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EDITORIAL

Re-evaluating the role of pelvic radiation in the age of modern precision medicine and systemic therapy

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Abstract

The efficacy of pelvic radiation in the management of locally advanced stage rectal cancer has come under scrutiny in the context of modern precision medicine and systemic therapy as evidenced by recent clinical trials such as FOWARC (*J Clin Oncol* 2019; 37: 3223-3233), NCT04165772 (*N Engl J Med* 2022; 386: 2363-2376), and PROSPECT (*N Engl J Med* 2023; 389: 322-334). In this review, we comprehensively assess these pivotal trials and offer additional insights into the evolving role of pelvic radiation in contemporary oncology.

Key Words: Radiotherapy; Locally advanced stage rectal cancer; Precision medicine; Systemic therapy; Clinical trial

Core Tip: Neoadjuvant systemic therapy alone without radiation represents a viable option for locally advanced rectal cancer patients, particularly when organ preservation is not a priority. Nevertheless, it is crucial to engage in multidisciplinary discussions, especially considering the limited long-term experience.

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INTRODUCTION

Pelvic radiation has traditionally played an essential role in neoadjuvant therapy for locally advanced rectal cancer (LARC) in the past, either as neoadjuvant concurrent chemoradiotherapy (nCCRT) or neoadjuvant short course radiotherapy (nSCRT)[1-3]. However, its efficacy has come under scrutiny in the context of modern precision medicine and systemic therapy as evidenced by recent clinical trials[4-6] and a systematic review[7]. Consequently, the use of neoadjuvant systemic therapy alone without radiation has emerged as one of the alternatives in contemporary guidelines for patients with certain genetic mutations who achieved a complete clinical response after immunotherapy or patients with a good response (> 20%) after chemotherapy[8]. In addition, patients with high-risk features such as threatened mesorectal fascia, N2 stage, or extramural vascular invasion were not good candidates for the use of chemotherapy without radiation[6,8].

MAIN BODY

In this editorial, we have summarized select relevant trials in Table 1[4-6,9,10], which provide the rationale for employing neoadjuvant systemic therapy alone without radiation in specific LARC cases. However, we would like to highlight two additional considerations regarding the omission of pelvic radiation for LARC.

Table 1 Key characteristic of trials investigating neoadjuvant systemic therapy alone without radiation in locally advanced rectal cancer

Study	ID	Design	LARC	Study group	Comparator group(s)	mFU	pCR (%)	Local control (%)	OS (%)
FOWARC[4]	NCT01211210	Phase 3	Suitable for curative resection	FOLFOX	CCRT	45.2	6.5 *vs* (14 or 27.5); *P* 0.05	3-year LRR 8.3 *vs* (8 or 7); *P* = 0.873	3-year 90.7 *vs* (91.3 or 89.1); *P* = 0.971
PROSPECT [6]	NCT01515787	Phase 3	T2N1, T3N0, T3N1	FOLFOX	CCRT	58	21.9 *vs* 24.3; *P* value NA	5-year LR 1.8% *vs* 1.6%; *P* value > 0.05	5-year 89.5 *vs* 90.2; *P* value > 0.05
GRECCAR4 [9]	NCT01333709	Phase 2 RCT	T3d with predictive CRM 1 mm	FOLFIRINOX	CCRT	65.7	(10 or 13.5) *vs* (58 or 20); *P* value NA	NA	5-year (90 or 84.3) *vs* (93.3 or 86.1); *P* value > 0.05
CONVERT [10]	NCT02288195	Phase 3	cT2N+ or cT3-4Nany uninvolved mesorectal fascia	CAPOX	CCRT	NA	11 *vs* 13.8; *P* = 0.33	NA	NA
19-288[5]	NCT04165772	Phase 2	Mismatch repair–deficient	Dostarlimab	NA	NA	NA	100	100

LARC: Locally advanced rectal cancer; LR: Local recurrence; LRR: Locoregional recurrence; mFU: Median follow up (in months); pCR: Pathological complete response; OS: Overall survival; CCRT: Concurrent chemoradiotherapy; CRM: Circumferential resection margin; NA: Not available; RCT: Randomized controlled trial.

First, it is imperative to await long-term follow-up results from the aforementioned studies. For instance, the initial publication of the RAPIDO trial reported no statistically significant difference in locoregional failure between nSCRT followed by chemotherapy and nCCRT (P = 0.12)[11]. However, the disparity in locoregional failure became more pronounced with borderline statistical significance after extended follow-up (P = 0.07)[12]. This finding has led to nSCRT being less favored by certain experts[13] and in the current guidelines[8]. It is worth noting that the biological equivalent dose in radiotherapy of nCCRT is higher than that of nSCRT [EQD2(10) 50 Gy *vs* 37.5 Gy][14].

Second, one of the potential objectives in modern LARC management is organ preservation, for which nCCRT in the context of total neoadjuvant therapy has shown great promise[15,16]. Therefore, when sphincter or organ preservation is the goal, concerns may arise about the suitability of neoadjuvant systemic therapy alone without radiation[13].

CONCLUSION

In summary, neoadjuvant systemic therapy alone without radiation represents a viable option for LARC patients, particularly when organ preservation is not a priority. Nevertheless, it is crucial to engage in multidisciplinary discussions, especially considering the limited long-term experience. We eagerly anticipate the results of ongoing trials, such as NCT04495088 and NCT04749108, which will provide further insights into this evolving treatment approach.

FOOTNOTES

Co-first authors: Tao-Wei Ke and Yu-Min Liao.

Author contributions: Ke TW and Liao YM contributed equally to this work; Ke TW, Liao YM, Chang SC, Chen WTL, Liang JA, and Chien CR made substantial contribution to the design of the work, to the interpretation of data, and to revise the manuscript; all have read and approve the final manuscript. The choice of these researchers (Ke TW and Liao YM) as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Ke TW and Liao YM as co-first authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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