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Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer

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QUESTION: A 64-year-old male with no significant medical history was referred for further evaluation of suspected rectal cancer identified during an external colonoscopy. Endoscopic examination revealed an ulcerofungating lesion located 5 cm from the anal verge, and the biopsy confirmed moderately differentiated adenocarcinoma (Fig. 1A). Initial staging with computed tomography and rectal magnetic resonance imaging (MRI) indicated cT3/T4N1 disease with threatened circumferential resection margin (CRM) and extramural venous invasion (EMVI) positivity (Fig. 1B). The serum carcinoembryonic antigen level was 5.03 ng/ml. The patient is currently asymptomatic for bowel obstruction, with an Eastern Cooperative Oncology Group performance status of 0. What would be the most appropriate treatment strategy?

ANSWER: Based on recent clinical data and guidelines, following assessment with MRI, for patients with microsatellite stable or proficient mismatch repair locally advanced rectal cancer (LARC), total neoadjuvant therapy (TNT) should be offered as initial treatment for patients with tumors located in the lower rectum and/or patients who are at higher risk for local and/or distant metastases. This case represents high-risk LARC, characterized by cT3/T4, N+ status, threatened CRM and EMVI positivity on MRI. To maximize both systemic and local disease control, a TNT strategy is the most appropriate approach for this patient. The TNT approach can be tailored according to the risk of locoregional recurrence and distant metastasis. In the present case, a higher risk of locoregional recurrence was anticipated than the risk of distant metastasis based on MRI findings, including threatened CRM. Therefore, following multidisciplinary

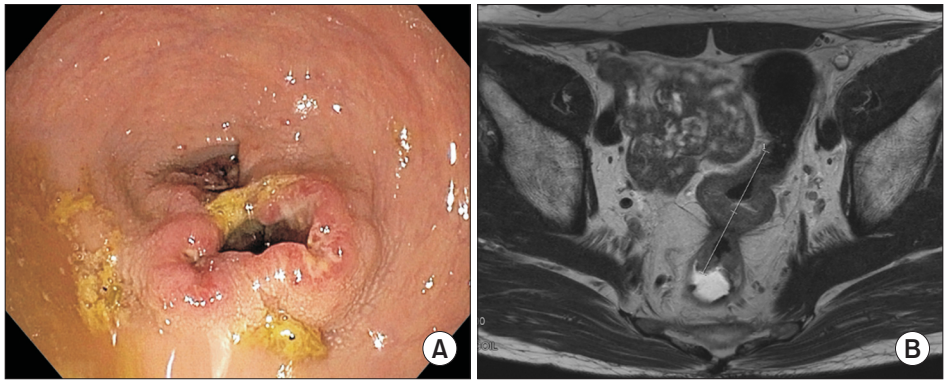

Fig. 1. Initial imaging findings of the patient.

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team discussion, TNT approach was selected, initiating with long-course chemoradiotherapy (CRT) to maximize locoregional control, followed by systemic chemotherapy to address potential micrometastatic disease and enhance tumor response prior to surgery. Treatment consisted of long-course concurrent CRT with capecitabine, followed by eight cycles of preoperative modified FOLFOX (mFOLFOX) chemotherapy, and subsequent laparoscopic low anterior resection with diverting loop ileostomy. Postoperative management was to be determined based on the final surgical pathology, with consideration of additional postoperative chemotherapy (approximately four cycles), taking into account national health insurance policies in Korea.

REVIEW: LARC has traditionally been managed with preoperative long-course CRT followed by radical surgery, specifically total mesorectal excision, and adjuvant chemotherapy. Numerous clinical trials have established long-course CRT as the preoperative standard of care, owing to its efficacy in reducing local recurrence and enhancing the probability of successful surgical resection.

However, this traditional CRT-based paradigm has faced significant limitations, most notably the inadequate prevention of distant metastasis. A persistent clinical challenge is that only approximately half of the patients are able to complete the planned adjuvant chemotherapy cycles due to physical debilitation or postoperative complications following major surgery. Furthermore, since systemic treatment is deferred until the postoperative phase, effective control of micrometastases is often delayed. Consequently, distant metastasis rates of 25–30% have been reported despite conventional CRT, underscoring the urgent need for novel therapeutic strategies.

In this context, TNT has emerged as a contemporary strategy. TNT involves the intensive delivery of both CRT and systemic chemotherapy prior to surgery, aiming for early locoregional control as well as the early eradication of distant micrometastases. The clinical benefits of TNT have been validated through several large-scale randomized controlled trials, including RAPIDO, PRODIGE, STELLAR, and OPRA.

The RAPIDO trial, focused on high-risk patients, defined by pelvic MRI with at least one of the following criteria: clinical tumor (cT) stage cT4a or cT4b, extramural vascular invasion, clinical nodal (cN) stage cN2, tumor or lymph node ≤ 1 mm from the mesorectal fascia, or enlarged lateral lymph nodes considered to be metastatic. This study demonstrated that preoperative short-course radiotherapy (5 × 5 Gy within 8 days) followed by systemic chemotherapy (CAPOX or FOLFOX4) significantly improved both 3-year disease-related treatment failure (DRFS) and pathologic complete response (pCR) rates compared to conventional CRT [1]. pCR was defined as the complete absence of viable tumor cells in the surgical specimen upon microscopic examination by a pathologist (ypT0N0). Similarly, the PRODIGE 23 study showed that induction FOLFIRINOX followed by preoperative CRT significantly increased 3-year disease-free survival (DFS) and pCR rates compared to the standard of care (long-course chemoradiotherapy followed by surgery and adjuvant chemotherapy); notably, 7-year long-term follow-up further confirmed a significant improvement in overall survival (OS) [2]. The STELLAR trial, involving distal or middle-third cT3–4/N+ rectal cancer, applied short-course radiotherapy (5 × 5 Gy) followed by systemic chemotherapy (CAPOX or FOLFOX4). This study demonstrated that while TNT showed no significant difference in metastasis-free survival or locoregional recurrence compared to CRT, it achieved superior 3-year OS. In the OPRA trial, patients achieving a clinical complete response (cCR) after TNT were able to undergo organ preservation via a watch and wait (WW) approach, yielding favorable long-term organ preservation and DFS. cCR was defined as the disappearance of all detectable tumor based on clinical, endoscopic, and radiological evaluations following neoadjuvant therapy, without surgical intervention. Furthermore, the PROSPECT and CONVERT trials provided evidence that neoadjuvant chemotherapy alone can ensure comparable oncologic outcomes in carefully selected low-to-intermediate risk patients, thereby suggesting that omission of radiotherapy may be feasible in carefully selected patients.

The integration of TNT has been proactively reflected in international clinical guidelines. The 2024 National Com-

prehensive Cancer Network guidelines recommend TNT as a standard of care for T3–4, T1–2/N1–2, or unresectable LARC, permitting both short-course radiotherapy combined with systemic chemotherapy and long-course CRT preceded or followed by systemic chemotherapy [3]. The 2025 European Society for Medical Oncology [4] and American Society of Clinical Oncology [5] guidelines also strongly recommend TNT for high-risk rectal cancer and suggest its application in conjunction with non-operative management strategies.

How is TNT currently implemented within the South Korean health insurance system? As of October 1, 2024, national health insurance coverage for TNT in rectal cancer has been officially implemented in South Korea. According to these criteria, patients with locally advanced stage II or III rectal cancer are eligible for reimbursement when receiving 12 cycles of FOLFOX or 8 cycles of CapeOx treatment regimen that incorporates both neoadjuvant and adjuvant components of TNT. These standards are based on the primary clinical trial results and the latest international guidelines discussed previously.

In clinical practice, the optimal number of preoperative chemotherapy cycles and their integration with postoperative adjuvant therapy in TNT remain variable, as a range of treatment schedules has been explored across clinical trials. However, concentrating systemic chemotherapy during the neoadjuvant phase when the patient's general condition is relatively favorable appears to be an effective strategy. From a practical perspective, it may be reasonable to deliver at least 6–8 cycles of FOLFOX or 4–6 cycles of CAPOX systemic chemotherapy prior to surgery. This strategy may improve chemotherapy compliance and overall treatment completion rates, while enhancing tumor response and facilitating early control of micrometastatic disease. Following completion of preoperative TNT and surgical resection, the remaining chemotherapy cycles may be administered in the adjuvant setting, with the exact number tailored according to the final pathological findings, including the presence or absence of pCR, as well as the patient's postoperative recovery and tolerance. The application of TNT in rectal cancer treatment should be determined through thorough multidisciplinary discussions that evaluate the extent of tumor progression, the patient's performance status, and specific treatment goals.

In conclusion, the TNT approach has demonstrated several advantages, including early prevention or eradication of micrometastases, higher rates of pCR and prolonged DFS, facilitation of surgical resection, and improved tolerance and completion rates of chemotherapy. In selected patients, surgery may even be omitted if a cCR is achieved following neoadjuvant therapy [3]. The incorporation of TNT should be offered in the management of high-risk rectal cancer.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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