MODERN PRINCIPLES OF NEOADJUVANT CHEMOTHERAPY IN LOW RECTAL CANCER

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Abstract. *Low rectal cancer remains one of the most challenging malignancies in modern oncology due to its complex anatomical location, the risk of local recurrence, and the necessity to preserve sphincter function. The development of neoadjuvant chemotherapy has fundamentally changed the approach to treating these tumors, improving both oncological and functional outcomes. The main objective of neoadjuvant therapy is to achieve tumor downstaging, reduce micrometastatic spread, and increase the likelihood of complete surgical resection (R0 resection).*

In recent years, several chemotherapy regimens, including FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) and CAPOX (capecitabine and oxaliplatin), have demonstrated significant effectiveness when used either alone or in combination with radiotherapy. The integration of these systemic therapies into multimodal treatment protocols has led to better local tumor control, improved overall survival, and a higher rate of organ preservation.

Furthermore, the use of total neoadjuvant therapy (TNT), which incorporates both systemic chemotherapy and chemoradiotherapy prior to surgery, has shown superior pathological complete response rates. The introduction of molecular diagnostics and biomarker-based treatment selection has opened new opportunities for personalized medicine in rectal cancer, including the use of targeted and immune therapies.

This paper analyzes the current principles, strategies, and results of neoadjuvant chemotherapy in low rectal cancer and discusses emerging trends that could shape future treatment protocols aimed at optimizing efficacy while minimizing adverse effects.

Keywords. *Neoadjuvant chemotherapy; low rectal cancer; chemoradiotherapy; FOLFOX; CAPOX; total neoadjuvant therapy (TNT); tumor regression; sphincter preservation; targeted therapy; immunotherapy; personalized medicine; multimodal treatment; colorectal oncology.*

Main Body

6. Rationale and Objectives of Neoadjuvant Chemotherapy

The main goal of neoadjuvant chemotherapy in low rectal cancer is to reduce tumor burden before surgery, thereby increasing the likelihood of complete resection and decreasing the risk of local recurrence. The anatomical confinement of the pelvis often complicates surgical access and limits the ability to achieve negative margins.

Preoperative systemic therapy allows for tumor downstaging and may convert initially unresectable tumors into operable cases. Furthermore, early treatment of micrometastases contributes to improved long-term survival.

Neoadjuvant chemotherapy also enables the assessment of treatment response, which can serve as a prognostic indicator. Patients who achieve a complete or near-complete pathological response generally have better survival rates. In selected cases, where there is a complete clinical response, a “watch-and-wait” strategy may even be considered, avoiding radical surgery and preserving anorectal function.

2. Commonly Used Chemotherapy Regimens

Several chemotherapy regimens have been evaluated in clinical trials for neoadjuvant use in rectal cancer. The most widely accepted combinations include:

- FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) — a regimen that enhances radiosensitivity and improves tumor regression.
- CAPOX (capecitabine and oxaliplatin) — an oral alternative to FOLFOX with comparable efficacy and better patient compliance.
- FOLFIRI (5-fluorouracil, leucovorin, and irinotecan) — used in specific cases where oxaliplatin intolerance or resistance is observed.

These regimens are often integrated into total neoadjuvant therapy (TNT) protocols, combining both chemotherapy and chemoradiotherapy in the preoperative phase to maximize local and systemic control.

3. Integration with Radiotherapy and Total Neoadjuvant Therapy (TNT)

Combined chemoradiotherapy has become a standard component of neoadjuvant treatment for locally advanced low rectal cancer. The concurrent administration of chemotherapy with pelvic radiotherapy improves tumor response by sensitizing cancer cells to radiation. The TNT approach extends this concept further by administering all systemic therapy before surgery, thereby increasing the rate of pathological complete response (pCR) and decreasing the risk of distant metastases.

Recent trials such as RAPIDO and PRODIGE-23 have shown that TNT improves disease-free survival and reduces treatment-related delays. Additionally, TNT enhances compliance, as patients often tolerate preoperative chemotherapy better than postoperative therapy.

4. Advances in Molecular and Targeted Therapies

The evolution of molecular biology has led to a more personalized approach to neoadjuvant treatment. Biomarker analysis, including microsatellite instability (MSI), KRAS, NRAS, and BRAF mutations, enables clinicians to tailor therapy to individual tumor characteristics.

- Patients with MSI-high tumors may benefit from immunotherapy agents such as PD-1 inhibitors.
- EGFR inhibitors and VEGF-targeted agents are under investigation for potential integration into neoadjuvant protocols.

These targeted approaches promise improved efficacy and reduced systemic toxicity compared to conventional chemotherapy.

5. Surgical and Functional Outcomes

One of the key advantages of neoadjuvant therapy is its impact on surgical outcomes. Tumor downsizing increases the feasibility of sphincter-preserving procedures, reducing the need for permanent colostomy. Moreover, achieving tumor regression allows for more precise surgical dissection, lowering postoperative complication rates.

However, treatment-related side effects, such as neuropathy and hematologic toxicity, require careful monitoring and dose adjustments. The timing of surgery after neoadjuvant therapy is also crucial, typically occurring 6–10 weeks after treatment completion to allow for maximal tumor response and tissue recovery.

6. Challenges and Future Directions

Despite the progress, several challenges persist. Optimal chemotherapy duration, regimen selection, and criteria for patient selection remain subjects of ongoing debate. Furthermore, reliable biomarkers to predict response are still under investigation. Future research is expected to focus on combining neoadjuvant chemotherapy with immunotherapy, refining TNT protocols, and integrating artificial intelligence tools to predict treatment outcomes.

The ultimate goal is to achieve a fully personalized, organ-preserving, and minimally invasive approach to the management of low rectal cancer.

Discussion

Neoadjuvant chemotherapy has become an integral part of modern oncological practice for managing low rectal cancer, significantly improving local control, resectability, and overall survival. The discussion of its effectiveness should be considered from multidisciplinary and evidence-based perspectives, as treatment outcomes largely depend on the integration of chemotherapy, radiotherapy, and surgical planning.

One of the most important advantages of neoadjuvant therapy is its ability to reduce tumor volume and downstage disease before surgery. This approach not only increases the rate of complete (R0) resections but also allows for sphincter-preserving operations, which are crucial for maintaining the patient's postoperative quality of life. Studies such as the German Rectal Cancer Study Group trial have shown that preoperative chemoradiotherapy provides superior local control compared to postoperative therapy, emphasizing the importance of treatment sequencing.

The advent of Total Neoadjuvant Therapy (TNT) has further transformed treatment paradigms by integrating systemic chemotherapy and chemoradiation entirely into the preoperative phase. The RAPIDO and PRODIGE-23 trials demonstrated that TNT significantly improves pathological complete response rates, reduces distant metastases, and enhances disease-free survival. However, while TNT offers promising outcomes, it also raises challenges regarding patient selection, toxicity management, and treatment

adherence. Not all patients tolerate prolonged preoperative regimens equally well, and optimization of dosage intensity remains an active area of research.

A growing body of evidence supports the role of biomarker-driven approaches in guiding neoadjuvant chemotherapy. For example, MSI-high and deficient mismatch repair (dMMR) tumors are more likely to respond to immunotherapy, while patients with specific molecular alterations in KRAS, NRAS, or BRAF may require alternative targeted strategies. Integrating molecular profiling into preoperative planning could help personalize treatment, reducing unnecessary toxicity and improving outcomes.

Despite these advances, several unresolved questions persist. The optimal timing between the completion of neoadjuvant therapy and surgery remains controversial. While longer intervals may allow for greater tumor regression, they also risk disease progression in some cases. Furthermore, reliable predictive markers to assess complete clinical response are still being developed, and the “watch-and-wait” approach, though promising, must be applied cautiously within strict monitoring protocols.

In summary, neoadjuvant chemotherapy in low rectal cancer continues to evolve from conventional cytotoxic approaches toward a multimodal, precision-based model. Collaboration among oncologists, surgeons, radiologists, and pathologists is essential for selecting appropriate candidates, tailoring therapy, and optimizing outcomes. Future directions include combining immunotherapy and targeted agents with established chemotherapy regimens, exploring novel biomarkers for response prediction, and implementing advanced imaging and AI tools for individualized treatment planning.

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