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Consensus guidance of immune checkpoint inhibitors in locally advanced rectal cancer

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ABSTRACT

In the past 5 years, clinical trials on immune checkpoint inhibitors (ICIs) for the treatment of locally advanced rectal cancer (LARC) have flourished globally, and China has become one of the leading regions in this field. In response to the breakthrough progress and accumulation of evidence from key clinical trials, the Chinese Society of Colorectal Surgery has recognised the need for updated consensus guidance on the development of perioperative and organ-preserving treatment strategies for LARC. This expert consensus guidance provided unified standards for the indications, medication regimens, efficacy evaluations and follow-up of ICIs in this population, with a focus mainly on perioperative management and organ-sparing strategies. The diagnostic part of this consensus guidance is based on the internationally recognised definition of mismatch repair/microsatellite instability detection and emphasises the importance of multidisciplinary teams in treatment decision-making. In terms of treatment, based on the results of key trials that have changed clinical practice in the past 5 years, this expert consensus provides graded recommendations for the duration of preoperative immunotherapy and the necessity of postoperative adjuvant therapy, local resection and organ preservation strategies. Moreover, we refined the management process for the safety of perioperative immunotherapy. This document aims to provide a reference for surgeons; internal medicine, radiation therapy, pathology and imaging physicians; patients and nursing staff involved in the treatment of LARC, as well as health policy makers.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, while rectal cancer accounts for nearly half of CRC cases.¹ Locally advanced rectal cancer (LARC) typically refers to stage II–III disease characterised by T3–4 tumours or a node-positive status (N+) without metastases.² Prior to the emergence of immune checkpoint inhibitors (ICIs), the standard treatment for LARC was neoadjuvant concurrent chemoradiotherapy (CRT) combined with total mesorectal excision (TME). However, the pathological complete response (pCR) rate is less than 20%, which does not satisfy clinical application.^{3–4} Postoperative complications, including anastomotic leakage, urinary system dysfunction, sexual dysfunction and anterior resection

syndrome, occur in approximately 40% of patients who undergo CRT with TME. Some patients may also risk the conversion of their temporary stomas to permanent stomas, resulting in not only a significant decrease in quality of life but also social adaptation challenges.^{5–10}

Deficient DNA mismatch repair (MMR) leads to the accumulation of mismatches, insertions and deletions within repetitive sequences, a phenomenon known as microsatellite instability (MSI).¹¹ High-level microsatellite instability (MSI-H) is a well-defined genetic hallmark of a distinct cancer subgroup characterised by a deficient mismatch repair (dMMR) system and the consequent inability to correct DNA damage—primarily single-base-pair insertions or deletions that may occur during DNA replication by DNA polymerase.^{12–13} According to the patient's MMR function and microsatellite status, rectal cancer can be divided into three types: dMMR/MSI-H, proficient mismatch repair (pMMR)/microsatellite instability-low (MSI-L) or microsatellite stability (MSS). Approximately 5%–15% of patients with rectal cancer have the dMMR/MSI-H type, particularly those with earlier stages of the disease; the remaining patients (more than 80%) have the pMMR/MSI-L or MSS type.^{14–16} In the vast majority of cases, dMMR and MSI-H represent the same biological event. Therefore, dMMR and MSI-H are often considered equivalent biomarkers in clinical practice, whereas pMMR is usually equivalent to MSS or MSI-L.^{17–18} Notably, the rate of inconsistency between the results of dMMR and MSI-H detection is approximately 10%.¹⁹

Multiple studies have suggested that the application of ICIs during neoadjuvant therapy for dMMR/MSI-H LARC can significantly increase the pCR rate and allow some patients to achieve a clinically complete response (cCR). This strategy allows patients to be treated during remission while avoiding surgery so that the rectal and anal function can be completely preserved. Patients with pMMR/MSS or MSI-L have a poor response to immunotherapy, whereas immunotherapy alone is essentially ineffective in patients with metastatic rectal cancer.¹⁹ In the CheckMate 142 study, the response was limited, with only 1 of 20 patients responding to combination therapy with programmed cell death protein-1 (PD-1) and



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cytotoxic T lymphocyte-associated protein 4 (CTLA-4) blocking antibodies.²⁰ However, many factors affect the efficacy of immunotherapy, including the immune microenvironment and intestinal flora, in patients with LARC.^{21–23} Moreover, radiotherapy has a sensitisation effect on the immune microenvironment.^{24–26} Therefore, immunotherapy combined with radiotherapy still has great potential for patients with pMMR/MSS or MSI-L LARC. Numerous studies have shown that immunotherapy combined with concurrent CRT or short-course radiotherapy (SCRT) for this type of LARC can significantly increase the pCR and cCR rates and allow more patients to achieve potential organ preservation.

This consensus guidance elaborates on and forms recommendations for the application of immunotherapy based on published research and the clinical experience of the consensus guidance expert group members, with the goal of helping clinicians worldwide safely implement this technology and laying a foundation for gathering additional evidence of its efficacy against LARC.

METHODOLOGY

Search strategy and selection criteria

A consensus literature search of the English databases Medline, Embase, Web of Science and the Cochrane Library and the Chinese databases CNKI, Wanfang and VIP were conducted. The search strategies are described in online supplemental appendix 1. Studies were included if they were prospective or retrospective clinical trials involving patients with LARC who received neoadjuvant or perioperative immunotherapy with ICIs and were published in English journals, Chinese core journals or the official websites of international conferences from January 2016 to December 2025. Literature reviews, meta-analyses and case reports were excluded from this study (figure 1). The included studies are displayed in online supplemental appendix 2.

Establishing a consensus

The consensus guidance panel comprised a multidisciplinary and interprofessional team, including 34.1% (63/185) colorectal surgical oncologists, 28.6% (53/185) medical oncologists and

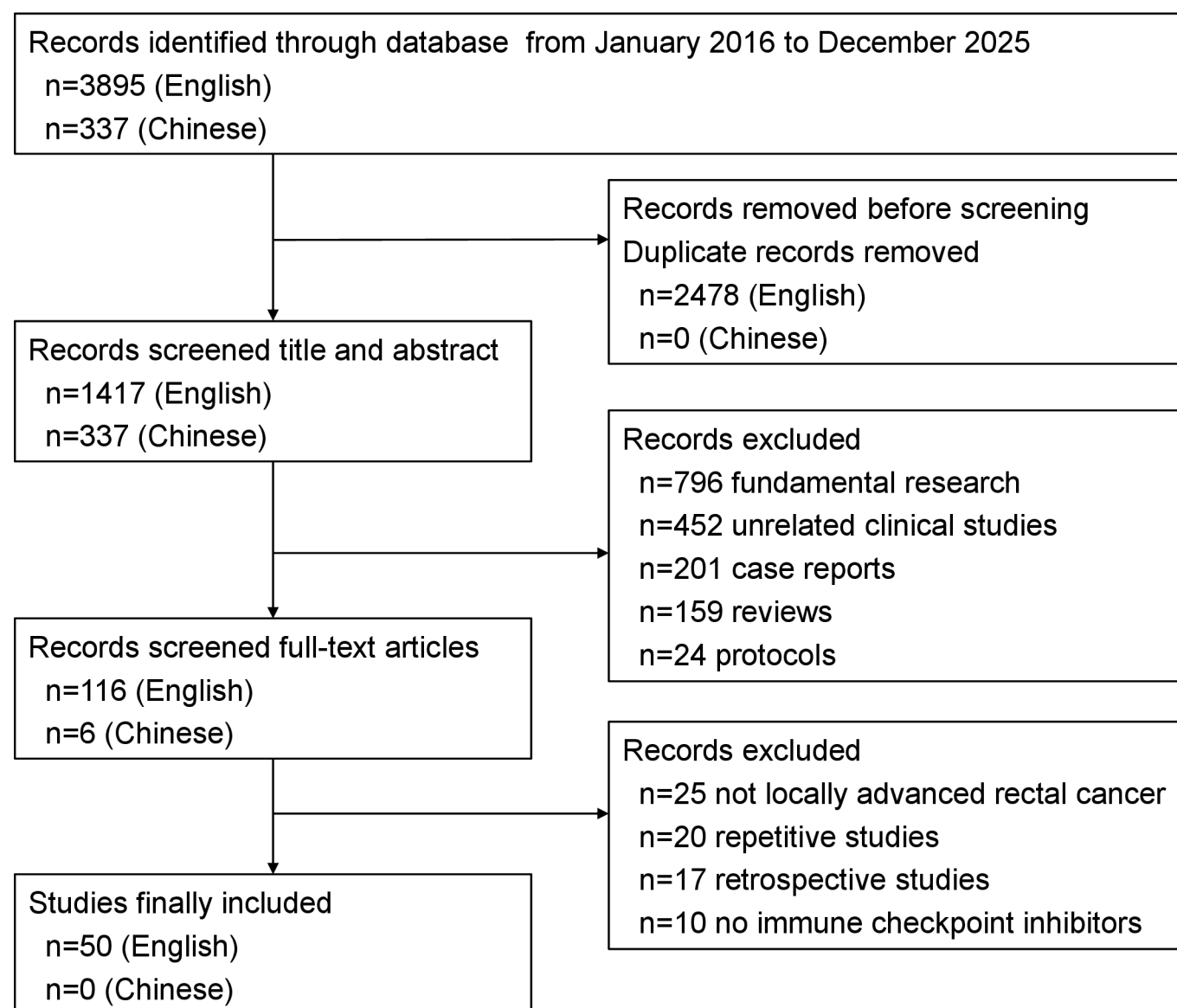


Figure 1 Literature screening and inclusion/exclusion procedure. From January 2016 to December 2025, a total of 3895 English and 337 Chinese literatures were retrieved. After reading the abstract and full text, 50 English studies were ultimately included.

37.3% (69/185) radiation oncologists. The Delphi method was used to achieve consensus recommendations based on the voting options of agreement, disagreement and conditional agreement from all the panellists. This process was conducted anonymously to ensure the independence of each expert's opinion. The strength of the recommendations was classified as strong ($\geq 90\%$ agreement) or weak (75%–90% agreement).²⁰ The Grading of Recommendations Assessment, Development and Evaluation quality assessment²⁷ (high, moderate, low and very low) was used to rate the quality of the available evidence in this consensus. The detailed progress of consensus formation and the Delphi method is provided in online supplemental appendix 3 and online supplemental appendix 4. A summary of the 18 recommendations reached in this consensus and the associated level of supporting evidence is provided in [table 1](#).

RECOMMENDATIONS

MMR/MSI detection

Recommendation 1: The MMR and MSI statuses of patients should be routinely determined before treatment (evidence quality: high; strength of the recommendation: strong).

MMR and MSI detection can be performed for prognostic stratification and provide guidance for immunotherapy for patients with LARC and to screen patients for conditions such as Lynch syndrome.^{28–31} dMMR/MSI-H tumours harbour many mutations and present extensive immunogenicity and therefore respond well to ICIs. Multiple studies have shown that the effectiveness of PD-1 inhibitors in patients with dMMR/MSI-H LARC is significantly better than in similarly treated patients with pMMR/MSS.^{32–33} The MMR/MSI status is thus an important biomarker for guiding the choice of immunotherapy.

All patients with LARC are recommended to routinely have their MMR/MSI statuses monitored prior to the start of treatment. In general, dMMR is equivalent to MSI-H, whereas pMMR is equivalent to MSI-L or MSS. However, the rates of MSI and MMR detection are naturally inconsistent, with an inconsistency rate of 10%–15%. The MMR and MSI statuses should be detected simultaneously for conditional patients to avoid missed detection and to provide patients the opportunity to receive the optimal immunotherapy regimen.^{34–35}

Recommendation 2: Immunohistochemistry (IHC) should be used to detect MMR, while PCR should be used to determine MSI (evidence quality: high; strength of the recommendation: strong).

The IHC method is recommended for determining a patient's MMR status. The absence of any one of the four MMR proteins (MLH1, MSH2, MSH6 and PMS2) is considered to indicate dMMR, whereas the detection of the expression of all four MMR proteins indicates pMMR. PCR capillary electrophoresis is recommended for determining a patient's MSI status. The current international gold standard method, '2B3D (BAT25, BAT26, D2S123, D17S250 and D5S346)', is recommended for locus detection; specifically, this method includes five microsatellite loci, consisting of two single-nucleotide loci (BAT-25 and BAT-26) and three dinucleotide loci (D2S123, D5S346 and D17S250).^{34–35} The evaluation criteria are divided into three groups: (1) MSS is defined as no unstable loci; (2) MSI-L is defined as instability in one locus and (3) MSI-H is defined as instability in >2 or more loci.

Given the simplicity and feasibility of the IHC method, if the patient's MMR and MSI statuses cannot be detected simultaneously, the MMR status should be determined first; if the test result is pMMR, the MSI status should be checked afterwards.

In recent years, with the widespread application of high-throughput sequencing platforms, target region sequencing on next-generation sequencing platforms, whole-exome sequencing and whole-genome sequencing has begun to be applied to determine the MSI status. The use of a certified testing platform or testing at a qualified testing centre is recommended to ensure that the results are suitably accurate.

The importance of an MDT in treatment decision-making

Recommendation 3: An MDT team should be established before treatment. The treatment strategies should be dynamically adjusted according to continuous assessments (evidence quality: high; strength of the recommendation: strong).

A growing body of clinical evidence suggests that the use of ICIs in neoadjuvant and organ-sparing therapy for patients with LARC can significantly improve the pCR, cCR and R0 resection rates, indicating that ICIs are promising treatment options for achieving the goals of each treatment. Efforts are being made in China, as well as worldwide, to accumulate experience in the clinical application of PD-1/programmed cell death ligand 1 (PD-L1) inhibitors, with the expectation that these novel treatments can help patients with LARC achieve better survival and quality of life. However, surgeons are not relatively familiar with some key clinical issues, such as accurate disease staging, cCR assessment and management of adverse events (AEs). Thus, the MDT team is extremely needed.

We recommend the formation of an MDT to comprehensively evaluate the patient's general condition, diagnose the disease, determine the stage/range of tumour invasion and assess the suitability for immunotherapy according to his or her treatment goals and to participate in the full treatment decision-making process, including drug selection, the duration of treatment, the evaluation of the treatment response, the timing of TME and the choice between local resection or a watch-and-wait (W&W) approach and whether to administer adjuvant therapy so that the patient can receive the most suitable treatment. The MDT should include staff from the departments of colorectal surgery, medical oncology, radiation oncology, radiology, pathology and gastroenterology. Conditional centres can also invite experienced pharmacy experts to join the MDT. The responsibilities of these corresponding departments are suggested and shown in [table 2](#). All recommendations for treatment decisions in this consensus guidance must be based on the results of the MDT assessments and discussions.

Patients with dMMR/MSI-H LARC

Neoadjuvant therapy

Recommendation 4: Patients should receive 3 months of treatment with PD-1/PD-L1 inhibitors and/or CTLA-4 inhibitors, and the therapeutic effect should be immediately evaluated. Patients who have not achieved cCR may undergo another 3 months of ICI treatment before their efficacy is reassessed (evidence quality: moderate; strength of the recommendation: strong).

Numerous small-sample phase 2 studies^{36–39} have shown that patients with resectable stage IIIII dMMR/MSI-H CRC who receive PD-1 inhibitors followed by TME achieve a pCR rate $>50\%$, while few patients have reported AEs. In phase 2, single-arm RATIONALE214 clinical study,^{36–33} patients with stage II/III dMMR/MSI-H CRC received three cycles of tislelizumab treatment, among whom 29 (87.9%) underwent surgery. A pathological examination of the resected samples revealed that the major pathological response (MPR) rate was 89.7% (26/29 patients), while the pCR rate was 62.1% (18/29 patients). The

Table 1 Summary of 18 recommendations for the use of immune checkpoint inhibitors in locally advanced rectal cancer

No.	Recommendation	Evidence quality	Strength of recommendation
1	The MMR and MSI statuses of patients should be routinely determined before treatment.	High	Strong
2	Immunohistochemistry (IHC) should be used to detect MMR, while PCR should be used to determine MSI.	High	Strong
3	An MDT team should be established before treatment. The treatment strategies should be dynamically adjusted according to continuous assessments.	High	Strong
4	Patients should receive 3 months of treatment with PD-1/PD-L1 inhibitors and/or CTLA-4 inhibitors, and the therapeutic effect should be immediately evaluated. Patients who have not achieved cCR may undergo another 3 months of ICI treatment before their efficacy is reassessed.	Moderate	Strong
5	No acknowledged postoperative adjuvant regimen is recommended for patients who have received neoadjuvant ICI therapy. Patients who cannot achieve a pCR can continue with the original regimen or switch to standard adjuvant chemotherapy.	Very low	Strong
6	Adjuvant ICI therapy should not be administered routinely to patients who do not receive neoadjuvant ICI therapy. Patients with LARC with a high risk of recurrence can actively participate in clinical trials.	Very low	Strong
7	Middle and low patients with dMMR/MSI-H have a strong desire for anal preservation and should receive neoadjuvant ICIs therapy for at least 6 months, and patients who achieve a cCR can be managed with the W&W strategy.	Low	Strong
8	CRT is recommended for patients with a high risk of recurrence who have not achieved cCR after 6 months of ICI treatment. Patients reached cCR after CRT can still choose the W&W strategy.	Low	Strong
9	Patients should be fully informed of the benefits and risks of immunotherapy and the W&W strategy. Close monitoring should be required during the W&W period to assess potential tumour regrowth and metastasis.	Low	Strong
10	LCRT can be performed concurrently or sequentially with 3–6 cycles of ICI neoadjuvant therapy before TME. Adjuvant chemotherapy can be routinely administered after surgery.	Moderate	Weak
11	Patients with a high risk of recurrence at baseline or high motivation for anal preservation but difficult cases can be treated with TNT plus ICIs, followed by TME surgery.	Moderate	Weak
12	Patients can be treated with SCRT plus ICIs and 2–6 cycles of CAPEOX before TME. The total duration of immunotherapy should not be more than 6 months.	Moderate	Strong
13	Patients with a strong desire for anal preservation can choose W&W after achieving cCR, while clinicians should fully inform them of the possibility of not achieving cCR.	Low	Strong
14	Dual immunotherapy regimen is not recommended for neoadjuvant or organ-sparing therapy. Considering the possible benefits, patients may be recommended to actively participate in clinical trials.	Very low	Strong
15	After neoadjuvant ICIs, ypT1N0M0 or high motivation for anal preservation but difficult ypT2N0M0 cases can receive LE through a careful MDT assessment. TME is recommended for ypT1–2 patients with a high risk for recurrence at baseline, whereas the W&W strategy is recommended for ypT0 patients after fully informing benefits and risks.	Very low	Strong
16	Specific populations should be identified and undergo complete baseline examinations and irAE monitoring during neoadjuvant therapy. Particular attention should be given to immune-mediated myocarditis and pneumonitis, as both conditions are associated with high mortality.	High	Strong

Continued

Guideline

Table 1 Continued

No.	Recommendation	Evidence quality	Strength of recommendation
17	MDTs should be formed to address irAEs and improve the efficiency and accuracy of the diagnosis and treatment of irAEs.	Very low	Strong
18	Standardised handling of irAEs during neoadjuvant therapy may not typically affect surgical safety, but the risk of postoperative complications exists. Surgery after irAE recovery to grade ≤ 1 is recommended.	Very low	Strong

cCR, clinically complete response; CRT, chemoradiotherapy; CTLA-4, cytotoxic T lymphocyte-associated protein 4; dMMR, deficient mismatch repair; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; LARC, locally advanced rectal cancer; LE, local excision; MDT, multidisciplinary team; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability-high; pCR, pathological complete response; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand 1; TME, total mesorectal excision; W&W, watch-and-wait.

PICC study³⁷ included 34 patients with dMMR/MSI-H locally advanced CRC who randomly received toripalimab alone or combined with celecoxib and revealed that after six cycles of neoadjuvant therapy, the pCR rate of the combination group reached 88%, whereas that of the toripalimab group was 65%. Phase 2 NEOCAP study³⁶ included 53 patients with either dMMR/MSI-H or POLE/POLED-1-mutant locally advanced CRC. After 3 months of neoadjuvant treatment with camrelizumab plus apatinib, 23 patients underwent surgery, and 14 (61%) patients achieved pCR. In another phase 2 study involving 35 patients with locally advanced unresectable or high-risk resectable MSI-H/dMMR solid tumours, 27 patients with CRC were enrolled and treated with 6 months of pembrolizumab, followed by surgical resection.³⁸ Among the 17 patients who underwent surgery, the pCR rate was 65%.

Several studies^{40–41} have explored the preliminary efficacy of PD-1 inhibitors combined with CTLA-4 inhibitors as a short-cycle neoadjuvant therapeutic strategy for patients with dMMR/MSI-H LARC. Although the NICHE trial series are pioneering studies in this field, their specific conclusions are focused primarily on dMMR colon cancer.⁴⁰ In a phase 1b study⁴² in which 101 patients with stage II B–III dMMR CRC were randomised at a 1:1 ratio to receive two doses of sintilimab (day 1, day 22) combined with one dose of IBI310 (a CTLA-4 inhibitor, day 1) or two doses of sintilimab monotherapy, among whom 96 received surgery, the pCR rate in the dual immunotherapy group

was significantly higher than that in the monotherapy group (80% vs 47.7%, $p=0.0007$). Another study from Denmark evaluated the efficacy and tolerability of one cycle of nivolumab and ipilimumab in patients with early-stage dMMR rectal cancer. Five patients achieved cCR, while all patients chose the W&W strategy and avoided radiotherapy and surgery.⁴²

In these studies, the majority of patients who received ICI neoadjuvant therapy had stage II–III (cT3/cT4 or N+) CRC. Specifically, the proportions of patients with cT4 in the PICC study reached 65% and 88%, respectively. A retrospective analysis of 73 patients with dMMR CRC⁴³ revealed that the radiological response rates of patients with cT4 and patients with cT2/cT3 following neoadjuvant immunotherapy were not significantly different (84.0% vs 85.4%; $p=0.999$), and the pCR rates of patients with cT4 were comparable to those of all patients (59.5% and 57.1%, respectively). In a phase 2 single-arm study,³⁹ 32 patients with high-recurrence-risk stage II or stage III dMMR/MSI-High CRC were treated with pembrolizumab for 1–3 cycles and then underwent surgery, ultimately achieving a pCR rate of 59% (19/32 patients). The results of a single-centre retrospective observational study⁴³ revealed that the pCR rate of patients with stage cT4bM0 dMMR CRC who received neoadjuvant immunotherapy was significantly higher than that of patients who received neoadjuvant CRT (70.0% vs 0.0%, $p=0.004$). Furthermore, compared with neoadjuvant CRT, neoadjuvant immunotherapy significantly reduced the rates of open surgery

Table 2 Definition of roles and responsibilities of MDT teams

Department	Responsibilities
Colorectal surgery	Leads the MDT discussion, assesses the feasibility, timing and extent of surgery. Evaluates the oncologic safety of the W&W strategy. Manages perioperative complications and leads communication with patients and their families.
Medical oncology	Leads the formulation of the immunotherapy regimen (drug selection, combination strategies). Assesses the indications for and potential benefits of immunotherapy. Manages trAEs throughout the course of therapy and provides timely intervention when they occur.
Radiation oncology	Develops and evaluates radiotherapy regimens (long-course or short-course), defining the time and sequence in combination with immunotherapy. Defines the radiotherapy target volume and dose, balancing efficacy and adverse events.
Radiology	Provides precise baseline staging and assessment of response to neoadjuvant therapy. Differentiates true tumour progression and pseudo-progression. Promptly identifies irAEs such as immune-related pneumonitis.
Pathology	Provides accurate detection of MMR/MSI status, PD-L1 expression, etc. Assesses the degree of pathological response after neoadjuvant therapy (TRG stage, pCR).
Gastroenterology	Evaluates tumour response at the mucosal level through endoscopic examination. Performs endoscopic biopsies to acquire tissue samples for pathological evaluation.

irAE, immune-related adverse event; MDT, multidisciplinary team; MMR, mismatch repair; MSI, microsatellite instability; pCR, pathological complete response; PD-L1, programmed cell death ligand 1; trAE, treatment-related adverse event; TRG, tumour regression grade; W&W, watch-and-wait.

($p=0.000$) and multiorgan resection ($p=0.025$) and significantly improved disease-free survival (DFS) ($p=0.0078$). Therefore, patients with cT4 tumours, especially those with cT4b tumours, benefit from PD-1 inhibitor neoadjuvant therapy to the same extent as patients with cT2/cT3 tumours and can achieve better short- and long-term efficacy than with concurrent CRT.

However, whether the increase in the pCR rate caused by neoadjuvant immunotherapy can lead to an extension of overall survival (OS) remains uncertain. Several studies have retrospectively analysed the recurrence and survival rates of patients with dMMR CRC who received neoadjuvant PD-1 inhibitor therapy over a median follow-up duration of 17.1–27 months.^{43–45} The 2-year tumour-related DFS rate, 2-year local recurrence-free survival (RFS) rate, 2-year distant metastasis-free survival rate and 2-year OS rate for patients who received surgical treatment were all 100%. In the PICC study, the 3-year follow-up data, which were updated in 2024, included an event-free survival (EFS) rate of 100% for the PD-1 inhibitor combined with celecoxib group and 94% for the PD-1 inhibitor monotherapy group.⁴⁶ Currently, two phase 3 trials are underway, the Neoshot study (NCT05890742) and the AZUR-2 study (NCT05855200), which are exploring the combination of sintilimab with IBI310 (a CTLA-4 inhibitor) and dostarlimab (a PD-1 inhibitor), respectively, for the neoadjuvant and perioperative treatment of patients with locally advanced dMMR/MSI-H CRC. The publication of these two studies will provide an additional basis for the perioperative application of immunotherapy.

The optimal duration of neoadjuvant ICIs has not yet been conclusively determined. In current studies, PD-1 inhibitors are typically used as a monotherapy for 9–18 weeks (3–6 cycles, Q3W)^{36–39} or in combination with CTLA-4 inhibitor treatment for 4–6 weeks (2 doses of the PD-1 inhibitor, Q2W or Q3W; one dose of the CTLA-4 inhibitor) after surgery.^{40,41} It was reported that after 1 cycle of neoadjuvant therapy with pembrolizumab, the pCR rate following surgery can reach 44%–46%,⁴⁷ whereas the inclusion of additional cycles of neoadjuvant ICIs therapy can increase the pCR rate.^{48,49} However, these studies are all single-arm studies, and the relationship between the pCR rate and the number of treatment cycles needs to be further confirmed with randomised controlled trials (RCTs). Based on the above considerations, this writing team recommends conducting an efficacy assessment on the completion of 3 months of neoadjuvant ICIs to facilitate the early identification of disease progression and the incidences of AEs and delayed surgery. For patients who cannot achieve a cCR, an additional 3-month course of ICIs may be administered, followed by a reassessment.

Adjuvant therapy

Recommendation 5: No acknowledged postoperative adjuvant regimen is recommended for patients who have received neoadjuvant ICI therapy. Patients who cannot achieve a pCR can continue with the original regimen or switch to standard adjuvant chemotherapy (evidence quality: very low; strength of the recommendation: strong).

The evidence on the optimal postoperative adjuvant therapy for patients with dMMR/MSI-H who have received neoadjuvant therapy with PD-1 inhibitors is insufficient. According to the 'effective preoperative regimens can be used for postoperative treatment' principle, the preoperative regimen can be used for patients without disease progression after preoperative treatment. However, the outcomes of patients who achieve pCR are excellent; thus, these patients can opt not to receive any adjuvant therapy. For patients with positive lymph nodes who do

not achieve pCR, preoperative ICI treatment can be continued or adjuvant chemotherapy can be administered. The decision to administer adjuvant chemotherapy should be fully discussed with the patient.

Recommendation 6: Adjuvant ICI therapy should not be administered routinely to patients who do not receive neoadjuvant ICI therapy. Patients with a high risk of recurrence can actively participate in clinical trials (evidence quality: very low; strength of the recommendation: strong).

The ATOMIC trial is the first phase 3 clinical study to evaluate the efficacy of ICIs as an adjuvant therapy for dMMR CRC. In this study, patients with stage III dMMR colon cancer were enrolled to investigate the efficacy and safety of atezolizumab in combination with mFOLFOX6 chemotherapy. The 3-year DFS rate was 76.6% in the mFOLFOX6 alone group, whereas it was 86.4% in the atezolizumab plus mFOLFOX6 group. No significant difference was observed in the incidence of grade 3–4 immune-related adverse events (irAEs) between the two groups.⁵⁰ However, the use of immunotherapy in adjuvant therapy for patients with dMMR/MSI-H LARC is still being explored, and several studies are in progress. For example, a phase 3 study (NCT06520683) is investigating tislelizumab vs standard treatment (chemotherapy or observation) as the post-operative adjuvant therapy for patients with stage II dMMR/MSI-H CRC who have not received immunotherapy and are at high risk of tumour recurrence. No published long-term survival data are available on the use of ICIs; thus, clinical treatment is not routinely recommended. Patients are encouraged to actively participate in clinical trials of adjuvant immunotherapy.

Organ preservation for patients with dMMR/MSI-H LARC

5–10 years ago, total neoadjuvant therapy (TNT) and neoadjuvant therapy were considered the standard treatments for patients with LARC.⁵¹ However, the latest NCCN guidelines recommend neoadjuvant immunotherapy instead of TNT as the preferred treatment strategy for patients with dMMR/MSI-H LARC.⁵² Radiotherapy and surgery may cause permanent damage, such as urinary system injury and sexual dysfunction, which significantly reduce the quality of life of patients.^{8–10} The W&W strategy or local resection after neoadjuvant therapy for LARC can help patients achieve greater survival while retaining rectal and anal function and preserving quality of life. In view of the strong demand for the preservation of rectal and anal function in patients with low and middle rectal cancer, numerous recently published and ongoing clinical trials investigating neoadjuvant therapies have set the complete response (CR) rate, defined as the cCR+pCR rate, as the primary study endpoint. After receiving several cycles of neoadjuvant therapy, patients can choose TME surgery or the W&W strategy to avoid surgical complications.

Recommendation 7: Middle and low patients with dMMR/MSI-H have a strong desire for anal preservation should receive neoadjuvant ICIs therapy for at least 6 months, and patients who achieve a cCR can be managed with the W&W strategy (evidence quality: low; strength of the recommendation: strong).

Multiple small phase 2 studies and retrospective studies^{53–55} have shown that treatment with PD-1 inhibitors alone or in combination with other drugs can result in a high cCR rate and prolonged remission for patients with dMMR/MSI-H LARC. No disease recurrence or metastasis occurred during the W&W period. A milestone study sponsored by the Memorial Sloan Kettering Cancer Center (MSKCC)^{53,54} revealed that the cCR rate of the first 12 patients with dMMR/MSI-H rectal cancer

who were treated with dostarlimab for 6 months reached 100%. All patients were subsequently managed with the W&W strategy, and no local tumour regrowth or distant metastasis occurred during the follow-up period (6–25 months). Further analysis revealed that 49 patients with dMMR LARC all achieved cCR and underwent non-operative management. Another phase 2 trial including 16 patients with T3–T4 stage or lymph node-positive dMMR/MSI-H rectal cancer showed that after receiving eight cycles of sintilimab treatment, 9 patients achieved cCR.⁵⁵ After the W&W strategy for a median of 17.2 months, all patients survived with no recurrence.

Conclusive results concerning the optimal duration of PD-1 inhibitor use for organ-sparing therapy are unavailable, but sufficient drug exposure may lead to a higher cCR rate. Another neoadjuvant dual immunotherapy study in patients with dMMR LARC showed that 2/7 patients did not achieve cCR after 1 month, whereas all 7 patients achieved cCR after an additional month of dual immunotherapy.⁴¹ Current studies mostly use PD-1 inhibitor monotherapy for 6 months, which is longer than the duration of neoadjuvant therapy. The results of the NEOCAP study indicated that the cCR rate after 6 months of PD-1 monotherapy reached 54%, whereas in the MSKCC study, 100% of patients achieved cCR after 6 months of treatment. Several studies have shown^{36 44 55} that the median time from the start of PD-1 inhibitor treatment to the achievement of cCR is 3.8–5.8 months; patients treated with PD-1 inhibitors for 1 year are less likely to experience disease progression.³⁸ Therefore, treatment for 6 months or longer can provide sufficient time for tumour regression, allowing a greater proportion of patients to achieve cCR and thus be managed with a W&W strategy. If the patient achieves cCR after treatment for less than 6 months, PD-1 treatment should continue for up to 6 months.

Most patients with dMMR/MSI-H rectal cancer included in the aforementioned studies had stage II–III disease, and few patients with stage I disease were included. However, the consensus focuses and recommendations are specifically on stage II–III disease. In the MSKCC study, the proportion of T0–2 patients was 21% (10/48), and the proportion of patients with negative lymph nodes was 15% (7/48). In a retrospective study,⁴⁴ among the 19 included patients, only one patient with stage I disease was included, whereas no patients with stage I disease were included in the NEOCAP study. Clinical evidence for the use of PD-1 inhibitors in patients with stage I tumours to allow organ preservation is insufficient. Moreover, both local resection and concurrent CRT can be adopted to achieve anal preservation, improving the cCR rate and feasibility of the W&W strategy, with a favourable prognosis. Therefore, we do not recommend the use of PD-1 inhibitors for patients with stage I disease. Additionally, a considerable proportion of the patients in these studies had cT4 disease managed with the W&W strategy. No current evidence suggests that patients with cT4 tumours who undergo immunotherapy have a higher risk of recurrence or shorter OS after the W&W strategy. Therefore, this approach can be safely offered to patients with cT4 tumours. The majority of recent research employs PD-1 inhibitor monotherapy. Whether PD-1 inhibitors combined with other drugs can achieve cCR faster or yield better long-term survival data remains unclear. Therefore, active clinical research is encouraged.

Recommendation 8: CRT is recommended for patients with a high risk of recurrence who have not achieved cCR after 6 months of ICI treatment. Patients reached cCR after CRT can still choose the W&W strategy (evidence quality: low; strength of the recommendation: strong).

One study enrolled 16 patients who received PD-1 inhibitors, 13 of whom received treatment for at least 6 months. Among the 6 patients who underwent TME, 3 achieved pCR, and another 9 (56%) achieved cCR and received follow-up. The median time to achieve complete remission (pCR or cCR) was 5.2 months. Two of these patients achieved a near clinical complete response (ncCR) after 6 months of PD-1 inhibitor treatment and chose to continue treatment; one patient underwent surgery and achieved pCR after 25 cycles of treatment, and the other patient achieved pCR after 12 cycles of treatment alone.^{55 56} These results suggest that flexibility in determining the duration of treatment may be necessary in individual cases. Another phase 2 trial involving patients with dMMR solid tumours included 8 (23%) patients with rectal cancer. The planned course of neoadjuvant pembrolizumab therapy was 6 months, followed by surgical or nonsurgical treatment, after which the patients continued to receive pembrolizumab for another 6 months. Two patients underwent surgical resection, one due to disease progression after receiving two cycles of treatment and postoperative pathology confirmed residual cancer, while the other patient achieved pCR after surgery. Among the 6 patients who received nonsurgical treatment, 2 achieved cCR, 3 achieved a partial response and 1 had stable disease. After 9 months of pembrolizumab treatment, 1 patient experienced disease progression, another patient withdrew informed consent, and the remaining patients completed or are continuing with 12 months of treatment.^{38 57}

These results suggest that an imaging evaluation should be performed within 3 months after the start of treatment for early detection of local recurrence and distant metastasis. For patients exhibiting a suboptimal response to neoadjuvant therapy or failing to achieve cCR within 6 months, particularly those at high risk of recurrence, prompt TME is warranted. Based on the National Comprehensive Cancer Network (NCCN) guidelines,⁵⁸ patients with dMMR/MSI-H LARC who are immunotherapy-naïve should receive neoadjuvant PD-1 inhibitor monotherapy for 6 months. During treatment, restaging via imaging is recommended every 2–3 months. Patients who achieve a cCR are eligible for active surveillance. For those exhibiting poor tumour regression, CRT is advised. If cCR is attained following CRT, a W&W strategy remains a viable option. Currently, no evidence supports extending immunotherapy beyond 6 months for patients who fail to achieve cCR with initial immune checkpoint inhibition.

Due to the particularities of immunotherapy, evaluating its efficacy faces unique challenges. Imaging examinations (MRI/Positron Emission Tomography-CT) have significant limitations in distinguishing pathological complete remission from pseudoprogression on imaging. This challenge is due to the sustained inflammatory response, fibrosis and immune cell infiltration within the tumour bed after immunotherapy, which can appear as persistent masses or abnormal signals on imaging, and thus distinguishing them from active tumour cells is difficult.^{59 60} A cohort study of 13 patients revealed that the proportion of patients who received neoadjuvant immunotherapy with false residues was as high as 76.9%. Three patients who achieved pCR were diagnosed with progressive disease and experienced pseudoprogression (23.1%, 3/13). In addition, four patients (30.8%) in the immunotherapy group had newly swollen lymph nodes, while postoperative pathology suggested that they were non-metastatic.⁶¹ If a patient still cannot achieve cCR after 6 months of immunotherapy, the possibility of a pseudoresidual tumour should be considered. If the patient has a strong willingness for organ preservation, local

resection is recommended. If the result is negative, local resection or the W&W strategy can be selected after careful consideration and full communication with the patient and his or her family.

Recommendation 9: Patients should be fully informed of the benefits and risks of immunotherapy and the W&W strategy. Close monitoring should be required during the W&W period to assess potential tumour regrowth and metastasis (evidence quality: low; strength of the recommendation: strong).

The phase 2 study of dostarlimab for patients with dMMR LARC remains the most influential clinical study of the W&W strategy following immunotherapy,⁵³ and all 12 initially recruited patients have achieved cCR and have entered the monitoring stage. 81% of patients reported that their symptoms were relieved within 9 weeks. The latest results were reported in 2025, with a total of 103 patients who completed treatment.⁶² After 6 months of dostarlimab treatment, 49 patients with dMMR LARC (cohort 1) achieved cCR and underwent non-operative management. Among the patients in cohort 2, which included 54 patients with dMMR non-rectal solid tumours, 35 patients achieved a cCR, and 33 elected to proceed with non-operative management. Among all 117 included patients, the RFS at 2 years was 92%, with a median follow-up for recurrence of 20.0 months. This study represents a landmark in dMMR solid tumour therapy, particularly given the outstanding outcomes in patients with rectal cancer. We look forward to observing further significant results in the larger-scale, phase 2 AZUR-1 trial (NCT05723562).

Another multicentre retrospective cohort study⁶³ enrolled 61 patients with dMMR/MSI-H LARC, among whom 44 (72.1%) met the cCR criteria, with a median follow-up time of 29.1 months. No local recurrence or distant metastasis was observed in any of the patients during the follow-up period, and the 3-year DFS and OS rates were both 100%. In this study, one patient had suspected para-aortic and common iliac artery lymph node metastasis according to CT imaging and an elevated serum carcinoembryonic antigen level 11 months after treatment cessation. However, lymph node biopsy indicated inflammation with immune cell infiltration rather than tumour cells. The presence of swollen lymph nodes after immunotherapy may be due to granulomatous/sarcoid-like lesions or nodal immune flares.^{64–67} Another retrospective study involving 73 patients showed that one patient who died of cardiovascular disease and one patient with an unresectable tumour experienced disease progression after a median follow-up time of 17.2 months. The 2-year tumour-specific OS and DFS rates were both 100%.⁴³

Existing studies have shown that the W&W strategy remains safe and that the resection rate after local tumour regrowth is high. The results of the OPRA study^{68,69} revealed that the oncological safety of patients managed with the W&W strategy after achieving cCR or nCR was similar to that of patients who received TME surgery during the 5-year follow-up. After local tumour regrowth, 80–91% of patients who underwent TME achieved R0 resection. Nevertheless, patients undergoing W&W remain at increased risk for local regrowth and distant metastasis, mandating closer follow-up (online supplemental appendix 5).⁵ While evidence from small phase 2 and retrospective studies suggests this strategy may be relatively safe post-immunotherapy, the associated risks cannot be overlooked. Crucially, large-scale trial data confirming its long-term oncologic safety are currently lacking.

Patients with LARC with an unknown pMMR/MSS or MMR/MSI status

Numerous clinical trials have explored the use of PD-1/PD-L1 inhibitors as elements of neoadjuvant and organ-sparing therapy for patients with pMMR/MSS LARC. PD-1/PD-L1 inhibitors can improve the pCR rate of patients receiving neoadjuvant therapy; however, few studies have suggested that PD-1/PD-L1 inhibitors can prolong DFS. However, these studies were mostly phase 2 trials with small sample sizes. Clinicians should carefully consider the use of PD-1/PD-L1 inhibitors in neoadjuvant and organ-sparing therapy for patients with pMMR/MSS LARC. However, when ICIs are combined with TNT or neoadjuvant therapy, close monitoring of the potential cumulative toxicity risk is still necessary. irAEs may be superimposed on or confounded by side effects such as chemotherapy-induced myelosuppression, gastrointestinal reactions and radiotherapy-induced radiodermatitis or enteritis.^{70,71} These side effects complicate the attribution and management of AEs. Therefore, conducting a comprehensive baseline assessment before treatment and implementing close monitoring during therapy are strongly recommended. For related content, please refer to Section “Managing the safety of perioperative immunotherapy”.

Neoadjuvant therapy for patients with pMMR/MSS LARC LCRT combined with ICIs

LCRT (1.8–2 Gy/dose × 22–25 fractions, with concurrent oral capecitabine) is the standard neoadjuvant therapy for patients with pMMR/MSS or MMR/MSI status-unknown LARC, but the pCR rate is less than 20%. In terms of TNT, including long-term radiotherapy, the addition of several cycles of induction chemotherapy or consolidation chemotherapy before and after CRT can increase the pCR rate.^{72–75} Numerous studies have shown that the use of PD-1/PD-L1 inhibitors combined with CRT or LCRT TNT is a safe and effective form of neoadjuvant therapy for patients with pMMR/MSS LARC and can increase the likelihood of tumour regression and organ preservation.^{76–86}

Recommendation 10: LCRT can be performed concurrently or sequentially with 3–6 cycles of ICI neoadjuvant therapy before TME. Adjuvant chemotherapy can be routinely administered after surgery (evidence quality: moderate; strength of the recommendation: weak).

Several single-arm phase 2 trials have explored the preliminary efficacy of CRT concurrently or sequentially with 3–6 cycles of PD-1/PD-L1 inhibitor therapy in patients with LARC, resulting in a pCR rate between 22% and 34.5%.^{76–81} The AVANA study⁷⁶ explored the efficacy of preoperative chemotherapy and radiotherapy combined with avelumab in the treatment of LARC. Among the 96 patients with an evaluable pathological response, 22 (23%) achieved pCR and 59 (61.5%) achieved MPR. The phase 2 single-arm trials VOLTAGE, NSABP-FR2 and PANDORA^{77–79} explored the efficacy of the sequential use of five cycles of nivolumab, four cycles of duvalumab and three cycles of duvalumab, respectively, with reported pCR rates of 30%, 22.2% and 32.7%, respectively. In the CHOICE I study,^{75,87} the efficacy of sintilimab administered concurrently with four cycles of LCRT was explored in the treatment of LARC. The cCR rate was 38.9%, the CR rate was 52.2%, the organ preservation rate was 61.1% and the anus preservation rate was 94.4%.

The multicentre NECTAR trial reported that patients with LARC received CRT combined with 3 cycles of tislelizumab as neoadjuvant therapy.⁸⁸ Among the 50 patients included in the study, the pCR rate reached 40%. Further RCTs enrolled 186 patients with LARC, who were randomly divided into groups

receiving CRT combined with concurrent tislelizumab (group A), sequential tislelizumab (group B) or CRT alone.⁸⁹ The results revealed that the pCR rates of groups A and B were 27.1% and 32.7%, respectively. With respect to combination therapy, a retrospective study explored CRT combined with tislelizumab and thymalfasin as a neoadjuvant treatment for patients with LARC.⁹⁰ The pCR rate reached 61.5%, which was higher than that of 38.5% in the group treated with CRT combined with tislelizumab. The above studies preliminarily explored LCRT combined with ICI neoadjuvant therapy, which can significantly increase the pCR rate with no substantial safety issues. Thus, this combination therapy could be considered in clinical practice.

Recommendation 11: Patients with a high risk of recurrence at baseline or high motivation for anal preservation but difficult cases can be treated with TNT plus ICIs, followed by TME surgery (evidence quality: moderate; strength of the recommendation: weak).

A phase 2 RCT included 134 patients with LARC, among whom nearly 80% of the high-risk patients were randomly assigned to the experimental group (four cycles of sintilimab combined with the capecitabine plus oxaliplatin (CAPEOX) regimen for concurrent LCRT) or the control group (four cycles of the CAPEOX regimen alone for concurrent LCRT); the patients who achieved cCR continued to receive four cycles of the CAPEOX regimen consolidation therapy, while the remaining patients underwent TME surgery and received four cycles of adjuvant CAPEOX chemotherapy after surgery.⁸² The primary endpoint, the CR rate (cCR rate + pCR rate), was significantly greater in the experimental group than in the control group (44.8% vs 26.9%). In the PKUCH04,⁸³ DUREC⁸⁴ and NRG-GI002 studies,⁸⁵ camrelizumab, durvalumab and pembrolizumab, respectively, were combined with LCRT-based TNT for patients at high risk of recurrence, resulting in pCR rates of 33.3%, 39% and 31.9%, respectively. The follow-up data from the NRG-GI002 study⁸⁶ revealed that the 3-year OS rate of patients treated with pembrolizumab combined with TNT was significantly higher than that of patients in the TNT group (95% vs 87%), confirming for the first time that neoadjuvant immunotherapy may improve long-term survival.

The above studies have enrolled patients with LARC with at least one high-risk factor for recurrence, including cT3c-d/4, extramural venous invasion (EMVI), mesorectal fascia (MRF), N2, low-lying or rectal preservation that is not feasible through surgery, to explore the preliminary efficacy of LCRT-based TNT combined with ICIs as neoadjuvant therapy. The neoadjuvant schemes used in these studies differ and include induction chemotherapy + CRT alone, combination with consolidation chemotherapy or CRT + consolidation chemotherapy. PD-1/PD-L1 inhibitors could be used throughout the entire course of TNT or in one or two stages. However, many clinical issues, such as the optimal combination of CRT or TNT with PD-1/PD-L1 inhibitors, the interval between preoperative radiotherapy and surgery, systemic treatment cycles and the uncertainty of the effect of the addition of PD-1/PD-L1 inhibitors on prolonging survival, still need to be verified by performing clinical trials with larger sample sizes. In view of the substantial increase in the pCR rate, clinicians could implement this regimen based on the specific conditions of the patient or recommend that patients participate in related clinical trials.

SCRT combined with immunotherapy

Recommendation 12: Patients can be treated with SCRT plus ICIs and 2–6 cycles of CAPEOX before TME. The total duration

of immunotherapy should not be more than 6 months (evidence quality: moderate; strength of the recommendation: strong).

SCRT followed by CAPEOX is also a standard treatment regimen for LARC. The UNION phase 2 prospective single-arm trial investigated the preliminary efficacy of SCRT followed by two cycles of CAPEOX chemotherapy combined with camrelizumab and TME for LARC.⁹¹ The pCR rate in the MSS/pMMR group was 46%, with an R0 resection rate of 100% and an anal preservation rate of 89%. Further phase 3 RCTs (UNION-III) included 231 patients with LARC, with 113 patients in the experimental group receiving SCRT followed by two cycles of camrelizumab combined with CAPEOX as neoadjuvant therapy.⁹² Patients in the control group received conventional concurrent CRT followed by two cycles of neoadjuvant CAPEOX therapy. The pCR rate in the experimental group was significantly higher than that in the control group (39.8% vs 15.3%), while the median EFS and OS were not reached after the 3-year follow-up. In addition, several phase 2 trials^{93–95} have employed a similar regimen, that is, SCRT followed by 2–4 cycles of PD-1/PD-L1 inhibitor therapy combined with the CAPEOX or mFOLFOX6 regimen as neoadjuvant therapy, and have achieved a pCR rate ranging from 37.5% to 58.5%.

The multicentre, open-label, single-arm phase 2 Averectal study⁹³ evaluating the efficacy and safety of mFOLFOX6 followed by six cycles of avelumab treatment for LARC indicated a pCR rate of 37.5% and an MPR rate of 67.5%. The PERCAM study⁹⁴ enrolled 32 patients with MSS LARC who received SCRT followed by two cycles of CAPEOX and six cycles of the PD-L1 inhibitor (enfafolimab); the pCR rate was 62.5%, and the MPR rate was 75%. Another single-centre, open-label RCT⁹⁵ involved 111 patients with pMMR/MSS LARC who were randomised to receive SCRT followed by four cycles of tislelizumab plus CAPEOX (experimental group, n=53) or SCRT followed by four cycles of CAPEOX (control group, n=58). Among the 82 patients who received TME, the pCR rate was 58.5% (23/42) in the experimental group and 37.5% (15/40) in the control group. The incidence of grade 3–4 AEs was comparable between the two groups. In addition, a single-arm phase 2 trial⁹⁶ explored the efficacy of CAPEOX plus six cycles of tislelizumab in combination with 5-fraction split-course hypofractionated radiotherapy. TME was performed 2–4 weeks after the end of the neoadjuvant treatment. Among the 23 patients who underwent surgery, the pCR rate was 56.5%, and the R0 resection rate was 100%.

Some perspectives suggest that radiotherapy is delivered to the mesorectum and regional lymph nodes, which may damage T lymphocytes and lead to radiotherapy-induced fibrosis. Based on this consideration, an open-label, multicentre, phase 2 trial^{97,98} enrolled patients with MSS/pMMR LARC who received lymph node-sparing modified SCRT (the irradiated target area included only the primary tumour, without the draining lymph nodes of the tumour) followed by four cycles of CAPEOX plus tislelizumab. A total of 46 patients, 80% of whom had positive lymph nodes, were enrolled. Among them, 33 patients underwent surgery, with R0 resection, pCR and MPR rates of 100%, 78.8% and 90.9%, respectively. Therefore, for patients with pMMR/MSS or MMR/MSI-unknown LARC, SCRT followed by immunotherapy and chemotherapy can be considered as a neoadjuvant therapy. Alternatively, patients can be recommended for participation in similar clinical trials. However, the long-term survival benefits of this regimen remain unclear, and long-term follow-up data from confirmatory phase 3 trials are needed.

Organ preservation for patients with pMMR/MSS LARC

Given that patients with pMMR/MSS or MMR/MSI-unknown LARC who are treated with immunotherapy achieve obviously lower pCR and cCR rates than those with dMMR/MSI-H tumours, researchers have become more cautious about conducting explorations aimed at organ preservation in such patients. Hence, relevant clinical evidence is lacking. Clinicians should also be more cautious when implementing PD-1/PD-L1 inhibitor-based regimens for organ preservation therapy. This section only provides recommendations for organ-sparing treatment regimens for such patients. Other recommendations for organ-sparing therapy are the same as those for patients with dMMR/MSI-H LARC (see the 'Organ preservation for patients with dMMR/MSI-H LARC').

Recommendation 13: Patients with a strong desire for anal preservation can choose W&W after achieving cCR, while clinicians should fully inform them of the possibility of not achieving cCR (evidence quality: low; strength of the recommendation: strong).

Clinical trials aiming to investigate the W&W strategy or organ preservation are limited. Most studies use the CR (cCR+pCR) rate or survival indicators as the endpoint. Currently, phase 3 clinical trials are lacking, and the relevant data are limited by considerable heterogeneity and small sample sizes. Nevertheless, LCRT combined with immunotherapy has shown great potential for organ preservation and prolonged survival. A single-arm phase 2 clinical trial⁷⁵ included 23 patients with stage I–III MSS low rectal cancer (<5 cm from the anal verge) without risk factors to receive LCRT combined with sintilimab. The results revealed that the cCR rate was 43.5% (10/23). The overall anal preservation rate was 95.5% (21/22), whereas the rectal preservation rate was 59.1% (13/22). Similarly, in another single-arm, open-label phase 2 trial,⁸⁷ 18 patients with very low rectal cancer (≤2 cm from the dentate line) who underwent LCRT were included. The 2-course PD-1 inhibitor regimen was added 2 weeks after the first radiotherapy. After the end of radiotherapy, capecitabine or CAPEOX was administered, followed by a 2-course PD-1 inhibitor treatment. A total of 7 patients (38.9%) achieved cCR, with an organ preservation rate of 61.1% and an anal preservation rate of 94.4% (17/18). Another phase 2 RCT⁸² revealed that 44.8% of patients with LARC achieved CR after LCRT combined with immunotherapy. These patients have achieved preservation of important organs, such as the rectum and anus, but long-term survival data have not been disclosed.

The TORCH study, the first trial to explore the efficacy of SCRT combined with immunotherapy for organ preservation in patients with LARC, enrolled 130 patients with LARC who were randomly assigned 1:1 to the consolidation group (Group A) or the induction group (Group B).⁹⁹ Patients in Group A received SCRT followed by six cycles of toripalimab combined with CAPEOX chemotherapy. Patients in Group B received two cycles of toripalimab plus CAPEOX followed by SCRT, after which four cycles of toripalimab plus CAPEOX were administered as consolidation treatment. Among the 121 patients who were ultimately included in the analysis, the CR rate in Group A (n=62) reached 56.5% (15 cCR+20 pCR), whereas that in Group B (n=59) reached 54.2% (15 cCR+17 pCR). Patients in Group A had a higher cCR rate (43.5% vs 35.6%), suggesting that the consolidation neoadjuvant immunotherapy scheme may provide more opportunities for the W&W strategy and organ preservation.

In summary, LCRT or SCRT combined with ICIs could improve the rate of cCR and organ preservation. However, a

consensus on whether the use of the W&W strategy will lead to an increased risk of distant metastasis or a reduced OS is still lacking. Clinicians should consider this strategy carefully after fully assessing the risk of disease recurrence. Therefore, investigators are encouraged to conduct additional clinical trials aimed at organ preservation strategies, with the W&W strategy or organ preservation rate as one of the study endpoints, with the hope that patients with LARC can achieve improved quality of life while prolonging their OS. According to clinical assessment, contraindications for adopting a W&W strategy include: (1) rectal cancer with a high risk of local recurrence or distant metastasis; (2) intolerance to neoadjuvant therapy; (3) reluctance toward or inability to accept the risks associated with W&W and (4) inability to adhere to close surveillance due to poor compliance. Additionally, patient preference must be respected, and treatment alternatives, follow-up protocols, as well as potential risks of recurrence and metastasis, should be thoroughly discussed with the patient.

Dual immunotherapy

Recommendation 14: Dual immunotherapy regimen is not recommended for neoadjuvant or organ-sparing therapy. Considering the possible benefits, patients may be recommended to actively participate in clinical trials (evidence quality: very low; strength of the recommendation: strong).

Current clinical trials involving dual immunotherapy as a neoadjuvant therapy for patients with pMMR/MSS LARC are scarce and have very small sample sizes. The NEST-1 study¹⁰⁰ enrolled 10 patients with CRC who received one dose of BOT (a CTLA-4 antibody) combined with two doses of BAL (a PD-1 antibody). Among the 7 patients with MSS LARC, two experienced grade 3 AEs, and only one achieved pCR. In the NEST-2 study,¹⁰¹ the number of BAL treatment cycles was increased to four cycles. Among the 15 patients with MSS LARC, 6 achieved cCR, and 7 did not complete all four cycles. An interim analysis of the results of the CHINOREC study¹⁰² revealed that among the 10 patients with LARC who received nivolumab combined with ipilimumab treatment, 8 had grade 1–2 surgical complications, and no grade 3 surgical complications occurred.

Given that the number of AEs associated with dual immunotherapy for metastatic CRC is greater than that associated with single immunotherapy,^{42 103 104} caution is needed to determine whether patients with LARC need to be treated with dual immunotherapy. Due to the lack of efficacy data and the possibility of irAEs, dual immunotherapy is not recommended for these patients. Active participation in clinical trials is encouraged.

Local excision

Recommendation 15: After neoadjuvant ICIs, ycT1N0M0 or high motivation for anal preservation but difficult ycT2N0M0 cases can receive LE through a careful MDT assessment. TME is recommended for ypT1–2 patients with a high risk for recurrence at baseline, whereas the W&W strategy is recommended for ypT0 patients after fully informing benefits and risks (evidence quality: very low; strength of the recommendation: strong).

Local excision (LE) methods, such as endoscopic resection or transanal resection, are the primary forms of radical treatment for early-stage rectal cancer. A systematic review and meta-analysis that included 20 clinical trials and compared the oncological outcomes of LE and TME in the treatment of early-stage rectal cancer revealed that¹⁰⁵ LE is more suitable for patients with rectal cancer with no risk factors. Patients with rectal cancer

treated with LE who underwent monitoring of the clinical stage had a satisfactory therapeutic effect, with a 96.7% R0 resection rate, 93.0% 5-year DFS rate and 81.6% 5-year OS rate. Due to the ability to better preserve the structure and function of the rectum and anus than TME, the use of LE after neoadjuvant therapy is becoming increasingly common.

The milestone GRECCAR2 study¹⁰⁶ enrolled 186 patients with cT2-3N0-1 rectal cancer. Among them, 145 responded well to neoadjuvant therapy and were randomly assigned to the LE and TME groups. No significant differences were observed in terms of the 5-year local recurrence rate, metastatic disease, OS or DFS between the two groups. The multicentre, randomised controlled, non-inferiority phase 3 TAU-TEM trial¹⁰⁷ included patients with cT2-3aN0M0 rectal cancer. A total of 173 patients were randomly assigned to the neoadjuvant therapy combined with LE group or TME group. Ultimately, 82.7% (67/81) of patients in the neoadjuvant therapy combined with LE group achieved organ preservation, with a pCR rate of 44.3% (35/79). In addition, the CARTS trial¹⁰⁸ enrolled 55 patients with cT1-3N0M0 rectal cancer who underwent LE after receiving neoadjuvant CRT, with an organ preservation rate of 63.6% (35/55). The long-term oncological outcomes were satisfactory, with a 5-year local recurrence rate of 7.7%, a 5-year DFS rate of 81.6% and a 5-year OS rate of 82.8%.

The key to performing LE after neoadjuvant therapy is to identify suitable patients and closely follow them. Only patients with ycT1N0M0 tumours are recommended for the W&W strategy after receiving LE, which should be performed in high-quality centres to ensure accurate pathological staging and good patient management. Studies have shown that neoadjuvant therapy containing PD-1 inhibitors can significantly promote tumour regression and increase the cCR rate and the percentage of patients managed with the W&W strategy. Thus, for patients with a small residual tumour after neoadjuvant therapy, the use of W&W after LE may be a safe and effective organ-preserving strategy. Currently, long-term follow-up data concerning the use of LE after neoadjuvant immunotherapy are lacking, but more clinical trials are encouraged.

Managing the safety of perioperative immunotherapy

While immunotherapy can improve the pCR and cCR rates, it can also induce a series of irAEs of different degrees. The time of occurrence, the organs involved and the clinical manifestations of irAEs are diverse. In addition, in patients with pMMR/MSS LARC, neoadjuvant immunotherapy is typically used in combination with chemotherapy and radiotherapy; consequently, irAEs may be confused with adverse reactions caused by radiotherapy and chemotherapy. Clinicians should strive to identify irAEs more accurately and implement strict management of the whole treatment process.

Recommendation 16: Specific populations should be identified and undergo complete baseline examinations and irAE monitoring during neoadjuvant therapy. Particular attention should be given to immune-mediated myocarditis and pneumonitis, as both conditions are associated with high mortality (evidence quality: high; strength of the recommendation: strong).

The safety of immunotherapy is relatively good. According to multiple studies, most irAEs are grade 1/2, and the incidence of grade ≥ 3 irAEs is relatively low. The immunotherapy regimen should be chosen carefully for patients who may be at potential risk of ICI-related toxicity or other unexpected toxicity, such as those who have undergone organ transplantation, are elderly or have autoimmune diseases (psoriasis, rheumatoid arthritis,

etc).^{109–112} A comprehensive baseline evaluation can help identify patients at high risk of irAEs, including routine measurements of vital signs and physical examinations (particular attention to skin and mucosal conditions); haematological and biochemical tests (complete blood count, tests of liver and kidney function, and electrolyte levels); cardiac enzyme profile (a special emphasis on troponin I/T and creatine kinase-MB levels); thyroid function (thyroid stimulating hormone, FT3 and FT4 levels); adrenal cortical hormones (serum cortisol levels); pituitary function tests; ECG and echocardiography (patients with risk factors); pulmonary function; urinalysis; and infectious disease screening.

Several studies have shown that the development of irAEs in patients with rectal cancer treated with immunotherapy combined with radiotherapy and chemotherapy is related mainly to the endocrine system, liver, skin, gastrointestinal tract and skeletal muscular system. The irAEs can occur at any stage of immunotherapy but are usually delayed and long-lasting, and delayed irAEs may even occur 1 year after the end of ICI treatment.¹¹³ Haematological toxicity is the most common AE, which is caused mainly by cytotoxic chemotherapeutic drugs and is often classified as a chemotherapy-related AE. Most irAEs can be detected in a timely manner through regular monitoring. Prior to treating an event, a differential analysis should be conducted to determine whether the event is an irAE, an AE caused by radiotherapy and chemotherapy, or a symptom of the disease itself. Although the incidence of immune myocarditis is low, it has a high mortality rate, and its clinical manifestations are nonspecific. In clinical practice, immune myocarditis can be detected early through regular monitoring of myocardial enzyme levels and ECG.¹¹⁴ Although pneumonia associated with ICIs occurs infrequently, when it occurs, the patient's condition is often severe. New or worsening cough and difficulty breathing are the most common clinical symptoms of immune pneumonia and require sufficient clinical attention and timely intervention.¹¹⁵

Recommendation 17: MDTs should be formed to address irAEs and improve the efficiency and accuracy of the diagnosis and treatment of irAEs (evidence quality: very low; strength of the recommendation: strong).

Unlike chemotherapeutic drugs, which act on metabolically active cells, irAEs can occur in any tissue or organ in the body. Many problems have been noted among surgeons, such as a lack of understanding and insufficient specialist experience. Therefore, an MDT that includes the departments of medical oncology, respiratory medicine, rheumatology and immunology is recommended for scientific guidance and management. Through a multidimensional discussion of irAEs by an MDT, the diagnosis can be confirmed as soon as possible. The MDT can also provide organisational assurance and a platform for doctors of different specialties to jointly develop treatment plans, allowing the quick determination of the best treatment strategy, shortening of the treatment time and improvements in the treatment effect.

Domestic and international guidelines for grading and classification must be followed when dealing with irAEs, such as the 2024 Chinese Society of Clinical Oncology Guidelines for the Management of Immune Checkpoint Inhibitor-Associated Toxicity and the NCCN Guidelines.^{116–118} For irAEs of grade ≥ 2 , prompt MDT consultation involving oncology, relevant specialties (eg, cardiology, endocrinology, respiratory medicine), critical care and clinical pharmacy is recommended. In patients whose immunotherapy was withheld due to irAEs, a comprehensive MDT evaluation should be conducted to assess the feasibility of resuming treatment. Particularly for pMMR/MSS patients, alternative treatment options are recommended as the priority. MDT collaboration can fully leverage the advantages of experts from different disciplines to analyse and determine the patient's condition from different perspectives, thereby

Table 3 Summary of phase 3 clinical trials on immune checkpoint inhibitors for locally advanced rectal cancer

Study title (ClinicalTrials.gov ID)	Phase	Patients	N	Treatment	Primary endpoint	Study start	Country of primary investigator
STELLAR II (NCT05484024)	III	Locally advanced rectal adenocarcinoma, cT3–T4N0/cT2–4N+, M0	588	Experimental arm: short-course radiotherapy followed by neoadjuvant chemotherapy and PD-1 inhibitor. Control arm: short-course radiotherapy followed by neoadjuvant chemotherapy.	CR	August 2022	China
PKUCH R07 (NCT06229041)	II/III	T4b, or mrN2, or positive MRF, or positive EMVI rectal cancer	472	Experimental arm: Camrelizumab+Immunotherapy. Control arm: total neoadjuvant treatment.	pCR	March 2023	China
MODIFI-RC-II (NCT06958432)	III	Mid/low pMMR/MSS rectal cancer	430	Experimental: node-sparing radiotherapy plus chemotherapy and PD-1 inhibitor. Control arm: conventional radiotherapy plus chemotherapy and PD-1 inhibitor.	CR, EFS	May 2025	China
NCT07277842	III	Locally advanced low rectal adenocarcinoma, pMMR	382	Experimental arm: Serplulimab+FOLFOXIRI+Radiotherapy. Control arm: active comparator: CAPOX+Radiotherapy.	3 year EFS	December 2025	China
BFH-niCRT-04 (NCT06312982)	III	T1-2N1-2M0 or T3N0-2M0, locally advanced rectal cancer	375	Experimental arm: NCRT, tislelizumab and CAPOX. Control arm: NCRT and CAPOX.	CR	February 2024	China
NeoCaCRT-III (NCT06832917)	III	Locally advanced rectal cancer, cT 3-T4/N+M0	238	Experimental arm: SCRT followed by AK104 plus chemotherapy. Control arm: Chemo only.	DFS	March 2025	China
UNION (NCT04928807)	III	Resectable T3-4 and/or N+rectal cancer	231	Experimental arm: short course radiotherapy sequential camrelizumab and chemotherapy. Control arm: long-term concurrent chemoradiotherapy and sequential chemotherapy.	pCR	July 2021	China
PALACE Study (NCT07020247)	III	Locally advanced rectal cancer	184	Experimental arm: total neoadjuvant chemoradiotherapy+Serplulimab. Control arm: total neoadjuvant chemoradiotherapy	pCR+cCR	November 2024	China
CHCRS-Immunity (NCT05215379)	III	MSS ultra-low rectal cancer	180	Experimental arm: xintilimab injection. Control arm: neoadjuvant chemoradiation therapy	cCR	October 2022	China
mRCAT-III (NCT06507371)	III	cT3-4bN0/+M0, MSS middle and low rectal cancer	170	Experimental arm: participants will receive radiation with CAPOX and tislelizumab. Control arm: participants will receive radiation and CAPOX	pCR	July 2024	China
PKUCH-R09 (NCT06443671)	III	Mid-high pMMR/MSS locally advanced rectal cancer	132	Experimental arm: Fruquintinib and Tislelizumab combined with mCapeOX. Control arm: CapeOX group	pCR	June 2024	China
BASKETIII (NCT06791512)	III	dMMR/MSI-H colorectal cancer	122	Experimental arm: neoadjuvant therapy of mFOLFOX6+Bevacizumab+PD-1 monoclonal antibody. Control arm: neoadjuvant therapy of mFOLFOX6	DFS	January 2025	China
PRECAM-R (NCT05752136)	III	Locally advanced rectal cancer, cT2-4a N+, cT3/T4a N0	108	Experimental arm: neoadjuvant chemoradiotherapy combined with immunotherapy and total mesorectal excision. Control arm: neoadjuvant chemoradiotherapy and total mesorectal excision	pCR	April 2023	China

cCR, clinically complete response; CR, complete response; DFS, disease-free survival; dMMR, deficient mismatch repair; EFS, event-free survival; EMVI, extramural venous invasion; MRF, mesorectal fascia; MSI-H, microsatellite instability-high; MSS, microsatellite stability; NCRT, neoadjuvant chemoradiotherapy; pCR, pathological complete response; PD-1, programmed cell death protein-1; pMMR, proficient mismatch repair; SCRT, short-course radiotherapy.

reducing the possibility of misdiagnosis. Therefore, forming management opinions based on an MDT is the key to ameliorating irAEs.

Recommendation 18: Standardised handling of irAEs during neoadjuvant therapy may not typically affect surgical safety, but the risk of postoperative complications exists. Surgery after irAE recovery to grade ≤ 1 is recommended (evidence quality: very low; strength of the recommendation: strong).

In accordance with the Common Terminology Criteria for Adverse Events, grade 1 AEs do not require special treatment, and immunotherapy can be continued. For grade 2 adverse reactions of the skin and endocrine system, ICIs can be used continuously based on symptomatic treatment. If the AEs persist, treatment should be discontinued, and glucocorticoids should be used. For other systemic grade 2 AEs, immunotherapy should be suspended until the symptoms

are alleviated. In the event of grade 3–4 AEs, the patient should receive glucocorticoid treatment, while immunotherapy should be suspended or even permanently discontinued. If the symptoms do not improve significantly or significantly worsen after 48–72 hours of glucocorticoid treatment, immunosuppressants, immunoglobulin, plasma exchange and novel biological agents such as infliximab should be considered.

Most current guidelines recommend against restarting ICIs for all patients who develop grade 4 irAEs. For patients with grade 1–3 AEs, the benefits of restarting ICI treatment should be re-evaluated after the irAEs are downgraded to grade 1. The final decision on restarting treatment should be made after a discussion by the MDT. No evidence has indicated that neoadjuvant immunotherapy affects the safety of surgery or increases the incidence of postoperative complications.^{119–120} However, surgery should be performed only after irAEs have resolved to $\leq$ grade 1 and the risks are deemed manageable following an MDT assessment, with enhanced perioperative monitoring to ensure safety. Previous studies have shown that long-term use of glucocorticoids can increase the incidence of surgical site infections.¹²¹ However, patients with irAEs use glucocorticoids for only a short time before surgery, which may not have a significant effect on surgical outcomes.

While immunotherapy has good efficacy, it can also lead to irAEs. Although the prognosis of most irAEs is good, some may cause permanent damage to the patient and even lead to death. Clinicians should weigh the benefits and harms and carefully use immunotherapy based on a comprehensive consideration of the treatment needs and the patient's own condition and wishes and closely monitor and address irAEs during treatment.

OUTLOOK

The modulatory effect of the gut microbiota on the efficacy of ICIs has emerged as a new research hotspot.¹²² Preliminary studies of advanced melanoma, non-small cell lung cancer and other cancer types have suggested that modulating the gut microbiome through faecal microbiota transplantation (FMT) may reverse resistance to immunotherapy and increase response rates.^{123–125} A notable phase II trial (ChiCTR2100046768) in refractory MSS metastatic CRC demonstrated that combining FMT with ICIs and anti-angiogenic therapy yielded promising survival benefits.¹²⁶ However, in the field of LARC, relevant clinical evidence remains scarce. Furthermore, this consensus is based mainly on existing evidence obtained using PD-1/PD-L1 and CTLA-4 inhibitors.^{127–129} Although novel targets such as 'lymphocyte-activation gene 3' and 'T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains' have shown great potential, this consensus was unable to include them because of the limited number of clinical trials in the perioperative setting for LARC. We look forward to further clinical evidence to continuously improve treatment strategies in these related fields.

This consensus was formed by systematically searching and incorporating relevant literature published globally and using the internationally recognised Delphi method. We noticed that a significant portion of the high-quality studies included in the analysis were from the Chinese population (online supplemental appendix 2). This distribution reflects the active clinical research contributions of Chinese scholars in this field, but it may also constitute potential selection bias. In addition, all the experts who participated in Delphi voting and developed this consensus were from China. The final recommendation is influenced to some extent by the clinical practice model, drug accessibility and regional diagnosis and treatment experience in China (online supplemental appendix 4). Therefore, we suggest that international peers make final decisions based on their local diagnostic

and treatment guidelines, drug accessibility and the specific situation of patients when they refer to this consensus. We will invite globally renowned experts from North America, Europe, Asia, etc, with extensive clinical experience in this field to draw up the development of a further international version of the consensus.

This consensus has reviewed research data on the use of various ICIs to treat LARC. However, we must explicitly emphasise that the current evidence remains insufficient to support direct comparisons of the efficacy of different drugs. Most existing studies are single-arm, phase 2 trials and head-to-head RCTs that compare different ICIs are lacking. Additionally, considerable differences in the tumour stage, treatment regimens (number of immunotherapy cycles, chemotherapeutic agents and radiotherapy modalities), and primary endpoints have been observed across studies. Thus, this consensus is primarily grounded in the overall strength of evidence for the use of ICIs to treat patients with dMMR/MSI-H LARC rather than being specific to any particular agent. Future trials should focus on comparing the relative efficacy of different ICIs through RCTs.

Rapid developments in medical technology have helped demonstrate the great potential of ICIs in the perioperative and organ-sparing treatment of LARC, but room for additional developments in the future still exists (table 3). First, the long-term survival data are limited. Additional multicentre clinical trials will provide a greater evidence base for the application of ICIs. Large-scale clinical trials can better evaluate the efficacy and safety of different treatment options and provide a more reliable basis for clinical decision-making. In addition, individualised treatment will be important in the future. An individualised treatment plan is developed based on the patient's genetic signature, tumour biological characteristics and other factors to improve the pertinence and effectiveness of treatment. Moreover, the optimal combination of ICIs and other treatments still needs to be explored. Finally, optimising patient management is very important.^{90 130–132} In addition to pretreatment evaluations, monitoring during treatment and follow-up after treatment, timely detection and treatment of adverse reactions can improve patients' quality of life. In conclusion, ICIs have great potential in the perioperative and organ-sparing treatment of LARC. In the future, continuous exploration and innovation are needed to improve treatment efficacy and patients' quality of life.

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