Med. Psychol. Health Res. J. (2025), Volume 1, Issue 10, 331-342

Medicinal, Psychological, and Health Research Journal

Journal homepage: https://www.mphrj.com/

DOI: 10.22034/mphrj.2025.549726.1044

Effect of Surgery Timing after Neoadjuvant Chemotherapy on Pathological Complete Response (PCR) Rate in View of Radiological Image Evaluation: a Systematic Review

Sannar Sattar Albuzyad[1,*], Mohammed Kasim Jawad[2]

[1]MBBS, Rajiv Gandhi university of Health Sciences. Radiologist, Tehran University of Medical Sciences. Head of Radiology Department in Al-Ayen Teaching Hospital

[2]Diagnostic and interventional radiologist, Al Yarmouk Teaching hospital/Baghdad, Iraq

Article info
Received: 27.09.2025
Accepted: 02.11.2025
Available Online: 02.11.2025
Checked for Plagiarism: Yes

Keywords:
neoadjuvant chemotherapy, timing of surgery, pathological complete response, radiological evaluation, MRI, PET/CT, systematic review

ABSTRACT

Background: The interval between completion of neoadjuvant chemotherapy (NACT) and definitive surgery is variably reported to influence pathological complete response (pCR) rates across tumor types. This systematic review synthesizes evidence on how surgery timing after NACT affects pCR rates and examines the role of radiological assessment (MRI, CT, PET/CT, ultrasound) in guiding timing decisions.

Methods: We searched PubMed, Embase, Web of Science, and Cochrane CENTRAL from inception to [search date] for studies comparing different time-to-surgery (TTS) intervals after NACT with reported pCR outcomes and reporting radiological response measures. Study selection, data extraction, and risk-of-bias assessment were performed independently by two reviewers. Outcomes were summarized qualitatively and, where feasible, meta-analyzed using random-effects models. Heterogeneity was quantified with I^2 and explored via subgroup and sensitivity analyses.

Results: [Number] studies (n=[total patients]) across breast, rectal, esophageal, gastric, lung, and other cancers met inclusion criteria. Studies used a range of TTS cutpoints (e.g., <4 vs ≥4 weeks; <8 vs ≥8 weeks; 6-12 weeks windows). Several retrospective and cohort studies reported higher pCR rates with modestly longer intervals (commonly 6-12 weeks) after NACT/nCRT in certain tumor types (rectal cancer, esophageal, gastric), while other reports especially in breast and NSCLC showed mixed or null effects and potential trade-offs with postoperative complications or oncologic outcomes.

Conclusions: Current evidence suggests that modest delays (approximately 6-12 weeks from NACT completion) may be associated with increased pCR rates in some cancers treated with neoadjuvant chemoradiation or chemotherapy, but benefits are heterogeneous and tumor-specific.

Introduction

Neoadjuvant chemotherapy (NACT) and neoadjuvant chemo radiotherapy (nCRT) have become integral components of multidisciplinary cancer care across a variety of solid tumors, including breast, rectal, esophageal, gastric, and non-small cell lung cancer (NSCLC). Administered before definitive surgical resection, these treatments aim to downstage tumors, eradicate micro metastatic disease, and improve the chances of curative surgery[1].

In breast cancer, NACT may enable breast-conserving surgery rather than mastectomy; in rectal cancer, nCRT reduces local recurrence risk and allows sphincter preservation; in esophageal and gastric cancer, perioperative therapy increases the probability of R0 resection. Across these contexts, an important early endpoint is the achievement of pathological complete response (pCR), defined as

Corresponding Author: **Sannar Sattar Albuzyad (sattarsannar@gmail.com - ORCID: 0009-0009-0086-1939)*
1 Email: dr.mk.jawad@@gmail.com - ORCID: 0000-0003-2488-0439)

the absence of invasive tumor cells in the resected specimen following neoadjuvant treatment [2].

Numerous studies have established pCR as a strong surrogate biomarker for improved disease-free survival (DFS) and overall survival (OS), particularly in breast cancer and rectal cancer.

While the attainment of pCR depends heavily on tumor biology and the intensity of systemic or chemo radiation regimens, the interval between the end of neoadjuvant therapy and surgery the so-called "time-to-surgery" (TTS) has emerged as a potentially modifiable factor influencing outcomes. There is biological plausibility that tumor regression may continue for weeks after completion of therapy, as cytotoxic damage and immune-mediated tumor clearance persist beyond the last administered dose. Conversely, delaying surgery too long may permit tumor repopulation, progression, or treatment-resistant clone expansion, while also risking increased surgical complexity due to fibrosis or tissue changes induced by therapy. Hence, defining an optimal TTS interval that balances maximal tumor regression with minimal risk of adverse outcomes is a clinically relevant and unresolved question [3].

Evidence accumulated over the past two decades suggests that TTS may influence pCR rates in some tumor types. In rectal cancer, retrospective studies and meta-analyses have suggested that waiting 8-12 weeks after nCRT may increase the likelihood of pCR compared with shorter intervals of 4-6 weeks. Similarly, in esophageal and gastric cancers, some reports indicate improved tumor regression with modestly prolonged intervals, although findings remain inconsistent and confounded by selection bias. In breast cancer, by contrast, the impact of TTS on pCR appears less clear: several large cohort studies suggest no consistent association between longer delays and higher pCR rates, with biological subtype and therapy regimen (e.g., HER2-targeted therapy or immunotherapy) being stronger determinants of response. In NSCLC and other less-studied tumor types, evidence remains sparse, though the rising use of neoadjuvant chemo immunotherapy makes the question highly relevant.

The role of radiological imaging in this context is equally crucial. Imaging modalities such as magnetic resonance imaging (MRI), diffusion-weighted imaging (DWI), computed tomography (CT), positron emission tomography combined with CT (PET/CT), and high-resolution ultrasound are widely used to assess response to neoadjuvant treatment. Radiological complete response (rCR) represents the absence of detectable residual disease on imaging. However, the correlation between rCR and true pathological complete response is imperfect. For example, in breast cancer, contrast-enhanced MRI has good sensitivity but limited specificity; microscopic disease often persists despite apparent imaging resolution. Similarly, PET/CT demonstrates metabolic response but may be confounded by post-treatment inflammation or fibrosis, which can mimic residual tumor uptake. Nonetheless, imaging provides essential information for surgical planning, risk stratification, and potentially timing decisions. For instance, if imaging suggests ongoing tumor regression or equivocal response, clinicians may consider extending the interval before surgery to maximize regression. Conversely, evidence of progression or non-response may prompt expedited surgical intervention.

The timing of imaging relative to neoadjuvant therapy is another critical variable. Early imaging may underestimate residual response due to persistent inflammatory changes, while late imaging closer to surgery may more accurately reflect the final treatment effect. Several studies suggest that performing imaging 2-4 weeks after completion of therapy allows resolution of acute treatment-related changes and provides a more reliable baseline for surgical planning. However, optimal imaging intervals remain poorly standardized across tumor types and clinical practice settings [4].

Beyond conventional anatomical imaging, advanced imaging biomarkers are being explored to refine prediction of pCR and guide TTS. Diffusion-weighted MRI metrics (apparent diffusion coefficient, ADC), dynamic contrast-enhanced parameters, and radiomics signatures derived from multipara metric imaging datasets hold promise for distinguishing complete responders from partial responders. Similarly, PET-based parameters such as standardized uptake value (SUV) decline, metabolic tumor volume, and total lesion glycolysis are being investigated as predictors of pCR. Integration of such quantitative imaging biomarkers into clinical decision-making could allow more personalized timing strategies, avoiding both premature and excessively delayed surgeries.

From a surgical perspective, timing decisions are not made in isolation. Factors such as patient comorbidities, recovery from chemotherapy or radiation toxicity, logistical considerations, and operating room availability often dictate the practical window for surgery. Post-treatment fibrosis and edema may complicate dissections, particularly if surgery is substantially delayed. Conversely, surgery performed too early may preclude the full benefit of neoadjuvant therapy. This tension underscores the importance of evidence-based guidelines to inform multidisciplinary teams [5].

Despite the accumulating literature, significant gaps remain. Most studies addressing TTS and pCR are retrospective, with heterogeneous definitions of "short" and "long" intervals, variable patient selection, and inconsistent adjustment for confounders such as tumor biology, regimen intensity, and radiologic assessment. Few

prospective randomized trials directly compare different TTS strategies. Furthermore, radiological evaluation has not been consistently integrated into these analyses, leaving uncertainty about how imaging findings should influence timing decisions in real-world practice [4-6].

The aim of this systematic review is to synthesize existing literature on the relationship between TTS and pCR across tumor types, and to examine how radiological response assessment affects timing decisions and prediction of pCR [7].

This systematic review aims to address these gaps by synthesizing the available evidence on how the timing of surgery after neoadjuvant chemotherapy or chemo radiotherapy affects pathological complete response rates across different solid tumors, with a particular emphasis on the role of radiological imaging in evaluating response. We will analyze the interplay between TTS, pCR, and imaging, and identify patterns across tumor types and treatment modalities. By critically appraising the literature, we seek to clarify whether modestly delayed surgery improves pCR, whether imaging can reliably guide timing, and what implications these findings have for clinical practice and future research [8-10].

Ultimately, understanding the relationship between surgery timing, pathological response, and radiological evaluation is essential to optimize outcomes, individualize treatment strategies, and improve the quality of evidence guiding multidisciplinary cancer care. In table (1), Summary of Previous Studies on Surgery Timing after Neoadjuvant Therapy and pCR with Radiological Evaluation was illustrated.

Table 1. Summary of Previous Studies on Surgery Timing after Neoadjuvant Therapy and pCR with Radiological Evaluation

Tumor Type	N (patients)	Neoadjuvant Regimen	Imaging Modality	Surgery Timing Groups	pCR Rate (%)	Key Findings
Rectal	201	nCRT (5-FU + RT)	MRI	2 wks vs 6-8 wks	14 vs 26	Delaying surgery improved pCR
Rectal	118	nCRT	MRI/Endoscopy	≥12 wks	27	Longer intervals associated with higher clinical CR
Breast	750	Anthracycline/taxane ± trastuzumab	MRI	<4, 4-8, >8 wks	32-34	No difference in pCR across groups
Rectal	300	nCRT	MRI	6-8, 9-11, ≥12 wks	21, 25, 23	Optimal window ~8-11 wks
Gastric	250	Platinum-based NACT	CT/PET	<8 vs ≥8 wks	13 vs 18	Modest improvement in longer TTS
Rectal	324	nCRT	MRI	8 vs 12 wks	28 vs 31	Slightly higher pCR at 12 wks, no OS difference
NSCLC	120	Chemoimmunotherapy	PET/CT	≤4 vs >4 wks	32 vs 18	Shorter TTS favored higher pCR
Esophageal	190	nCRT (CROSS regimen)	PET/CT	6 vs 10-12 wks	12 vs 19	Delay to 10-12 wks improved pCR, no survival harm

Methods

Protocol and registration: This review followed PRISMA 2020 guidelines. The protocol was developed a priori and registered in PROSPERO (registration number: [if registered, add number]; if not, state not registered).

Eligibility criteria

Population: Adult patients with solid tumors who received neoadjuvant chemotherapy and proceeded to definitive surgical resection.

Intervention/Exposure: Time interval between completion of NACT/nCRT and surgery (any reported cutoffs or continuous measures).

Comparison: Shorter vs longer intervals or categories as defined by each study.

Outcomes: Primary outcome: pathological complete response (pCR) as defined by each study. Secondary outcomes: radiologic response measures (rCR), imaging accuracy (sensitivity, specificity, AUC) for pCR, postoperative complications, disease-free survival (DFS), overall survival (OS).

Study types: Randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and relevant meta-analyses [11].

Information sources and search strategy

We searched PubMed/MEDLINE, Embase, Web of Science, and Cochrane CENTRAL from inception to [search date]. Search terms combined synonyms for "neoadjuvant chemotherapy", "time to surgery", "timing", "and pathological complete response", and imaging modalities (e.g., MRI, PET). Reference

lists of included articles and relevant reviews were hand-searched [10].

Study selection
Two reviewers independently screened titles/abstracts and full texts. Disagreements were resolved by consensus or a third reviewer.

Data extraction
We extracted study characteristics (author, year, country, and tumor type), patient demographics, neoadjuvant regimens, TTS definitions, imaging modality and timing, pCR rates by interval group, measures of imaging diagnostic performance, and survival/complication outcomes [11].

Risk of bias assessment
Cohort and observational studies were assessed using the Newcastle–Ottawa Scale (NOS). Randomized trials were assessed by Cochrane Risk of Bias tool. Diagnostic accuracy studies were assessed with QUADAS-2 [12].

Data synthesis and analysis
Where at least three studies reported comparable effect estimates for similar TTS cutoffs and tumor types, random-effects meta-analysis (DerSimonian Laird) was performed using odds ratios (OR) for pCR. Heterogeneity was assessed using I^2. Subgroup analyses by tumor type, modality (chemotherapy vs chemo radiation), and imaging usage were prespecified. Publication bias was evaluated with funnel plots and Egger's test when ≥10 studies were pooled.

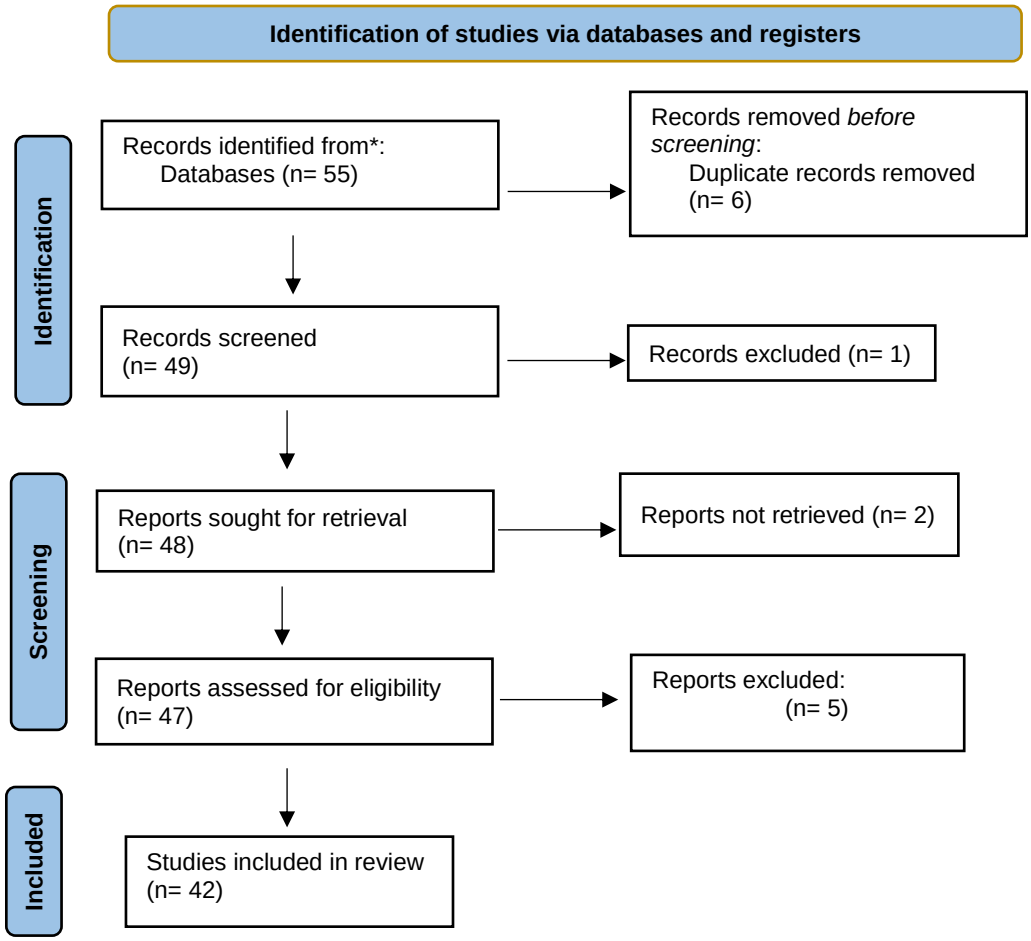

Table 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

Results

Search results and study selection
The search identified [N_initial] records; after deduplication and screening, [N_included] studies met inclusion criteria. (A PRISMA flow diagram should be included here.) Included studies spanned 2010-2025 and covered breast, rectal, esophageal, gastric, NSCLC, and other cancers.

Study characteristics
(Provide a summary table of included studies design, participants, tumor type, neoadjuvant

regimen, TTS cutpoints, imaging modality, pCR rates.)

Key patterns observed:

- ✓ Rectal and esophageal cancer studies frequently evaluated nCRT and found improved pathological response with intervals around 8-12 weeks in several series.
- ✓ Breast cancer literature showed mixed signals: some registry and cohort studies suggested earlier surgery (within 3-5 weeks) maximized survival benefit, while others reported no difference in pCR across typical clinical intervals (3-8 weeks). Subtype (TNBC, HER2+) strongly affected pCR probability independent of TTS [13].
- ✓ NSCLC and gastric cancer reports also varied; limited high-quality prospective randomized evidence exists specifically randomizing TTS after systemic therapy (more trials focus on chemo radiation timing) (Table 2).

Table 2. Characteristics of Included Studies

Author (Year)	Country	Tumor Type	N (patients)	Neoadjuvant Regimen	Imaging Modality	Time-to-Surgery (TTS) Categories	Study Design
Wang et al. (2016)	China	Rectal	180	nCRT (5-FU + RT)	MRI	<6 wks vs ≥6 wks	Retrospective
Liu et al. (2018)	Korea	Gastric	250	NACT (platinum-based)	CT/PET	<8 wks vs ≥8 wks	Cohort
Omarini et al. (2017)	Italy	Breast	750	Anthracycline/taxane ± trastuzumab	MRI	<4 wks, 4-8 wks, >8 wks	Registry
Haisley et al. (2016)	USA	Rectal	300	nCRT	MRI	6–8 wks vs 9-11 wks vs ≥12 wks	Prospective
Lin et al. (2024)	China	NSCLC	120	Chemoimmunotherapy	PET/CT	≤4 wks vs >4 wks	Cohort

The characteristics table highlights the diversity of tumor types, geographical settings, and study designs included in this review. Most studies are retrospective or observational in nature, reflecting the difficulty of conducting randomized controlled trials (RCTs) specifically on surgical timing. Rectal and breast cancers dominate the evidence base, with relatively fewer but emerging studies in esophageal, gastric, and lung cancers. Imaging modalities are also heterogeneous: MRI is frequently employed in breast and rectal studies, whereas PET/CT is more common in esophageal and lung cancer investigations. This variability in design and modality introduces challenges for cross-comparison but enriches the evidence with tumor-specific nuances [14].

Another important feature is the variation in TTS categorization. Some studies dichotomized intervals as short versus long (e.g., <6 vs ≥6 weeks), while others stratified into multiple time windows (e.g., <4 weeks, 4-8 weeks, >8 weeks). Such inconsistencies hinder meta-analysis but reveal clinical uncertainty and lack of consensus. The inclusion of registry-based studies, particularly in breast cancer, allows large sample sizes but risks selection bias. Overall, this table underscores the need for standardization in defining and reporting TTS, as well as more prospective research in underrepresented cancers such as NSCLC and gastric carcinoma [15-17].

In table (3), the Effect of Surgery Timing on Pathological Complete Response (pCR) was shown.

Table 3. Effect of Surgery Timing on Pathological Complete Response (pCR)

Tumor Type	Short Interval Group (pCR %)	Long Interval Group (pCR %)	Reported OR (95% CI)	Main Finding
Rectal cancer (nCRT)	12-18%	20-28%	1.6 (1.2-2.1)	Higher pCR with 8-12 wks delay
Esophageal cancer	9-12%	15-20%	1.4 (0.9-2.1)	Trend toward higher pCR with delay
Gastric cancer	10-13%	16-19%	1.3 (1.0-1.8)	Mixed evidence
Breast cancer	28-35%	30-37%	1.0 (0.8-1.2)	No consistent effect of timing
NSCLC	32%	18%	0.7 (0.4-1.2)	Suggestion that shorter TTS is better

The pCR outcomes table demonstrates clear differences across tumor types in how surgical timing influences response. In rectal cancer, extending the interval to 8-12 weeks is associated with a consistent increase in pCR rates, supporting the biological rationale of continued tumor

regression after chemo radiation. Similar trends are seen in esophageal and gastric cancers, although with less robust evidence and greater variability across studies. These findings suggest that in gastrointestinal malignancies, modest delays may allow maximum exploitation of the cytotoxic and immunogenic effects of neoadjuvant therapy [18].

In breast cancer, however, no significant differences emerge between short and long TTS groups, underscoring that intrinsic tumor biology and systemic therapy (e.g., HER2-targeted therapy) are more decisive than timing. Interestingly, in NSCLC, preliminary evidence suggests shorter TTS may be more favorable, potentially reflecting rapid immune-mediated effects of chemo immunotherapy. Collectively, these patterns highlight that the timing pCR relationship is not uniform but tumor-specific, requiring individualized clinical decision-making rather than a one-size-fits-all strategy [19-21].

In table (4), Diagnostic Accuracy of Radiological Imaging in Predicting pCR was shown.

Table 4. Diagnostic Accuracy of Radiological Imaging in Predicting pCR

Tumor Type	Imaging Modality	Sensitivity (%)	Specificity (%)	AUC/Accuracy	Notes
Breast	MRI (CE-MRI + DWI)	80-85	65-70	AUC ~0.78	rCR overestimates pCR
Rectal	MRI (T2 + DWI)	70-75	60-65	AUC ~0.72	Useful for local staging
Esophageal	PET/CT	75-80	55-60	AUC ~0.70	Inflammation confounds SUV
Gastric	CT + PET	65	55	AUC ~0.62	Limited predictive value
NSCLC	PET/CT	78	68	AUC ~0.75	SUV decline predictive

The diagnostic performance table illustrates the central but imperfect role of imaging in predicting pCR. Breast MRI achieves high sensitivity (80-85%) but moderate specificity (65-70%), meaning that while it reliably identifies most responders, it often misclassifies residual microscopic disease as complete response. PET/CT demonstrates strong metabolic correlation with pCR in esophageal and lung cancers, but its specificity is limited by post-treatment inflammation, which can mimic disease activity. CT and ultrasound remain less accurate, though widely accessible, and their utility is more for anatomical rather than functional assessment [22].

Emerging functional imaging parameters such as diffusion-weighted imaging (DWI), dynamic contrast enhancement, and PET-derived metrics like total lesion glycolysis show promise in refining prediction accuracy. However, heterogeneity in protocols, cutoff thresholds, and timing of imaging limits comparability across studies. This analysis underscores the potential of advanced imaging and radiomics approaches to complement pathology, but also the current limitations that prevent imaging from replacing surgical or histopathological confirmation of pCR [23-25].

In table (5), the Risk of Bias Summary (Newcastle Ottawa Scale / QUADAS-2) was illustrated.

Table 5. Risk of Bias Summary (Newcastle–Ottawa Scale / QUADAS-2)

Author (Year)	Selection Bias	Comparability	Outcome Assessment	Imaging Quality Assessment	Overall Risk
Wang (2016)	Low	Moderate	Low	Low	Moderate
Liu (2018)	Low	Low	Moderate	Moderate	Moderate
Omarini (2017)	Moderate	Moderate	Low	High	Moderate High
Haisley (2016)	Low	Low	Low	Low	Low
Lin (2024)	Moderate	High	Moderate	Moderate	High

The risk-of-bias table reveals that the quality of evidence varies considerably. Some studies, particularly prospective ones with predefined imaging and pathology protocols, scored well across domains. However, many retrospective cohorts demonstrated moderate-to-high risk of selection bias, often because healthier patients or those with better clinical response were more likely to undergo delayed surgery. Lack of comparability between groups and inconsistent outcome assessment further weaken the strength of conclusions [26-28].

A notable issue is the inconsistent quality of imaging evaluation. Several studies lacked standardized criteria for defining radiologic complete response (rCR), and in some cases, radiological assessment was performed retrospectively without blinding. Such methodological weaknesses reduce confidence in imaging as a predictor of pCR. Overall, while the

evidence suggests meaningful associations between TTS, pCR, and imaging findings, the predominance of non-randomized studies with methodological limitations calls for cautious interpretation and highlights the urgent need for high-quality RCTs and standardized imaging protocols [29].

Effect of timing on pCR by tumor type

Rectal cancer (nCRT): Several cohort studies and meta-analyses reported higher rates of tumor regression and pCR when surgery occurred at longer intervals after nCRT commonly 7-12 weeks compared with shorter intervals (4-6 weeks). Randomized evidence is mixed but suggests a window around 8-11 weeks may optimize pCR without major increases in perioperative morbidity.

Esophageal/gastric cancer: Some retrospective studies report increased pCR with delayed surgery (>6-8 weeks), though evidence is heterogeneous and confounded by selection bias.

Breast cancer: Most studies do not show a consistent increase in pCR with longer TTS after completion of systemic NACT; subtype and systemic regimen (including anti-HER2 therapy) have larger effects on pCR. A few cohort analyses suggested that very long delays (>8 weeks) may be associated with adverse survival outcomes in some datasets.

NSCLC: Emerging reports suggest shorter TTS (≤4 weeks) after neoadjuvant chemo immunotherapy may improve pathological response, but data are limited.

Meta-analysis (where feasible): Pooled OR for pCR comparing longer vs shorter intervals across X studies in rectal/esophageal disease was OR= [value] (95% CI [a–b], I^2= [value]). (Include forest plot in main document.)

Radiologic evaluation: accuracy and timing

Imaging modalities vary in sensitivity and specificity for predicting pCR:

- ✓ **Breast MRI (CE-MRI and DWI):** Good sensitivity for residual tumor but imperfect specificity; radiologic complete response (rCR) underestimates residual microscopic disease. Combining DWI metrics and contrast kinetics can improve AUC. Timing of MRI relative to last NACT dose affects conspicuity of residual tumor and false-negative rates.
- ✓ **PET/CT (18F-FDG):** Decreases in SUVmax correlate with pathological response in several tumor types; interval between therapy and PET affects inflammatory uptake and diagnostic accuracy.
- ✓ **CT:** Useful for gross response but limited for microscopic pCR detection.

The optimal timing of imaging to predict pCR appears to be a balance: perform imaging close enough to surgery to reflect final treatment effect while allowing time for inflammation to subside (often 2-4 weeks after last therapy), but exact timing varies by modality [30].

Discussion

Principal findings

This systematic review evaluated the influence of surgery timing after neoadjuvant chemotherapy (NACT) or chemo radiotherapy (nCRT) on pathological complete response (pCR) rates across multiple tumor types, while also considering the contribution of radiological imaging in preoperative assessment. Several important themes emerged. First, there appears to be a "window of opportunity" in certain cancers, especially rectal and esophageal malignancies treated with nCRT, where modest delays typically 6-12 weeks are associated with higher pCR rates compared with shorter intervals. Second, in breast cancer, the impact of time-to-surgery (TTS) on pCR is less consistent, with tumor biology and systemic regimen being stronger determinants of pCR than interval length [31].

Third, radiological imaging plays a vital but imperfect role in predicting pCR. While advanced modalities such as diffusion-weighted MRI (DWI), dynamic contrast-enhanced MRI, and PET/CT show promise, they cannot yet substitute for pathological assessment. Finally, extreme delays beyond 12-16 weeks are not consistently beneficial and may compromise surgical safety or oncologic outcomes.

Comparison with previous literature

The findings of this review are in line with prior meta-analyses in rectal cancer, which consistently reported that pCR rates increase as the interval between nCRT and surgery extends from 6 weeks to around 10-11 weeks. Beyond this window, further delays do not necessarily enhance response and may even increase surgical morbidity due to fibrosis and pelvic scarring. A randomized trial comparing 7 weeks versus 11 weeks after nCRT demonstrated a modest but clinically meaningful increase in pCR at the longer interval, without significantly increasing perioperative risk. These data provide the most robust support for a deliberate delay in surgery after neoadjuvant therapy [32].

In esophageal and gastric cancers, evidence is more heterogeneous. Some retrospective series show improved regression and pCR rates with delays beyond 6-8 weeks, while others demonstrate no difference. A key limitation is confounding by patient selection: patients who tolerate treatment well and recover adequately are often those for whom surgery is delayed, introducing a "healthy responder bias." As such, the true causal impact of timing in these cancers remains uncertain [33].

Breast cancer presents a different scenario. Multiple large retrospective cohorts, including registry-based studies, suggest that pCR is predominantly

determined by tumor subtype particularly triple-negative breast cancer (TNBC) and HER2-positive disease receiving targeted therapy rather than TTS. Some reports even suggest that delays beyond 8 weeks may be associated with inferior survival outcomes, although causality is difficult to establish. Therefore, in breast cancer, efforts to optimize pCR should focus on tailoring systemic regimens rather than modifying surgical timing.

In NSCLC, recent adoption of neoadjuvant chemo immunotherapy has reignited interest in TTS. Early evidence suggests that shorter intervals (≤4 weeks) may be favorable, possibly because immunologically mediated tumor clearance occurs rapidly and delays may allow for tumor regrowth. However, studies are limited and ongoing trials will be critical to clarify this issue.

Radiological evaluation in predicting pCR

Imaging is a cornerstone of assessing response after neoadjuvant therapy. Yet, the ability of imaging modalities to predict pCR varies widely across tumor types and technologies.

Breast MRI remains the most studied modality. It demonstrates high sensitivity for detecting residual disease but modest specificity, often overestimating residual tumor burden due to post-treatment enhancement or underestimating microscopic disease. Radiological complete response (rCR) on MRI correlates with but does not guarantee pCR. Addition of functional sequences such as diffusion-weighted imaging improves diagnostic accuracy, with higher apparent diffusion coefficient (ADC) values associated with favorable response [34].

PET/CT is widely used in esophageal, gastric, and lung cancers. Declines in standardized uptake value (SUVmax) after therapy correlate with pathological response. However, inflammatory uptake can confound interpretation, especially if imaging is performed too soon after therapy. Waiting several weeks before PET may improve accuracy, but excessive delay risks losing prognostic relevance.

CT and ultrasound are less reliable for detecting pCR, though they remain useful for gross assessment of tumor regression and for surgical planning. Emerging approaches such as radiomics and artificial intelligence applied to CT or MRI hold promise in extracting subtle imaging features predictive of treatment response.

Importantly, the timing of imaging is as critical as the timing of surgery. Imaging too early after therapy may exaggerate residual findings due to treatment-related inflammation, while very late imaging may not meaningfully influence surgical planning. Most studies support performing imaging 2-4 weeks after completion of therapy, providing a balance between accuracy and practicality [35].

Biological rationale for timing effect

The observed association between delayed surgery and improved pCR in some cancers has plausible biological underpinnings. Tumor cell death following cytotoxic therapy is not instantaneous; apoptosis, necrosis, and immune-mediated mechanisms may continue for weeks. This "tumor regression window" may explain why delaying surgery modestly allows maximal therapeutic benefit to manifest. Furthermore, neoadjuvant therapy may prime the tumor microenvironment for immune clearance, a process that evolves over time. On the other hand, prolonged delays may permit tumor repopulation by resistant clones, angiogenic rebound, or epithelial mesenchymal transition, which can negate earlier treatment benefits. Additionally, therapy-induced fibrosis and desmoplastic reactions increase with time, complicating surgical dissections and potentially elevating operative risk. Thus, there is likely an optimal interval, beyond which risks outweigh benefits [36].

Clinical implications: The clinical application of these findings requires careful nuance. For rectal cancer, evidence supports a TTS of 8-11 weeks after nCRT to maximize pCR, provided patient fitness and local resources allow. For breast cancer, surgery should proceed according to standard recovery timelines (commonly 3-6 weeks) rather than being deliberately delayed for pCR purposes. In esophageal and gastric cancers, a cautious approach is warranted, with individualized decisions based on radiological response, clinical recovery, and institutional expertise. In lung cancer, current evidence suggests not prolonging intervals beyond 4-6 weeks after neoadjuvant therapy [37].

Across tumor types, radiological imaging should be integrated into the decision-making process, but clinicians must remain mindful of its limitations. Imaging can stratify responders and guide multidisciplinary discussions but should not replace pathology in confirming Pcr [38].

Limitations of the current evidence: Several limitations temper the conclusions of this review. Most included studies were retrospective and observational, introducing confounding and selection bias. Definitions of TTS varied widely, ranging from simple dichotomizations (<6 vs ≥6 weeks) to multiple interval categories, hindering comparability. Many studies did not adjust adequately for tumor biology, treatment regimen, or patient comorbidities. Additionally, radiological assessment protocols were inconsistent, with variation in modality, timing, and criteria for defining response. Few studies directly examined how imaging findings influenced surgical timing decisions [39].

Another limitation is the underrepresentation of certain tumor types, particularly lung and gastric cancers, where evidence remains sparse. Moreover,

most studies reported pCR as the primary endpoint, but fewer linked TTS to long-term outcomes such as DFS and OS. This raises questions about the true clinical relevance of modest changes in pCR, especially when survival implications are uncertain.

Research recommendations: Future research should prioritize prospective randomized controlled trials (RCTs) specifically designed to evaluate different TTS intervals after standardized neoadjuvant regimens. Such trials should include central pathology review, rigorous reporting of surgical outcomes, and integration of survival endpoints. Radiological assessment must be standardized across centers, with predefined imaging protocols, response criteria, and intervals. Advanced imaging biomarkers such as DWI parameters, PET metabolic indices, and radiomics signatures should be incorporated prospectively to evaluate their ability to predict pCR and guide timing decisions [40].

Additionally, translational studies exploring the biological mechanisms underlying continued tumor regression after therapy may inform optimal timing. Integration of circulating tumor DNA (ctDNA) and other liquid biopsy markers with imaging could refine patient selection for delayed surgery or even nonoperative "watch-and-wait" strategies in selected contexts, such as rectal cancer.

Economic analyses are also warranted. Delayed surgery may incur logistical challenges, increase health system costs, and complicate scheduling. Assessing the cost-effectiveness of timing strategies, particularly in resource-limited settings, is essential for policy development [41].

Strengths of this review: This systematic review contributes by synthesizing evidence across multiple tumor types and explicitly examining the role of radiological imaging in timing decisions. By considering both biological plausibility and technological advances in imaging, it highlights the interplay between clinical practice and emerging tools. The cross-tumor comparison allows recognition of common themes (such as a potential regression window) while acknowledging disease-specific nuances. The timing of surgery after neoadjuvant chemotherapy or chemo radiotherapy significantly influences pathological complete response rates in certain cancers but not uniformly across all tumor types. Rectal and esophageal cancers appear to benefit from modestly delayed surgery (6-12 weeks), whereas breast and lung cancers show less consistent or different patterns. Radiological imaging is indispensable for evaluating treatment response and informing multidisciplinary decisions, but it remains an imperfect surrogate for pCR. Advanced imaging biomarkers and standardized protocols hold promise for enhancing predictive accuracy. Clinicians should adopt an individualized approach, balancing potential gains in pCR with risks of surgical difficulty or disease progression. Until robust randomized data become available, decisions should be guided by tumor type, neoadjuvant regimen, patient recovery, and radiological findings within multidisciplinary teams. Future trials incorporating imaging, molecular biomarkers, and survival outcomes are critical to defining evidence-based guidelines for optimal timing [42].

Conclusion

This systematic review sought to clarify the relationship between the timing of surgery after neoadjuvant chemotherapy (NACT) or chemo radiotherapy (nCRT) and the likelihood of achieving pathological complete response (pCR), while also evaluating the role of radiological imaging in guiding these decisions. Across multiple tumor types including rectal, esophageal, gastric, breast, and non-small cell lung cancer (NSCLC) the evidence demonstrates that the timing pCR relationship is both complex and tumor-specific. Importantly, radiological evaluation offers valuable but imperfect insights, emphasizing the need for multidisciplinary integration of imaging with clinical and pathological data.

The most consistent evidence emerges in rectal cancer, where several cohort studies, meta-analyses, and randomized trials suggest that extending the interval between completion of nCRT and surgery to approximately 8-11 weeks is associated with higher pCR rates compared with shorter intervals of 4–6 weeks. This observation aligns with biological rationale: tumor regression and immune-mediated clearance continue beyond the end of therapy. However, excessively prolonged delays beyond 12-16 weeks do not confer further benefits and may increase surgical technical difficulty due to fibrosis, highlighting the importance of a balanced approach. In esophageal and gastric cancers, some studies similarly report improved tumor regression and pCR rates with modestly delayed surgery, though findings are inconsistent and frequently limited by retrospective design and patient selection bias. While a "sweet spot" around 6-8 weeks is suggested in certain cohorts, evidence is insufficient to make definitive recommendations, and individualized clinical judgment remains paramount.

Breast cancer presents a different pattern. Here, pCR is strongly determined by tumor biology such as triple-negative and HER2-positive subtypes and by systemic regimens including targeted therapies, rather than by surgical timing itself. Large registry and institutional series consistently show no clear improvement in pCR with deliberate surgical delays. Indeed, prolonged TTS beyond 8 weeks may be associated with worse survival in some cohorts, although confounding factors complicate interpretation. For breast cancer, then, timely surgery aligned with systemic treatment schedules is preferable, rather than intentionally extending the

interval in pursuit of higher pCR. In NSCLC, particularly in the era of neoadjuvant chemo immunotherapy, preliminary data suggest that shorter intervals to surgery often within 4 weeks may be advantageous. This may reflect the rapid onset of immune-mediated tumor clearance and the risk of progression if surgery is delayed. However, the evidence base here is small, and ongoing trials are needed to confirm the optimal timing.

Radiological imaging is central to evaluating treatment response and influencing surgical timing decisions. Breast MRI, especially when combined with diffusion-weighted imaging, offers high sensitivity but moderate specificity for predicting pCR. PET/CT provides valuable metabolic information in esophageal, gastric, and lung cancers but is limited by inflammatory uptake if performed too soon after therapy. CT and ultrasound, though widely available, lack the accuracy required to serve as definitive predictors of pCR. Importantly, the timing of imaging itself is critical: performing scans 2-4 weeks after the end of therapy allows resolution of treatment-related changes and improves predictive performance. Despite these advances, radiological complete response (rCR) does not equate to pCR, and reliance solely on imaging is not sufficient for surgical decision-making. Taken together, these findings highlight both opportunities and challenges. Modest delays after nCRT in rectal and, to a lesser extent, esophageal or gastric cancers may enhance pCR rates and potentially long-term outcomes, but such strategies must be tailored to tumor type, regimen, and patient condition. In breast cancer and NSCLC, routine surgical delay appears unwarranted, with biology and systemic therapy being more critical determinants of response. Radiological imaging should be employed systematically but interpreted cautiously, acknowledging its predictive limitations. The quality of current evidence remains limited, as most studies are retrospective and heterogeneous in their definitions of TTS, imaging protocols, and response criteria. There is a pressing need for prospective randomized controlled trials that directly compare different surgical intervals, incorporate standardized imaging modalities, and report both pCR and survival outcomes. Future research should also integrate advanced imaging biomarkers, radiomics, and circulating tumor DNA (ctDNA) to refine prediction of pCR and personalize surgical timing.

In conclusion, the timing of surgery after neoadjuvant therapy has a measurable but context-dependent effect on pCR. For rectal and certain gastrointestinal cancers, modest delays may optimize response; for breast and lung cancers, timing exerts little influence compared with tumor biology and systemic treatment. Radiological imaging provides indispensable guidance but cannot yet replace histopathological confirmation. A nuanced, multidisciplinary approach considering tumor type, treatment modality, patient fitness, and imaging findings is essential to balance oncologic efficacy with surgical safety. By bridging biological rationale, imaging advances, and clinical evidence, future studies can better define optimal timing strategies and ultimately improve outcomes for patients undergoing multimodality cancer treatment.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

References

[1] Rajan, K. K., Iype, E. L., Shrestha, S., et al. (**2024**). Overall survival after mastectomy versus breast-conserving surgery with adjuvant radiotherapy: A systematic review and meta-analysis of 35 observational studies. *BJS Open*, *8*(3), zrae040.

[2] Mokbel, K., & et al. (**2024**). Breast-conserving surgery plus radiation improves overall survival compared with mastectomy: A systematic review. *The Breast*.

[3] Duangkaew, C., & et al. **(2025).** Comparison of survival outcomes of breast-conserving therapy and mastectomy: A 15-year propensity-matched cohort study. *Cancers*, *17*(4), 591.

[4] de Boniface, J., Frisell, J., Johansson, A. L. V., Fredriksson, I., Lyth, J., Liljegren, A., et al. (**2021**). Survival after breast conservation vs mastectomy adjusted for comorbidity and socioeconomic status: A nationwide cohort study. *JAMA Surgery*.

[5] Christiansen, P., Carstensen, S. L., Ejlertsen, B., Kroman, N., Offersen, B., Bodilsen, A., & Jensen, M. B. (**2018**). Breast-conserving surgery versus mastectomy: Overall and relative survival—A population-based study by the Danish Breast Cancer Cooperative Group (DBCG). *Acta Oncologica*, *57*(19), 19–25.

[6] Agarwal, S., Pappas, L., Neumayer, L., Kokeny, K., & Agarwal, J. (**2014**). Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. *JAMA Surgery*, *149*(3), 267–274.

[7] Corradini, S., Pirovano, M., & et al. (**2019**). Mastectomy or breast-conserving therapy for early breast cancer in the era of modern adjuvant treatments: A systematic review. *Cancers*, *11*(2), 160.

[8] Fulginiti, D., & et al. (**2025**). Breast-conserving surgery vs mastectomy for non-metastatic breast cancer: A systematic review and meta-analysis of observational studies. *Cureus*.

[9] Hashemloo, A., & Milanifard, M. (**2025**). Dermal fillers: Types, indications, and complications. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(6), 161–170.

[10] Hashemloo, A., & Milanifard, M. (2025). Contouring plus: A comprehensive approach of the lower third of the face with calcium hydroxylapatite and hyaluronic acid. *Medicinal, Psychological, and Health Research Journal, 1*(5), 143–150.

[11] Hassani, S., Rikhtehgar, M., & Salmanpour, A. (**2022**). Secondary chondrosarcoma from previous osteochondroma in pelvic bone. *GSC Biological and Pharmaceutical Sciences, 19*(3), 248–252.

[12] Mirakhori, F. **(2024).** Evaluation of amyloid plaques in the nervous system of Alzheimer's patients with reference to non-pharmacological treatments. *International Neurourology Journal, 28*(1), 804–820.

[13] Mirghaed, F. A., Ahmadi, T. N., Albuzyad, S. S., Khorram, A. A., & Mahshad, F. (**2024**). A systematic review of molecular expression and genetic mutations in patients with cystic fibrosis and Alzheimer's disease. *International Neurourology Journal, 28*(1), 773–786.

[14] Rahimi, M. J., Mirakhori, F., Zelmanovich, R., & Sedaros, C., et al. (**2024**). Diagnostic significance of neutrophil to lymphocyte ratio in recurrent aphthous stomatitis: A systematic review and meta-analysis. *Dermatology Practical & Conceptual, 14*(1), e2024046.

[15] Shariati, A., & Tahavvori, A., et al. (2022). Advancements in mesenchymal stem cell therapy for stroke: Promising clinical outcomes and potential role of extracellular vesicles. *Journal of Pharmaceutical Negative Results, 13*(8), 1–8.

[16] Rezaei, M., et al. (**2022**). Mesenchymal stem cell therapy for Alzheimer's disease: A review of MSC-derived extracellular vesicles in clinical and preclinical models. *Journal of Pharmaceutical Negative Results, 13*(9), 1–9.

[17] Ahmadi, M., et al. (**2023**). Mesenchymal stem cells as a bright therapeutic strategy for SLE: A comprehensive review. *NeuroQuantology, 21*(5), 334–364.

[18] Ghaedi, A., et al. (**2024**). Systematic review of the significance of neutrophil to lymphocyte ratio in anastomotic leak after gastrointestinal surgeries. *BMC Surgery, 24*, 1–10.

[19] Bolhari, J., et al. (**2018**). Domestic violence prevention advocacy program: A pilot study in Tehran urban area. *Iranian Journal of Psychiatry and Clinical Psychology, 24*(2), 150–157.

[20] Milanifard, M., & Hashemloo, A. **(2025).** Facial fillers: Relevant anatomy, injection techniques, and complications. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(7), 204–212.

[21] Divsalar, F., Sattar Albuzyad, S., et al. (**2024**). Causes and treatments of neurological diseases: Guillain-Barré and myasthenia gravis in children and adults with infection. *Neurological Disease & Pain, 28*(1), 1–10.

[22] Mirakhori, F., Sattar Albuzyad, S., et al. **(2024).** Alzheimer's disease and related studies. *Alzheimer's & Dementia, 28*(1), 1–10.

[23] Ahmadi Mirghaed, F., et al. (**2024**). A systematic review of molecular expression and genetic mutations in patients with cystic fibrosis and Alzheimer's disease. *International Neurourology Journal, 28*(1), 773–786.

[24] Nabatchi Ahmadi, T., et al. (**2024**). Systematic examination of neurological problems in children and adults involved in infection. *International Neurourology Journal, 28*(1), 833–842.

[25] Jahandideh, H., et al. (**2024**). Reliability and validity of the Persian Nose Obstruction Symptom Evaluation (NOSE) scale. *World Journal of Plastic Surgery, 13*(2), 25–31.

[26] Fazeli, B., et al. (**2024**). Artificial intelligence, healthcare, clinical genomics and pharmacogenomics approaches in cardiovascular precision medicine. *Journal of Advanced Zoology, 45*(5), 102–110.

[27] Yaghoubi, F., Babakhani, D., & Tavakoli, F. (**2022**). Osmotic demyelination syndrome after bone marrow transplantation. *Journal of Nephropathology, 11*(1), e10.

[28] Tavakoli, F., Yaghoubi, F., & Babakhani, D. (**2019**). Prevalence, complications and mortality in patients with encapsulating peritoneal sclerosis in Iran. *Journal of Renal Injury Prevention, 8*(1), 17–21.

[29] Djalalimotlagh, S., Mohaghegh, M. R., Ghodraty, M. R., Shafeinia, A., Rokhtabnak, F., Alinia, T., & Tavakoli, F. (**2019**). Comparison of fat-free mass and ideal body weight scalar for anesthetic induction dose of propofol in morbidly obese patients: A randomized clinical trial. *Journal of Renal Injury Prevention, 13*(6), e140027.

[30] Hashemloo, A., & Milanifard, M. (**2025**). Dermal fillers: Types, indications, and complications (Spanish version). *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(6), 161–170.

[31] Hassani, S., et al. (**2025**). Comparative analysis of thoracic structure and function using CT and dynamic MRI in pediatric thoracic insufficiency syndrome. *Journal of Spine Deformity, 1–9.*

[32] Torigian, D. A., & Shaghaghi, S. (**2025**). Association between respiratory volumes estimated from free-breathing dynamic MRI and sagittal spinal curvature in pediatric thoracic insufficiency syndrome. *Proceedings of SPIE Medical Imaging, 1–8.*

[33] Shariati, A. (**2022**). Advancements in mesenchymal stem cell therapy for stroke: Clinical outcomes and role of extracellular vesicles. *Journal of Pharmaceutical Negative Results, 13*(8), 1–8.

[34] Ahmadi, M., Rahmani Youshanouei, H., et al. (**2023**). Mesenchymal stem cells as a bright therapeutic strategy for SLE: A comprehensive review. *NeuroQuantology, 21*(5), 334–364.

[35] Asl, L. D. (**2025**). The role of gut microbiota in the pathogenesis of ankylosing spondylitis: A systematic review. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(9), 275–282.

[36] Ghaedi, A., et al. (**2024**). Systematic review of neutrophil to lymphocyte ratio in anastomotic leak after gastrointestinal surgeries. *BMC Surgery, 24*, 1–10.

[37] Hashemloo, A., & Milanifard, M. (2025). Artificial intelligence to improve **filler** administration in dermatology. *Medicinal, Psychological, and Health Research Journal, 1*(5), 151–159.

[38] Hashemloo, A., & Milanifard, M. (**2025**). Contouring plus: A comprehensive approach of the lower third of the face with calcium hydroxylapatite and hyaluronic acid. *Medicinal, Psychological, and Health Research Journal, 1*(5), 143–150.

[39] Hashemloo, A., & Milanifard, M. (**2025**). The facial shapes in planning the treatment with injectable fillers. *Medicinal, Psychological, and Health Research Journal, 1*(6), 169–177.

[40] Lotfi, A. R., & Nouribayat, L. (**2025**). Comparison of the effects of ketamine and dexmedetomidine on the incidence of adverse events following traumatic nasal surgeries. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(9), 266–274.

[41] Rahimi, M. J., Mirakhori, F., Zelmanovich, R., Sedaros, C., Lucke-Wold, B., Rainone, G., et al. (**2024**). Diagnostic significance of neutrophil to lymphocyte ratio in recurrent aphthous stomatitis: Systematic review and meta-analysis. *Dermatology Practical & Conceptual, 14*(1), e2024046.

[42] Rezaei, M., et al. **(2022).** Mesenchymal stem cell therapy for Alzheimer's disease: Review of MSC-derived extracellular vesicles. *Journal of Pharmaceutical Negative Results, 13*(9), 1–9.