasiveness and preservation of renal parenchyma, whereas stereotactic body radiotherapy provides local ablation through high-precision image guidance without requiring a puncture route. (Huang RS, Chow R, Benour A, et al., 2025; Siva S, Bressel M, Sidhom M, et al., 2024) However, evidence remains based mainly on systematic reviews, cohort studies, and single-arm prospective studies rather than randomized head-to-head comparisons with surgery.

Percutaneous ablation is currently the most established non-surgical local treatment, particularly in cT1a disease, small peripheral tumors, technically feasible lesions, and patients in whom renal preservation is critical. A recent meta-analysis comparing non-surgical ablative strategies showed that these modalities can achieve consistently high local control with low

rates of severe adverse events, supporting their role in selected localized tumors. (Huang RS, Chow R, Benour A, et al., 2025) In a propensity score-matched SEER-based study of cT1a solid renal cell carcinoma, Guo et al. found shorter overall survival with heat-based thermal ablation than with cryoablation, although cancer-specific outcomes did not differ significantly. (Guo RQ, Peng JZ, Sun J, et al., 2024) A systematic review of percutaneous cryoablation further showed that renal functional decline was generally small, including in patients with T1b disease. (David-Dimitris Chlorogiannis, Anargyros Chlorogiannis, Dimitrios K. Filippiadis, Alexis Kelekis, Gregory C. Makris & Christos Georgiades, 2024) Together, these findings support a relatively well-defined role for percutaneous ablation, especially cryoablation, in selected small renal masses.

At present, however, the indications for ablative treatment remain concentrated in patients with small, technically accessible lesions who are not suitable for surgery. Long-term oncologic evidence and the ability to obtain complete pathological assessment remain inferior to surgery. Ablation is therefore better regarded as an important alternative rather than a replacement for standard surgical treatment.

Compared with percutaneous ablation, stereotactic body radiotherapy entered the local treatment framework later. Renal cell carcinoma was previously considered relatively insensitive to conventionally fractionated radiotherapy, but advances in image guidance, motion management, and dose delivery have enabled high biologically effective doses to achieve meaningful local ablation. (Siva S, Louie AV, Kotecha R, et al., 2024) Current evidence from systematic reviews, practice guidelines, and prospective studies supports its feasibility and local efficacy, although direct comparative evidence against surgery remains limited.

Prospective studies have strengthened the clinical role of SBRT for primary renal tumors. FASTRACK II reported excellent short-term local control and favorable intermediate clinical outcomes in patients with primary kidney cancer who were unsuitable for surgery. (Siva S, Bressel M, Sidhom M, et al., 2024) Long-term follow-up data also suggest that renal functional decline after primary tumor SBRT is generally moderate, with a low incidence of dialysis, including in patients with a solitary kidney. (Vivian S. Tan et al., 2024) These results support SBRT as a noninvasive local treatment option for elderly patients, those with substantial comorbidity, and those with anatomical features unfavorable for surgery or percutaneous ablation.

Percutaneous ablation and SBRT should therefore be viewed as complementary rather than competitive. Percutaneous ablation remains more established for small peripheral tumors with a safe puncture route, whereas SBRT offers an important noninvasive option for larger tumors, lesions near the renal hilum, bowel, or major vessels, tumors with high puncture-related risk, or patients unable to tolerate anesthesia or invasive procedures. The clinical question is not which modality is universally superior, but how to match each modality more precisely to tumor burden, anatomy, and patient condition.

In addition to local ablation, SBRT may also exert immune-modulating effects. High-dose radiotherapy can promote tumor antigen release and alter the tumor microenvironment, thereby enhancing antitumor immune responses. Existing reports have suggested a potential interaction between radiotherapy and immunotherapy, including occasional observations of the abscopal effect. (Feinaj A, Fox E, Sinibaldi V, et al., 2024; Hori K, Hirohashi Y, Aoyagi T, et al., 2020) However, in renal cell carcinoma this evidence remains limited to mechanistic inference and case-based observations. The present role of SBRT is therefore supported primarily by its local control, tolerability, and increasingly defined indications, whereas its potential systemic immune effects remain to be validated.

Taken together, non-surgical local treatment in localized renal cell carcinoma has become increasingly stratified. Percutaneous ablation remains a mature option for patients who are not surgical candidates or who require maximal nephron preservation, while the evidence supporting primary tumor SBRT continues to strengthen for larger tumors, lesions unsuitable for puncture, or patients requiring a fully noninvasive pathway. Future studies should focus on direct comparisons among techniques, long-term renal and quality-of-life outcomes, and more precise definition of indications by tumor size, location, and baseline renal function.

4. The Evolving Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma

In metastatic renal cell carcinoma, the role of

cytoreductive nephrectomy has shifted from broad routine use to selective application. This change reflects the combined influence of randomized trials, systematic reviews, and retrospective evidence from the immunotherapy era. Local surgery is no longer viewed as a fixed initial step for all patients with synchronous metastatic disease, but as an intervention that must be interpreted within the context of systemic therapy, disease burden, performance status, and treatment goals.

In the phase III CARMENA trial, sunitinib alone achieved survival outcomes that challenged the traditional paradigm of immediate nephrectomy followed by systemic therapy. (Méjean A, Ravaud A, Thezenas S, et al., 2018) In SURTIME, a deferred strategy after initial systemic treatment was associated with more favorable overall survival than immediate cytoreductive nephrectomy, supporting the value of treatment sequencing and response-based patient selection. (Bex A, Ghanem YA, Albiges L, et al., 2025) These studies indicate that initial systemic therapy can identify patients most likely to benefit from subsequent surgery while avoiding ineffective operations in rapidly progressive disease.

A 2024 Cochrane systematic review concluded that the highest-level evidence, derived mainly from the targeted therapy era, supports a cautious and selective rather than routine use of cytoreductive nephrectomy in patients requiring systemic therapy. (Dahm P, Ergun O, Uhlig A, et al., 2024) Retrospective evidence from the immunotherapy era suggests that cytoreductive nephrectomy may still provide benefit in selected patients. Fallah et al. reported better outcomes among patients treated with immune checkpoint inhibitors plus antiangiogenic therapy who underwent cytoreductive nephrectomy, while also emphasizing the persistent impact of prognostic selection factors that cannot be fully controlled in retrospective analyses. (Fallah J, Gittleman H, Weinstock C, et al., 2024) Recent reviews have similarly argued that the role of cytoreductive nephrectomy should now be interpreted in relation to patient selection, systemic treatment background, and timing rather than as a routine upfront procedure. (Hara T & Miyake H., 2025)

Overall, cytoreductive nephrectomy remains part of the treatment framework for metastatic renal cell carcinoma, but its role has fundamentally changed. It is no longer a relatively fixed treatment step, but a selective local intervention requiring careful patient selection and timing judgment. It appears most appropriate in patients with symptomatic primary tumors, disease control after initial systemic therapy, good performance status, and limited metastatic burden. The key question has therefore shifted from whether cytoreductive nephrectomy should be performed to which patients should undergo it, when it should be undertaken, and how it should be integrated into the overall treatment sequence.

5. Metastasis-Directed Local Treatment in Oligometastatic and Oligoprogressive Disease

Metastasis-directed local treatment has become an increasingly important component of oligometastatic and oligoprogressive renal cell carcinoma management. In contrast to widely metastatic disease, where systemic therapy remains central, the main value of local treatment in this setting lies in regulating treatment tempo and extending the duration of benefit. Interpretation therefore depends not only on local control, but also on the specific therapeutic objectives of different clinical scenarios.

In oligometastatic disease, prospective studies suggest that metastasis-directed radiotherapy can produce durable local control and prolong the interval before systemic therapy is required. Tang et al. reported encouraging progression-free and systemic therapy-free outcomes with metastasis-directed radiotherapy in oligometastatic clear-cell renal cell carcinoma. (Tang C, Sherry AD, Seo A, et al., 2025) In a phase IIb study of systemically untreated oligometastatic kidney cancer, Hannan et al. further showed that most patients had still not initiated systemic therapy at 1 year and that local control remained excellent. (Hannan R, Assadi R, Christie A, et al., 2026) Although these studies are mainly single-arm, they support the conclusion that carefully selected patients with low-volume disease may achieve a prolonged systemic therapy-free interval after metastasis-directed local treatment.

In oligoprogressive disease, the value of local treatment lies primarily in maintaining the benefit of ongoing systemic therapy. Current evidence suggests that the clinical goals of oligometastatic and oligoprogressive disease are distinct: the former focuses on delaying systemic therapy initiation, whereas the latter aims to eradicate a limited number of resistant lesions and prolong the efficacy of the current regimen.

(Tang C, Sherry AD, Seo A, et al., 2025) This distinction also explains the use of different endpoints across studies, including progression-free survival, systemic therapy-free survival, and time to next-line treatment.

Despite consistent directionality, the evidence still relies heavily on single-arm and retrospective studies, and its conclusions remain strongly influenced by patient selection. Hoffer et al. reported better outcomes among patients receiving local therapy in addition to systemic treatment, but eligibility for local treatment was itself closely related to lesion number, metastatic site, general condition, and prior treatment response. (Hoffer S, Eggers H, Fröhlich T, et al., 2025) Metastasis-directed local treatment therefore appears most relevant in patients with low disease burden, controllable lesions, good performance status, and multidisciplinary confirmation that delaying treatment escalation is clinically meaningful. It should not be extrapolated directly to patients with widely metastatic disease.

Overall, current evidence suggests that metastasis-directed radiotherapy or metastasectomy may prolong the systemic therapy-free interval or delay switching systemic regimens in selected patients with low-volume disease. In oligoprogressive disease, local treatment appears particularly useful for preserving an effective systemic treatment pathway. Future research should standardize the definitions of oligometastatic and oligoprogressive disease, clarify patient selection criteria, and define the incremental value of local treatment across metastatic sites and systemic treatment contexts.

6. Current Limitations and Future Directions

Although research on local treatment for renal cell carcinoma has increased substantially, the maturity of evidence remains uneven across clinical scenarios. In localized disease, partial nephrectomy is already established as standard therapy. By contrast, although the value of ablation and SBRT is becoming clearer, evidence still depends largely on non-randomized comparisons, systematic reviews, and single-arm prospective studies. A recent ISRS systematic review and practice guideline confirmed that primary renal SBRT has achieved a meaningful level of technical maturity and clinical feasibility, but its long-term efficacy boundaries relative to surgery remain insufficiently defined. (Siva S, Louie AV, Kotecha R, et al., 2024)

In metastatic disease, the main controversy surrounding cytoreductive nephrectomy is no longer whether it has lost all value, but how to select patients and sequence treatment in the immunotherapy era. Current randomized evidence derives mainly from the targeted therapy era. Although retrospective studies suggest benefit in selected patients, selection bias remains difficult to eliminate. Future prospective studies should therefore focus on strategies that reassess surgical value after response to systemic therapy and incorporate variables such as risk stratification, disease burden, symptom control, and systemic treatment background.

In oligometastatic and oligoprogressive disease, a major challenge is incomplete standardization of the study population itself. The core issue is not merely to accumulate more survival data, but to determine how metastatic site, disease burden, tumor biology, and systemic treatment context shape the benefit of local treatment. Another important direction is to move beyond technique selection toward full-course treatment integration. Image-guided metastasis-directed therapy, molecular and imaging biomarkers, and more refined coordination with systemic therapy are increasingly relevant. (Vandaele S, Albersen M, Beuselinck B, et al., 2025) Future research should therefore focus less on technical feasibility alone and more on precisely defining treatment goals at different disease stages.

7. Conclusion

The role of local treatment in renal cell carcinoma continues to evolve. In localized disease, partial nephrectomy remains the central nephron-sparing treatment. Percutaneous ablation and SBRT provide established alternative pathways for elderly patients, those with substantial comorbidity, and those unsuitable for surgery. At present, the role of SBRT is supported mainly by high local control and favorable tolerability, whereas its potential systemic immune effects still require higher-level validation. In metastatic disease, cytoreductive nephrectomy has entered an era of selective use, and metastasis-directed local therapy in oligometastatic and oligoprogressive disease is acquiring clearer strategic significance. Overall, local treatment is shifting from isolated technical intervention toward precision-based and stage-specific integration, although evidence level, indication boundaries, and long-term outcomes still require

further clarification. Future evidence on patient selection, treatment timing, long-term functional outcomes, and prospective comparative studies will determine the ultimate role of local treatment in full-course renal cell carcinoma management.

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