



Prioritizing Chemotherapy in Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: A Policy Brief for Settings with Limited Timely Radiotherapy Access

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Dear Editor,

Locally advanced rectal cancer (LARC) remains a major oncologic challenge, requiring coordinated multimodal treatment to maximize tumor response, improve surgical outcomes, and reduce the risk of recurrence. Although conventional management historically consisted of neoadjuvant chemoradiotherapy followed by total mesorectal excision and postoperative chemotherapy, total neoadjuvant therapy (TNT) has increasingly become an established treatment strategy for many patients with LARC, particularly those with high-risk features or those requiring maximal tumor regression (1). Current international guidelines recognize TNT as an appropriate treatment approach, with the sequencing of chemotherapy and radiotherapy individualized according to tumor characteristics, treatment goals, and health care system factors (2).

However, in many low- and middle-income countries, including Iran, limited radiotherapy capacity, geographic disparities in access, and prolonged waiting times may delay the initiation of radiotherapy-based treatment pathways. National assessments of radiotherapy infrastructure in Iran have demonstrated substantial regional variation in available facilities and equipment, highlighting persistent challenges in ensuring equitable and timely access to radiotherapy services (3). Delayed treatment initiation is not only a logistical issue but also a

health care system challenge that may affect continuity of care, treatment completion, and the quality of cancer care.

The emergence of TNT provides an opportunity to adapt treatment sequencing to real-world health care constraints. In particular, chemotherapy-first TNT, in which systemic therapy is initiated before chemoradiotherapy, allows active oncologic treatment to begin while access to radiotherapy is arranged. International randomized trials have demonstrated that TNT improves the delivery of systemic therapy and may improve disease-related outcomes compared with conventional treatment sequences in appropriately selected patients (4, 5). The choice of TNT sequence remains individualized. Trials comparing induction chemotherapy followed by chemoradiotherapy with chemotherapy followed by consolidation chemotherapy have demonstrated comparable oncologic outcomes, whereas consolidation chemotherapy after chemoradiotherapy may offer advantages in pathological response and organ preservation strategies (6, 7).

Recent randomized studies from Iran have provided important context-specific evidence regarding the feasibility of chemotherapy-first TNT in settings where access to radiotherapy may be constrained. A randomized phase 3 trial evaluating TNT versus conventional chemoradiotherapy reported a numerically higher pathological complete response rate with TNT, although the difference was not statistically significant and survival outcomes require further evaluation (8). Subsequently, a

larger randomized controlled trial involving 202 patients reported that chemotherapy-first TNT significantly increased the pathological complete response rate compared with conventional treatment sequencing, without a major increase in treatment-related toxicity. However, survival outcomes from this study remain immature, and longer follow-up is required to determine whether improvements in pathological response translate into long-term survival benefits (9).

These findings support an important health policy principle: treatment sequencing should be considered both a biological or oncologic decision and a practical strategy for adapting evidence-based care to the realities of health care systems. In settings where patients may experience prolonged delays before accessing radiotherapy, chemotherapy-first TNT represents a pragmatic approach that enables the initiation of active systemic treatment while maintaining radiotherapy as an essential component of multimodality care.

The implications of this approach extend beyond individual patient outcomes. Initiating systemic therapy before radiotherapy becomes available may reduce periods during which patients receive no active treatment and may improve completion of planned multimodality therapy. In addition, chemotherapy-first TNT may offer greater flexibility in treatment coordination within health care systems facing radiotherapy capacity limitations. Nevertheless, these potential health system advantages should be evaluated prospectively through appropriate implementation studies assessing treatment waiting times, treatment completion rates, resource utilization, cost-effectiveness, and long-term oncologic outcomes.

From a health policy perspective, several complementary measures should be considered to support evidence-based implementation. National clinical guidelines should recognize TNT as an appropriate treatment option for selected patients with LARC, particularly in centers experiencing substantial radiotherapy delays. Clear multidisciplinary eligibility criteria should be developed to ensure that chemotherapy-first TNT is offered to patients who are medically suitable for systemic therapy and for whom subsequent access to radiotherapy can reasonably be secured.

Implementation requires coordinated action among multiple stakeholders. The Ministry of Health and Medical Education, including its Deputies for Treatment and for Research and Technology, the National Cancer Management Office, health care administrators, and professional societies should collaborate on standardized treatment pathways, referral networks, and monitoring systems. Public and complementary health insurers and reimbursement authorities should ensure appropriate

coverage of all components of TNT, including systemic chemotherapy, radiotherapy, imaging assessment, multidisciplinary evaluation, and supportive care, while preventing financial barriers that may compromise treatment completion.

Health technology assessment bodies and health care policymakers should support local evaluations of budget impact, cost-effectiveness, and equity outcomes before broad implementation. Cancer treatment centers should establish mechanisms for multidisciplinary decision-making, coordination of radiotherapy scheduling, and prospective monitoring of quality indicators. These indicators should include the time from diagnosis to therapy initiation, the time to radiotherapy access, completion of planned TNT, pathological and clinical response rates, surgical outcomes, toxicity, recurrence patterns, survival outcomes, and geographic equity in care delivery.

Despite encouraging evidence, several implementation barriers should be recognized. Limited radiotherapy infrastructure, unequal distribution of treatment resources, financial constraints, workforce limitations, and resistance to modifying established clinical pathways may delay the adoption of optimized treatment sequencing. Addressing these challenges requires coordinated national planning, investment in radiotherapy capacity expansion, workforce development, strengthened cancer registries, and continuous evaluation of real-world outcomes.

The experience of health care systems facing resource limitations highlights an important principle: improving cancer care does not always require entirely new therapeutic discoveries but often depends on implementing existing evidence in ways that reflect local health care capacity. In this context, chemotherapy-first TNT should be viewed as a context-adapted sequencing strategy for appropriately selected patients with LARC when timely access to radiotherapy is limited, rather than as a substitute for indicated radiotherapy. This approach can complement, but should not replace, long-term investment in radiotherapy infrastructure, equitable distribution of oncology services, and sustainable cancer care planning.

These considerations are particularly relevant to the Ministry of Health and Medical Education, the Deputy for Treatment, the Deputy for Research and Technology, the National Cancer Management Office, the Iranian Society of Radiation Oncology, the Iranian Colorectal Surgeons Society, medical oncology societies, public and complementary insurers, health technology assessment organizations, and administrators of cancer treatment centers. Policy development should focus on enabling equitable access to evidence-based TNT pathways while

ensuring appropriate patient selection, sustainable reimbursement mechanisms, multidisciplinary coordination, and continuous outcome monitoring. Future research should evaluate both traditional clinical endpoints and health system outcomes, including waiting times, treatment completion, cost-effectiveness, patient-reported outcomes, and equity of access. In parallel, continued investment in radiotherapy infrastructure and workforce capacity remains essential to ensure that adaptive treatment sequencing complements rather than replaces comprehensive cancer care development.

Footnotes

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