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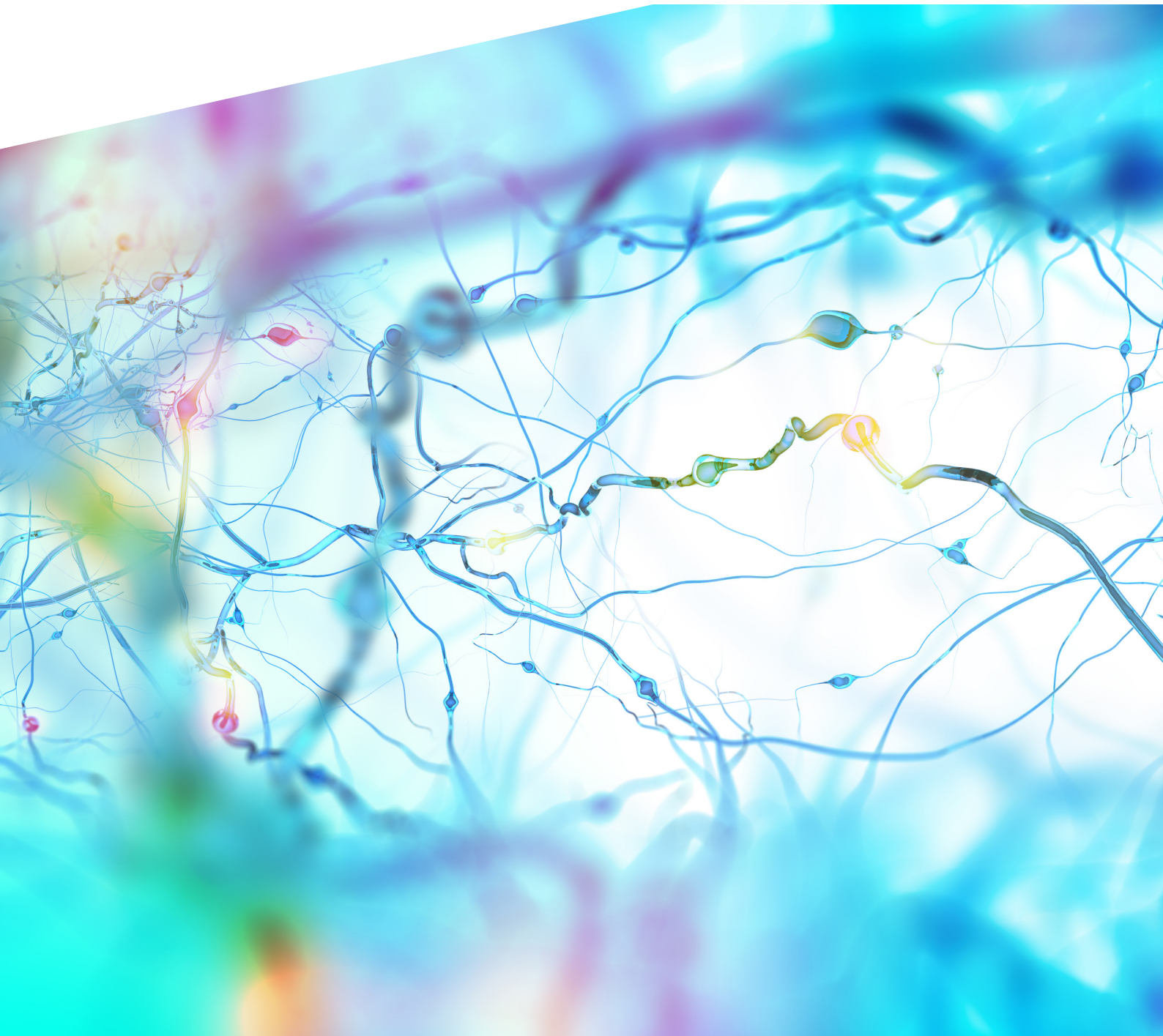

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Aims & Scope

The Ewha Medical Journal (Ewha Med J, http://www.e-emj.org), the official publication of Ewha Womans University College of Medicine and Ewha Medical Research Institute, is published quarterly a year, last day of January, April, July, and October. The first volume was published in March, 1978. It covers all fields of medical science including clinical research and basic medical science. The Journal aims to communicate new medical information between medical personnel and to help development of medicine and propagation of medical knowledges. All manuscripts should be creative, informative and helpful for diagnosis and treatment of the medical diseases and for communication of valuable information about all fields of medicine. Subscripted manuscripts should be written out according to the instructions for the Journal. Topics include original article, case report, images and solution, letter to the editor, invited review article and special issue in the respective field of medicine. The Ewha Medical Journal is indexed/tracked/covered by KoreaMed, KoMCI, KoreaMed Synapse, WPRIM, DOI/CrossRef, EMBASE and Google Scholar.

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Editorial

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Emerging Infectious Diseases at the End of the Fourth Year of the COVID-19 Pandemic and Recent Updates on Colorectal and Pediatric Endocrine Diseases

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Marking the End of the Fourth Year of the COVID-19 Pandemic

The year 2023 marks the fourth year of the COVID-19 pandemic, which has brought about multifaceted changes in health, healthcare systems, social structures, the economy, culture, and housing worldwide. In Korea, quarantine measures have been lifted, except in certain group living facilities such as hospitals and some nursing homes, signaling a shift toward pre-pandemic routines. Nevertheless, the pandemic's impact on daily life persists. Online meetings have become the norm, and it is now commonplace to conduct lectures and workshops virtually. This practice is also prevalent among several editorial committees of academic journals. In summary, these changes have been implemented across various sectors of our society.

In 2023, as COVID-19 cases decreased, there was a notable increase in other infectious diseases. Specifically, influenza cases surged to 3.5 times the number reported in 2022, with 61.3 cases per 1,000 population in the 49th week of 2023 compared to 17.3 per 1,000 population in the same week of 2022 [1]. Additionally, instances of mycoplasma pneumonia more than tripled in 2022 [2]. An imported infectious disease, mpox, was detected in the country but remained contained, primarily affecting specific groups within the homosexual community [3]. In the realm of veterinary health, Korea saw the introduction of an infection caused by the lumpy skin disease virus in cows, which is transmitted by vectors [4]. Although the specific vectors present in the field have not been reported, laboratory studies have shown that *Aedes aegypti* mosquitoes, ixodid ticks (*Amblyomma hebraeum*, *Rhipicephalus appendiculatus*, and *Rhipicephalus* [*Boophilus*] *decoloratus*), biting flies (*Stomoxys calcitrans*), and horseflies (*Haematopota* spp.) can potentially act as vectors [5]. Consequently, it is presumed that the domestic introduction of the virus occurred through these infected vectors, as the mode of transmission is not airborne. This raises the concern that various mosquitoes, ticks, and flies native to Africa and the Middle East could potentially introduce not only cattle diseases but also human infections caused by vector-borne

viruses, bacteria, and parasites into Korea. Given the changing climate and Korea's shift towards a more subtropical environment, it is crucial for government surveillance and clinical practice to intensify monitoring of these vector-borne imported diseases. Without vigilant oversight, there is a risk that these diseases could become endemic as the vectors establish themselves domestically.

This issue of *Ewha Medical Journal* features a collection of insightful articles that explore significant advancements in the fields of colorectal surgery and pediatric endocrinology.

Advancements in Colorectal Surgery and Colorectal Cancers

Clinical guidelines for enhanced recovery following colorectal surgery have been introduced. A review published in this issue compares elements from two sets of guidelines: those of the Enhanced Recovery After Surgery (ERAS) Society and the American Society of Colon and Rectal Surgery [6]. Key elements of the ERAS guidelines include preoperative optimization, anemia management, antimicrobial prophylaxis, prevention of intraoperative hypothermia, and thromboprophylaxis. In contrast, the guidelines from the American Society of Colon and Rectal Surgery highlight preadmission orders and discharge criteria. This comparison acquaints readers with the current guidelines for improved postoperative recovery.

In the diagnosis of colorectal cancer, markers of the inflammatory response have become increasingly recognized as important prognostic tools. Elevated preoperative levels of the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and C-reactive protein–albumin ratio have been identified as predictors of poor outcomes. Understanding these inflammatory markers is crucial for improving the management of colorectal cancer [7].

Five therapeutic approaches for colorectal cancer have been introduced. These include preoperative chemoradiotherapy for advanced local rectal cancer, transanal local excision for early-stage rectal cancer, cytoreductive surgery coupled with hyperthermic intraperitoneal chemotherapy for colorectal cancer with peritoneal metastases, and an examination of the impact of the COVID-19 pandemic on treatment modalities. These insights are invaluable for colorectal surgeons, patients, and their families.

Methods to prevent anastomotic leakages, a common complication of colorectal surgery, have been elucidated. These methods encompass intraoperative reinforcing sutures, the application of fluorescence angiography, transanal drainage, and the use of diverting stomas. The selection of these techniques should be tailored to each patient, taking into account specific risk factors and the clinical context [8].

Innovations in Pediatric Endocrinology

Four themes in pediatric endocrinology are discussed. The first theme is endocrine hypertension in children related to adrenal gland disorders. These disorders are categorized into three types: mineralocorticoid-related hypertension, which includes conditions such as primary aldosteronism, congenital adrenal hyperplasia, and apparent mineralocorticoid excess; glucocorticoid-related hypertension, exemplified by Cushing syndrome; and catecholamine-related hypertension, which encompasses pheochromocytoma and paraganglioma. Although these disorders are rare, they are significant causes of endocrine hypertension in children and require prompt investigation for swift diagnosis and appropriate treatment [9].

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The second theme reviewed contemporary advancements in managing childhood Graves' disease, with a focus on emerging targeted therapies. Treatment options such as antithyroid drugs, radioactive iodine ablation, and thymectomy were compared, alongside ongoing research into the long-term outcomes of these approaches in pediatric patients. Considering the autoimmune nature of Graves' disease, which involves B and T lymphocytes and the thyroid-stimulating hormone receptor, research is being conducted on therapies targeting these pathways. Adequately sized randomized controlled trials are crucial to establish the efficacy of these novel treatments [10]. The third theme addressed Prader-Willi syndrome (PWS), a prevalent genetic cause of obesity. This syndrome occurs in approximately 1 out of every 10,000 to 30,000 births, making immediate diagnosis essential. Beyond obesity, the syndrome is associated with developmental delays, learning difficulties, and behavioral issues. The management of obesity in PWS is particularly challenging, which highlights the importance of early diagnosis for effective intervention [11].

PWS is caused by one of three genetic mechanisms: 65%–70% of cases are due to a paternal deletion of the 15q11.2–13 region of chromosome 15, 20%–30% result from maternal uniparental disomy, and 2%–5% are caused by imprinting defects or rearrangements. At the heart of PWS is the *SNORD116* gene located in the paternal chromosome 15 region; a deficiency in this gene leads to hypothalamic imbalances that manifest in typical PWS symptoms, such as abnormal eating and sleep patterns [12].

I trust that the recent advancements in colorectal surgery and pediatric endocrinology, as described above, will prove valuable to surgeons, pediatricians, and practicing physicians.

Appreciation to Authors and Reviewers

In my first year volunteering as the editor of the *Ewha Medical Journal*, I endeavored to publish a substantial number of manuscripts from various Korean medical societies. I am deeply grateful to the authors for their willingness to share their exceptional knowledge and expertise in their respective fields, as well as to the reviewers who generously dedicated their time to the journal. Looking ahead, I aim to attract and publish articles on more current and relevant topics that resonate with both the Korean and international medical communities.

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Conflict of Interest

Sun Huh has been an editor-in-chief of the *Ewha Medical Journal* since September 2023. However, he was not involved in the review process. No other potential conflict of interest relevant to this editorial was reported.

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Author Contribution

The article is prepared by a single author.

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Not applicable.

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Review Article

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The Latest Results and Future Directions of Research for Enhanced Recovery after Surgery in the Field of Colorectal Surgery

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Key Words
Enhanced recovery after surgery; Colorectal surgery; Perioperative care; Postoperative complications

Enhanced recovery after surgery (ERAS) aims to promote postoperative recovery in patients by minimizing the surgical stress response through evidence-based multimodal interventions. In 2023, updated clinical practice guidelines were published in North America, potentially superseding the most recent guidelines previously announced at the ERAS Society in 2019. This review compares and reviews these two guidelines to examine the principle of ERAS and items related to colorectal surgery and to introduce the latest relevant study results published within the last 5 years. In the pre-hospitalization stage, the concept of pre-hospitalization is emphasized; this involves checking and reinforcing the patient's nutritional status and physical functional status before surgery. In the preoperative stage, large-scale studies have prompted a change in the recommendation of mechanical bowel preparation combined with oral antibiotics in elective colorectal surgery. In the intraoperative stage, laparoscopic surgery has become a widespread and important component of ERAS, and more technologically advanced single-incision laparoscopic surgery and robotic surgery are the focus of active research. Ileus-prevention items, such as opioid-sparing multimodal pain management and euvolemic fluid therapy, are recommended in the postoperative stage. The adoption of ERAS protocols is expanding to encompass a wide range of surgical procedures, clinical scenarios, healthcare institutions, and professional medical societies. In order to maximize the effect by increasing adherence to ERAS, medical staff must fully understand the clinical basis and meaning of each item, and the protocol must be maintained and developed steadily through a team approach and audit system.

Introduction

Enhanced recovery after surgery (ERAS) constitutes a comprehensive set of evidence-based practices, collaboratively administered by a diverse healthcare team, aimed at facilitating swift postoperative recovery for patients. It has been proven to be associated with faster recovery of bowel function, reduced postoperative length of hospital stay (LOS), and a lower rate of postoperative complications compared to traditional perioperative care [1,2].

However, ERAS is relatively difficult to introduce and maintenance efforts are also required. In addition, the degree to which various items of ERAS are accepted by institutions or medical staff varies [3].

The aim of this review is to enhance readers' understanding of ERAS and facilitate future research in this field. This will be achieved by presenting recently published papers (within the

last 5 years) on relevant topics. Additionally, we will provide a schematic comparison of the recently updated clinical practice guidelines for enhanced recovery after colon and rectal surgery from the American Society of Colon and Rectal Surgeons (ASCRS) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) [4] with the existing ERAS Society guidelines [5].

Main Text

1. Composition of enhanced recovery after surgery items: practice guidelines from the Enhanced Recovery after Surgery Society and American Society of Colon and Rectal Surgeons

ERAS guidelines for colorectal surgery were first published in 2005 and have been updated as recently as 2019 by the ERAS Society. Meanwhile, the ASCRS and SAGES, primarily based in North America, issued their initial practice guidelines in 2017, with updates made in 2023. While these two sets of guidelines share many similar principles and protocol items, the ERAS Society guidelines are slightly more comprehensive. In contrast, the ASCRS guidelines contain less detail on individual items but incorporate the most recent research findings (Table 1).

In brief, the ASCRS guidelines advocate for the use of mechanical bowel preparation (MBP) in conjunction with oral antibiotics for colorectal resections. This differs from the ERAS Society guidelines, which suggest considering MBP (coupled with oral antibiotics) solely for rectal surgery. Furthermore, the ASCRS guidelines diverge from the ERAS Society guidelines in their approach to thoracic epidural analgesia (TEA). While the ERAS Society guidelines endorse TEA for open surgery, the ASCRS guidelines suggest considering TEA selectively, only if the surgery is open and a dedicated pain team is available. The ASCRS guidelines also underscore

Table 1. Brief comparison of current clinical guidelines from the Enhanced Recovery after Surgery Society and the American Society of Colon and Rectal Surgery-Society of American Gastrointestinal and Endoscopic Surgeons

Stage	ERAS Society guidelines [5]	ASCRS guidelines [4]
Preadmission		
Preadmission orders		Standardized order sets should be utilized
Information, education, and counseling	Patients should receive dedicated preoperative counseling routinely	A preoperative discussion regarding clinical milestones and discharge criteria should be performed. Stoma teaching and counseling regarding how to avoid dehydration should be provided for patients undergoing ileostomy.
Preoperative optimization	Medical risk assessment Smoking cessation at least 4 weeks prior to surgery	
Nutrition	Preoperative nutritional assessment should be offered. Patients at risk of malnutrition are recommended to have oral nutritional supplementation for 7–10 days.	Oral nutritional supplementation is recommended in malnourished patients (targeting a protein intake of 1.2–1.5 g/kg/day for 1–2 weeks).
Prehabilitation	May reduce complications. Patients who are less fit may be more likely to benefit.	May be considered for patients with multiple comorbidities or significant deconditioning.
Anemia management	If possible, anemia should be corrected with intravenous iron preoperatively prior to surgery, and blood transfusion should be avoided.	

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Table 1. Continued

Stage	ERAS Society guidelines [5]	ASCRS guidelines [4]
Preoperative		
Prevention of PONV	A multimodal approach to PONV prophylaxis should be considered.	Similar (recommendations for PONV, pain, SSI prevention, and fluid management are stated in the Perioperative Interventions section).
Pre-anesthetic medication	Sedative medication should be avoided if possible before surgery.	A multimodal, opioid-sparing, pain management plan should be implemented before the induction of anesthesia.
	Opioid-sparing multimodal re-anesthetic medication can be used.	
Antimicrobial prophylaxis	Intravenous antibiotic prophylaxis should be given within 60 min before incision as a single-dose administration.	
	In patients receiving oral mechanical bowel preparation, oral antibiotics should be given.	
Skin preparation	Chlorhexidine-alcohol-based preparation	A bundle of measures (preoperative: chlorhexidine shower, bowel preparation, antimicrobial prophylaxis, chlorhexidine/alcohol skin preparation; operative: wound protector, gown and glove changes before fascial closure, antimicrobial sutures, maintaining euglycemia and normothermia) should be in place to reduce SSI perioperatively
Bowel preparation	MBP alone with IV antibiotic prophylaxis may be used for rectal surgery.	MBP combined with preoperative oral antibiotics is typically recommended.
Preoperative fasting and carbohydrate loading	The patient should be allowed to eat up until 6 h and take clear fluids up until 2 h before anesthetic induction.	Clear liquids may be continued up to 2 h before surgery.
	Patients with delayed gastric emptying and emergency patients should fast overnight or 6 h before surgery.	
Intraoperative		
Standard anesthetic protocol	Avoidance of benzodiazepines	Similar recommendation
	Use of short-acting anesthetics	
	Cerebral function monitoring	
	Monitoring of the level and complete reversal of neuromuscular block	
Fluid and electrolyte management	Maintain fluid homeostasis	Even a short duration of MAP<65 mmHg should be avoided (associated with adverse outcomes, in particular myocardial injury and acute kidney injury).
	GDFT should be adopted, especially in high-risk patients	Similar recommendation
Prevention of intraoperative hypothermia	Reliable temperature monitoring should be undertaken.	
Surgical access	Minimally invasive surgery is recommended.	Similar recommendation
Drain	Pelvic and peritoneal drains should not be used routinely.	Similar recommendation
Postoperative		
Nasogastric tube	Should not be used routinely	Similar recommendation
	If inserted during surgery, it should be removed before reversal of anesthesia.	

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Table 1. Continued

Stage	ERAS Society guidelines [5]	ASCRS guidelines [4]
Postoperative		
Pain control	Avoid opioids and apply multimodal analgesia.	Similar recommendation
	TEA is recommended in open colorectal surgery.	TEA is an option for open colorectal surgery (if dedicated pain team is available)
Abdominal wall blocks	TAP blocks can reduce opioid consumption and improve recovery.	Laparoscopic-guided TAP block is safe and effective, and seems to be as effective as US-guided TAP block.
Thromboprophylaxis	Mechanical prophylaxis by compression stockings and/or intermittent pneumatic compression until discharge	
	Pharmacological prophylaxis with LMWH for 28 days after surgery	
Fluid and electrolyte management	Net "near-zero" fluid and electrolyte balance should be maintained.	Similar recommendation
	Balanced solutions are preferred.	Similar recommendation
		Intravenous fluids should be routinely discontinued in the early postoperative period in the absence of surgical complications or hemodynamic instability
Foley catheter	Recommended for 1–3 days	Removed within 24 h for colon–upper rectal resection Removed within 24–48 h for mid/lower rectal resection
Nutritional care	Early resumption of oral intake with oral supplementation from the day of surgery.	Patient should be offered a regular diet with 24 h.
	Perioperative immunonutrition for malnutrition.	The efficacy of immunonutrition over standard high-protein oral nutritional supplements remains controversial.
Early mobilization	Through patient education and encouragement	Early and progressive patient mobilization are associated with a shorter length of stay.
Discharge criteria		Hospital discharge prior to return of bowel function may be offered for selected patients.
Audit	Collection of key outcome and process data used for repeated audits and feedback is essential	

ERAS, Enhanced Recovery after Surgery; ASCRS, American Society of Colon and Rectal Surgeons; PONV, postoperative nausea and vomiting; SSI, surgical site infection; MBP, mechanical bowel preparation; MAP, mean arterial pressure; GDFT, goal-directed fluid therapy; TEA, transthoracic epidural analgesia; TAP, transversus abdominis plane; US, ultrasonography.

the importance of comprehensive preoperative education about the stoma and the potential for dehydration. They suggest that early discharge may be considered even for patients whose bowel function has not yet returned to normal. Conversely, the ERAS Society guidelines address issues such as abstaining from alcohol and smoking, correcting anemia, and thromboprophylaxis, which are not mentioned in the ASCRS guidelines. In this review, the author will sequentially present the latest research findings in accordance with the topics covered by both sets of guidelines.

2. Pre-admission issues

1) Prehabilitation

Prehabilitation is defined as "a process in the continuum of care that occurs between the time of diagnosis and the beginning of acute treatment and includes physical, nutritional and psychological assessments that establish a baseline functional level, identify impairments, and provide interventions that promote physical and psychological health to reduce the incidence and/or severity of future impairments" [5] or simply "enhancement of the patient's preoperative condition" [4].

With the rise in the elderly population, there is an increasing focus on pre-habilitation. McLennan et al. [6] presented the results of a study involving 199 patients who underwent elective colorectal surgery and received ERAS perioperative care. The study found that patients with a poor preoperative physical status, specifically those unable to climb two flights of stairs, had significantly higher postoperative complications (OR, 6.64; 95% CI, 1.51–29.13, P=0.012) than those who did not exhibit such physical limitations.

However, even though preoperative prehabilitation may enhance physical function, it remains a topic of debate whether this improvement translates into tangible outcomes such as reducing postoperative complications and shortening the LOS [4]. Consequently, the recommendations of the two guidelines are confined to suggesting that prehabilitation might be beneficial for patients with multiple comorbidities or poor physical performance.

Additionally, given that nutrition has been identified as a significant factor in postoperative outcomes and has its own set of recommendations, the term "prehabilitation" should be narrowly defined to focus on exercise capacity or frailty. As a result, it is crucial to pursue research efforts that investigate preoperative evaluations, prehabilitation methods, and their respective effects.

2) Nutrition

Both guidelines suggest assessing the preoperative nutritional status and administering oral nutritional supplementation to malnourished patients for an approximate duration of 1–2 weeks. Evidence exists that the preoperative nutritional status is linked to complications, and enhancements in nutritional status can result in a reduction of postoperative infectious complications [7].

Lorenzon et al. [8] conducted a study involving 1,648 patients who underwent digestive tract surgery, of which 1,041 were colorectal cancer patients. The authors discovered a significant interrelation among ERAS care, minimally invasive surgery (MIS), and nutritional screening. They found that these factors significantly impacted 30-day mortality and LOS.

3. Preoperative issues

1) Bowel preparation

There are ongoing debates regarding the method and impact of bowel preparation in relation to surgical site infection (SSI). The ASCRS guidelines typically recommend the use of MBP in conjunction with preoperative oral antibiotics prior to elective colorectal surgery. However, the 2019 ERAS Society guidelines suggest bowel preparation only as an optional measure for rectal surgery [4,5]. Consequently, in recent studies on ERAS in colorectal surgery, many researchers have incorporated a "no MBP" approach into their ERAS protocols.

Further research is needed to address several issues related to bowel preparation. These

include the development of less invasive and more comfortable methods for MBP that do not significantly disturb homeostasis prior to surgery. Additionally, the selection of suitable oral antibiotics, the determination of the most beneficial bowel preparation method in MIS, and the investigation of pre- or probiotics that can aid in restoring the normal gut microbiome following bowel preparation and throughout perioperative care, all merit further investigation [9].

2) Preoperative oral carbohydrate loading

The recommendation to mitigate the detrimental effects of overnight fasting by consuming oral carbohydrates two hours prior to surgery is quite robust, and there is consensus between the two guidelines on this matter. However, there is a lack of evidence regarding this issue for patients with diabetes.

3) Surgical site infection prevention bundles

The ERAS Society guidelines incorporate a section on antimicrobial prophylaxis and skin preparation. In contrast, the ASCRS guidelines utilize a bundle concept, amalgamating various preoperative and intraoperative measures into a single comprehensive package. This discrepancy may stem from the ERAS Society guidelines' uncertainty regarding the validity of each prophylactic item, as they evaluated the evidence for each individually. Recent evidence suggests that various SSI prevention bundles are effective in reducing SSI. Notably, the prevention effect increases with higher adherence to the various bundle items [10].

4) Postoperative nausea and vomiting

Guidelines suggest the preventive use of anti-emetic agents, combining two or more with different mechanisms, prior to surgery. An observational study involving 806 consecutive patients enrolled in the colorectal ERAS program demonstrated the varied use of these agents and the outcomes achieved through multimodal approaches [11]. In this study, the incidence of postoperative nausea and vomiting (PONV) was reported as 7%, 7%, and 10% on postoperative days 0, 1, and 2, respectively. However, the authors stressed the need for further development, as the increased rate of PONV on the second postoperative day led to an extended LOS by two nights due to poor oral intake and a delayed soft diet.

4. Intraoperative issues

1) Fluid management

The recommendations of both guidelines for perioperative fluid therapy are similar, and the summary is as follows: The first choice is typically a balanced chloride-restricted crystalloid, with the general aim being to maintain euvolemic status. For high-risk patients, or during high-risk procedures that may result in significant intravascular losses, goal-directed fluid therapy can be employed. If there are no surgical complications and the patient remains hemodynamically stable post-surgery, fluid therapy should be discontinued as soon as possible.

In this regard, recent studies [12–14] have investigated whether the risk of acute kidney injury (AKI) increases when applying the ERAS protocol (Table 2). These studies explored the association between AKI and patients undergoing colorectal surgery with ERAS perioperative care. Despite similar baseline characteristics, the incidence of AKI was consistently higher in the ERAS group compared to the non-ERAS group, resulting in an increase in complications. Additionally, the LOS was longer for AKI patients within the ERAS group.

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Table 2. Studies dealing with the occurrence of acute kidney injury among colorectal surgery patients receiving enhanced recovery after surgery perioperative care

Author	Year	Study design	Group	No. of patients	Population	AKI (%)	LOS (days)	LOS (days) of AKI patients vs. non-AKI in ERAS group	Other significant factors for AKI
Marcotte et al. [12]	2018	Retrospective cohort	ERAS vs. matched pre-ERAS	132 vs. 132	Colorectal resection (laparoscopy: 72.3%)	11.4 vs. 2.3, P<0.0001	5.5 vs 7.7, P<0.0001	8.40 vs. 5.11 (P=0.0037)	
Wiener et al. [13]	2020	Retrospective cohort	ERAS vs. pre-ERAS (in the NSQIP registry)	572 vs. 480	Colorectal resection	13.64 vs. 7.08, (OR 2.31, 95% CI 1.48–3.59, P<0.01)	7 (5–12) vs. 3 (2–6), P<0.01	Median 4 (IQR 4–9) vs. 3 (2–5), P=0.04	Smoking, ASA grade ≥3
Drakeford et al. [14]	2022	Retrospective cohort	AKI vs. non-AKI	n=555	Colorectal surgery +ERAS	13.4 (stage I: 11.2%, II: 2.0%, III: 0.2%)		Median 11 (IQR 5–17) vs. 6 (4–8), P<0.001	High preoperative creatinine level, open surgery, long anesthesia duration, major complications
Shim et al. [15]	2020	Retrospective cohort	(Intraoperative) oliguria* vs. matched non-oliguria	125 vs. 125	Laparoscopic colorectal cancer resection+ERAS	26.4 vs. 11.2, (OR 2.708, 95% CI 1.354 –5.418, P=0.005)			

AKI, acute kidney injury; LOS, length of hospital stay; ERAS, enhanced recovery after surgery; NSQIP, National Surgical Quality Improvement Program; ASA, American Society of Anesthesiologists.
*Defined as <0.5 mL/kg/h.

However, in a study by Drakeford et al. [14], which analyzed 555 patients undergoing laparoscopic colorectal resection with the ERAS protocol, it was highlighted that while 13.4% of AKI cases occurred, only 2.2% of these were moderate to severe AKI (as classified by the Kidney Disease Improving Global Guidelines stage 2 and 3). The authors noted that many similar studies often neglect to provide detailed information on ERAS adherence, such as whether preoperative oral carbohydrate loading was carried out or the volume of perioperative fluid administered (including oral intake). This omission makes it challenging to accurately interpret or compare the results. However, the findings of this study revealed that even though 83.6% of the cases were mild AKI (stage 1), the major complication and 1-year mortality rates were significantly higher than in patients who did not develop AKI.

Another study [15] compared 125 patients experiencing intraoperative oliguria (<0.5 mL/kg/h) during laparoscopic colorectal cancer surgery with ERAS perioperative care to another 125 patients, matched based on propensity scores. The findings indicated a significantly higher occurrence of AKI in the oliguria group, which was associated with an increased rate of surgical complications (18.4% vs. 9.6%, P=0.045). Consequently, it is crucial to adhere to the ASCRS guidelines. These guidelines emphasize the importance of avoiding a mean arterial pressure of less than 65 mmHg during the perioperative period, maintaining euvolemia, and properly addressing or preparing for the risk factors of AKI as identified in various studies.

2) Surgical approach

MIS is associated with fewer wound-related complications, reduced pain, and faster recovery compared to open surgery, all of which contribute to improved adherence to ERAS. Consequently, both ERAS Society guidelines advocate for the implementation of MIS where

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feasible. There is an increasing interest within the MIS field to investigate whether technological advancements have resulted in variations in the effectiveness of ERAS protocols across different methods. Recent studies have examined whether single-port laparoscopic surgery and robotic surgery have a more beneficial impact on ERAS than conventional laparoscopic surgery (Table 3).

Research on robotic surgery has yielded conflicting results. In patients who underwent robotic right colonic resection with intra-corporeal anastomosis, there was no difference in postoperative complications and LOS, but the operation time was notably longer compared to those who underwent laparoscopic surgery [16]. Conversely, a large-scale population cohort study by Asklid et al. [17] and a study by Hung [18] that tracked the increasing rate of robotic surgery over time, found that robotic surgery was significantly associated with a reduced LOS. Furthermore, Hung's study indicated that a higher rate of robotic surgery was associated with greater adherence to the ERAS protocol.

This discrepancy in study results may be due to the differences in the surgical sites examined in each study. Robotic surgery tends to offer more advantages if the lesion is closer to the anus, as it facilitates precise operations within the narrow confines of the pelvis, thereby promoting quicker recovery. Conversely, in right colonic surgery, which is performed in the abdominal cavity, robotic surgery does not present a clear advantage over laparoscopic surgery.

With advancements in laparoscopic techniques and tools, single-incision laparoscopic

Table 3. Studies investigating the effect of new surgical techniques among the patients who underwent colorectal surgery with an enhanced recovery after surgery protocol

Author	Year	Study design	Technique	No. of patients	Population	LOS	Complications	Other notes
Migliore et al. [16]	2021	Retrospective cohort	Lap. vs. Robot	170 vs. 46	Right hemicolectomy with intracorporeal anastomosis +ERAS	OR 0.16, 95% CI 0.79–1.10, P=0.74	No difference	No difference in conversion, readmission, 30-day morbidity, and major morbidity. Operative time was longer in robotic surgery (P<0.001)
Asklid et al. [17]	2022	Retrospective cohort (the Swedish part of the international ERAS Interactive Audit System)	Open vs. Lap. vs. Robot	3,125 (1,429 vs. 869 vs. 827)	Rectal tumor resection +ERAS	Robotic was the shortest (median 9 vs. 7 vs. 6 days)	No difference (40.9% vs. 31.2% vs. 35.9%)	Similar preoperative and intraoperative compliance to the ERAS protocol
Hung et al. [18]	2023	Retrospective cohort	Lap. vs. Robot	155 (31 cases/ quintile)	Colorectal resection +ERAS	For ≤5 days, robotic surgery: OR 5.029, 95% CI 1.321–19.421, P=0.018		The more recent the period, the higher the rate of robotic surgery, the higher median compliance rate of ERAS protocol, and the shorter LOS.
Kim et al. [19]	2019	Retrospective cohort	Lap./ERAS vs. SILS/Cv. Lap./Cv.	91 vs. 83 vs. 96	Colon cancer	ERAS was a significant factor (in multiple regression analysis, P<0.001)	No difference among the groups	No difference in reoperation and readmission among the groups

LOS, length of hospital stay; Lap., laparoscopic surgery; ERAS, enhanced recovery after surgery; SILS, single incision laparoscopic surgery; Cv., conventional perioperative treatment.

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surgery (SILS) has also been developed. Some studies have compared operative outcomes among various combinations of surgical methods and conventional or ERAS care [19,20]. Although no difference was observed in complications or readmission rates, the group that received ERAS care demonstrated a significantly shorter LOS than the other two groups receiving conventional perioperative care. This was according to a study comparing outcomes among three groups: multiport laparoscopy+ERAS care, SILS+conventional care, and multiport laparoscopy+conventional care. In the multivariable analysis, perioperative ERAS care was a significant factor in reducing LOS, while SILS was not. Another study [20] compared SILS and multiport laparoscopic surgery while implementing ERAS perioperative care in gastric cancer cases. However, only the C-reactive protein level was significantly lower in the SILS group on the third postoperative day. No differences were identified in complications, recovery time for walking/eating after surgery, and LOS.

However, even in the case of laparoscopic appendectomy, which typically has a relatively short LOS, a study found that the LOS of the SILS group was significantly shorter than that of the multiport group within the same ERAS protocol [21]. Furthermore, the application of SILS has been extended to various procedures [22]. Therefore, additional research is needed to evaluate the impact of SILS on the outcomes of ERAS perioperative care in diverse types of surgery.

5. Postoperative issues

1) Pain management

A multimodal, opioid-sparing pain management approach, which can facilitate early postoperative ambulation without adversely affecting bowel movement recovery, is one of the most crucial and highly recommended components of the ERAS protocol. Thoracic epidural analgesia (TEA), once a significant protocol, is now only considered for open surgery due to potential side effects and diminished effectiveness in laparoscopic surgery.

Recent studies have highlighted potential analgesic procedures or agents that could serve as alternatives to TEA. This is because methods previously effective in open surgery may no longer yield significant differences, given the rise of MIS and the multimodal analgesic pain management approach of ERAS.

The guidelines mention the transversus abdominis plane block. A randomized controlled trial (RCT) compared its effects with TEA using only ropivacaine without opioids. The total opioid consumption up to 48 hours post-surgery was found to be similar (29 mg vs. 40 mg, P=0.3) [23]. There was no significant difference in the time to first postoperative bowel movement, complications, or LOS among patients who underwent laparoscopic colon resection and followed the same ERAS protocol, with the exception of the regional block method used. However, the authors favored the transversus abdominis plane block, which demonstrated superior analgesia over time post-surgery, over TEA, whose efficacy has been questioned in existing studies.

An RCT [24] focusing on the quadratus lumborum block found no significant reduction in postoperative opioid use (129 mg vs. 127.2 mg in the first 24 hours, P=0.93) with this block. Furthermore, it did not accelerate recovery when compared to a placebo in the context of laparoscopic colon resection with ERAS perioperative care.

2) Other ileus-prevention items

In addition to multimodal pain management, ERAS incorporates a variety of measures to prevent postoperative ileus. These measures, commonly recommended in guidelines, include

early ambulation, prompt resumption of diet, timely withdrawal of fluids, early removal or avoidance of nasogastric tubes, early removal of urinary catheters, and minimal use of drains.

Sato et al. [25] analyzed 289 patients who had undergone surgery for colorectal cancer following the ERAS protocol. Their objective was to determine which elements of the ERAS protocol primarily influenced complications and LOS. They discovered that ceasing intravenous fluid infusion on the first postoperative day was a significant factor associated with complications and LOS. Additionally, they found that preventing intraoperative fluid overload (less than 2 L) had a substantial impact on LOS. This underscores the importance of fluid therapy within the ERAS protocol.

Regarding the timing of postoperative urinary catheter removal, the ERAS Society guidelines recommend 1–3 days after elective colorectal surgery, while the ASCRS guidelines recommend catheter removal within 24 hours for colon-upper rectal resection and within 24–48 hours after mid-lower rectal surgery. Meillat et al. [26] reported the outcomes of Foley catheter removal on the third postoperative day in 135 patients who underwent surgery under the ERAS protocol, in accordance with the ERAS Society recommendation. This study found successful removal in 88.9% of cases, with risk factors for failure including obesity, an American Society of Anesthesiologists grade greater than II, anti-aggregation platelet medication, absence of anastomosis, and extended operation time. Although the study demonstrated that early removal of the primary catheter could be safely carried out, it also revealed that 5 out of 7 patients who experienced failure developed a urinary tract infection, and 2 experienced urinary retention. This suggests a need for even more prompt removal.

Schreiber et al. [27] compared patients who underwent colorectal surgery and were administered the same ERAS protocol. These patients were divided into two groups based on the timing of Foley catheter removal. Approximately 73% of the patients in this study underwent open surgery, and TEA was applied to all patients. The conventional group, consisting of 116 patients, had the Foley catheter removed when TEA was terminated. Conversely, the catheter was removed on the first postoperative day in the early removal group. Although the early removal group experienced a higher rate of urinary retention (7.8% vs. 2.6%), the incidence of catheter-related urinary tract infections was significantly higher in the conventional treatment group (30.4% vs. 13.8%). This suggests that early removal of the catheter is a feasible option.

3) Discharge criteria

The ASCRS guidelines deal with discharge criteria, whereas the ERAS Society guidelines do not. Until now, the readiness for discharge in patients receiving colorectal ERAS perioperative care has typically been assessed based on factors such as bowel recovery, the ability to tolerate an oral diet, effective pain management, and self-mobility. However, these conditions may only be met 1–2 days post-surgery. In a study of 788 ERAS colorectal surgical patients, Biondi et al. [28] compared 146 (18.5%) who were discharged within 72 hours post-surgery to the remaining patients. They reported that over 80% adherence to ERAS was a positive factor for early discharge. Conversely, living outside the hospital area, being female, having a long operation time, drain installation, a postoperative stay in the intensive care unit, and postoperative complications were identified as negative factors.

While some research has been conducted on the practice of discharging patients before bowel recovery is achieved, a key component of the general ERAS discharge criteria, this approach has gained more traction due to the scarcity of medical resources amid the COVID-19 pandemic. This protocol, often referred to as "same day discharge" (SDD), "ambulatory colectomy" (in the

context of colectomy), or "hyper-ERAS," involves discharging patients within 24 hours post-surgery. A systematic review [29] analyzed 38,854 patients who underwent elective colorectal surgery patients with the ERAS protocol, of whom 1,622 (4.2%) were managed using the SDD protocol. Of these, 1,590 (98%) successfully completed SDD. The authors concluded that, despite variability in the type of surgery or discharge criteria, SDD reduced LOS and enhanced patient satisfaction without increasing 30-day readmission or postoperative complications.

With advancements in surgical techniques, multimodal pain management, and video-telecommunication technology, the LOS in ERAS is progressively being minimized. Despite this, it remains crucial to carefully select patients using a scoring system. Additionally, providing an evidence-based, multi-dimensional team approach and close monitoring for adherence is essential. However, there is also a need for further patient education on how to respond to various medical situations that may potentially arise after discharge.

6. Outcomes of enhanced recovery after surgery

1) Effect of overall adherence on outcomes of enhanced recovery after surgery protocol

ERAS perioperative care typically encompasses approximately 20 distinct elements. The number of these elements that a patient successfully completes is referred to as compliance or adherence, which is significantly associated with surgical outcomes.

Table 4 summarizes recent studies on the outcomes of the ERAS protocol, based on adherence. The POWER study [30] conducted a prospective collection and analysis of the perioperative care protocol for local surgical procedures across 80 Spanish hospitals, using the ERAS items as a basis. This study, which involved 2,084 patients, categorized participants into quartiles according to their adherence to the standard ERAS protocol. The results showed that the top quartile, which had the highest adherence, demonstrated significantly better outcomes in terms of major complications (grade 3 or higher according to the Clavien-Dindo classification), overall complications, and mortality, than the bottom quartile.

Previously, a similar trend was observed in a smaller patient cohort (n=196) with major morbidity, anastomotic leakage, and overall LOS, when patients following the ERAS protocol were categorized according to their adherence rate (<80%, 80%–89%, and ≥90%) [31]. This observation raises the question of whether the ERAS protocol would yield optimal results if adherence reaches 100%. In a study conducted by Milone et al. [32], only 8.9% of patients achieved 100% adherence. However, even when adherence was above 75%, functional recovery indicators such as ambulation, bowel movement, and tolerable diet were significantly higher than in those who did not achieve this level of adherence.

Several studies have indicated that high adherence rates can positively impact not only short-term performance, but also oncologic outcomes. It has been reported that a high adherence rate (≥80%) significantly contributed to a favorable 3-year survival rate in patients who underwent laparoscopic colorectal cancer surgery with ERAS perioperative care [33]. The authors hypothesized that maintaining a low inflammatory state post-surgery through ERAS perioperative care could have contributed to improved survival outcomes.

Conversely, a study that included 3,830 patients undergoing colorectal surgery with ERAS perioperative care found no association between overall or postoperative adherence to the ERAS protocol and major morbidity or anastomotic leak [34]. Another study [35] involving 1,900 patients who underwent anterior resection found that neither preoperative nor intraoperative adherence rates were associated with anastomotic leak. Given that significant complications

Table 4. Studies investigating the association between adherence to the enhanced recovery after surgery protocol and outcomes

Author	Year	Study design	Group	No. of patients	Population	Main finding	Other notes
Ripollés-Melchor et al. [30]	2019	National multicenter prospective cohort	Adherence rate Q1 (>77.3%) vs. Q2 (>63.6%, <73.7%) vs. Q3 (>54.5%, <63.6%) vs. Q4 (<54.5%)	521×4	Colorectal surgery (MIS: 59.21%)	Q1 compared with Q4: moderate to severe complications (OR 0.34, 95% CI 0.25–0.46, P<0.001), overall complications (OR 0.33, 95% CI 0.26–0.43, P<0.001), mortality (OR 0.27, 95% CI 0.07–0.97, P=0.06).	Adherence to 22 ERAS items
Catarci et al. [31]	2020	Prospective cohort (two centers)	Adherence rate <80% vs. 80%–89% vs. ≥90%	196	Minimally invasive colorectal surgery	Overall morbidity (%/10): 5.1 vs. 3.7 vs. 2.9 (P=0.04), major morbidity (%/10): 2.2 vs. 0.3 vs. 0.3 (P=0.0002), anastomotic leakage (%): 14.7 vs. 2.8 vs. 2.5 (P=0.013), median overall LOS (days): 6 vs. 5 vs. 4 (P=0.05)	Mean adherence rate: 85.4%, a significant dose–effect curve for overall and major morbidity rates, anastomotic leakage rates and LOS
Milone et al. [32]	2022	National multicenter prospective cohort	Single-arm	1,138	Minimally invasive colorectal surgery	100% adherence: 8.9%, 75% adherence: 64.7%, Adherence of >75% was associated with significantly better functional recovery (90.2±98.8 vs 95.9±33.4 h, P=0.003)	Definition of functional recovery: complete mobilization+stool passage +tolerance of a solid diet
Pisarska et al. [33]	2019	Prospective cohort	Adherence rate <80% vs. ≥ 80%	109 vs. 241	Laparoscopic colorectal cancer resection	<80% compliance with ERAS protocol: a significant factor associated with poor 3-year survival (HR 3.38, 95% CI 2.23–5.21, P=0.0102)	<80% adherence was associated with a longer hospital stay (6 vs. 4 days, P<0.0001), higher rate of postoperative complications (44.7% vs. 23.3%, P<0.0001), poor functional recovery parameters on POD #1: tolerance of oral diet (53.4% vs. 81.5%, P<0.0001) and mobilization (77.7% vs. 96.1%, P<0.0001)
Catarci et al. [34]	2022	Multicenter prospective cohort	Single-arm	3,830	Colorectal surgery (MIS: 79.7%)	Overall or postoperative ERAS adherence higher or lower than the median level was not significant for major morbidity or anastomotic leak	Significant factors for major morbidity: perioperative transfusion (OR 7.79, 95% CI 5.46–11.10; P<0.0001), standard anesthetic protocol (OR 0.68, 95% CI 0.48–0.96; P=0.028) Significant factors for anastomotic leak: male sex (OR 1.48, 95% CI 1.06–2.07; P=0.021), perioperative transfusions (OR 4.29, 95% CI 2.93–6.50; P<0.0001), non-standard resections (OR 1.49, 95% CI 1.01–2.22; P=0.049)
Asklid et al. [35]	2021	Retrospective cohort (the Swedish part of the international ERAS Interactive Audit System)		1,900	Anterior resection	Effect of mean preoperative and intraoperative compliance rate to ERAS on anastomotic leak: OR 0.99, 95% CI 0.97–1.01	Significant predictors for AL in multivariate analysis: male sex, obesity, peritoneal contamination, year of surgery 2016–2020, age, duration of primary surgery

MIS, minimally invasive surgery; ERAS, enhanced recovery after surgery; LOS, length of hospital stay; POD, postoperative day; AL, anastomotic leak.

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after surgery may already indicate low adherence to postoperative ERAS items, it seems reasonable to exclude postoperative adherence when calculating the overall adherence rate.

The inconsistent results can be attributed to the fact that these studies are observational, each employing a different ERAS protocol (e.g., bowel preparation policy). There may have been shifts in emphasis on certain items or surgical techniques over the course of the study, and adherence may vary depending on the location of colorectal disease. Additionally, each item may have a different degree of impact on the outcome [36]. Future well-designed research taking into account the factors mentioned above is warranted.

7. Enhanced recovery after surgery in specific situations

1) Enhanced recovery after surgery for elderly patients

ERAS perioperative care requires a multidisciplinary team approach. The ability to introduce, sustain, and enhance ERAS protocols is indicative of a relatively advanced stage in a society's healthcare system. In such developed societies, the proportion of elderly patients is bound to increase. For instance, in South Korea, one of the fastest-aging societies, a study conducted on 4,326 patients with colorectal cancer from 2006 to 2019 found that 23.9% were aged between 70 and 79, while 7.5% were 80 or older [37]. Research has indicated that aging is a significant factor contributing to ERAS failure, such as complications or increased LOS. This is because aging can often be accompanied by a decline in physical function, the presence of comorbidities, and malnourishment [38]. Furthermore, older patients exhibited a high incidence of postoperative ileus and a relatively high rate of stoma formation. These conditions can be associated with high output and may increase the likelihood of low adherence to the ERAS protocol [39].

In patients who underwent colorectal surgery with ERAS perioperative care, studies [40–42] have shown that adherence with individual items tends to be lower in elderly patients compared to younger ones, leading to an increase in LOS and overall complications. However, there was no difference in major complications (as classified by Clavien-Dindo grade 3 or higher) and no significant difference in overall adherence between the two age groups. A recent study [42] found no difference in complications or LOS between patients aged 70 or older and younger patients, despite a significantly higher rate of comorbidities in the elderly (Table 5).

Studies comparing elderly patients who underwent colorectal surgery divided into ERAS and non-ERAS groups have demonstrated the validity of implementing ERAS perioperative care in elderly patients. Tejedor et al. [43] compared the outcomes of 156 ERAS patients aged 70 or older with 156 non-ERAS patients matched based on age, sex, location (colon or rectum), and temporary stoma. They found a significantly shorter LOS and a significantly lower complication rate in the ERAS group. Notably, the rate of adherence to the ERAS protocol was only 42%. Martínez-Escribano et al. [44] compared colorectal surgery outcomes before and after the introduction of ERAS in patients over 70 years of age. They reported a significant decrease in postoperative ICU admissions and transfusions in the ERAS group, although there was no observed decrease in complications and LOS.

While the benefits of ERAS are less pronounced in the elderly compared to younger patients, there is still a distinct advantage in applying ERAS perioperative care when compared to conventional care in the same elderly population. Therefore, the implementation of ERAS should be considered in appropriately selected elderly patients.

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Table 5. Studies on the enhanced recovery after surgery protocol in elderly colorectal resection patients

Author	Year	Study design	Group	No. of patients	Population	LOS	Complications	Other notes
Pedrazzani et al. [40]	2019	Retrospective cohort	Aged ≤65 vs. 66–75 vs. ≥76	112 vs. 57 vs. 56	Laparoscopic colorectal resection +ERAS	No difference	Overall: 25.9% vs. 36.8% vs. 42.9%, Major: 4.5% vs. 3.5% vs. 1.8% (NS) anastomotic leak : 2.7% vs. 1.8% vs. 1.8% (NS)	Lower compliance in the elderly group with early ambulation, early Foley removal, stopping fluids, and opiate avoidance
Chan et al. [41]	2020	Retrospective cohort	Aged <65 vs. ≥65	75 vs. 97	Colorectal cancer resection (laparoscopy 83.7%)	6.7 vs. 10.9 days, P=0.007	16.0% vs. 33.0%, P=0.011	Deviation from ERAS: 6.7% vs. 15.5% (P=0.074)
Koh et al. [42]	2022	Retrospective cohort	Aged ≤70 vs. >70	237 vs. 98	Colorectal cancer surgery (MIS: 95.8%)	No difference	Morbidity calculated by the CCI score, no difference	Significantly more comorbidities in the older group
Tejedor et al. [43]	2018	Retrospective cohort	ERAS vs. non-ERAS (case-matched)	156 vs. 156	Colorectal surgery, aged ≥70 (laparoscopy 59% vs. 21%, P<0.0001)	6 (5.25) vs. 8 (6.75) days P<0.0001	Major complications: 10.3% vs. 21.8%, P=0.020 Mortality: 1.9% vs. 11.5%, P=0.001	Compliance with the ERAS protocol in the ERAS group: 42%
Martínez -Escribano et al. [44]	2022	Retrospective cohort	Pre-ERAS vs. ERAS	158 vs. 213	Colorectal cancer resection (aged ≥70, laparoscopy 46.5% vs. 65.7%)	No difference, lower ICU admission in ERAS (OR 0.42, 95% CI 0.27–0.65, P<0.001)	No difference	A lower transfusion rate in ERAS (OR 0.26, 95% CI 0.14–0.48, P<0.001)

LOS, length of hospital stay; ERAS, enhanced recovery after surgery; NS, no significance; CCI, Charlson comorbidity index; MIS, minimally invasive surgery; ICU, intensive care unit.

2) Spread of enhanced recovery after surgery coverage and circumstances

In light of consistent reports on the short- and long-term effects of ERAS, it is being applied to a variety of diseases and situations beyond the realm of elective colorectal surgery, as well as in a wider range of countries. A brief assessment of this evolving status provides valuable insights into the future direction of ERAS development.

In the field of colorectal surgery, ERAS protocol adoption was reported in clinically suspected T4 colorectal cancer [45] and in Crohn's disease [46], for which surgery is relatively difficult and the complication rate is higher. An RCT [47] reported that the application of modified ERAS reduced PONV, SSI, and LOS (by about 3 days) even when open laparotomy was performed as an emergency procedure in cases of perforation peritonitis, as opposed to being elective. In these instances, the ERAS protocol differs from that of elective surgery in that a nasogastric tube is routinely inserted prior to surgery, and a liquid diet is resumed following the first passage of flatus. However, key characteristics such as non-opioid multimodal analgesia, expedited resumption of ambulation, and swift drain removal are preserved as part of the standard ERAS protocol.

The utility of ERAS, as reported in numerous medical scenarios, extends beyond large hospitals to also include small and medium-sized hospitals [48]. Even in countries where healthcare systems are not yet fully developed, ERAS [49] is becoming more widespread [50].

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3) Future directions

As discussed above, the adoption of ERAS is expanding across a range of diseases, medical scenarios, and diverse types of medical institutions and societies. Furthermore, the evolution of various medical and surgical techniques, aging, and the emergence of pandemics are generating new evidence. While the principle of ERAS is proliferating and being adapted for various situations, this not only benefits many patients and reduces social costs, but it can also complicate comparisons and analyses between studies when determining the most appropriate and effective changes.

It is necessary to establish and develop ERAS protocols tailored to specific institutions and diseases, based on international guidelines. However, it is equally important to create a network with a system capable of assessing the scientific validity of any modifications, while also selecting and managing essential items that are recorded.

Conclusion

The treatment of surgical patients necessitates a multidisciplinary approach that extends beyond surgical techniques. In response to societal changes, there is a need for treatments that can optimize the use of medical resources while ensuring the best outcomes for patients. Familiarity with the guidelines for ERAS perioperative care, as well as an understanding of the latest relevant research, can provide a solid foundation for systematically addressing these needs. To maximize the effectiveness of ERAS, it is crucial that medical staff fully comprehend the clinical basis and significance of each component. Furthermore, the protocol must be consistently upheld and progressively developed through team-based approaches and an audit system.

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Conflict of Interest

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Review Article

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Inflammatory Response Markers as Predictors of Colorectal Cancer Prognosis

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Colorectal neoplasms; Inflammatory response marker; Prognosis

Colorectal cancer (CRC) is a globally prevalent and challenging malignancy. Accurate prognosis prediction is essential for optimizing patient care. This comprehensive review discusses the intricate relationships between inflammatory response markers and CRC prognosis. Inflammatory response markers have gained prominence as a prognostic tool. Elevations in the preoperative neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and C-reactive protein-albumin ratio predict a poor prognosis for patients with CRC. A decreased lymphocyte-monocyte ratio is also a poor prognostic factor. A high Glasgow prognostic score and a high modified Glasgow prognostic score are associated with adverse outcomes, including reduced survival. While significant progress has been made, challenges remain in standardizing the clinical application of these inflammatory response markers. Prospective research and further investigations are warranted to refine the prognostic models. Enhanced understanding and utilization of these inflammatory response markers will help advance personalized treatment strategies, refine surveillance protocols, and improve the management of CRC.

Introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed malignancies and a leading cause of cancer-related death worldwide [1,2]. Advances in screening and treatment modalities have improved the survival of patients with CRC; however, the mortality rate remains high in cases of metastasis or recurrence [1,3]. The complexity of tumor progression—including, for instance, tumor heterogeneity, resistance mechanisms, genetic alterations, and micromolecular biology—contributes to the difficulty of achieving improvements in prognosis; therefore, more sophisticated and tailored treatment strategies are needed [4–7]. It is thus important to identify factors associated with a poor prognosis in patients with CRC. The conventional prognostic model for CRC is the TNM staging system, which was proposed by the American Joint Committee on Cancer. Clinical characteristics and additional pathologic features are also used to predict the patient's prognosis [5,6,8,9]. However, patients with a similar clinicopathologic status and staging may have different prognoses.

Biomarkers are quantifiable and measurable indicators that reflect normal biological processes, pathological conditions, or responses to therapeutic interventions. Biomarkers serve as diagnostic tools that provide early disease detection and act as prognostic markers to offer insights into disease progression and potential outcomes [9–12]. Inflammatory response markers, which are among the most easily measurable biomarkers, reflect the body's immune response and provide

insights into the tumor microenvironment and its impact on the prognosis of CRC. Numerous previous studies have reported that inflammatory response markers, such as the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR), can be useful for predicting the CRC prognosis [3,10,13,14]. The purpose of this study was to review inflammatory response markers that, according to current research, exhibit potential for predicting the prognosis of patients with CRC. This review summarizes the inflammatory response markers that can be obtained from routinely performed blood tests before CRC treatment, with the aim of offering an understanding of how inflammatory response markers may predict the prognosis of CRC and contribute to advances in the field of precision medicine in CRC [7].

Inflammatory Response Markers

1. Inflammation and cancer

Chronic inflammation has been recognized as an important factor in cancer initiation and progression [15]. It induces tissue damage, in response to which cell proliferation is activated as a part of the healing process. When chronic inflammation persists, there is a repeated cycle of tissue damage and regeneration, leading to the occurrence of genetic mutations. Inflammatory cells, such as macrophages and T cells, secrete cytokines and chemokines in response to tissue damage [16]. These signaling molecules (such as tumor necrosis factor-alpha and CXCL8) can affect tumor biology, including growth, migration, and differentiation, by releasing growth factors, promoting angiogenesis, and causing DNA damage [17]. Table 1 summarizes the inflammatory response markers and the prognosis of CRC.

2. Neutrophil-lymphocyte ratio

The NLR is a widely used biomarker to predict prognosis in CRC; it is defined as the absolute neutrophil count divided by the absolute lymphocyte count. Several studies have shown that a high preoperative NLR is associated with a poor prognosis in patients with stage I–III CRC who underwent curative resection. The cutoff values were different depending on the study and ranged from 2.05–5.00 [18–23]. Chiang et al. analyzed 3,857 patients with stage I–III CRC who underwent curative resection and found that a preoperative NLR>3 was a significant predictor of disease-free survival (DFS) [18]. Li et al. reported that a preoperative NLR>2.72 was associated with significantly lower DFS and overall survival (OS) rates in 5,336 patients with stage I–III CRC who underwent curative resection [21]. Some studies have concluded that a high preoperative NLR predicted a poor prognosis in patients with CRC who underwent curative-intent resection, including stage IV patients [23,24]. Song et al. reported that a preoperative NLR>2 was associated with lower cancer-specific survival (CSS) and OS rates in patients with stage I–IV CRC who underwent resection [23]. Several studies have focused on high NLR values and the prognosis of rectal cancer [25–28]. Zhang et al. analyzed 472 patients with advanced rectal cancer who underwent preoperative chemoradiotherapy followed by curative resection. A high NLR before chemoradiotherapy was significantly associated with worse DFS and OS [26]. Yosida et al. reported that a preoperative NLR>2.58 was associated with a lower DFS in patients with stage I–II rectal cancer who underwent curative resection [27]. Other studies have focused on high NLR values and the prognosis of colon cancer [28,29]. Hung et al. analyzed 1,040 patients with stage II colon cancer who underwent curative resection and found that a preoperative NLR>5 was associated with a lower OS rate [29].

Several studies have investigated the role of pretreatment NLR in colon cancer with distant

metastasis [30–33]. A study by Halazun et al. demonstrated that a preoperative NLR>5 had a poor prognostic impact in patients with concurrent CRC liver metastasis who underwent curative-intent resection [30]. Mao et al. analyzed 183 patients who were diagnosed with CRC with liver metastasis and performed neoadjuvant chemotherapy followed by surgery. An NLR>2.3 before chemotherapy was associated with poor recurrence-free survival and OS [31]. Casadei-Gardini et al. performed a randomized-controlled trial in patients with Stage IV CRC who underwent chemotherapy and reported that a pretreatment NLR>3 was associated with poor progression-free survival and OS [33] .

Table 1. Inflammatory response markers associated with the prognosis of CRC

Author	Year	Population	Patients (n)	Main outcome	HR (95% CI)	P-value	Cut-off
Neutrophil–lymphocyte ratio							
Halazun [30]	2008	CRLM following curative-intent resection	440	DFS	2.26 (1.65–3.13)	<0.001	5
Ding [28]	2010	CC following curative resection (stage IIA)	141	RFS	4.88 (1.73–13.75)	0.003	4
Hung [29]	2011	CC following curative resection (stage II)	1,040	OS	1.29 (1.07–1.80)	0.012	5
Chiang [18]	2012	CRC following curative resection (stage I-III)	3,857	DFS	1.31 (1.09–1.57) (especially CC)	0.013	3
Guthrie [19]	2013	CRC following curative resection (stage I-III)	206	CSS	3.07 (1.23–7.63)	<0.05	5
Malietzis [20]	2014	CRC following curative resection (stage I-III)	506	DFS	2.41 (1.12–5.15)	0.024	3
Nagasaki [25]	2015	RC following nCRT and curative resection (stage I-III)	201	OS	3.38	0.012	3
Li [21]	2016	CRC following curative resection (stage I-III)	5,336	DFS OS	1.20 (1.05–1.37) 1.23 (1.01–1.50)	0.009 0.047	2.72
Song [23]	2017	CRC following resection (stage I-IV)	1,744	CSS OS	0.74 (0.57–0.95) 0.76 (0.60–0.96) (reference: NLR≥2)	0.018 0.021	2
Pedrazzani [24]	2017	CRC following curative resection (stage I-IV)	603	CSS OS	1.22 (0.77–1.93) 1.15 (0.86–1.54)	0.40 0.003	3.5
Mao [31]	2019	CRLM following nCT and resection	183	RFS OS	1.53 (1.08–2.18) 2.43 (1.49–3.94)	0.017 <0.001	2.3
Casadei-Gardini [33]	2019	CRC following CT (stage IV)	276	PFS OS	2.27 (1.59–3.23) 14.4 (11.4–17.1)	<0.001 <0.001	3
Inamoto [22]	2019	CRC following curative resection (stage I-III)	448	DFS CSS OS	1.71 (1.12–2.66) 2.11 (0.96–5.05) 2.04 (1.11–3.96)	0.01 0.06 0.02	2.05
Erstad [32]	2020	CRLM following curative-intent resection	151	OS	2.46 (1.08–5.60)	0.032	5
Yosida [27]	2020	RC following curative resection (T1-2)	151	DFS	5.11 (1.84–16.4)	0.002	2.58
Zhang [26]	2020	RC following nCRT and curative resection (stage II-III)	472	DFS OS	1.71 (1.02–2.87) 1.80 (1.01–3.20)	0.044 0.046	2.3

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Table 1. Continued

Author	Year	Population	Patients (n)	Main outcome	HR (95% CI)	P-value	Cut-off
Platelet–lymphocyte ratio							
Pedrazzani [24]	2017	CRC following curative resection (stage I-IV)	603	CSS OS	1.64 (0.74–3.62) 1.86 (1.05–3.32)	0.22 0.034	350
Erstad [32]	2020	CRLM following curative-intent resection	151	OS	2.10 (1.04–4.23)	0.037	220
An [14]	2022	RC following nCRT and curative resection (stage I-III)	168	OS	1.79 (1.01–3.17)	0.047	170
Lymphocyte–monocyte ratio							
Li [21]	2016	CRC following curative resection (stage I-III)	5,336	DFS OS	0.77 (0.67–0.88) 0.76 (0.62–0.93)	<0.001 0.008	2.83
Chan [35]	2017	CRC following curative resection (stage I-III)	1,623	OS	0.57 (0.48–0.68)	<0.001	2.38
Chen [37]	2019	Obstructive CRC with stent insertion following resection	128	DFS OS	0.42 (0.17–1.07) 0.40 (0.18–0.92)	0.068 0.031	1.67
Glasgow prognostic score							
Choi [39]	2014	CRC following resection (stage I-IV)	105	CSS	5.17 (1.76–15.18)	0.003	
Inamoto [22]	2019	CRC following curative resection (stage I-III)	448	DFS CSS OS	1.68 (1.03–2.67) 2.17 (1.03–4.49) 1.73 (0.97–3.02)	0.04 0.04 0.06	
Lee [40]	2020	CRC following curative-intent resection (stage I-IV)	1,590	DFS OS	1.71 (1.23–2.38) 2.34 (1.62–3.39)	0.001 0.001	
Modified Glasgow prognostic score							
Leitch [43]	2007	CRC following curative-intent resection (stage I-IV)	149	CSS	1.44 (1.01–2.04)	0.043	
Roxburgh [41]	2009	CRC following curative resection (stage I-III)	287	CSS	2.65 (1.66–4.25)	<0.001	
Park [44]	2016	CRC following curative-intent resection (stage I-IV)	1,000	CSS OS	1.28 (1.09–1.52) 1.28 (1.13–1.45)	0.003 <0.001	
Tokunaga [42]	2017	CRC following curative resection (stage I-III)	468	RFS OS	2.14 (1.40–3.24) 2.45 (1.53–3.88)	<0.001 <0.001	
Suzuki [45]	2018	CRC following curative-intent resection (stage I-IV)	727	OS	2.01	0.005	

CRC, colorectal cancer; HR, hazard ratio; CRLM, colorectal cancer with liver metastasis; DFS, disease-free survival; CC, colon cancer; RFS, recurrence-free survival; OS, overall survival; CSS, cancer-specific survival; RC, rectal cancer; nCRT, neoadjuvant chemoradiotherapy; NLR, neutrophil-lymphocyte ratio; PFS, progression-free survival.

3. Platelet-lymphocyte ratio

The PLR, which is defined as the ratio of the platelet count to the lymphocyte count, has also been suggested as a prognostic marker for CRC. Several studies have reported that a high preoperative PLR was associated with a poor prognosis in patients with CRC [24,32,34]. Pedrazzani et al. analyzed 603 patients with CRC who underwent curative resection and found that a preoperative PLR>350 was a significant predictor of CSS and OS [24]. Erstad et al. reported that a preoperative PLR>220 in patients with concurrent CRC liver metastasis who underwent curative-intent resection was associated with a worse OS [32].

4. Lymphocyte-monocyte ratio

The lymphocyte-monocyte ratio (LMR), which is defined as the ratio of the lymphocyte count to the monocyte count, can predict the prognosis of CRC. Several studies have shown that a high preoperative LMR is associated with a poor prognosis in patients with CRC who underwent curative resection [21,35,36]. Chan et al. analyzed 1,623 patients with stage I–III CRC and the prognostic impact of LMR. A preoperative LMR<2.38 was an independent prognostic factor and was superior to other biomarkers, such as the NLR and PLR [35]. Li et al. also reported that a preoperative LMR<2.83 was associated with lower DFS and OS in patients with stage I–III CRC who underwent curative resection [21]. A study by Chen et al. focused on obstructive CRC and the prognostic impact of the pretreatment LMR. An LMR<1.67 before endoscopic stenting was associated with poor DFS and OS [37].

5. Glasgow prognostic score and modified Glasgow prognostic score

The combination of a higher CRP value and hypoalbuminemia can be a sensitive biomarker for prognosis of CRC. The Glasgow prognostic score (GPS) is a useful scoring system for predicting the prognosis of patients with CRC, as well as other malignant tumors [38]. The GPS is based on the combination of hypoalbuminemia (<3.5 g/dL) and elevated CRP (>10 mg/L); if both are abnormal, the score is 2; if one or the other is abnormal, the score is 1; if neither is abnormal, the score is 0. Multiple studies have shown that a high GPS before surgery was associated with a poor prognosis for patients with stage I–III CRC who have undergone curative resection [22,38]. Choi et al. reported that a preoperative GPS of 2 was associated with a worse CSS in patients with stage I–IV CRC who underwent resection [39]. A study by Lee et al. evaluated 1,590 patients with CRC, including stage IV, who underwent curative-intent resection and revealed that a GPS of 1 or 2 was associated with DFS and OS rates [40]. The modified GPS (mGPS) is defined as follows: patients with a CRP level ≤10 mg/L and an albumin level ≥3.5 g/dL are scored as 0; those with a CRP level >10 mg/L are scored as 1; and those with a CRP level >10 mg/L and an albumin level <3.5 g/dL are scored as 2. Several studies have demonstrated that the preoperative mGPS was associated with the prognosis in patients with stage I–III CRC who underwent curative resection [41,42]. Roxburgh et al. reported that a preoperative mGPS of 1 or 2 was associated with lower CSS rates in patients with stage I–III CRC who underwent curative resection [41]. Other studies have evaluated the association between the prognosis of patients with CRC (including stage IV) who underwent curative-intent resection and had a preoperative mGPS [43–45]. Leitch et al. reported that a preoperative mGPS of 1 or 2 was associated with lower CSS rates in patients with stage I–IV CRC who underwent curative-intent resection [43]. A study by Park et al. analyzed 1,000 patients with stage I–IV CRC who underwent curative-intent resection and reported that a preoperative GPS of 1 or 2 was associated with poor CSS and OS [44]. A study by Suzuki et al. evaluated 737 patients with stage I–IV CRC who underwent curative-intent resection and concluded that a preoperative mGPS of 1 or 2 was associated with poor CSS [45].

Conclusion

In summary, our comprehensive review has shed light on the complex interplay between the prognosis of CRC and the roles of inflammatory response markers. These non-invasive biomarkers are easily accessible both before and after surgery. The findings discussed herein collectively highlight the critical significance of considering these inflammatory response

markers when assessing the clinical prognosis of patients with CRC.

The evidence presented suggests that elevated levels of inflammatory response markers are associated with a poor prognosis in patients with CRC. These markers reflect the systemic inflammation that often accompanies malignancies, as well as the intricate relationship between the tumor microenvironment and the host immune response. Incorporating these markers into clinical practice could enhance the precision of prognosis prediction and inform treatment decisions. When used in combination with clinical assessments, these markers offer valuable insight into the management of patients with CRC.

Despite significant progress in understanding the relationship between these inflammatory response markers and the prognosis of CRC, challenges remain. The heterogeneity of CRC and the influence of various factors on inflammatory response marker levels underscore the need for continued research. Prospective studies, multi-center trials, and the exploration of emerging inflammatory response markers hold promise for refining prognostic models and improving patient outcomes. Ultimately, the integration of these inflammatory response markers into the clinical evaluation of patients with CRC is a promising way to improve personalized treatment strategies, optimize surveillance protocols, and advance the field of CRC management. As our understanding of these inflammatory response markers continues to evolve, so will our ability to predict, prevent, and effectively treat malignancies.

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Conflict of Interest

Bo Young Oh serves as the editorial board members of the *Ewha Medical Journal*, but had no role in the decision to publish this article. No other potential conflict of interest relevant to this article was reported.

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Review Article

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How Can We Improve the Tumor Response to Preoperative Chemoradiotherapy for Locally Advanced Rectal Cancer?

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Preoperative chemoradiotherapy (pCRT) followed by total mesorectal excision is the accepted standard treatment for patients with locally advanced rectal cancer. The purpose of pCRT is to prevent the spread of viable tumor cells within the local area during surgical procedures. Additionally, pCRT can facilitate the resection of locally advanced tumors that are otherwise challenging to remove, thereby enabling a radical resection. Although a pathologic complete response is observed in fewer than 20% of patients, the reasons for the variability in tumor response to pCRT are not fully understood. Several techniques have been researched with the aim of improving the tumor response to pCRT. These techniques include intensifying or combining chemotherapy, either simultaneously or sequentially, increasing radiation dose, modifying radiation mode or schedule, adjusting the interval between radiation and surgery, and incorporating multiple agents to increase the efficacy of pCRT. This review discusses various strategies that may improve tumor response outcomes following pCRT.

Introduction

Rectal cancer is often diagnosed at a locally advanced stage and ranks as the third most common cancer globally. Despite significant efforts to enhance oncological outcomes for rectal cancer, the mortality rate associated with this disease in South Korea continues to increase [1].

Preoperative chemoradiotherapy (pCRT), followed by total mesorectal excision, is now considered the standard treatment strategy for patients with locally advanced rectal cancer (LARC) [2,3]. The purpose of pCRT is to inhibit the dissemination of locally viable tumor cells during surgery. Additionally, pCRT can facilitate the resection of locally advanced tumors that are difficult to remove, thereby enabling radical resection.

pCRT has become increasingly important in the treatment of tumors, offering a definitive alternative to radical surgery by achieving a complete response in some cases [4,5]. Although a small subset of patients with microsatellite instability has shown promising responses to immunotherapy [6], the response to pCRT remains a critical prognostic factor. Achieving a pathologic complete response (pCR) can significantly reduce the risk of local recurrence and improve both disease-free survival (DFS) and overall survival (OS) [2,4]. However, pCR is achieved in fewer than 20% of patients, and the reasons for the variability in tumor response to pCRT are not fully understood [2,7]. Consequently, further efforts are needed to improve tumor response to pCRT, which could help predict patient prognosis and tailor treatment strategies.

Several strategies have been researched with the goal of improving tumor response outcomes following pCRT, such as intensifying or combining chemotherapy agents either concurrently or sequentially, optimizing the radiation dose, delivery method, or schedule, adjusting the interval between radiation and surgery, or incorporating additional agents to enhance the efficacy of pCRT (Figs. 1, 2) [7–11]. This review investigates different approaches to enhance tumor response outcomes in patients with LARC after pCRT.

Radiotherapy

1. Pathological complete response

pCR is defined as the absence of viable tumor cells upon a gross histopathological examination of the resected specimen, classified as pT0N0M0 [12]. The tumor regression grade (TRG) serves as a method to categorize the primary tumor's response to pCRT by histopathologically assessing residual tumor cells and the extent of tumor regression and replacement. Various TRG classification systems are in use, including those by Mandard (1994), Dworak (1997; modified in 2003), the Memorial Sloan-Kettering Cancer Center (MSKCC) classification (2008), and the Ryan/American Joint Committee on Cancer (AJCC) 7th Edition (2010), as outlined in Table 1 [13–16].

The Mandard system is a TRG system used for esophageal carcinoma and other digestive tract malignancies. The TRGs in the Mandard classification are divided into five grades. Complete regression (CR) is designated as TRG1, characterized by fibrosis throughout multiple layers of the wall with an absence of viable cancer cells. The Dworak system classifies TRGs into four grades and defines CR as TRG4, which is identified by the lack of tumor cells and may include fibrotic masses or pools of cell-free mucus. Another classification system, currently

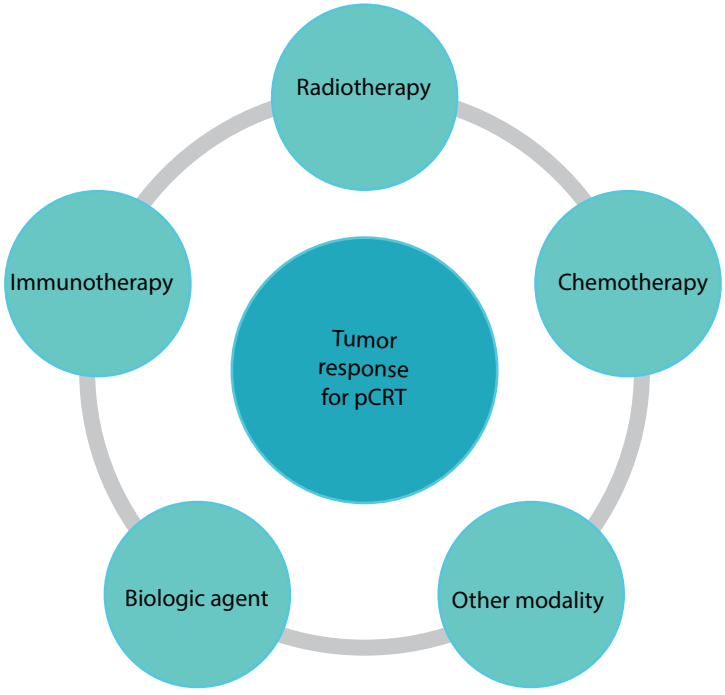

Fig. 1. Various techniques used to improve the tumor response to preoperative chemoradiotherapy. pCRT, preoperative chemoradiotherapy.

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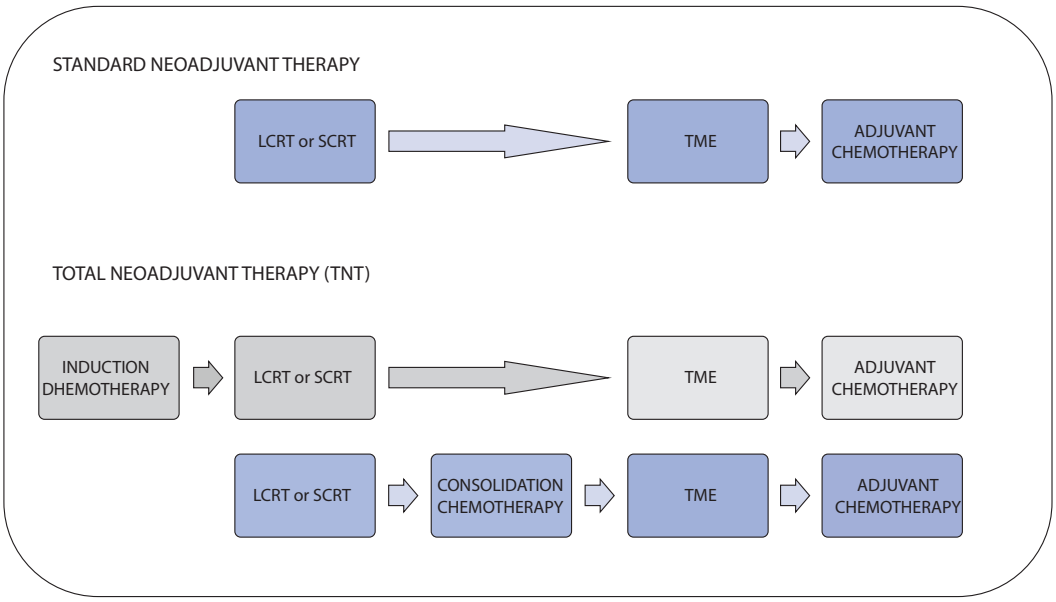

Fig. 2. Schematic overview of regimens for standard neoadjuvant therapy and total neoadjuvant therapy for locally advanced rectal cancer (LARC). LCRT, long-course chemoradiotherapy; SCRT, short-course chemoradiotherapy; TME, total mesorectal excision.

recommended by the AJCC, is the Ryan classification. This system also categorizes TRGs into four grades, with CR defined as TRG0, indicating the complete absence of viable cancer cells. Meanwhile, the MSKCC classification separates tumors into three groups based on the response

Table 1. TRG classification systems

TRG	TRG 0	TRG 1	TRG 2	TRG 3	TRG 4	TRG 5
Mandard		CR, no viable cancer cells, fibrosis extending through the different layers of the wall	Rare residual cancer cells scattered through the fibrosis	Increased number of residual cancer cells, fibrosis predominates	Residual cancer outgrowing fibrosis	Absence of regressive changes
Dworak	No response	Minimal response (dominant tumor mass with obvious fibrosis, vasculopathy); fibrosis <25% of tumor mass	Moderate response (dominant fibrotic changes with a few easy-to-find tumor cells in groups); fibrosis 25%–50% of tumor mass	Near CR (few microscopically difficult-to-find tumor cells in fibrotic tissue with or without mucous substance); fibrosis >50% of tumor mass	CR (no tumor cells, only fibrotic mass or acellular mucin pools)	
Ryan/AJCC	CR, no viable cancer cells	Near-CR, single cells, or rare small groups of cancer cells	Partial response, residual cancer with evident tumor regression but more than single cells or rare small group of cancer cells	Poor or no response, extensive residual cancer with no evident tumor regression		
MSKCC		100% tumor response	86%–99% tumor response	≤85% tumor response		

TRG, tumor regression grade; CR, complete response; AJCC, American Joint Committee on Cancer; MSKCC, Memorial Sloan-Kettering Cancer Center.

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rate and defines CR as TRG1, which corresponds to a 100% tumor response.

2. Dose of radiation

In theory, the effectiveness of pCRT could be enhanced by escalating the radiation therapy (RT) dose through external beam irradiation, brachytherapy, or contact therapy, shortening the overall treatment duration, or administering simultaneous consolidation boosts. Although multiple studies on pathological complete response (pCR) have shown a significant dose-response relationship for tumor regression following pCRT [8,9], randomized trials have not confirmed an increase in pCR rates with higher RT doses within pCRT [10]. A phase 3 randomized trial demonstrated a significant improvement in the primary endpoint, pCR [11], when comparing a novel regimen that included the addition of oxaliplatin and an increase to 50 Gy of external-beam RT, versus the standard pCRT treatment with capecitabine and 45 Gy. Modern RT techniques, including intensity-modulated RT, volumetric arc RT, and image-guided RT, can reduce the involvement of vulnerable organs such as the small bowel, bladder, and femoral head, while precisely targeting the anal sphincter with the radiation dose.

The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) consensus guidelines recommend a radiation dose of 45–54 Gy for the treatment of LARC. However, Appelt et al. [8] have demonstrated a significant dose-response relationship for tumor regression following pCRT for LARC, with radiation doses ranging from 50.4 to 70 Gy. Moreover, LARC patients who received radiation doses of 60 Gy or higher experienced a pCR rate of 20.4%. This rate corresponded with a lower incidence (10.3%) of grade 3 or higher acute toxicity and a high probability (89.5%) of successful surgical resection, as reported in a meta-analysis [9]. These findings suggest that RT exceeding 50 Gy can be clinically beneficial with an acceptable level of toxicity. Nonetheless, there is a lack of large-scale prospective studies investigating doses above 50 Gy. Consequently, additional research is warranted to validate the safety and efficacy of higher dose escalation.

3. Duration of radiation

External beam RT is the primary radiation technique used in pCRT. It delivers radiation to the entire mesorectum and rectal wall, aiming to eradicate tumor deposits within the field. Both preoperative short-course chemoradiotherapy (pSCCRT) and preoperative long-course chemoradiotherapy (pLCCRT) are standard pCRT schedules. Traditional pSCCRT, also known as 5×5 Gy therapy, administers five daily doses of 5 Gy (totaling 25 Gy) and is typically followed by radical resection within one week of completing RT (less than 10 days from the first radiation fraction). Recently, pSCCRT with delayed surgery has emerged as a beneficial alternative to conventional pSCCRT with immediate surgery, demonstrating comparable oncological outcomes and reduced postoperative complications [17]. The pLCCRT regimen administers a daily dose of RT in smaller fractions (approximately 1.8 to 2 Gy) over a longer period of 25 to 28 days. Patients receive a total RT dose ranging from 45 Gy to 54 Gy, which is considered equivalent to a short-course dose of 25 Gy [2]. Research comparing pSCCRT with pLCCRT in early-stage resectable cancer found no significant differences in outcomes [18–20]. However, in more advanced cases, pSCCRT combined with immediate surgery may not allow sufficient time to achieve a significant down-staging response [18,19]. Conversely, if surgery is delayed for an extended period, pSCCRT might be comparable to pLCCRT [21,22]. Nonetheless, it is quite challenging to precisely define the T and N sub-stages that necessitate pSCCRT or pLCCRT [17]. The decision to use pSCCRT versus pLCCRT should be made by a multidisciplinary team, taking into account

the potential for long-term toxicity and the need for preoperative tumor down-staging [23].

4. Interval between radiation and surgery

The optimal timing for surgery in patients with LARC following pCRT or pSCCRT remains a contentious issue in clinical trials. It is crucial to find a balance between the acute tissue response and allowing enough time for the maximum effects of CRT to manifest, thereby facilitating safe surgical intervention [17]. This period is designed to enhance tissue response and foster recovery from radiation, while simultaneously preventing radiation-induced tissue fibrosis. The tumor's response to pCRT can fluctuate over time, with peak tumor regression often taking several months to occur. In clinical practice, the timing of surgery post-pCRT can vary significantly (from 4 to 12 weeks) due to a variety of factors, such as recovery from treatment, surgeon preference, and waiting list issues [17–20]. However, retrospective studies have indicated a higher rate of pCR when surgery is postponed following pCRT [24]. A Dutch study corroborated that pSCCRT did not significantly decrease tumor stage when the gap between pCRT and surgery was less than 10 days [25]. Conversely, pSCCRT followed by delayed surgery (5–13 weeks) resulted in a higher rate of pCR (11.8% vs. 1.7%) and a higher rate of Dworak TRG4 (10.1% vs. 1.7%) compared to immediate surgery (within 1–2 weeks) [26]. Given that radiation-induced necrosis requires time to develop, prolonging the interval between CRT and surgery could potentially increase the incidence of pCR.

If the objective is to preserve the sphincter, it is advisable to wait for six weeks after pCRT to initially assess the tumor's response. If the tumor does not respond adequately to pCRT, surgery should be performed within two weeks. In cases where clinical complete regression (cCR) or near cCR is achieved, restaging should be done after six weeks to decide whether to adopt the watch-and-wait treatment approach [27]. The Lyon R 90-01 clinical trial found that pCRT increased the rate of pCR or near-pCR from 10.3% at two-week intervals to 26% at six to eight-week intervals. As a result, the optimal interval between CRT and surgery is currently considered to be six to eight weeks to improve pCR rates and reduce postoperative complications [28,29]. Despite encouraging results from trials that have extended the time between pCRT and surgery, there is still no definitive consensus on the time between the completion of pCRT and surgery, with current studies showing a cautious trend towards delaying surgery.

The impact of the time interval from the completion of pCRT to surgery on pCR rates in rectal cancer remains a topic of ongoing debate [18–32]. The GRECCAR-6 study, however, found no significant difference in pCR occurrence between intervals of 11 and 7 weeks, although patients with an 11-week interval experienced a higher rate of surgical complications [30]. A study using the National Cancer Database (NCDB) sought to identify the optimal timing for surgery following pCRT in patients with stage II-III rectal cancer who received pCRT treatment between 2006 and 2012. This study involved 11,760 participants. The authors found that delaying surgery beyond 8 weeks offered no additional benefit, despite an observed increase in tumor downstaging during the waiting period [31]. A meta-analysis of 13 studies, involving 19,652 patients, showed that patients with a waiting interval of more than 8 weeks between pCRT and surgery had a significantly higher incidence of pCR compared to those with a waiting interval of less than 8 weeks. However, no significant differences were noted in operative time, OS, DFS, local recurrence rate, postoperative complications, or sphincter-sparing surgery [32]. A multicenter study examined outcomes for rectal cancer patients who underwent surgery more than 12 weeks after completing pCRT. The histopathologic examination of resected surgical specimens revealed that the pCR rate was 8.3% for patients who had surgery within 12 weeks and 15.8%

for patients whose surgery was delayed beyond 12 weeks. Moreover, no significant differences were found in morbidity and mortality between the two groups [33]. Another study indicated that patients who underwent surgery after 12 weeks of pCRT therapy, and progressively longer preoperative intervals, had similar postoperative complication rates to patients with a 6-week interval. This study categorized the period between pCRT and surgery into longer intervals of 6, 12, 18, and 24 weeks. Despite the administration of additional systemic chemotherapy to patients who underwent surgery after the longer interval, the group that delayed surgical resection to 20 weeks showed significantly higher pCR rates, with no change in postoperative complications [34].

Chemotherapy

1. Oxaliplatin and irinotecan

Concurrent chemotherapy during pCRT offers a significant advantage in terms of improved tumor regression and local control, compared to RT alone [34]. This is evident in various phase 2 trials involving patients with LARC who underwent preoperative RT alone. These patients exhibited significantly lower rates of pCR (4%–13%) compared to those treated with pCRT (9%–31%). Numerous randomized trials have demonstrated that the addition of concurrent chemotherapy to pSCCRT and pLCCRT enhances local sensitization and systemic control of the disease [27,35,36].

In four out of five randomized phase 3 trials evaluating the addition of oxaliplatin as a radiation enhancer to preoperative fluoropyrimidine-based CRT (STAR-01, ACCORD 12/0405-Prodige 2, NSABP R-04, PETTAC-6), the oxaliplatin chemoradiotherapy arm led to a significant increase in grade 3–4 toxicity, up to approximately 25%. However, there was no notable benefit in terms of complete response, R0 resection, local control, or survival [11,35,36]. In the CAO/ARO/AIO-04 study, the group treated with oxaliplatin demonstrated a significantly higher pCR rate than the control group, but without substantial increases in toxicity [35]. There was also a minor advantage in 3-year DFS [36]; however, despite the slight increase in pCR (17%–13%), there was no difference in R0 resection. Given the increased toxicity without a clear benefit in outcomes, the addition of oxaliplatin to fluoropyrimidine-based CRT is currently not recommended outside of clinical trials. The primary question is whether adding oxaliplatin at a full systemic dose (85–130 mg/m^2) to pCRT can improve pCR rates and oncological outcomes, including DFS and OS. Although most trials show little or no difference in response rates between the two groups, patients receiving oxaliplatin experienced more severe toxicities and adverse events [36].

Irinotecan is a promising radiosensitizer that has been evaluated in multiple published phase 2 trials. The CinClare study confirmed that adding irinotecan to pCRT could increase the pCR rates when compared to the standard pCRT group (30.0% vs. 15.0%) [37]. Some studies [38,39] have reported increased rates of acute toxicities in the irinotecan arm, but did not identify any significant differences in pCR or tumor regression between treatments. Conversely, a handful of non-randomized phase 2 studies suggested that the integration of irinotecan into standard fluoropyrimidine-based CRT could boost response rates to roughly 14% to 22% [39]. Currently, there is insufficient evidence to propose that irinotecan effectively increases the pCR rate, and further research is required to confirm its potential as a radiosensitizer.

2. Total neoadjuvant therapy

Despite the significant improvement in outcomes for rectal cancer patients treated with

pCRT, there is still a 25%–30% risk of recurrence within 5 years [19]. The creation of more intensive neoadjuvant strategies has facilitated the progression of all systemic therapies to total neoadjuvant therapy (TNT). It is hypothesized that TNT can decrease the risk of distant recurrence by providing early treatment and eliminating systemic micrometastases, thereby improving OS. Furthermore, administering chemotherapy and RT prior to surgery, as opposed to post-surgery recovery, results in a significantly higher completion rate of the full dose and schedule. The RAPIDO trial, a phase 3 randomized controlled study, compared pSCCRT followed by systemic chemotherapy with FOLFOX or CAPOX (capecitabine, oxaliplatin) for 18 weeks before surgery to conventional pCRT in high-risk patients (T4, N2, epidural vascular invasion, positive mid-rectal fascia, positive side nodes) [40]. After 5 years, the study showed a doubling of the pCR rate from 13.8% to 27.7%, and a 6.7% decrease in disease-related treatment failure. However, the 5-year update on the RAPIDO trial revealed a statistically significant increase in local recurrence (8% vs. 12%, P=0.07) and breached mesorectum (4% vs. 21%, P=0.048) in the experimental arm [41]. Contrary to mid-term results, this raised concerns that short-course TNT might lead to inferior surgical quality, which could offset the benefits of an increased pCR rate with short-course TNT.

Another recent phase 3 trial, PRODIGE 23, explored the efficacy of TNT in treating T3 or T4 rectal cancer. This trial differed from the RAPIDO trial in that it included both T3 and T4 rectal cancer. The experimental group demonstrated a higher pCR rate (27.5% vs. 11.7%, P<0.001), coupled with a 7.2% rise in 3-year DFS. Furthermore, the experimental group showed superior metastasis-free survival. Surgical morbidity rates were comparable in both groups [42].

Targeted Agents

Numerous phase 1 and 2 trials have reported a range of outcomes concerning pCR rates and safety when integrating angiogenic inhibitors or epidermal growth factor receptor (EGFR) inhibitors into pCRT using 5-fluorouracil (5-FU) for LARC treatment [43,44,45]. The pairing of bevacizumab with pCRT has shown tolerable toxicity in some trials [46,47,48], while other studies have consistently indicated more severe toxicity, increased surgical morbidity, and unfavorable healing outcomes [43,44]. Sorafenib has shown promising results, but its use is still limited to small cohorts and phase I studies [49]. Despite veliparib and capecitabine-based CRT achieving a pCR rate of only 28%, the potential radiosensitizers in this category are cause for concern. Further research is essential to clarify their role in rectal cancer treatment [49].

The addition of cetuximab to 5-FU-based chemoradiation regimens has produced disappointing results, with complete remission rates of less than 10% for the combined regimen, according to a pooled analysis of existing studies. This is in contrast to standard 5-FU regimens, which have shown rates of 15%–30%. Moreover, the combined regimen has shown unacceptably high levels of toxicity. Numerous phase 1-2 trials involving the addition of cetuximab to chemoradiation with fluoropyrimidines have generally led to more instances of diarrhea, without significantly increasing pCR rates or survival [44]. In the only randomized phase 2 trial (EXPERT-C), adding cetuximab to the induction neoadjuvant chemotherapy with capecitabine and oxaliplatin, or to the capecitabine chemoradiotherapy regimen, did not result in a significant improvement in pCR rates (18% vs. 15%) or DFS or OS. This was also the case in the subgroup with *RAS* or *BRAF* wild-type tumors [45]. EGFR inhibitors, including panitumumab and cetuximab, are approved for treating wild-type metastatic colorectal cancer involving RAS. However, their effectiveness in treating LARC remains uncertain. Only a handful of phase 2 trials using panitumumab have been

published. The authors concluded that adding panitumumab to pCRT did not achieve the expected primary endpoint of pCR due to additional toxicity [49]. Therefore, currently, there is no role for EGFR-targeted agents as radiosensitizers in the treatment of LARC.

Immunotherapy

Currently, immunotherapy is evolving from a post-diagnosis treatment for metastatic cancers to a primary treatment option. It is also being incorporated into adjuvant and neoadjuvant therapies for early-stage cancers. Patients in the neoadjuvant phase are generally healthier but are at a higher risk of experiencing side effects from the treatment. In the context of neoadjuvant therapy for rectal cancer, immunotherapy has shown remarkable results in patients with high microsatellite instability or deficient mismatch repair. Researchers at MSKCC reported that administering PD-1 monotherapy to individuals with high microsatellite instability/deficient mismatch repair LARC resulted in a complete clinical response (cCR) of 100% (14/14) [50]. Many researchers are investigating the promising results of combining PD-1/PD-L1 inhibitors with chemoradiotherapy for patients with microsatellite-stable LARC.

The addition of immunotherapy has led to more promising results in the modern era. At present, the reported findings are primarily from small-scale phase 2 studies. However, studies with similar designs corroborate these results. In trials based on pCRT, the CR rate can surpass 30% when combined with immunotherapy, as evidenced by Voltage-A, NSABP FR-2, and PANDORA [51–53]. Therefore, the combination of pCRT and PD-1 monoclonal antibodies can attain CR rates that are comparable to those of the TNT model.

Conclusion

The field of surgical treatment for rectal cancer has consistently evolved with the introduction of new techniques such as laparoscopic, robotic, transanal robotic/laparoscopic total mesorectal excision, and image-guided surgery. These advances have not only improved oncological outcomes but also highlighted the importance of functional preservation [3,54–58]. However, despite these developments, complications related to surgery and the onset of postoperative bowel dysfunction [59,60]—often viewed as an unavoidable result of rectal resection—remain significant concerns in rectal cancer surgery.

In light of these considerations, there has been a growing interest in recent years in increasing the rates of pCR and cCR achieved through pCRT, with the ultimate goal of preserving the rectum. The refinement of pCRT, which includes intensifying concurrent chemotherapy, increasing the frequency of interval chemotherapy, and implementing TNT, has gradually improved tumor regression effectiveness in patients. Research suggests that the TNT model can significantly boost the rate of pCR to over 30%. In instances where a high likelihood of achieving pCR is initially assessed, a treatment approach involving local excision may be considered. This is akin to the management of early-stage cancer, although the complications of local excision after pCRT should not be overlooked [34,60]. Furthermore, a watch-and-wait strategy can be adopted by more patients with cCR to enhance organ preservation and improve quality of life. The use of this strategy is also anticipated to reduce the incidence of distant metastases and improve long-term survival. Therefore, the focus of pCRT for LARC is shifting from the traditional approach, which primarily aimed to control local recurrence, to a new approach that emphasizes enhancing tumor regression, preserving organs, and promoting long-term survival.

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Conflict of Interest

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

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Review Article

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Surgical Techniques for Transanal Local Excision for Early Rectal Cancer

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Rectal neoplasms; Local excision; Transanal excision; Transanal endoscopic microsurgery; Transanal endoscopic surgery

The primary objective in the treatment of early rectal cancer is to achieve optimal oncological control while minimizing the long-term impact of therapeutic interventions on patients' quality of life. The current standard of care for most stage I and II rectal cancers involves radical surgery, specifically total mesorectal excision. Although total mesorectal excision is generally curative for early rectal cancers, it can significantly affect patients' quality of life by potentially necessitating a permanent colostomy and causing bowel, bladder, and sexual dysfunction. Given the morbidity associated with radical surgery, alternative approaches to managing early rectal cancer, such as local excision through transanal excision, transanal endoscopic microsurgery, and transanal minimally invasive surgery, have been investigated. If these surgical approaches are applied cautiously to carefully selected cases of early rectal cancer, it is anticipated that these local procedures will achieve comparable oncological outcomes to the established standard of radical surgery, potentially offering superior results regarding morbidity, mortality, and overall quality of life.

Introduction

Total mesorectal excision (TME) is established as the prevailing therapeutic approach for rectal cancer, facilitating comprehensive tumor eradication through excision of the primary tumor along with the enveloping mesorectum and associated regional lymph nodes. This technique has demonstrated commendable outcomes in terms of local disease control and prolonged survival rates. Nevertheless, notable morbidities have been documented, including anastomotic leakage, genitourinary impairment, and the necessity for temporary or permanent stoma formation [1–3].

There has been a growing interest in the exploration of local treatment options for rectal cancer due to the significant morbidities associated with TME. This interest stems from the possibility of curing some patients without resorting to radical surgery, which often comes with its own set of disadvantages [4,5]. Local excision (LE) is an appealing choice for early rectal cancer, as it can potentially spare patients from unnecessary extensive rectal resection and the related complications. This approach offers several potential advantages, including reduced postoperative pain, quicker recovery, and the preservation of anorectal function without the need for a stoma. Additionally, new techniques for LE, such as transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS), have been introduced to address the limitations

of conventional transanal excision (TAE).

Notwithstanding its advantages, there exists a concern regarding the potential risk of lymph node metastasis associated with transanal LE, which may hinder its ability to deliver oncologic outcomes equivalent to those of TME [6]. Multiple studies have reported a higher incidence of local recurrence with LE than with TME in the treatment of early rectal cancer [7,8]. These observations underscore the pivotal role of meticulous patient selection in guiding the choice of appropriate treatment modalities.

This review article seeks to provide a comprehensive overview of the various surgical techniques utilized in transanal LE for early rectal cancer, delving into indications, patient selection criteria, and technical considerations, while also emphasizing both their advantages and limitations.

Patient Selection

Precise patient selection, coupled with the meticulous execution of full-thickness, margin-free excisions, has a major effect on patient outcomes following LE for rectal cancer. In appropriately chosen individuals, the incidence of local recurrence has been documented to fall below 4%, rendering LE a potentially curative treatment option that yields comparable oncological results to radical surgery [4]. Consequently, it is imperative for surgeons to endeavor to differentiate between patients who are at high or low risk for local recurrence and lymph node metastasis prior to considering LE as a therapeutic approach for rectal cancer.

To ensure the appropriate selection of patients who are likely to benefit the most from LE, it is imperative to commence with a digital rectal examination, which clarifies key parameters such as tumor mobility, the distance from the anal verge, and the condition of the anal sphincter. Subsequently, proctoscopy aids in the evaluation of more proximal tumors, providing valuable insights into their dimensions and proximity to the anal verge. LE is generally considered technically feasible if the tumor occupies a maximum of 30% of the bowel circumference, measures no more than 3 cm, and exhibits mobility.

Preoperative investigations in the evaluation of rectal cancer encompass a range of diagnostic modalities, including radiological, endoscopic, and histological approaches where feasible. Typically, a comprehensive assessment involves CT scans of the chest, abdomen, and pelvis, complemented by PET scans when equivocal CT findings are present, to determine the presence of distant metastasis. For the locoregional evaluation of rectal cancer, MRI and endo-rectal ultrasonography (ERUS) or their combination is employed. ERUS has been proposed to exhibit superior accuracy in early disease staging when compared to MRI, albeit with reduced precision in assessing lymph node involvement. Conversely, MRI demonstrates superior accuracy in assessing lymph node status compared to ERUS [9,10].

An endoscopic examination serves the purpose of localizing lesions from the anal verge, conducting biopsies for histological evaluation, and estimating the degree of submucosal invasion through the analysis of glandular crypt patterns. Historically, rectal lesions situated within 10 cm of the anal verge were deemed suitable candidates for LE due to the limitations of surgical access and suboptimal tumor visualization. However, advances in technology and instrumentation have made it possible to reach higher lesions with improved visualization using the endoscopic approach. Innovative techniques such as TEM and TAMIS have extended access to lesions located up to 15 cm within the rectum. During an endoscopic evaluation for a primary rectal lesion, the submucosal invasion depth can be estimated by evaluating glandular crypt

patterns. The presence of regular pit patterns typically signifies lesions confined to the mucosal layer, which makes them amenable to endoscopic resection. Conversely, the identification of irregular pit patterns, characterized by architectural distortion and amorphous structures, suggests an elevated risk of deep submucosal invasion [11,12].

Several histological parameters have demonstrated predictive value in assessing the likelihood of invasive disease and the risk of lymph node metastasis after endoscopic biopsy or resection. A consensus exists that resection margins equal to or greater than 1 mm are generally deemed sufficient, while margins less than 1 mm have been associated with recurrence rates of up to 33% [13,14]. Of paramount importance among these risk factors is the depth of tumor infiltration, as the risk of lymph node metastases steadily escalates with increased submucosal infiltration in early rectal cancer. The subclassification of T1 cancers into three tiers of submucosal invasion has shown a correlation with lymph node metastatic risk: 0%–3% for sm1, 8%–11% for sm2, and 11%–25% for sm3 invading tumors [15]. In accordance with a comprehensive cohort study, T2 rectal cancers exhibit a 21% risk of lymph node metastasis [16]. Furthermore, other indicators of aggressive tumor behavior include suboptimal histological grade, mucinous tumors, signet ring cell tumors, and the presence of lymphovascular invasion or perineural invasion [17]. Lastly, the presence of isolated clusters of malignant cells at the leading edge of the tumor, referred to as tumor budding, has also demonstrated a significant association with unfavorable oncological outcomes [14]. Occasionally, these characteristics are only definitively identified through pathological specimen review following LE, making it necessary to consider additional treatment modalities.

In summary, the optimal candidate for a LE procedure is a rectal adenocarcinoma smaller than 3 cm, classified as T1 and limited to the sm1 layer, exhibiting well-differentiated characteristics, and devoid of tumor budding, lymphovascular invasion, or perineural invasion, with an exceedingly low likelihood of lymph node metastasis. Conversely, if preoperative assessments reveal the presence of high-risk features, careful consideration should be given to the appropriateness of pursuing LE, and it may be regarded as an indication for palliative management.

Surgical Techniques of Transanal Local Excision

1. Transanal excision

Tumors located within 10 cm of the anal verge can be surgically resected using conventional TAE. This procedure necessitates prior bowel preparation and the administration of prophylactic antibiotics. The patient's positioning during surgery is determined by the tumor's specific location; posterior tumors require lithotomy positioning, while anterior and lateral tumors are excised with the patient in the prone jackknife position. Anesthesia options encompass both general and regional techniques. To facilitate exposure, anal dilation is achieved using instruments like a Parks retractor or lone-star retractor, with the potential addition of lateral traction sutures to enhance visibility. Electrocautery is employed to create a radial line of dissection, ensuring a 1 cm margin. The rectal excision is performed as a full-thickness procedure, reaching the mesorectal fat. The closure of the rectal wall defect is transverse to prevent luminal narrowing, employing either a continuous or interrupted absorbable suture. Finally, the specimen is securely affixed to a board to facilitate a precise pathological assessment of the oriented margins.

2. Transanal endoscopic microsurgery

In the 1980s, Buess et al. introduced TEM, employing a 4-cm-diameter rigid rectoscope equipped with a magnified binocular viewer, which facilitated a three-dimensional stereoscopic visualization of the rectum [18]. This instrument was inserted into the anus, creating an airtight seal to permit rectal insufflation using CO_2 at pressures ranging from 10 to 15 mmHg, achievable through conventional laparoscopic CO_2 insufflators [5,19]. The magnified view enabled the examination of approximately 220° s of the rectum simultaneously, with frequent repositioning of the rectoscope to optimize lesion visualization during the procedure. Prior to the intervention, patients underwent bowel preparation and received prophylactic antibiotics. Patient positioning was determined by tumor location to ensure optimal access [20]. Although general anesthesia was recommended, regional anesthesia was not contraindicated. Tumor resection was executed through endoscopic instruments introduced via the rectoscope, allowing access to proximal rectal lesions up to 15 cm from the anal verge. It was deemed advisable to mark a 1 cm circumferential margin around the tumor prior to resection to prevent misorientation. However, tumors located very low in the rectum (below 5 cm from the anal verge) were challenging to visualize adequately due to the rectoscope's distal seal formation. Full-thickness resection was accomplished using electrocautery, avoiding direct tumor manipulation. Subsequently, the excised rectal wall defect was closed transversely with a continuous absorbable suture, and the specimen was oriented for pathological examination.

The transanal endoscopic operation (TEO) platform closely resembles the setup of TEM, featuring a 4-cm-diameter rigid rectoscope securely affixed to the operating table via an articulated support arm. These rectoscopes are available in various lengths to accommodate procedures at different depths within the rectum. The primary distinction between the two techniques lies in the method of image acquisition, with TEO employing a high-definition camera to present two-dimensional images on a dedicated monitor, akin to the configuration commonly found in laparoscopic surgery. Notably, the TEO platform allows the utilization of standard laparoscopic instruments and associated devices.

3. Transanal minimally invasive surgery

The technique of TAMIS, which was initially described in 2009, applies single-port laparoscopic surgery principles to transanal microsurgery, offering the potential to perform TEM using standard laparoscopic instruments, including a laparoscopic scope [21]. This approach aims to eliminate the necessity for specialized TEM equipment by utilizing readily available laparoscopic tools, thereby achieving comparable efficacy. TAMIS procedures typically involve the use of single-access ports made of flexible materials, which can be securely anchored to the anorectal ring to establish the required pneumo-rectum seal. Bowel preparation and prophylactic antibiotics are typically administered. Patients are positioned in the dorsal lithotomy position, with a preference for general anesthesia, although regional anesthesia is not contraindicated. A lubricated single-access port is introduced into the anal canal, and pneumo-rectum is established using a standard laparoscopic CO_2 insufflator [22,23]. Notably, the straightforward design and concept of the TAMIS platform significantly reduce setup time compared to TEM and TEO [24]. A 5 mm laparoscopic scope, along with instruments like laparoscopic graspers, electrocautery tools, and needle drivers, are introduced through the single-access port. The procedural steps closely resemble TEM techniques, involving the marking of 1 cm circumferential margins around the tumor and performing full-thickness resection, followed by transverse closure of the defect. TAMIS offers access to proximal rectal lesions located up to 15 cm from

the anal verge, and operators can work in all four quadrants of the rectum without needing to reposition the patient, thanks to the platform's flexibility and the ability to adjust the camera port position [25].

More recently, the introduction of robot-assisted TAMIS (rTAMIS), initially described in 2013, has incorporated the advantages of robotic surgery into the traditional TAMIS approach by utilizing a single access port [26]. Robotic surgery in this context offers improved ergonomics and operator dexterity through the use of articulated instruments. Additionally, it enhances image acquisition with a three-dimensional magnification view and surgeon-controlled camera, resulting in higher-quality and more stable images than can be achieved in conventional TAMIS procedures [27]. Motion scaling and tremor reduction further enhance precision, which is particularly beneficial in the constrained rectal environment. Moreover, rTAMIS demonstrates advantages in terms of ease of suturing and excision aggressiveness, especially in the upper rectal regions [28]. Another notable advantage of rTAMIS is the ability to maintain pneumo-rectum due to lower torque at the ports, as opposed to conventional TAMIS [29]. However, it should be noted that rTAMIS faces limitations related to robotic arms colliding within the narrow working area and challenges associated with lengthy docking times [30]. To address these issues, the introduction of the da Vinci SP robotic system in 2018, specifically designed for single-port use, has proven to be a significant advancement (Fig. 1) [31]. This single-port robotic platform employs a single 25 mm cannula, housing a surgeon-controlled 3D camera and three double-jointed articulated arms. Importantly, the platform offers 360° rotation of the robotic boom and instruments, enabling access to all rectal quadrants without necessitating patient or robot repositioning [32]. The availability of three arms is advantageous, as the third arm can be utilized for tissue retraction and applying suture tension during defect closure.

Outcomes of Transanal Local Excision

1. Postoperative and pathological outcomes

Postoperative complications following LE are relatively rare and are less frequent than after TME. Moreover, LE demonstrates a significant advantage over TME with respect to parameters such as length of hospital stay, incidence of postoperative complications, and the occurrence of bleeding [33]. Postoperative complications following TAE predominantly include bleeding, which is the most prevalent, along with rectal stenosis, urinary retention, fecal incontinence, and the development of rectovaginal fistulas [34]. The prevalent post-procedural complications following

Fig. 1. Robot-assisted transanal minimally invasive surgery (rTAMIS) with the da Vinci SP robotic system. (A,B) The da Vinci SP robotic system is established for rTAMIS (remote view and close view, respectively). (C) Three articulated robotic arms can be applied for rTAMIS within the rectal lumen.

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TEM and TAMIS procedures are bleeding, urinary tract infections, and suture line dehiscence [22].

Comparing surgical outcomes among the various operative techniques (namely, TAE, TEM, and TAMI), no statistically significant disparities were observed in terms of overall postoperative morbidity [35]. Although minimally invasive approaches tend to be associated with shorter hospital stays, statistical significance has not been achieved [35]. Moreover, no statistically significant differences were found in the duration of surgical procedures according to the surgical approach used [35]. The incidence of anorectal dysfunction following TEM and TEO procedures can be partially attributed to the utilization of a rectoscope with a 4 cm diameter, which may impact the dilatation of the anal sphincter complex. Nevertheless, it is noteworthy that the reported occurrence of fecal incontinence subsequent to the insertion of the resectoscope is 1%, and this complication is typically transient [36]. Furthermore, a systematic review assessing functional outcomes and quality of life after TEM and TAMIS observed that neither technique exhibited a significant impact on continence, with exceptions observed only in a minority of instances [37].

In the context of the learning curve, it is evident that TAMIS exhibits a comparatively shorter trajectory, potentially attributable to the pre-existing familiarity of surgeons with laparoscopic and single-access port laparoscopic techniques, unlike TEM [38]. A cohort analysis revealed that the learning curve for experienced colorectal experts in TEM was estimated to be 36 cases [36]. Additionally, the learning curve cutoff for TAMIS has been reported to be significantly shorter, ranging from 12 to 24 cases [38].

In an assessment of complication rates among patients undergoing rTAMIS, it was observed that 10.5% experienced complications. When comparing short-term outcomes between rTAMIS and conventional laparoscopic TAMIS, no statistically significant differences were detected, with the exception of an increase in procedural costs [39].

In the context of pathological outcomes, conventional TAE exhibits a notably higher positive resection margin rate (10%), which stands in stark contrast to TEM and TAMIS [25,40]. Moreover, it is essential to highlight that TAE is associated with significantly higher rates of specimen fragmentation than TAMIS procedures [35]. Specifically, the incidence of positive margins following TAMIS was reported to be 4.4%, with a concomitant tumor fragmentation rate of 4.1% [22]. This disparity may be attributed to suboptimal visualization and the utilization of non-ergonomic instruments during TAE procedures. Importantly, it is worth noting that attempts to identify differences in resection quality between TAMIS and TEM have yielded no significant differences [41].

In the context of rTAMIS, a study revealed a positive resection margin rate of 3.7%, demonstrating a modest decrease compared to the corresponding rates observed in conventional laparoscopic TAMIS, where positive resection margins typically range from 7% to 8.6% [39,42]. Lesion fragmentation was observed in 0.9% of rTAMIS cases, a rate lower than that of 5% reported for conventional TAMIS [39]. Additionally, it is worth noting that rTAMIS demonstrated a higher R0 resection rate (94.74%) than the conventional approach (90.48%), although this difference did not reach statistical significance [28].

2. Oncological outcomes

Numerous studies have consistently reported that the incidence of postoperative local recurrence after LE for T1 rectal cancer typically ranges from 4% to 24%, whereas after TME, it is typically 0% to 7% [5,43–45]. When contrasting the outcomes of LE with those of TME,

there is a considerably higher local recurrence rate among patients with T1 (ranging from 8.2% to 23%) and T2 rectal cancer (ranging from 13% to 30%) who undergo LE, as opposed to those who undergo TME for T1-T2 disease (ranging from 3% to 7.2%) [7,46,47]. A recent meta-analysis comparing TEM and TME for T1 rectal cancer found that the incidence of local recurrence following TEM was significantly greater than after TME [8]. Nevertheless, a study assessing the prognosis after LE did not find a notable difference in disease-free survival (DFS) compared to TME. Among individuals undergoing LE for T1-T2 disease, the 5-year DFS rates ranged from 55% to 93%, which was comparable to patients undergoing TME, who had a 5-year DFS rate of 77%–97% [46,48].

Comparing oncologic outcomes among various LE techniques, TEM exhibited a notably lower local recurrence rate than TAE [25]. This disparity in recurrence rates can primarily be attributed to the enhanced visibility achieved through TEM. A comparative analysis between TAE, TEM, and TAMIS found that TEM and TAMIS exhibited a lower recurrence rate when contrasted with TAE, while no significant difference in recurrence rates was identified between TEM and TAMIS [35]. In the context of rTAMIS, the observed local recurrence rate of 4.1% closely approximated the corresponding rate of 6% observed in conventional laparoscopic TAMIS [22,39].

A recent meta-analysis analyzed local recurrence rates in patients with T1 and T2 rectal cancers who underwent LE [49]. The study revealed that T1 lesions exhibited an 8.1% local recurrence rate. Subsequent subgroup analysis focused on low-risk T1 tumors, characterized by the absence of lymphovascular invasion, poor differentiation, deep submucosal invasion, tumor budding, or positive resection margins, and found a lower recurrence rate of 6.7%. Conversely, high-risk T1 lesions, defined by the presence of one or more high-risk features, displayed a higher local recurrence rate of 13.6%. In contrast, T2 tumors exhibited a notably higher local recurrence rate of 28.9%. Additionally, a predictive model estimated 5-year local recurrence rates of 18.6% for pT1 lesions and 29.3% for pT2 lesions [50]. Notably, independent predictors of local recurrence encompassed depth of invasion, increasing tumor size diameter, lymphovascular invasion, and tumor differentiation status.

Conclusion

Multiple techniques currently exist for the minimally invasive LE of early rectal cancer, each possessing distinct advantages. Despite the heightened risk of local recurrence, a less invasive procedure linked to significantly reduced morbidity and mortality, as well as enhanced functional outcomes, may hold appeal for certain patients. Therefore, it is imperative to provide thorough counseling to enable informed decision-making. The proposition of a minimally invasive procedure as an oncological compromise, yet still offering a substantial chance of cure, could be considered for a subset of patients burdened with substantial co-morbidities and limited physiological reserves, rendering them otherwise unsuitable candidates for conventional TME surgery.

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Conflict of Interest

Gyoung Tae Noh serves as the editorial board members of the *Ewha Medical Journal*, but had no role in the decision to publish this article. No other potential conflict of interest relevant to this article was reported.

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Review Article

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Advances in the Treatment of Colorectal Cancer with Peritoneal Metastases: A Focus on Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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In stage IV colorectal cancer (CRC), peritoneal metastasis is associated with a poor prognosis. Hyperthermic intraperitoneal chemotherapy (HIPEC) after cytoreductive surgery (CRS) is an effective treatment option that offers survival benefits in patients with peritoneal metastatic CRC. For over the past several decades, a multitude of studies have been conducted on CRS and HIPEC for peritoneal metastatic diseases, and research in this area is ongoing. Proper patient selection and a meticulous preoperative assessment are crucial for achieving successful postoperative outcomes. The completeness of cytoreduction and the surgical techniques employed are key factors in improving oncologic outcomes following CRS and HIPEC. The role of HIPEC for both therapeutic and prophylactic purposes is currently being evaluated in recent clinical trials. This article reviews the fundamental principles of CRS combined with HIPEC and discusses recent clinical trials concerning the treatment of CRS and HIPEC in CRC patients with peritoneal carcinomatosis.

Introduction

Colorectal cancer (CRC) is the third most common type of cancer worldwide [1]. Peritoneal carcinomatosis (PC) is the second most common cause of death in CRC, following hepatic metastasis [2,3]. Although the development of systemic chemotherapy has improved the survival of metastatic CRC patients, systemic chemotherapy has shown a relatively low drug transmission rate into the peritoneum. Thus, cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) was developed for peritoneal malignancies to overcome these limitations. Since colorectal surgical techniques have advanced over several decades [4–6], chemoradiotherapy and extensive lymphadenectomy involving multivisceral resection can be used to treat patients with CRC from the early stages to stage IV [7–9].

Several studies have reported that 4%–15% of CRC patients are diagnosed with either synchronous or metachronous peritoneal metastasis [10]. Franko et al. found that 17.4% of patients with metastatic CRC presented with PC, and for 2.1% of patients, PC was the only metastatic site [11]. Risk factors for peritoneal metastasis include advanced tumor or nodal stages, right-sided tumors, poor differentiation, and an initial emergency procedure for metachronous

cancer [12–14]. An analysis of the prognosis of CRC metastatic sites in patients undergoing conventional palliative systemic chemotherapy revealed that patients with peritoneal metastasis had a shorter overall survival than those with other isolated hematogenous metastatic sites [15]. In accordance with the tumor cell entrapment hypothesis proposed by Sugarbaker, surgical manipulation of the primary cancer can lead to locoregional spread of tumor cells. This results in the spillage of free cancer cells, leading to the implantation of these cells on the peritoneal surface, and the exfoliation of numerous cancer cells into the entire peritoneal space [16]. PC progresses rapidly, spreads widely, and induces intestinal obstruction, perforation, or fistula formation, all of which can lead to death.

In this context, CRS combined with HIPEC has been proposed as an alternative treatment option, given that the characteristics of PC differ from those of hematogenous metastasis. However, CRS remains a technically demanding procedure that should be carried out by a highly skilled surgical team to enhance postoperative clinical outcomes. In this study, we have reviewed the fundamental principles of CRS with HIPEC, key considerations, and recent clinical trials concerning the treatment of CRS with HIPEC in CRC patients who have PC.

Preoperative Assessment and Patient Selection

1. Assessment of peritoneal metastasis

The Peritoneal Cancer Index (PCI) score was developed by Jaquet and Sugarbaker in 1996 [16,17]. They divided the abdominopelvic cavity into nine regions, with four additional segments of the small bowel. The largest tumor lesion is scored from 0 to 3, according to its size, in the respective regions; consequently, the total PCI score ranges from 0 to 39 (3 points×13 regions). The PCI is advantageous for identifying the disease severity, distribution, and location. It is widely known that the PCI score is an important prognostic factor for peritoneal metastatic CRC [18].

The completeness of cytoreduction (CC) score is widely used to evaluate CRS [16]. It consists of four classifications, with each score referring to the remnant tumor burden after CRS (CC-0: no residual tumor, CC-1: <0.25 cm residual tumor, CC-2: 0.25–2.5 cm residual tumor, CC-3: >2.5 cm residual tumor). CC-0 and CC-1 are considered complete cytoreduction, and CC-2 and CC-3 are interpreted as incomplete cytoreduction. A tumor nodule smaller than 0.25 cm is thought to be penetrable by intraperitoneal chemotherapy; thus, CC-1 is regarded as complete cytoreduction if perioperative intraperitoneal chemotherapy is administered. A systematic review found that the median overall survival of complete cytoreduction in patients with PC from CRC was 33 months (range, 20–63 months), while that of patients with incomplete cytoreduction was 8 months (range, 8–17 months) [19]. Complete cytoreduction and a low PCI score are the most important prognostic factors in patients with PC [18].

The Peritoneal Surface Disease Severity Score system consists of the clinical symptom severity, PCI score, and primary tumor histology. The clinical symptoms include weight loss, abdominal pain, and ascites. Symptom severity is defined as follows: no symptoms, mild (weight loss <10% of body weight, mild abdominal pain, and asymptomatic ascites), and severe (weight loss ≥10% of body weight, unremitting pain, bowel obstruction, and symptomatic ascites). The PCI score is divided into three categories (PCI <10, 10–20, >20), and the aggressiveness of the primary tumor histology was classified into three categories (well to moderately differentiated/N0, moderately differentiated/N1 or N2, and poorly differentiated signet ring type). The nine

subsections of the Peritoneal Surface Disease Severity Score have their own points, and the total score represents the stage (score 2–3=stage I, score 4–7=stage II, score 8–10=stage III, and score >10=stage IV). This system could be a useful tool for the preoperative prediction of complete resectability in patients with PC [20,21].

2. Patient selection for cytoreductive surgery/hyperthermic intraperitoneal chemotherapy

Proper patient selection is crucial to avoid surgical morbidity or mortality and to improve the long-term outcomes of patients undergoing CRS and HIPEC. Several preoperative studies for metastatic CRC, including physical examinations; laboratory tests, especially tumor markers; CT of the chest, abdomen, and pelvis; and colonoscopy, should be performed, and additional imaging studies, such as transrectal ultrasonography, liver magnetic resonance imaging, or positron emission tomography-CT, are often performed. Various preoperatively assessable clinicopathological parameters have been evaluated as prognostic markers for CRS and HIPEC.

The best-known established prognostic factors are the PCI and CC scores. Elias et al. retrospectively analyzed 523 patients treated with CRS and intraperitoneal chemotherapy for peritoneal metastatic CRC and found that the PCI score (hazard ratio [HR]=1.052; P<0.001), CC score (HR=1.398; P<0.001), and lymph node invasion (HR=1.534; P<0.02) were associated with poor overall survival [18]. Adjuvant chemotherapy was a significant prognostic factor (HR=0.578; P<0.002). A sub-analysis of this study of 416 patients with CC-0 also found that the presence of liver metastasis and the experience of the center had a significant impact on the long-term prognosis. In a retrospective multicenter study, Glehen et al. reported similar results—namely, complete cytoreduction, treatment with a second procedure, limited extent of PC, age less than 65 years, and adjuvant chemotherapy were identified as positive independent prognostic factors. Preoperative systemic chemotherapy, lymph node invasion, synchronous resection of liver metastasis, and poor tumor differentiation were negative independent prognostic factors [22]. Another study by Elias et al. suggested that small-bowel involvement could be an independent prognostic factor. According to the analysis of 139 patients who had colorectal-origin peritoneal metastasis treated with CRS and HIPEC, a PCI score >15 was always involved in the small bowel, and these patients presented poorer overall survival than patients with a lower PCI score or non-small bowel involvement. Therefore, they proposed that a PCI score of >15 or invasion of the small bowel may be relative contraindications for CRS and HIPEC [23]. In a meta-analysis of the prognostic factors of patients with metastatic CRC who underwent CRS and HIPEC, 25 studies and 10 preoperatively assessable prognostic variables were analyzed and it was found that synchronous liver metastasis, low Eastern Cooperative Oncology Group (ECOG) performance status, lymph node metastasis, poor tumor differentiation, and signet ring cell histology were associated with negative outcomes [24]. Age alone should not be a contraindication for CRS treated with HIPEC, and it is important to select patients based on their performance status, nutritional status, quality of life, and institutional experience [25–27].

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

1. Cytoreductive surgery

The aim of CRS is to remove the entire gross tumor burden while avoiding organ dysfunction. A nasogastric tube is inserted within the stomach, and a Foley catheter is placed aseptically after surgical draping to prepare to expose the Foley catheter into the abdominal cavity during the

operation [28]. The operative time is commonly longer than that of standard colorectal surgery. Therefore, pneumatic compression devices and prophylactic heparin subcutaneous injection may help prevent deep vein thrombosis [29]. The lithotomy position is routinely used because a pelvic approach or rectal resection is often required. Even in patients who are not expected to undergo pelvic procedures, exploration of the abdominal cavity is crucial for the even distribution of intraperitoneal chemotherapeutic agents for HIPEC. Laparoscopic cytoreduction may be possible when patients have limited metastasis [30]. In patients with relatively high PCI scores or intraperitoneal adhesions, an open approach with a midline incision is preferred for complete CRS. Omentectomy is usually performed by saving the gastroepiploic arteries to avoid delayed gastric emptying. However, if the gastroepiploic arteries are invaded, resection is recommended. The stomach, small bowel, and large bowel, with their mesentery and parietal peritoneum, including the abdominal, subphrenic, and pelvic areas, should be explored and resected if they have tumor invasion. At least 150 cm of the small bowel must be saved to prevent short bowel syndrome. Intraperitoneal organs, including the spleen, gall bladder, uterus, ovaries, and vagina, can be excised during CRS. The feasibility and efficacy of synchronous resection of extraperitoneal metastases, including the liver or lung, in patients with peritoneal metastasis have not been established; however, several reports have demonstrated the feasibility of concurrent liver resection [31,32].

2. Technique and regimen of hyperthermic intraperitoneal chemotherapy

"HIPEC" was recommended as a standard acronym for hyperthermic intraperitoneal chemotherapy by the Fourth International Workshop on Peritoneal Surface Malignancy held in Madrid, Spain in December 2004. The temperature of the intraperitoneal antitumor agent is maintained at 41°C–43°C with a carrier solution (1.5% or 5% dextrose solution is often used) through a heat exchanger for 30–120 min. The inflow and outflow closed suction catheters are placed in the abdominal cavity and the chemical solution is circulated via a hyperthermia pump.

There are meaningful advantages to using heated cytotoxic drugs administered intraperitoneally. First, low systemic drug levels can be maintained despite high drug concentrations via intraperitoneal administration because of the peritoneal-plasma barrier. When macromolecular anticancer agents are administered into the peritoneum, the anticancer drugs can pass through the peritoneal interstitial layer, but cannot easily pass through the plasma endothelial layer because the gap in the intercellular space of the mesothelium, which composes the peritoneal layer, is wider (0.9 mm) than that of the endothelium (0.5 μm) [33]. It is possible to reduce the side effects of systemic antitumor agents while maximizing their cytotoxic effects on peritoneal tumors. Second, hyperthermia increases drug penetration into the tissues. Antitumor agents penetrate the tumor nodules through passive diffusion, convection, and recirculation [34]. Hyperthermia enhances the drug penetration rate and is expected to lead to a more potent antitumor effect. Third, several chemotherapeutic agents have been reported to exhibit increased cytotoxic effects under hyperthermic conditions. In addition, heat exerts a cytotoxic effect. Hyperthermia can destroy cancer cells not only by inhibiting RNA synthesis, but also by increasing lysosomal activity, which has selective cytotoxic effects on cancer cells [35].

Mitomycin-C (MMC) and oxaliplatin are widely used for HIPEC to treat CRC in patients with PC. They are suitable for intraperitoneal administration with macromolecular drugs (the molecular weights of MMC and oxaliplatin are 334.3 Da and 397.3 Da, respectively) and both are potentiated by hyperthermia. Recommended intraperitoneal regimens include 35 mg/m^2 of MMC in an isotonic salt solution for 90 minutes for the first 50% of the dose, followed

by 25% dose at 30 and 60 minutes, and 460 mg/m^2 of oxaliplatin in 5% dextrose solution for 30 minutes. According to a review article, the number of studies that enrolled more than 100 patients with CRC was approximately 20, and almost all of them used MMC or oxaliplatin (cisplatin and irinotecan are also used, but only in combination with MMC or oxaliplatin) [36]. Several comparative studies have analyzed the long-term outcomes of MMC and oxaliplatin; however, the overall superiority has not been identified yet [37].

HIPEC techniques are divided into the open coliseum technique and the closed technique (Fig. 1). The open coliseum technique has been previously described by Sugarbaker [16]. The major advantage of the open coliseum technique is that surgeons can distribute chemotherapy solutions manually; therefore, an even temperature and a proper distribution of antitumor agents are maintained. However, surgeons might be confronted with the potential hazard of exposure to the chemotherapy solution in its own form or as an aerosol. In contrast, the closed technique has the advantage of minimizing heat loss. A retrospective study that compared the hemodynamic distinction between open and closed HIPEC techniques showed no significant differences, except for the intraperitoneal temperature (more stable temperature maintenance in the closed technique) [38]. However, a major disadvantage of the closed technique is the non-homogeneous distribution of the chemotherapy solution and temperature. This may lead to uneven treatment effects in the intraperitoneal cavity or morbidity due to the overheated solution. Surgeons should consider the advantages and disadvantages of the two HIPEC techniques when choosing the method.

3. Postoperative morbidity and mortality

The morbidity of CRS and HIPEC is associated with postoperative surgery-related complications, including anastomotic leakage, wound infection, intra-abdominal sepsis, intestinal obstruction, and bleeding. Additionally, intraperitoneal chemotherapy-related complications, such as neutropenia, renal toxicity, and arrhythmia may occur. According to a systematic review of the efficacy of CRS and HIPEC for PC in CRC, the postoperative overall morbidity rates ranged from 23% to 44%, mortality rates ranged from 0% to 12%, and reoperation rates ranged from 4% to 11% based on nine studies [39]. Intraperitoneal MMC-induced neutropenia is a frequent complication that has been reported to occur in 39% to 40% of patients [40]. Lambert et al. reported an association between female sex and MMC-HIPEC-induced neutropenia, and they speculated that female patients have a larger peritoneal surface area with a smaller plasma volume than male patients, which may affect the pharmacological effect of MMC [40].

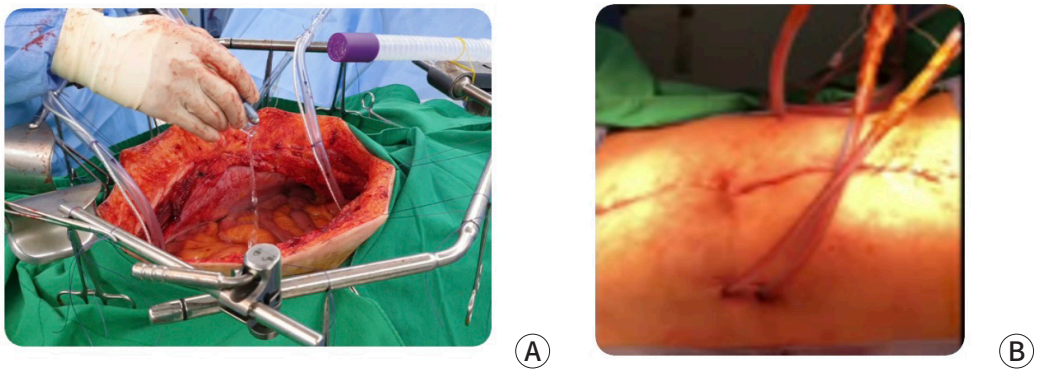

Fig. 1. Hyperthermic intraperitoneal chemotherapy methods. (A) Open technique, (B) closed technique.

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Recent Clinical Trials for Cytoreductive Surgery/Hyperthermic Intraperitoneal Chemotherapy

1. Trials of cytoreductive surgery/hyperthermic intraperitoneal chemotherapy for therapeutic aims

A randomized controlled trial compared CRC patients who received systemic chemotherapy using fluorouracil and leucovorin (n=51) and underwent CRS/HIPEC with or without adjuvant chemotherapy (n=54) from 1998 to 2001 in the Netherlands [2]. In this trial, HIPEC was performed using 35 mg/m^2 of MMC by a triple method over 90 minutes. The median overall survival was 22.3 months in the CRS/HIPEC group and 21.6 months in the CRS/HIPEC and systemic chemotherapy groups, respectively (P=0.032). Although this trial has some limitations due to its inclusion of patients with CRC and appendiceal neoplasms, it is the first randomized controlled trial to show a survival benefit of CRS/HIPEC compared with systemic chemotherapy only in CRC patients with peritoneal metastases.

The PRODIGE-7 trial was performed with 256 enrolled patients at 17 French centers from 2008 to 2014 [41]. The CRC patients with peritoneal metastases were randomly assigned to the CRS group (n=132) or the CRS/HIPEC group (n=133) by 1:1 allocation. HIPEC was intravenously administered using oxaliplatin (460 mg/m^2) mixed in a 5% dextrose carrier solution with bidirectional chemotherapy with folinic acid (20 mg/m^2) and 5-fluorouracil (400 mg/m^2) intravenously. In this study, the median survival was 41.7 months in the CRS/HIPEC group and 41.2 months in the CRS-only group (P=0.995). The 1-year survival rates in the CRS/HIPEC and CRS-only groups were 86.9% and 88.3%, respectively. The 5-year survival rates were 39.4% and 36.7% in the CRS/HIPEC and CRS-only groups, respectively. The relapse-free survival in the CRS/HIPEC group was 13.1 months, while that in the CRS-only group was 11.1 months (P=0.486). Thus, there was no significant difference in overall survival or relapse-free survival between the CRS/HIPEC and CRS-only groups. However, the hospital stay was longer in the CRS/HIPEC group than in the CRS-only group (18 vs. 13 days, P=0.0001). The rate of grade III postoperative adverse events was 26% in the CRS/HIPEC group, which was higher than that in the CRS group (15%; P=0.035). Therefore, the PRODIGE 7 trial concluded that no survival benefits were achieved by adding HIPEC after CRS in patients with CRC with peritoneal metastases.

Although the PRODIGE 7 trial failed to show a survival benefit from the addition of HIPEC to the treatment of CRC with peritoneal metastases, its results have been criticized. First, the prolonged overall survival in both the CRS and CRS/HIPEC groups was remarkable compared with the survival after palliative systemic chemotherapy. The overall survival of CRC with peritoneal metastasis in an analysis of the ARCAD database was 16.3 months, while the CRS and CRS/HIPEC groups showed overall survival of 41.2 months and 41.7 months, respectively [42]. Thus, the importance of surgical resection to reduce the tumor burden should be acknowledged when interpreting the results of the PRODIGE 7 trial [43]. In addition, the pharmacologic drawbacks of oxaliplatin with HIPEC are also criticized regarding the interpretation of the trial results. Specifically, the short half-life and rapid absorption of oxaliplatin into the plasma mean that it is not a suitable agent for increasing the efficacy of intraperitoneal chemotherapy. In addition, the carrier solution using 5% dextrose solution has disadvantages for use in the peritoneal cavity due to the influence of high glucose levels and delayed hemorrhagic complications [44]. Thus, there has been a trend to select MMC instead of oxaliplatin for the HIPEC regimen in CRC patients after CRS after the results of the PRODIGE 7 trial [45]. Nonetheless, the role of HIPEC and the appropriate chemotherapeutic agents in CRC patients are still debated.

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Table 1. Recent clinical trials of CRS/HIPEC

Trials	Enrollment period	Country	Published	Control vs. experimental arm	HIPEC (drug, dose)	Inclusion criteria
Netherland trial [2]	1998–2001	Netherlands	2003	Systemic CTx (n=51) vs. CRS/HIPEC+adjuvant CTx (n=54)	Mitomycin-C 35 mg/m^2	CRC PM
PRODIGE-7 [41]	2008–2014	France	2021	CRS (n=132) vs. CRS/HIPEC (n=133) followed by adjuvant CTx	Oxaliplatin 360–460 mg/m^2 +IV 5-FU/LV	CRC PM, PCI<26
ProphyloCHIP [46]	2010–2015	France	2020	Surveillance vs. Second-look surgery+HIPEC	Oxaliplatin 360–460 mg/m^2 +IV 5-FU/LV or Mitomycin-C 35 mg/m^2	Patients with resected synchronized localized CRC PM or perforated tumor
COLOPEC [47]	2015–2017	Netherlands	2019	Adjuvant CTx vs. Adjuvant HIPEC+adjuvant CTx	Oxaliplatin 360–460 mg/m^2 +IV 5-FU/LV	Resected T4N0-2M0 or perforated CRC
HIPECT4 [48]	2018–2021	Spain	2023	Adjuvant CTx vs. Adjuvant CTx+HIPEC	Mitomycin-C 30 mg/m^2, 60 min	Resected cT4NxMx CRC

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; CTx, chemotherapy; CRC, colorectal cancer; PM, peritoneal metastasis; PCI, peritoneal cancer index.

2. Trials for prophylactic hyperthermic intraperitoneal chemotherapy

The PROPHYLOCHIP-PRODIGE 15 trial was a randomized phase III trial to evaluate second-look surgery with HIPEC in CRC patients at high risk for peritoneal metastases compared with surveillance [46]. Patients who had synchronous or localized peritoneal seeding during primary tumor resection, a perforated tumor, or surgical removal of ovarian metastases were considered to have a high risk of peritoneal recurrence. Thus, 150 patients from 23 hospitals in France were randomly assigned to the second-look surgery group with HIPEC (oxaliplatin 460 mg/m^2 or oxaliplatin 300 mg/m^2 with irinotecan 200 mg/m^2 plus 5-fluorouracil 400 mg/m^2 intravenously or MMC 35 mg/m^2) or the surveillance group between 2010 and 2015. Second-look surgery was performed after 6 months of adjuvant chemotherapy with no signs of recurrence and continued to CRS/HIPEC when there was evidence of peritoneal recurrence during surgery. Interestingly, 71 patients experienced peritoneal recurrence in the surveillance group (48%) and the second-look surgery group (47%). The most common site of recurrence was the peritoneum, followed by the liver. However, there was no significant difference in overall survival and disease-free survival between the surveillance and second-look surgery groups with or without CRS/HIPEC. The 5-year overall survival rate was 72% in the surveillance group, which was not significantly different from that of 68% in the second-look surgery group. The 5-year disease-free survival rate was also not significantly different between the surveillance and second-look arthroscopy groups (49% and 42%, respectively; P=0.82). Therefore, this study showed no improvement in the outcomes of second-look surgery with HIPEC compared with surveillance. However, it is remarkable that this study suggested that peritoneal metastasis developed during the treatment of CRC patients with a high risk of recurrence, although radiologic results showed no evidence of recurrence.

The COLOPEC randomized multicenter trial aimed to evaluate the role of adjuvant HIPEC in preventing peritoneal metastases in CRC patients with a high risk of peritoneal recurrence [47]. A high risk of peritoneal recurrence was defined as T4N0-2M0 on the preoperative findings or pathologic T4 stages or a perforated primary tumor. In this study, the patients were stratified by tumor characteristics (T4 or perforation), age (≤65 years of >65 years), and the surgical

approach for primary tumor resection (laparoscopy or open surgery). From 2015 to 2016, 204 patients were randomly assigned to either the adjuvant systemic chemotherapy group (n=102) or the adjuvant HIPEC with systemic chemotherapy group (n=102). In this study, HIPEC was performed using oxaliplatin (460 mg/m^2) at 42°C–43°C for 30 minutes with bidirectional 5-fluorouracil (400 mg/m^2) and leucovorin (20 mg/m^2). The overall survival of the systemic chemotherapy group and 94.1% in the adjuvant HIPEC group was 93% (P=0.82) and disease-free survival of the systemic chemotherapy group and 69.3%, in the adjuvant HIPEC group was 69% (P=0.99). Thus, the COLOPEC trial did not show any benefits of adjuvant HIPEC in patients with T4 or perforated primary tumors.

The HIPECT 4 trial also aimed to evaluate the role of HIPEC in the prevention of peritoneal recurrence in patients with T4N0-2M0 CRC [48]. This study was designed to randomly allocate patients to a surgery with systemic chemotherapy group and a surgery with systemic chemotherapy and HIPEC (MMC 30 mg/m^2, 60 min, 42°C–43°C) group. The primary endpoint was locoregional control survival, and the secondary endpoints were perioperative morbidity/mortality, overall survival, and disease-free survival. Between 2015 and 2021, 184 patients at 17 Spanish centers were allocated to the surgery-alone group (n=95) and the surgery and HIPEC group (n=89). In this study, the 3-year locoregional control rate of surgery in the HIPEC group was 97.6%, which was significantly higher than that in the control group (87.6%, P=0.03); however, there was no significant difference in disease-free survival or overall survival between the two groups. There were no significant differences in adverse toxic events or morbidities between the groups. Notably, the HIPECT 4 trial used MMC as the chemotherapeutic regimen for HIPEC, whereas the COLOPEC and PROCHYLOCHIP trials used oxaliplatin. Although the HIPECT 4 trial showed the advantages of local control using MMC HIPEC, future studies are needed to determine the role of HIPEC in the prevention of recurrence in CRC patients with a high risk of peritoneal metastases (Table 1).

The current clinical trials for CRS/HIPEC have several issues regarding the selection of appropriate chemotherapeutic agents that are modified adequately for use in peritoneal chemotherapy. Careful patient selection to increase the efficacy of CRS/HIPEC is also important for improving the oncological outcomes. The development of intraperitoneal chemotherapeutic agents and genetic analyses based on individual tumor characteristics are needed to improve the oncologic outcomes after CRS/HIPEC.

Conclusion

CRC with peritoneal metastasis has a poor prognosis, underscoring the need to overcome the limitations of current treatments. Thus, CRS/HIPEC can be regarded as a treatment option for improving survival. Cytoreduction is thought to improve survival by reducing the tumor burden in patients with stage IV CRC. In addition, the principles and pharmacological characteristics of intraperitoneal chemotherapy have advantages over systemic chemotherapy. A more precise diagnosis, improved HIPEC techniques, and careful patient selection are needed for treatment with CRS/HIPEC. Ongoing clinical trials are expected to highlight the roles of CRS and HIPEC in patients with CRC and peritoneal metastases.

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

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Not applicable.

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Review Article

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Influence of the COVID-19 Pandemic on the Treatment Patterns and Outcomes of Colorectal Cancer

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COVID-19; Colorectal neoplasms; General surgery; Stage; Complication

Over the past 3 years, the COVID-19 pandemic has posed significant challenges to the healthcare system, leading to delays in the diagnosis and treatment of various diseases due to the need for social distancing measures. Colorectal cancer has not been immune to these disruptions, and research in various countries has explored the impact of COVID-19 on the diagnosis and treatment of colorectal cancer. One notable consequence has been the postponement of colorectal cancer screenings, potentially resulting in disease progression, which can adversely affect surgical and oncological outcomes. Furthermore, the treatment approach for colorectal cancer may vary depending on the extent of disease progression and the healthcare policies implemented in response to the COVID-19 pandemic. In this systematic review, we examine treatment strategies, surgical outcomes, and oncological variables across multiple studies focusing on colorectal cancer treatment during the COVID-19 pandemic. The purpose of this analysis was to assess how medical policies enacted in response to the COVID-19 pandemic have influenced the outcomes of colorectal cancer treatment. We hope that this review will provide valuable insights and serve as a foundational resource for developing guidelines to address potential medical crises in the future.

Introduction

Colorectal cancer ranks as the second leading cause of cancer-related death worldwide [1]. The crude mortality rate of colorectal cancer was 17.27 per 100,000 in 2020 [2]. Many efforts have been made to enhance the survival rates of colorectal cancer patients, including advancements in surgical procedures, adjuvant or neoadjuvant therapies, and early detection screening methods [3–8].

The World Health Organization declared COVID-19 a pandemic in March 2020 due to its rapid spread and high morbidity and mortality rates [9]. This pandemic has significantly impacted healthcare systems worldwide, presenting challenges across all disease types, including colorectal cancer. It has been reported that the COVID-19 pandemic has indeed affected the treatment patterns, surgical procedures, clinical practices, and oncological outcomes for patients with colorectal cancer [10–14]. A common theme across studies of colorectal cancer treatment during the COVID-19 pandemic has been the question of how to maintain care continuity beyond this pandemic era. In particular, the necessity of continuing appropriate screening is paramount. Research has been conducted to determine whether delays in the diagnosis and treatment of

colorectal cancer impact treatment outcomes, and whether there are viable alternatives when screening is delayed [14,15]. Some studies have reported that treatment delays in colorectal cancer during the COVID-19 pandemic have led to increased mortality rates [16]. In this pandemic era, concerns have also been raised about the timing of surgery and how to manage inevitable surgical delays. There has been a trend towards increased use of preoperative treatment under pandemic conditions, suggested as a safer treatment strategy depending on the stage of the disease [12–14]. These changes in treatment strategies may influence the long-term oncologic outcomes of colorectal cancer. Indeed, there remains a risk of new infectious diseases emerging and impacting colorectal cancer treatment in the future, even if the COVID-19 pandemic stabilizes. Therefore, it is crucial to carefully analyze treatment patterns and surgical and oncological outcomes during the pandemic to prepare for potential future medical crises.

This review aimed to analyze the published data regarding colorectal cancer treatment patterns, as well as surgical and oncological outcomes, during the COVID-19 pandemic. It offers insights into how we can formulate treatment strategies for colorectal cancer in potentially unpredictable situations within the medical community.

Methods

A literature search for relevant studies was conducted in August 2023 using the PubMed databases. The search keywords included "COVID," "COVID-19," "colorectal cancer," "colon cancer," "rectal cancer," "colorectal neoplasm," "surgery," "complication," "treatment," "recurrence," and "oncologic outcomes." Publications marked as e-pub ahead of print during the search period were also included. The search was performed using these keywords individually or in combination. The initial search yielded 708 published reports between 2021 and August 2023. From this extensive list of search results, studies that met the following criteria were included in this review: published after 2021, original articles, patient population with colorectal cancer, comparative studies between the COVID-19 period and pre-COVID-19 period, and those reporting at least one of the following results: treatment pattern, stage, operative method, and perioperative outcomes such as complications or mortality. Initially, the type of study was reviewed, followed by a screening of abstracts to identify suitable studies. Ultimately, 22 studies were included in this review and thoroughly evaluated in terms of treatment patterns, surgical procedures, and oncological outcomes (Table 1).

Changes in Treatment Strategies for Colorectal Cancer during the COVID-19 Pandemic

Screening plays a crucial role in reducing the incidence of colorectal cancer and improving patient survival rates. However, due to the fear of COVID-19, many medical complaints have been delayed, and screenings have been postponed. Indeed, it has been reported that the screening rate for colorectal cancer decreased during the COVID-19 pandemic [17,18]. In the USA, there was an observed 86% decline in colorectal screenings in 2020 [17]. As shown in Fig. 1, the rate of colonoscopies performed in Korea had been increasing by 5% annually until 2019. However, it appears that the outbreak of COVID-19 has reversed this trend, leading to a decrease in initiations (Fig. 1) [18].

The most concerning scenario arises when individuals with cancer miss their screenings, as this can cause a delay in cancer diagnosis and potentially lead to cancer progression. According

Table 1. Studies included in this review

Author	Publication year	Country	Type of study	Period		No. of patients		Comment for inclusion
				Pre-COVID-19	COVID-19	Pre-COVID-19	COVID-19	
Cano-Valderrama O [34]	2023	Spain	Retrospective Cohort Single center	2019.9–2020.1	2020.9–2021.3	169	220	Patients who were referred to a multidisciplinary team
Forse CL [24]	2021	Canada	Retrospective Cohort Single center	2019.8–2020.1	2020.8–2021.1	173	165	
Pirozzi BM [33]	2023	Italy	Retrospective Cohort Single center	2018.3–2020.2	2020.3–2022.2	147	133	
Miyo M [25]	2022	Japan	Retrospective Cohort Multicenter	2019.3–2020.2	2020.3–2021.2	3,569	3,198	
Freund MR [26]	2022	USA	Retrospective Cohort Single center	2016.3–2020.2	2020.3–2021.2	180	54	
Eklöv K [21]	2022	Sweden	NDB	2019.3–2019.8	2020.3–2020.8	590	550	
Eklöv K [22]	2022	Sweden	NDB	2019	2020	4,016	3,964	Compared with data from 2019
Rottoli M [27]	2022	Italy	Retrospective Cohort Multicenter	2019.3–12	2020.3–12	1,755	1,481	
Chen MZ [28]	2022	Australia	Retrospective Cohort Multicenter	2018.7–2019.2	2020.7–2021.6	700	906	
Tarta C [29]	2022	Romania	Retrospective Cohort Single center	2019	2020–2021	163	84	
Meijer J [20]	2022	Netherlands	NDB	2020 2–8 weeks	2020. 1) 9–11 weeks 2) 12–17 weeks 3) 18–26 weeks	410	161 231 385	Division of period: according to the proportion of expected colonoscopy performance
Ghosh S [30]	2022	USA	Retrospective Cohort Single surgeon	2019.4–2020.3	2020.4–2020.9	344	166	
Tang G [31]	2022	China	Retrospective Cohort Single center	2019.1–2019.3	2020.1–2020.3	136	68	
Uyan M [35]	2022	Turkey	Retrospective Cohort Single center	2019.3–2019.12	2020.3–2020.12	56	48	
Kudou M [44]	2022	Japan	Retrospective Cohort Single center	2018–2019	2020–2021	91	67	Only included minimally invasive surgery cases – emergency cases were excluded
Kiss BI [36]	2022	Romania	Retrospective Cohort Single center	2019.3–2020.3	2020–2021	160	142	
Choi JY [13]	2021	Korea	Retrospective Cohort Single center	2018.3–2018.9 2019.3–2019.9	2020.3–2020.9	1,985	916	
Kuryba A [40]	2021	England	NDB	2019.3–20.3.23	2020.3.23–	11,703	3,227	

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Table 1. Continued

Author	Publication year	Country	Type of study	Period		No. of patients		Comment for inclusion
				Pre-COVID-19	COVID-19	Pre-COVID-19	COVID-19	
Williams E [37]	2021	Australia New Zealand	Retrospective Cohort Multicenter	2017–2019	2020–	1,565		
Radulovic RS [45]	2021	Serbia	Retrospective Cohort Single center	2019	2020.3–2021.4	152	49	
Lee T [38]	2022	Singapore	Retrospective Cohort Single center	2019.10–2020.4	2020.4–2020.10	41	64	
Lim JH [39]	2021	Korea	Retrospective Cohort Single center	2017–2019	2020	2,514	715	

NDB, national database.

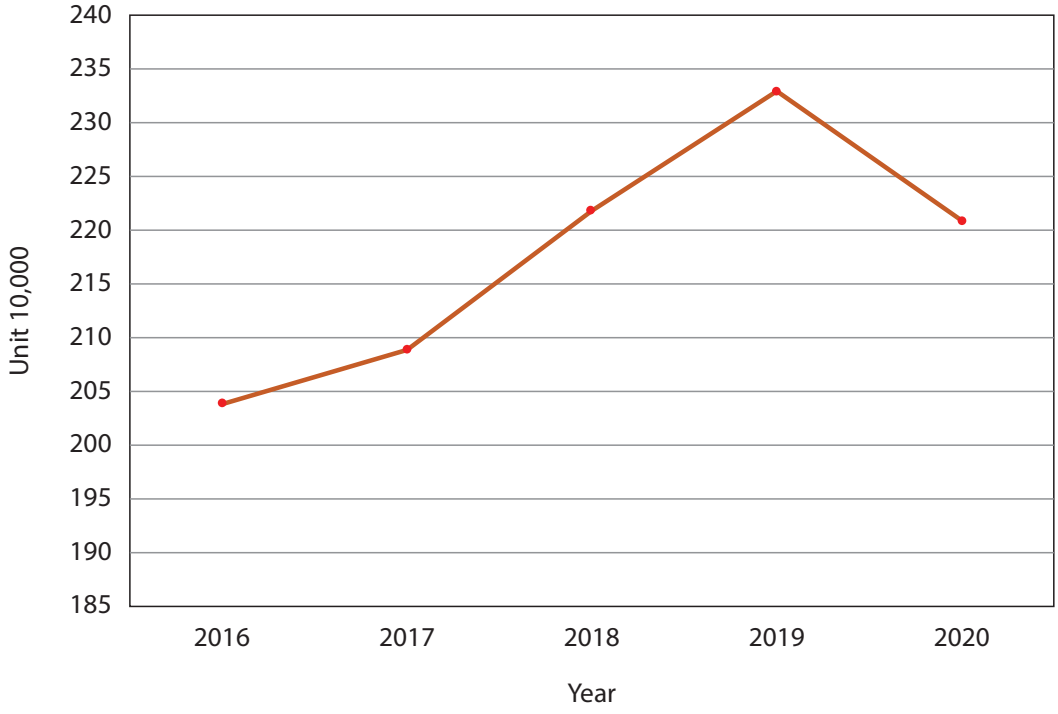

Fig. 1. Number of colonoscopies performed for screening purposes by year in South Korea.

to a meta-analysis of seven studies, it is recommended that elective surgery for colorectal patients not be postponed for more than four weeks. The available evidence suggests that extended delays from diagnosis are associated with poorer outcomes [14]. Neoadjuvant treatment is recommended for advanced disease to increase resectability. Conversely, several countries recommended a modified surgical approach during the initial stage of the 2020 pandemic, with the goal of reducing the workload in intensive care units by avoiding complications [12,19]. Therefore, changes in treatment patterns during the pandemic were not only a result of disease status but also of healthcare strategies.

The proportion of patients who received preoperative treatment during the pandemic,

Table 2. Treatment strategies for colorectal cancer during the COVID-19 pandemic compared to the pre-COVID-19 period

Author	Publication year	Proportion of patients treated with neoadjuvant treatment		P-value	Comment
		Pre-COVID-19	COVID-19		
Forse CL [24]	2021	19% 17%	11% 13%	<0.001 0.044	Chemotherapy post-shutdown Chemoradiotherapy post-shutdown
Miyo M [25]	2022	3.7%	3.7%	1	
Freund MR [26]	2022	65% TNT 15%	76% TNT 52%	0.0001	
Eklöv K [21,22]	2022	3.5%	5.1%	0.0016	Chemotherapy for colon cancer
		44%	45%	NS	Chemoradiotherapy for rectal cancer
Rottoli M [27]	2022	51.9%	52.2%	NS	Rectal cancer
Chen MZ [28]	2022	13.7%	16.2%		
Tarta C [29]	2022	7.2%	6.3% (2020) 9.5% (2021)	NS	
Meijer J [20]	2022	37.7%	1) 10.3% 2) 19.8% 3) 34.1%	NS	Chemoradiotherapy
Ghosh S [30]	2022	52.9%*	40.4%*	0.008	*Patients who could receive surgery
Tang G [31]	2022	7.4%	11.8%	NS	
Kiss BI [36]	2022	14.8%	17.6%	NS	
Choi JY [13]	2021	36%	38.7%	0.039	All kinds of neoadjuvant therapy

TNT, total neoadjuvant therapy; NS, non-specific.

compared to the pre-pandemic period, has been reported to vary. Some studies have indicated that a higher proportion of patients received neoadjuvant treatment during the pandemic, while others found no difference between the two periods (Table 2) [12,13,20–31]. According to data from the Netherlands Cancer Registry, there was no difference in the proportion of patients treated with (neo)adjuvant therapy between the two periods [20]. Eklöv et al. documented changes in the treatment patterns of colon cancer between the pre-pandemic and pandemic periods using the Swedish Colorectal Cancer Registry [21,22]. Their reports indicated that a higher percentage of patients received preoperative chemotherapy in 2022 (5.1%) compared to 2019 (3.5%; P=0.0016). However, in the case of rectal cancer, there was no significant difference in the number of patients who received neoadjuvant (chemo) radiotherapy between the two periods.

According to a multicenter study conducted in the UK, 22.3% of colorectal cancer patients experienced a change in the initial outcomes of management via a multidisciplinary team following the national lockdown. The use of short-course chemoradiotherapy increased from 15.4% to 45.2%, while the use of long-course chemoradiotherapy decreased from 56.3% to 14%. The researchers reported that this represented a significant deviation from standard practice in the UK [23].

Single-center cohort studies have reported a range of outcomes regarding neoadjuvant treatment (Table 2). Some studies have reported a significant increase in the use of neoadjuvant treatment, while others have found no difference in the proportion of patients undergoing preoperative treatment.

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Changes in Surgery for Colorectal Cancer during the COVID-19 Pandemic

Limited data exist concerning the safety of colorectal cancer surgery during the early stages of the COVID-19 pandemic. Initial reports suggested that cancer patients were at an increased risk of contracting COVID-19 and often experienced more severe outcomes. As a result, both surgeons and patients were hesitant to proceed with elective surgeries that could potentially be postponed to a more opportune time [32]. Therefore, the number of operations performed has decreased due to delays during the pandemic period, which also impacted the surgical approach, referral type, and tumor-related complications.

Most studies have reported fewer patients undergoing surgery during the pandemic compared to the pre-pandemic period (Table 1). Aside from a small number of studies, most have described a higher proportion of emergency or urgent operations during the pandemic period (Table 3) [33–39]. However, this was not directly associated with treatment delays from diagnosis to surgery [22,28,31,33]. Studies that showed a higher proportion of emergency operations did not demonstrate a significant delay in treatment [28,33].

During the pandemic, surgeons have expressed significant concern about the transmission of the virus. In the early stages of COVID-19, a study indicated that while there was insufficient evidence to confirm the safety of minimally invasive surgery in terms of transmission, it could still be performed provided that appropriate precautions were taken. Disease progression was a factor that interfered with laparoscopic surgery. The proportion of patients who underwent laparoscopic surgery during the pandemic was comparable to that of the pre-pandemic period, according to most reports (Table 3). However, some studies reported a significant decrease in the use of the laparoscopic approach for elective surgeries during the pandemic [13,40].

The frequency of stoma formation increased notably during the pandemic period. Additionally, there was a rise in the number of palliative resections during the same period [13,20,27,36]. Lim et al. [39] reported a significant decrease in the percentage of patients who were candidates for surgery during the pandemic (73.6%) compared to the pre-pandemic period (82.2%; P<0.001).

Surgical Complications after Colorectal Cancer Surgery during the COVID-19 Pandemic

After surgery, a higher disease severity often predicts an increased likelihood of post-surgical complications. However, numerous studies have reported comparable surgical complications between the pandemic and pre-pandemic periods (Table 3). Uyan et al. noted a significant increase in postoperative complications during the pandemic period (20% vs. 42%; P=0.014). Patients in the pandemic period experienced significantly more extraperitoneal complications (18.8%) compared to the 5.4% observed in the pre-pandemic period. Nevertheless, the length of postoperative hospital stay and early postoperative mortality rates did not differ between the two periods [35]. The enhanced recovery program, already adopted by many societies for colorectal cancer management, has been proven to be suitable even for fragile patients [41–43]. This could be one of the reasons why most studies did not show a difference in the length of hospital stay.

Several studies have reported increased mortality rates during the pandemic. Kuryba et al. observed a significant rise in surgical mortality following emergency surgery (5.6% vs. 8.9%, P=0.003), based on a national study in England that used administrative hospital data. Although

Table 3. Surgery patterns and complications after colorectal cancer surgery

Author	Publication year	Emergency surgery		Laparoscopic surgery		Surgical complications		Stoma formation	
		Pre-COVID-19	COVID-19	Pre-COVID-19	COVID	Pre-COVID-19	COVID-19	Pre-COVID-19	COVID-19
Cano-Valderrama O [34]	2023	9.5%	15.5%			-	-	-	
Pirozzi BM [33]	2023	49%*	67%*	63%	68%	8.8%	15.7%		
Miyo M [25]	2022	3.8%	4.1%	78.5% Ro 8.9%	75.6% Ro 13%	-	-		
Freund MR [26]	2022	-	-	8%	83%	-	-		
Eklöv K [21]	2022	10%	13%			14%+ 20%‡	11%+ 13%‡	-	
Eklöv K [22]	2022	14%	14%	54%*	58%*	12%	11%	-	
Rottoli M [27]	2022	91%	89.2%	51.9%‡	52.2%‡	34.3%	31.9%		
Chen MZ [28]	2022	19.8*	28.1%*	70.1%	73%	19.5%	16.3%		
Tarta C [29]	2022	68.7%*¶	50% (2020)*¶ 42.9% (2021)*¶	31.3%	23.8% (2020) 19% (2021)	163	84		
Meijer J [20]	2022	5.3%+ 1%‡	7.7%+ 1.3%‡	-	-	-	-	12.2%*	18.7%*
Ghosh S [30]	2022	12.7%	20.6%	59.5%	61.8%	Leakage 6.4%	5.9%		
Tang G [31]	2022	7.4%	8.8%	89%	88.2%	26.5%	30.9%		
Uyan M [35]	2022	23%*	52%*	29%	19%	20%*	42%*		
Kiss BI [36]	2022	27.5%*	40.8%*	8.8%	5.3%	-	-	31.9%*	43.7%*
Choi JY [13]	2021	-	-	88%	81.2%	-	-	1.8%*	4.1%*
Kuryba A [40]	2021	-	-	62.5%*	35.9%*	-	-		
Williams E [37]	2021	15.1%*	29.6%*	-	-	-	-		
Radulovic RS [45]	2021	-	-	23.7%	26.5%	-	-	21.7%	26.5%
Lee T [38]	2022	11.7%	17.1%	60.5%	71.7%	10.5%	3.8%		
Lim JH [39]	2021	0.3%	0.2%	-	-	-	-		

Ro, robotic surgery.
*Statistically significant.
+Colon cancer.
‡Rectal cancer.
¶Elective surgery.

there was a minor increase in mortality after elective surgery (0.9% vs. 1.2%, P=0.06), it was not as noteworthy [40]. Intriguingly, Chen et al. reported a significantly lower in-hospital mortality rate during the pandemic period (2.7% vs. 0.5%; P=0.003). They proposed that the allocation of additional resources and a higher staff-to-patient ratio during the pandemic may have contributed to the decrease in inpatient mortality, even during the pandemic period.

In general, surgical complications following colorectal cancer surgery did not significantly increase during the pandemic period.

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Changes in Tumor Stage and Oncological Variables of Colorectal Cancer during the COVID-19 Pandemic

Potential delays in the diagnosis of colorectal cancer could lead to disease progression and a higher proportion of advanced disease, which may be associated with worsening oncologic outcomes. Reports on stage migration during the pandemic period have been inconsistent. Many studies have reported an upshift in staging during the pandemic period, demonstrating a decrease in early-stage disease and an increase in metastatic disease (Table 4). In a study comparing patients who underwent minimally invasive surgery for colorectal cancer before and during the COVID-19 pandemic, Kuodo et al. [44] found a significantly higher number of cases with advanced tumor stage (pT4) in the COVID-19 group compared to the pre-COVID-19 group (P=0.026). Furthermore, the proportion of cases requiring combined resection of adjacent organs due to advanced T4 colorectal cancer was significantly greater in the COVID-19 group (16.4% vs. 4.4%, P=0.010). Kiss et al. [36] also reported an increased proportion of pT4b disease during the pandemic period, as well as a different stage distribution between the pandemic and pre-pandemic periods. Radulovic et al. [45] did not find differences in the proportion of emergency operations, surgical approaches, and stoma formation rates between the two periods. However, they reported a significantly increased incidence of T4b disease (3.3 % vs. 20.2%, P<0.01) during the COVID-19 pandemic and a decreased incidence of stage IIA disease

Table 4. Time to the initiation of treatment and stage distribution of colorectal cancer

Author	Publication year	Time to treatment start, days		P-value	Stage (%)			P-value
		Pre-COVID-19	COVID-19		Comparison	Pre-COVID-19	COVID-19	
Cano-Valderrama O [34]	2023	4.8	6.4	<0.001	Stage I/II/III/IV	36.7/24.3/22.5/16.6	23.6/22.7/30.0/23.6	0.019
Pirozzi BM [33]	2023	14	15	NS	Stage I/II/III/IV	15/31.6/38.1/15.6	18/36.1/34.6/3.6	NS
Miyo M [25]	2022				Stage I/≥II	26.9/73.1	24.2/75.8	0.0011
Freund MR [26]	2022	8.7	11.1	0.0068	Metastasis	3	9	0.05
Rottoli M [27]	2022	-	-		Multiple liver metastasis	72.1	82.2	0.09
Chen MZ [28]	2022	54.9	54.3	NS	-	-	-	
Tarta C [29]	2022	-	-		Stage IV	12	12 (2020) 20 (2021)	
Meijer J [20]	2022	-	-		Stage I/II/III/IV	29.8/26.6/22.2/19	20/25.5/26.8/26.2-	<0.01
Ghosh S [30]	2022	-	-		Stage I/II/III/IV	32.3/28.4/28.9/6	22.2/33.3/31.9/8.3	NS
Tang G [31]	2022	6.46	5.18	0.0016		-	-	
Kudou M [44]	2022	-	-		T4b	4.4	16.4	0.01
Uyan M [35]	2022	-	-		Stage I/II/III/IV	16/52/23/9	10/23/44/23	0.005
Kiss BI [36]	2022	-	-		T4b	12.4	18.9	0.026
Choi JY [13]	2021	-	-		Stage 0/I/II/III	3.1/25.1/34.2/37.7	4.3/26.7/31.2/37.8	NS
Kuryba A [40]	2021	-	-		Stage IV	37.8	24.9	
Radulovic RS [45]	2021	-	-		T4b Stage IIA	3.3 27.6	20.2 12.2	<0.01 0.033

NS, non-specific.

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(27.6% vs. 12.2%; P=0.033).

Even during the COVID-19 pandemic, the distribution of disease stages could be altered due to lockdown policies. Williams et al. [37] examined the trends in diagnosis and treatment of colorectal cancer during the pandemic, using data from the binational Colorectal Cancer Audit registry of Australia and New Zealand. They segmented the year 2020 based on the restrictions implemented across both countries. No difference in disease stage was observed during the period of bidirectional restrictions compared to the previous 3 years. However, fewer cases of stage I disease and more cases of stage II or III disease were identified in the last 3 months of 2020.

Some reports did not find any stage migration during pandemic periods [13,24,33,38,39]. However, other risk factors, previously reported as contributors to recurrence, were observed at higher rates during the pandemic. Choi et al. [13] found no difference in stage distribution, but there was a significant increase in lymphovascular invasion during the pandemic (37.3% vs. 45.2%, P=0.001). Pirozzi et al. [33] compared histopathological results during the pandemic, taking into account the strictness of lockdown measures. They found no differences in stage, nodal distribution, extra-mesorectal venous invasion, and tumor grading between two periods (peak-COVID-19 vs. post-peak-COVID-19) within the pandemic.

To date, no studies have reported on the recurrence or disease-free survival of colorectal cancer patients who received treatment during the COVID-19 pandemic. This may be due to the insufficient time that has elapsed since the onset of the pandemic to observe these long-term outcomes. It is crucial that we meticulously examine whether variations in pathological factors during the pandemic correlate with long-term cancer outcomes. This is a topic we hope to delve into in future studies.

Discussion

The COVID-19 pandemic has significantly impacted all aspects of our lives, including the healthcare system. COVID-19 has led to a decrease in cancer screenings, with colonoscopic screenings being particularly affected due to the necessity of visiting medical facilities. A decline in colorectal cancer screenings has been confirmed in many countries [17,18,28,33], and there is concern that this could impact the clinical, surgical, and oncologic outcomes of colorectal cancer [12,39]. The treatment patterns for colorectal cancer during the COVID-19 pandemic may vary greatly, depending on national and institutional policies and the healthcare system. Consequently, reports on disease progression, surgical outcomes, and oncologic variables have been quite diverse, even though most indicate a decrease in surgical volume during the pandemic period.

It is surprising that many studies have reported an increase in stoma formation, given that advancements in surgical techniques should enable sphincter preservation even in cases of very low rectal cancer [46–49]. Therefore, the higher rate of stoma formation during the pandemic period likely reflects disease progression rather than technical limitations. Neoadjuvant treatment, which can facilitate sphincter preservation, was even more commonly administered during the pandemic. It can be assumed that the proportion of laparoscopic procedures did not decrease, as suggested by many reports [26, 28–31]. Surgical complications typically remain stable in elective surgery. However, during the pandemic, there was a higher incidence of surgical complications, particularly in emergency cases, which are more prone to post-surgical complications [35–40]. This suggests that the overall increase in surgical complications during

the pandemic could be attributed to the higher proportion of emergency surgeries conducted within a specific medical community or facility.

The reporting of stage upshifting has been inconsistent. Some reports have indicated a higher proportion of advanced diseases, or conversely, a lower proportion of early-stage diseases. To determine whether the COVID-19 pandemic has compromised the long-term oncologic outcomes of colorectal cancer, we must await their long-term reports. Other factors, such as the number of harvested lymph nodes, lymphatic invasion, vascular invasion, perineural invasion, and preoperative obstruction, may also be associated with oncologic outcomes [13,39,50] in addition to the pathologic stage. However, many studies have not reported these variables. Furthermore, surgical difficulty, represented by operation time or the need for adjacent organ resection, may also be related to oncologic outcomes. Therefore, we must also carefully analyze these results in upcoming studies.

Conclusion

The COVID-19 pandemic has had various impacts on colorectal cancer treatment, affecting treatment patterns, surgical outcomes, and oncological factors. To formulate effective healthcare policies for future medical crises, it is crucial to thoroughly analyze the long-term consequences of the COVID-19 pandemic. As we transition into a post-mask era, which is gradually happening worldwide, it is important to prepare for potential future infectious diseases, including those transmitted through contact or droplets, much like COVID-19. Given the necessity of developing colorectal cancer treatment guidelines in anticipation of infectious disease pandemics, further research and considerations will be essential in the times ahead.

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

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Review Article

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Preventing Anastomotic Leakage, a Devastating Complication of Colorectal Surgery

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Anastomotic leakage (AL) after colorectal surgery is a significant concern, as it can lead to adverse functional and oncologic outcomes. Numerous studies have been conducted with the aim of identifying risk factors for AL and developing strategies to prevent its occurrence, thereby reducing the severe morbidity associated with AL. The intraoperative method for reducing AL includes a mechanical assessment of AL, an assessment of bowel perfusion, drain placement, and the creation of diverting stomas. The anastomosis technique is also associated with AL, and the appropriate selection and accurate application of anastomotic methods are crucial for preventing AL. Indocyanine green fluorescence imaging has recently gained popularity as a method for assessing bowel perfusion. While it is useful for detecting bowel perfusion, standardized protocols and measurement methods need to be established to ensure its reliability and effectiveness in clinical practice. The use of intraoperative drains to reduce AL has produced inconsistent results, and the routine adoption of this practice is not currently recommended. Diverting stomas can be used to help reduce the morbidity associated with AL. However, it is important to carefully consider the complications that can arise directly from the stoma itself. It should be noted that while a stoma can reduce AL, it cannot completely prevent it. This descriptive review examines various intraoperative methods aimed at reducing AL, discussing their effectiveness in reducing AL.

Introduction

Despite advancements in treatment and the establishment of a comprehensive nationwide screening program, the mortality rate from colorectal cancer (CRC) continues to be a significant concern in Korea [1]. Furthermore, the expenses related to the treatment of CRC and the management of its associated side effects pose a considerable societal burden.

Currently, the primary treatments for CRC include surgical procedures, radiotherapy, and chemotherapy [2,3]. Encouraging outcomes are being seen in a specific subgroup of patients through targeted therapy and immunotherapy [4,5]. Surgery is typically the first line of treatment for CRC. Significant advancements in the comprehensive management of CRC have been made due to improvements in surgical resection and anastomosis techniques, as well as the use of innovative instruments.

Nonetheless, surgical complications are an inherent part of the procedure, and among these, anastomotic leakage (AL) stands out as a particularly concerning complication following surgery for CRC. Studies have shown that AL can negatively impact functional outcomes and may

potentially contribute to cancer recurrence [6–8].

Over the past few decades, there has been a notable expansion in the use of minimally invasive procedures, including laparoscopic surgery, robotic approaches, and trans-anal mesorectal excision. These advancements have increased the likelihood of sphincter preservation [9–12]. Importantly, as the use of sphincter-preserving techniques continues to rise, so does the population of patients potentially at risk for AL. Consequently, efforts to predict, prevent, and appropriately treat AL following rectal cancer surgery have become increasingly critical.

In this descriptive review, we aim to explore the risk factors associated with AL following rectal cancer surgery and provide an overview of recent surgical techniques applied during and after surgery for prevention, as well as insights into treatment approaches.

Intraoperative Approach to Reduce Anastomotic Leakage

1. Anastomosis method and configuration

Hand-sewn and stapled anastomoses are still widely performed, with the choice between the two largely dependent on individual surgeons' preferences. This is due to the ongoing debate regarding which method is safer. The essential points for ensuring safe bowel anastomosis, whether hand-sewn or stapled, include meticulous technique, adequate blood supply, and the absence of tension [13]. The choice of anastomosis method and configuration is influenced by various factors, such as the surgical approach, intestinal tension, and the surgeon's level of experience.

There is no conclusive evidence supporting the superiority of any specific method of constructing colorectal anastomoses, including the side-to-side, end-to-side, side-to-end, or end-to-end techniques. At present, the double-staple technique is the most commonly employed method for colorectal anastomoses [14–16], especially given the widespread adoption of minimally invasive surgery. With regard to the double-staple technique, it has been suggested that the number of staple cartridges used for rectal division may be linked to AL, although the findings have not been consistently conclusive [17–19].

Some colorectal surgeons aim to minimize the number of cartridges used during rectal surgery by delicately trimming the rectum to allow for a single stapler firing to transect it. However, inserting a staple to transect the rectum can be particularly challenging in obese male patients with low, bulky tumors and narrow pelvises. It has been suggested that two cartridges be intentionally used for rectal transection, followed by the removal of the intersection of staple lines using a circular stapler. The use of a suprapubic port might be beneficial in reducing multiple stapler firings by facilitating vertical rectal division [20].

The "dog-ear" deformities created at both edges of the rectal stump after rectal division are considered a risk factor for AL in the double stapling technique. Some have demonstrated a technique that involves centrally invaginating the bilateral dog-ears using sutures to eliminate the dog-ears. Subsequently, both the staple line and the dog-ears are excised using a circular stapler [21,22]. In instances of proximal bowel dilation, to reduce the risk associated with anvil application, De Robles proposed a triple stapling technique [23]. This method involves using a linear stapler with an internal anvil to cut the proximal end, followed by creating an opening to remove the anvil spike prior to forming the anastomosis.

Intraoperative reinforcement of the anastomosis with sutures may be associated with a reduced occurrence of AL. However, the existing research evidence is somewhat constrained,

as many of the studies analyzed did not include patients with factors like neoadjuvant therapy or prophylactic stomas [24–28]. Recently, the use of intracorporeal circular reinforcing sutures has been introduced, utilizing barbed sutures for minimally invasive rectal surgery (Fig. 1). Although this technique could potentially be more easily implemented with a robotic approach, additional research is necessary to confirm its effectiveness in reducing AL.

2. Intraoperative assessment of bowel blood perfusion

Maintaining optimal blood flow is crucial for ensuring a safe anastomosis. Traditionally, surgeons have evaluated bowel perfusion during an anastomosis procedure by observing the bowel's color or the presence of pulsatile flow at the cut surface of the bowel or marginal vessel. However, these methods can be subjective and occasionally insufficient.

Ryu et al. [29] attempted to determine the perfusion status by grading the bleeding of marginal vessels during left colon cancer surgery. They proposed a visual grading system that categorizes the bleeding from the marginal vessel into four groups. Despite not observing a difference in the AL rate among the groups due to the absence of AL occurrences during the study period, they discovered a correlation between age and the perfusion status of the proximal bowel, as determined by the visual grading system.

The use of indocyanine green (ICG) to assess bowel perfusion during surgery has recently garnered increasing interest [30]. Fluorescence imaging with ICG facilitates the clear delineation of vascular and avascular segments. This assists in establishing a well-perfused anastomosis, which may help prevent AL. There is a growing body of evidence supporting its effectiveness in reducing AL following colorectal surgery [30–33].

The PILLAR study demonstrated a reduced incidence of AL when intraoperative angiography was utilized. Specifically, the study reported a 1.2% incidence rate for low-risk left-sided anastomoses, and a 1.9% rate for high-risk cases. High-risk cases were defined as those

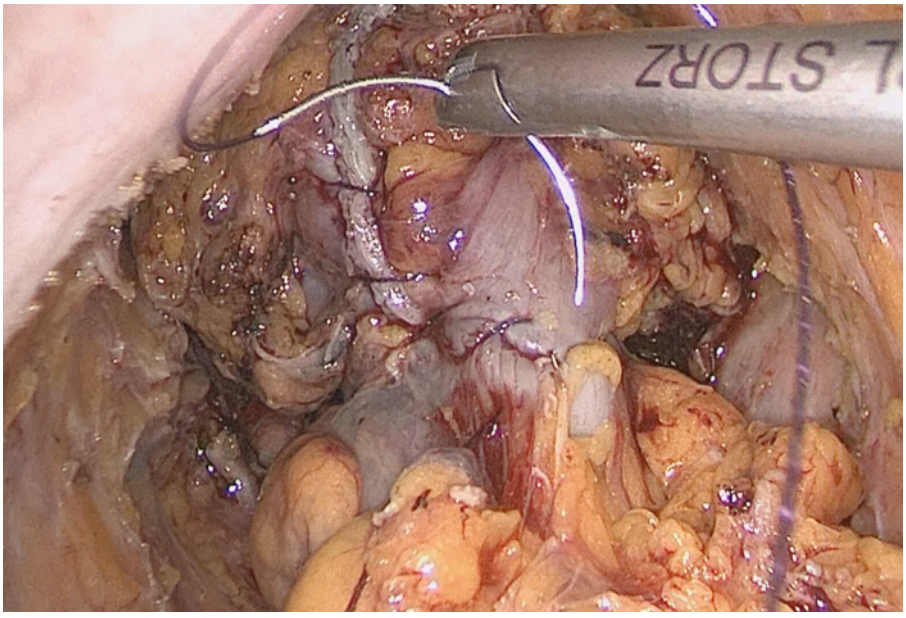

Fig. 1. Intracorporeal circular reinforcing sutures around a colorectal anastomosis following robotic low anterior resection. A continuous suture was done, including the linear-cut surface of rectal transection and circular anastomosis with a barbed suture. Unpublished photos of Sung Soo Yang with permission.

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involving anastomoses located less than 10 cm from the anal verge and/or in patients who had undergone pelvic radiation [32]. Shen et al. performed an analysis of four studies, which included a total of 1,177 patients. Their results indicated a combined OR of 0.27 (95% CI, 0.13–0.53) favoring intraoperative angiography (P<0.001) [33].

However, it should be noted that ICG imaging, while useful, has the limitation of not being able to objectively quantify the degree of perfusion. As a result, there have been studies conducted with the aim of establishing a grading system for perfusion assessment. A study by Kim et al. [34] proposed a five-tier grading system for this purpose, considering both perfusion time and intensity. This study involved 657 patients who underwent curative robot-assisted sphincter-saving surgery for rectal cancer. The findings revealed that delayed perfusion (>60 s) and low perfusion intensity (rated 1–2) were significantly more common in patients with anastomotic strictures and marginal artery defects, compared to those without these factors (P≤0.001).

These findings suggest that integrating ICG fluorescence angiography into colorectal surgery could potentially be beneficial for preventing AL. However, it is essential to establish standardized protocols and develop objective evaluation methods for its practical implementation.

3. Intraoperative assessment of anastomotic integrity

Surgeons have employed various mechanical intraoperative techniques to evaluate the integrity of anastomoses to reduce AL in colorectal surgery. The air leak test has traditionally been used during surgery as a method to evaluate the integrity of anastomosis. This test involves insufflating the bowel at the anastomotic site to identify any defects in the anastomosis, allowing for immediate repair if necessary. While this test can effectively detect mechanical faults intraoperatively, it has limitations in identifying anastomotic leaks caused by poor perfusion and its use in low colorectal or coloanal anastomosis. A modified method to address the limitations of the conventional air leak test has been suggested [35]. Crafa et al. [35] proposed the direct observation of air leaks within the anastomosis using a circular anal dilator under pneumoperitoneum (Fig. 2). However, as they also utilized ICG imaging, it is difficult to conclude that the modified air leak test alone was effective in reducing AL.

Intraoperative endoscopy has been used to evaluate the integrity of anastomoses, enabling the identification of bleeding at the anastomotic level or disruption of the anastomosis during surgery [36]. Endoscopy may also manage anastomotic bleeding, as it can be employed in a postoperative setting [37]. A systematic review and meta-analysis of six studies revealed that intraoperative endoscopy was linked with a decrease in postoperative AL (from 6.9% to 3.5%; OR=0.37; 95% CI, 0.21–0.68; P=0.001) and anastomotic bleeding (from 5.8% to 2.4%; OR=0.35; 95% CI, 0.15–0.82; P=0.02) in left-sided colon resection [36]. However, the air leak test using

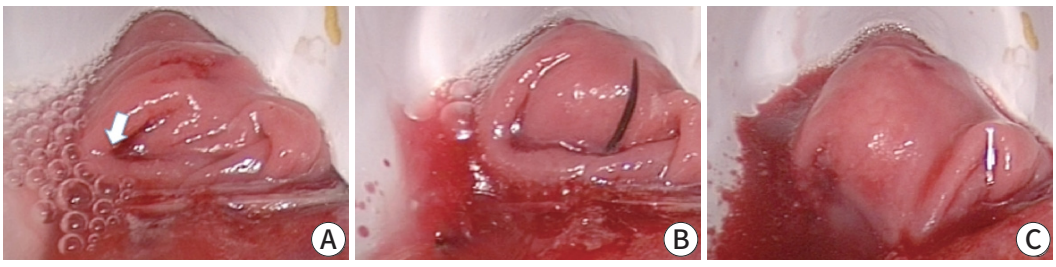

Fig. 2. Modified reverse air-leak test. (A) An air bubble is assessed within the rectum using circular anal dilator after filling the rectum with water. (B) A reinforcing suture is applied. (C) The absence of an air-leak is confirmed. Adapted from Crafa et al. [35] with CC-BY.

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endoscopy requires endoscopic skills, additional materials, and is time-consuming. Furthermore, its effectiveness in preventing AL in colorectal surgery requires further scientific validation.

While there may be debates about the effectiveness of mechanical intraoperative methods in reducing AL, they can still be valuable for identifying immediate technical issues.

4. Role of drainage in preventing or detecting anastomotic leakage

A trans-anal drain can potentially alleviate endo-luminal pressure at the anastomotic site and facilitate drainage on the proximal side of the anastomosis. It may also offer protection against watery stool or gas, and theoretically decrease bacterial contamination in the area, thus potentially preventing AL following rectal surgery. However, the outcomes of various studies have been inconsistent, casting doubt on the effectiveness and validity of trans-anal drainage [38,39]. A meta-analysis involving 909 participants (401 with trans-anal tubes and 508 without) from four trials concluded that the use of a trans-anal tube is an effective and safe procedure that can reduce the incidence of AL [38]. The group with the trans-anal drain exhibited a significantly reduced risk of AL compared to the group without the drain (OR=0.30; 95% CI, 0.16–0.55; P=0.0001). Additionally, there were notable differences between the two groups in terms of the reoperation rate (OR=0.18; 95% CI, 0.07–0.44; P=0.0002) in this meta-analysis. However, more recent analyses have presented contradictory findings [39]. These included three randomized controlled trials (RCTs) and 16 observational studies (both prospective and retrospective), involving a total of 4,560 patients. Interestingly, the impact of the trans-anal drain varied depending on the type of study. In the RCTs, the use of a trans-anal drain was not significantly associated with differences in AL (OR=0.67; 95% CI, 0.42–1.05; P=0.08). However, it was linked to a significant reduction in reoperation (OR=0.11; 95% CI, 0.03–0.51, P=0.004) and an increased rate of anastomotic bleeding (OR=2.36; 95% CI, 1.11–5.01; P=0.03). In observational studies, the use of a trans-anal drain was associated with a significant reduction in both AL (OR=0.44; 95% CI, 0.30–0.64; P<0.0001) and reoperation (OR=0.47; 95% CI, 0.33–0.69; P<0.0001). The conclusion drawn from these studies suggests that trans-anal drainage tubes may not clearly demonstrate superiority in reducing AL. Therefore, the use of trans-anal drainage to prevent AL is not currently recommended with a high level of evidence. However, well-designed future studies are warranted to evaluate its potential role.

The practice of prophylactic intra-abdominal drainage during elective colorectal surgery was once thought to be beneficial for the early detection of AL. However, recent studies have reported that this prophylactic measure does not reduce the incidence of AL [40,41]. The GRECCAR 5 trial, which compared 236 patients in the intra-abdominal drain group to 233 patients without drainage undergoing rectal cancer surgery, found that the use of intra-abdominal drainage did not result in a decrease in the rates of pelvic sepsis, postoperative morbidity, reoperation, length of hospital stay, or the rate of stoma closure [40]. A meta-analysis of a systematic review of four RCTs, including the GRECCAR 5 trial, compared patients undergoing colorectal resections with and without drainage. The results showed no significant differences between the groups in terms of clinical AL (8.5% vs. 7.6%; P=0.57), radiologic AL (4.2% vs. 5.6%; P=0.42), and pelvic sepsis (9.7% vs.10.5%, P=0.75) [41]. Therefore, the routine use of intra-abdominal drainage is currently not recommended.

5. The role of diverting stoma in anastomotic leakage reduction

While diverting stomas were initially intended to prevent AL and mitigate the severe morbidity associated with AL, their effectiveness in preventing AL remains unconfirmed. Furthermore, the

use of diverting stomas comes with the potential risks of dehydration and complications related to stoma closure [42,43].

A systematic review and meta-analysis, which solely focused on RCTs and included four RCTs with a total of 358 patients, found that the use of diverting stomas significantly diminished the risk of AL (OR=0.32) [44]. A more recent meta-analysis revealed that patients without diverting ileostomies experienced a significantly higher incidence of AL than those with a diversion (OR=0.292; 95% CI, 0.177–0.481) [45]. However, this study also discovered that the rate of complications other than AL was significantly higher in patients with diverting ileostomies than in those without (OR=3.337; 95% CI, 1.570–7.093).

A blow-hole type stoma was proposed as a method to reduce stoma-related complications in certain clinical settings [46]. However, it is not expected to prevent AL or reduce the morbidity associated with AL.

Therefore, in clinical practice, careful consideration of both the benefits and risks associated with diverting stomas is essential.

Conclusion

AL remains a significant concern in colorectal surgery. The method of anastomosis does not appear to be associated with AL, but the use of multiple cartridges in transecting the rectum during rectal surgery could be linked to AL. Several new techniques aimed at reducing cartridge use have been introduced and have shown promising results in small-scale studies. Intraoperative reinforcing sutures have also been effectively utilized to mitigate AL. The application of fluorescence angiography has demonstrated the potential to decrease AL. However, the use of intra-abdominal drains has proven ineffective in preventing AL and thus cannot be recommended. A recent meta-analysis has shown that trans-anal drains can have a positive effect in reducing AL, although the results have been inconsistent. The use of diverting stomas could potentially reduce AL-associated morbidity, but complications related to the stoma must also be considered.

Numerous efforts have been made to reduce AL in colorectal surgery. However, some of these approaches lack high-level evidence to support their effectiveness. To address this, well-designed studies should be conducted to determine the impact of both traditionally used and newly developed techniques in preventing AL. Moreover, the adoption of these techniques should be individualized, taking into account patient-specific risk factors and the clinical settings.

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

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Review Article

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Pediatric Endocrine Hypertension Related to the Adrenal Glands

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Endocrine causes of pediatric hypertension are relatively rare but important because of their distinct treatment options. Adrenal diseases accompanied by an excess of mineralocorticoids, glucocorticoids, and catecholamines are major causes of endocrine hypertension. Typical causes of mineralocorticoid-related hypertension include primary aldosteronism, congenital adrenal hyperplasia (11β- and 17 α-hydroxylase deficiencies), and apparent mineralocorticoid excess. Cushing syndrome and pheochromocytoma/paraganglioma are the primary causes of glucocorticoid- and catecholamine-related hypertension, respectively. This review provides an overview of the diagnostic evaluations, including hormonal assays and imaging studies, used to identify the underlying causes of pediatric endocrine hypertension, focusing on adrenal disorders. It presents details regarding the major adrenal disorders and recommended therapeutic approaches, emphasizing the importance of early detection and disease-specific management to prevent cardiovascular and metabolic complications in affected children.

Introduction

Pediatric hypertension is defined as systolic and/or diastolic blood pressure (BP) at or above the 95th percentile based on the normative distribution by age, sex, and height (or ≥130/80 mmHg for children aged ≥13 years) [1]. The recognition of hypertension in childhood is on the rise, with a global prevalence of approximately 4.0% [2]. Among pediatric hypertension cases, 50% are due to secondary causes, with endocrine hypertension comprising up to 6% [3]. Aside from obesity-related hypertension, the primary endocrine disorders that cause hypertension in children are adrenal diseases characterized by an overproduction of catecholamines, glucocorticoids, and mineralocorticoids [4]. Non-adrenal endocrine disorders such as excess growth hormone, thyroid dysfunction, and hyperparathyroidism also lead to hypertension [4]. When evaluating a patient with suspected endocrine-related hypertension, clinicians should obtain a detailed medical history, a review of systems including disease-specific symptoms and signs, and a family history of endocrine hypertension. Identifying an endocrine cause in children with hypertension not only opens the door to potential surgical cures or targeted pharmacological treatments but also aids in the prevention of metabolic and cardiovascular sequelae [5]. This review provides an overview of the biochemical and clinical features of childhood endocrine hypertension, with a particular emphasis on adrenal disorders and a discussion of their treatment options.

Biosynthesis and Action of Adrenal Hormones

The adrenal cortex produces three primary classes of steroid hormones that are essential for regulating a variety of physiological processes: mineralocorticoids from the zona glomerulosa, glucocorticoids from the zona fasciculata, and adrenal androgens from the zona reticularis [6]. Mineralocorticoids, with aldosterone being the most prominent, function by binding to the mineralocorticoid receptor (MR) and carry out a crucial role in BP regulation by modulating renal sodium reabsorption, as well as the release of hydrogen and potassium ions in the distal nephrons [7]. Glucocorticoids, predominantly cortisol, interact with the glucocorticoid receptor and are involved in regulating a wide range of bodily functions, including the mobilization of carbohydrates [8]. The adrenal medulla synthesizes and secretes catecholamines, including dopamine, norepinephrine, and epinephrine [9]. These catecholamines are released in response to stress, leading to an increase in BP, heart rate, and cardiac output, as well as alterations in smooth muscle tone [10]. Table 1 lists the major adrenal disorders that can lead to pediatric hypertension.

Mineralocorticoid-Related Hypertension

1. Primary aldosteronism

Primary aldosteronism (PA), the most prevalent type of secondary hypertension, accounts for approximately 10% of cases of pediatric hypertension [11]. In this condition, the adrenal glands autonomously produce aldosterone, resulting in low plasma renin activity, hypokalemic acidosis, polyuria, and hypertension. PA manifests with a wide range of severity, from mild to severe, and may initially present as elevated BP without concurrent hypokalemia or low renin activity [12].

The primary causes of PA are unilateral aldosterone-producing adenomas (also known as Conn syndrome, accounting for 30%–40% of cases), bilateral idiopathic hyperaldosteronism (comprising 60%–70% of cases), and less common forms (e.g., familial hyperaldosteronism [FH], representing 1%–5% of cases, and primary nodular adrenal hyperplasia). It is crucial to distinguish PA from physiological hyperreninemic hyperaldosteronism, which arises in response to sodium loss, potassium retention, or reduced blood volume. The diagnosis of PA is based on elevated plasma aldosterone levels and low plasma renin concentrations, resulting in an increased aldosterone-to-renin ratio (ARR). PA can be definitively diagnosed or excluded without the need for dynamic confirmatory testing in patients who present with an ARR greater than 27 ng/dL per ng/mL/h and a plasma aldosterone concentration exceeding 20 ng/dL, or in those with a normal ARR and a plasma aldosterone concentration below 9 ng/dL on two separate occasions [13]. For cases in the gray zone, dynamic aldosterone suppression tests are recommended, which may involve intravenous or oral saline loading, the administration of fludrocortisone, or captopril as an angiotensin-converting enzyme inhibitor [13]. PA is classified as either unilateral or bilateral using adrenal imaging and adrenal vein sampling [14]. The treatment of PA involves unilateral adrenalectomy in cases of lateralized aldosterone-producing adenoma or adrenal hyperplasia, and MR antagonists are used to treat bilateral PA [14].

Four subtypes of FH with autosomal dominant inheritance have been described. FH type I (OMIM 103900), caused by the chimeric *CYP11B1/CYP11B2* gene, can be treated with glucocorticoids [15]. FH type II (OMIM 605635) is associated with germline variants of *CLCN2* and does not respond to glucocorticoid administration [16]. FH type III (OMIM 613677) has been linked to germline variants of *KCNJ5* and is characterized by severe PA and hypokalemia due to

Table 1. Adrenal disorders causing pediatric hypertension

Disease	Gene	Inheritance	Clinical findings	Diagnostic tools
Mineralocorticoid-related hypertension				
Primary aldosteronism	–	–	Polyuria, myopathy cardiac dysrhythmias (in severe hypokalemia)	Increased aldosterone, suppressed PRA Increased aldosterone/renin ratio Low potassium
FH type I (OMIM 103900)	Chimeric *CYP11B1/CYP11B*	AD	Early and severe hyperaldosteronism relieved by treatment with glucocorticoids; variable presentation within the same family but associated with high morbidity and mortality at an early age	Germline mutation testing
FH type II (OMIM 605635)	*CLCN2*	AD	Early-onset hyperaldosteronism; variable phenotypic presentation, incomplete penetrance	
FH type III (OMIM 613677)	*KCNJ5*	AD	Severe early-onset resistant arterial hypertension and hypokalemia with massive bilateral adrenal hyperplasia; high levels of 18-oxocortisol and 18-hydroxycortisol; mild forms are also described	
FH type IV (OMIM 617027)	*CACNA1H*	AD	Early-onset hyperaldosteronism; developmental delay or attention-deficit disorder in some patients	
11β-Hydroxylase deficiency (OMIM 202010)	*CYP11B1*	AR	Virilization (female), pseudoprecocious puberty, sometimes prepubertal gynecomastia (male)	Increased 17-hydroxyprogesterone, DOC, 11-deoxycortisol, androstenedione, testosterone, DHEA-S Germline mutation testing
17α-Hydroxylase deficiency (OMIM 202110)	*CYP17A1*	AR	DSD (male), sexual infantilism, primary amenorrhea (female)	Low/low normal blood levels of androstenedione, testosterone, DHEA-S, 17-hydroxyprogesterone, aldosterone, cortisol Germline mutation testing
Apparent mineralocorticoid excess/11β -hydroxysteroid dehydrogenase deficiency (OMIM 218030)	*HSD11B2*	AR	Failure to thrive, delayed puberty, polydipsia, polyuria, muscle weakness, hypertension, nephrocalcinosis	Hypokalemia, metabolic alkalosis Low renin, low aldosterone Normal plasma cortisol levels High urinary cortisol-cortisone ratio
Glucocorticoid-related hypertension				
Cushing syndrome	–	–	Weight gain, growth failure, fatigue, round face, proximal myopathy, plethora, hirsutism, buffalo hump, central obesity	Elevated 24-hr urinary free cortisol excretion for 3 days Loss of circadian rhythm of serum cortisol 1 mg overnight dexamethasone suppression test
Catecholamine-related hypertension				
Pheochromocytoma and paraganglioma	*RET, VHL, NF1, SDHD, SDHC, SDHB, SDHA, SDHAF2*	AD	Headache, palpitation, sweating, pallor, paroxysmal blood pressure	Fractionated plasma or 24-hr urine metanephrines

PRA, plasma renin activity; FH, familial hyperaldosteronism; OMIM, Online Mendelian Inheritance in Man; AD, autosomal dominant; AR, autosomal recessive; DOC, deoxycorticosterone; DHEA-S, dehydroepiandrosterone sulfate; DSD, disorder of sexual development.

massive bilateral adrenal hyperplasia that cannot be treated with glucocorticoids [17]. FH type IV (OMIM 617027), caused by gain-of-function variants in *CACNA1H*, presents with PA in the first

decade of life but shows incomplete penetrance within affected families (Table 1) [18].

2. Congenital adrenal hyperplasia: 11β- and 17α-hydroxylase deficiencies

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder resulting from biochemical defects in steroid biosynthesis, leading to various alterations in mineralocorticoids, glucocorticoids, and adrenal androgens [19]. Hypertension is associated with CAH caused by 11β-hydroxylase deficiency (11OHD) and 17α-hydroxylase deficiency (17OHD) [20]. 11OHD (OMIM 202010), which results from variants in the *CYP11B1* gene, accounts for roughly 5% of all CAH cases [20]. The enzyme 11β-hydroxylase is responsible for converting 11-deoxycortisol to cortisol and deoxycorticosterone (DOC) to corticosterone. A deficiency in this enzyme causes the overproduction of steroid precursors, such as 11-deoxycortisol and DOC, as well as adrenal androgens, and results in increased secretion of adrenocorticotropic hormone (ACTH) [20]. The overproduction of DOC leads to hypertension, hypokalemia, and sodium retention, as well as suppressing aldosterone secretion and plasma renin activity to varying degrees [21]. Hypertension may be present in 30%–60% of cases during childhood, and can even be evident at birth. Excess androgens may cause prenatal virilization in females or precocious puberty in both sexes. The diagnosis is confirmed by elevated levels of DOC and 11-deoxycortisol, along with normal or suppressed plasma renin activity (Table 1) [21]. The treatment for 11OHD includes glucocorticoid replacement, using doses similar to the dosage for 21-hydroxylase deficiency, but there is no need for mineralocorticoid replacement [21].

17OHD (OMIM 202110), caused by variants in the *CYP17A1* gene involved in cortisol and androgen biosynthesis, is a highly uncommon type of CAH that is present in approximately 1% of all CAH cases [22]. The enzyme 17α-hydroxylase converts progesterone to 17-hydroxyprogesterone and pregnenolone to 17-hydroxypregnenolone. Deficient enzymatic activity results in decreased levels of 17-hydroxypregnenolone and 17-hydroxyprogesterone, reduced cortisol synthesis, overproduction of ACTH and elevated levels of DOC [22]. This impaired androgen production leads to the absence of secondary sexual characteristics during puberty in 46,XX individuals, who typically present as teenage girls with sexual infantilism and hypertension [23]. Individuals with a 46,XY karyotype may present with a disorder of sexual development, characterized by absent or incomplete development of the external genitalia (Table 1) [21]. Glucocorticoid replacement therapy is used to suppress hypertension induced by excess mineralocorticoids, and sex steroid replacement is initiated during adolescence, tailored to the individual's sex of rearing [24].

3. Apparent mineralocorticoid excess

Apparent mineralocorticoid excess (AME; OMIM 218030) is an autosomal recessive condition that results from pathogenic variants in the *HSD11B2* gene, which encodes the enzyme 11β -hydroxysteroid dehydrogenase type 2 (HSD11B2). This enzyme is responsible for converting active cortisol into its inactive counterpart, cortisone, in mineralocorticoid-responsive tissues [25]. Children affected by AME typically exhibit severe hypertension, muscle weakness, polyuria, polydipsia, delayed puberty, and failure to thrive, and this condition can lead to early-onset end-organ damage. AME is characterized biologically by hypokalemic alkalosis and low levels of renin and aldosterone. A diagnosis of defective HSD11B2 activity is made by identifying an elevated urinary cortisol-to-cortisone metabolite ratio (Table 1). Treatment options include MR antagonists, such as spironolactone or eplerenone, in combination with potassium-sparing diuretics, hypokalemia correction, and adherence to a low-salt diet. Despite these interventions,

treatment outcomes are not always successful, with a reported cardiovascular mortality rate of 19% among patients with AME [26].

Glucocorticoid-Related Hypertension

1. Cushing syndrome

Cushing syndrome (CS) is rare in childhood, with two to five new cases per million people annually, and is characterized by excessive production of glucocorticoids [27]. Pediatric CS most commonly arises iatrogenically due to the chronic administration of glucocorticoids. In rarer instances, it is caused by an over-secretion of endogenous cortisol, which can occur through either an ACTH-dependent or an ACTH-independent mechanism [28]. The secretion of excessive amounts of ACTH may be due to pituitary adenomas (known as Cushing disease), and, less commonly, by ectopic ACTH-secreting tumors. ACTH-independent CS takes place when adrenal neoplasms (e.g., carcinomas or adenomas) autonomously secrete cortisol. Another ACTH-independent cause is multinodular adrenal hyperplasia, including massive macronodular adrenal hyperplasia and primary pigmented nodular adrenocortical disease [29,30]. In children, CS typically presents with weight gain, central obesity, slowed growth, mood changes, altered facial appearance (including plethora, acne, and hirsutism), and muscle weakness. Overweight children who experience a halt in growth should be screened for CS, as weight gain coupled with growth failure are the most consistent and earliest signs [31]. Hypertension is present in about 63% of pediatric cases of CS [32]. When CS is clinically suspected, hypercortisolism is confirmed by a disruption in the normal circadian rhythm of serum cortisol, abnormally high 24-hour urinary free cortisol levels from three consecutive collections, increased levels of late-night salivary cortisol, and/or a lack of serum cortisol suppression following a low-dose dexamethasone suppression test (Table 1) [28,29].

After confirming the diagnosis, additional assessments are needed to determine ACTH dependence and localize the lesion responsible for cortisol secretion. The differential diagnosis should involve measuring plasma ACTH levels, conducting high-dose dexamethasone suppression tests (also known as the Liddle test), and performing a corticotropin-releasing hormone stimulation test [33]. Beyond laboratory tests, imaging studies play a crucial role in accurately diagnosing CS. CT or MRI can be employed to detect tumors of the adrenal cortex or to identify macroscopic or microscopic nodular adrenal hyperplasia. To locate an ectopic ACTH-producing source, CT or MRI scans of the neck, chest, abdomen, and pelvis, along with a labeled octreotide scan and fluorodeoxyglucose (FDG) PET, are utilized [27,29]. The primary treatment objective is the surgical removal of the lesion causing hypercortisolism [34]. While hypertension often improves after surgery, some patients may still need antihypertensive treatment. This can involve blocking the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, as well as targeting glucocorticoid receptors and MRs [35].

Catecholamine-Related Hypertension

1. Pheochromocytoma and paraganglioma

Pheochromocytoma (PCC) and paraganglioma (PGL) are highly uncommon catecholamine-secreting tumors, accounting for approximately 0.5%–2% of pediatric hypertension cases [36]. PCC originates from the adrenal medulla (more specifically, from chromaffin cells), while

PGLs develop in the autonomic nervous system outside the adrenal glands, arising from both parasympathetic and sympathetic paraganglia external to the cerebrospinal axis [37]. The clinical presentation of PCC and PGL can vary widely, typically involving symptoms and signs of catecholamine excess. The most common symptoms and signs include hypertension, diaphoresis, palpitations, and headache [38]. Occasionally, symptoms such as pain may arise due to the mass effect of the tumor. Some individuals may also be diagnosed incidentally during radiographic evaluations or through family screening for an associated hereditary syndrome [39].

PCC and PGL are diagnosed by measuring the concentrations of catecholamines and their metabolites in samples from the blood and urine. The initial laboratory work-up should include fractionated plasma and/or urine metanephrines (metanephrine and normetanephrine), which have a sensitivity close to 100% (Table 1) [40]. Assessing plasma dopamine or methoxytyramine (a dopamine metabolite) can be helpful for avoiding false-negative results, especially in the rare cases of extra-adrenal succinate dehydrogenase-associated PGLs [41]. Additionally, measurements of chromogranin A, which chromaffin cells store and release together with catecholamines, can serve as an additional diagnostic tool when plasma free metanephrine levels are only mildly elevated [42]. Once biochemical testing confirms catecholamine excess, the tumors can be located through radiographic imaging (typically CT or MRI of the abdomen and pelvis). If abdominopelvic imaging is inconclusive, the next step is to conduct examinations of the neck and chest [43]. Functional imaging can be particularly helpful for confirming extra-adrenal tumors or for evaluating patients for multifocal or metastatic disease, especially in patients who have a noradrenergic phenotype and risk factors for malignancy [44]. Functional imaging options include ^{123}I- or ^{131}I-metaiodobenzylguanidine (MIBG), which targets tissues that store catecholamines, and ^{18}F-FDG PET [45]. A recent study proposed ^{68}Ga-DOTATATE PET/CT as a first-line imaging modality due to its high affinity for somatostatin receptors, which are prevalent in neuroendocrine tumors like PCC and PGL, and its superior sensitivity compared to 18F-FDG PET/CT and ^{123}I-MIBG [46]. Genetic testing to identify common susceptibility genes is advised for all pediatric cases of PCC/PGL [44,47]. In pediatric patients with PCC/PGL, up to 80% of cases are linked to a hereditary predisposition syndrome, such as Von Hippel-Lindau disease, multiple endocrine neoplasia type 2, neurofibromatosis type 1, and familial PGL syndromes types 1 to 5. These syndromes are caused by variants of *RET*, *VHL*, *NF1*, and *SDH* subunit genes (*SDHD*, *SDHC*, *SDHB*, *SDHA*, and *SDHAF2*) [40,47]. Early identification of germline variants after diagnosis can positively influence management and clinical outcomes outcomes of patients with heritable diseases [48].

Surgical resection remains the cornerstone of treatment for both PCC and PGL, often resulting in the remission of hypertension [40]. For children who have adrenal PCC, laparoscopic adrenalectomy is the preferred procedure, with an emphasis on partial adrenalectomy as the initial strategy when feasible [49]. The preoperative management of hypertension is critical for minimizing morbidity associated with catecholamine release and typically requires a minimum of 10 to 14 days in pediatric patients. This management includes the use of α-1 receptor antagonists such as terazosin, prazosin, doxazosin, or phenoxybenzamine, and may also involve tyrosine hydroxylase inhibitors such as metyrosine. To prevent a hypertensive crisis, a regimen combining a calcium channel blocker with a β-blocker is recommended to counteract reflex tachycardia and prevent arrhythmias [50].

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Conclusion

Although adrenal disorders are rare, they are major causes of endocrine hypertension in children. These conditions are often associated with severe hypertension and may lead to end-organ damage at an early age if not promptly diagnosed and managed. Due to their potentially serious consequences, identifying adrenal diseases as a cause of hypertension in children is crucial for the effective treatment and prevention of long-term cardiovascular and metabolic complications. Moreover, recent advancements in genetic approaches have significantly improved our understanding of its pathophysiology, enabling more targeted management strategies by incorporating genetic information into the overall diagnostic and treatment process.

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Conflict of Interest

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

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Review Article

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Updates in the Management of Graves Disease in Children

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Graves disease (GD) is the primary cause of hyperthyroidism in children. The standard management options—namely, antithyroid drugs (ATD), radioactive iodine, and surgery—have not changed for many years. Although ATD therapy is often the first-line treatment for pediatric patients, the low likelihood of spontaneous remission means that most children will require a more permanent solution. Recent clinical trials and systematic reviews have shed light on the long-term outcomes of ATD therapy, radioactive iodine, and surgical interventions in managing pediatric GD. Additionally, novel therapies aimed at B-cells or the thyroid-stimulating hormone receptor, both implicated in the pathogenesis of GD, are under investigation. However, their definitive role in treating childhood GD has yet to be established. This review will cover the latest developments in the treatment of childhood GD, including information on emerging targeted therapies.

Introduction

Graves disease (GD) is the most common cause of hyperthyroidism in children and adolescents [1]. It is characterized by autoimmune mechanisms that involve thyroid receptor autoantibodies, which stimulate the thyroid-stimulating hormone receptor (TSHR). GD is more prevalent in children who have other autoimmune disorders, such as type 1 diabetes, rheumatoid arthritis, or celiac disease [2,3]. Although the prevalence of GD in children is much lower than in adults, studies from Western countries have indicated an increasing incidence of pediatric GD [2,4,5]. Environmental factors, including exposure to endocrine-disrupting chemicals and variations in iodine status, are thought to contribute to this trend [6,7].

The primary goal of treatment for pediatric GD is to restore normal thyroid function and maintain euthyroidism, while preventing disease recurrence. The approach to managing GD in children mirrors that of adults, including antithyroid drugs (ATD), radioactive iodine (RAI) therapy, and surgical intervention [8,9]. Typically, ATD is the initial treatment modality for children diagnosed with GD. However, the likelihood of spontaneous remission following ATD therapy is relatively low. Consequently, most pediatric patients with GD eventually require a definitive treatment, such as RAI or thyroidectomy [2,8–10].

This review focuses on the management of GD in children, including ATD, RAI, and surgery, and provides updated information on the outcomes associated with these treatment modalities. Furthermore, we summarize novel targeted therapies currently under investigation for GD.

Main Text

1. Antithyroid drug treatment

1) Initiation and monitoring of antithyroid drug treatment

Methimazole (MMZ) or carbimazole (CBZ) should be used for treating GD in children. Propylthiouracil (PTU) should be avoided due to its high risk of hepatotoxicity in pediatric patients. CBZ is a prodrug of MMZ and is rapidly converted to MMZ in the bloodstream. The initial dosing ranges from 0.15 to 0.5 mg/kg/day for MMZ and from 0.25 to 0.75 mg/kg/day for CBZ. These doses can be adjusted based on the clinical and biochemical severity of the disease [8,9]. While some clinicians prefer to divide the daily dose, MMZ can be administered once daily due to its long half-life of 3 to 5 hours [11]. Both the American Thyroid Association (ATA) and the European Thyroid Association (ETA) recommend obtaining a baseline white blood cell count with differential, as well as liver function tests, which should include measurements of transaminases, bilirubin, and alkaline phosphatase levels before starting ATD therapy [8,9]. Following the initiation of ATD treatment, thyroid function tests should be monitored at intervals of 2 to 6 weeks. It may take several months for thyroid hormone levels to normalize, and thyroid-stimulating hormone may remain suppressed for an extended period, regardless of the initial MMZ dose [12,13].

Approximately 20% of children may experience minor adverse effects from MMZ, including allergic reactions such as skin rash, pruritus, or dyspepsia, as well as myalgia and arthralgia [14]. Major side effects, which are rare, include agranulocytosis, Stevens-Johnson syndrome, vasculitis, and hepatic dysfunction [2,8,15]. Agranulocytosis is a particularly severe adverse event that requires patients on MMZ to stop the medication immediately and seek medical attention for a complete blood cell count if they present with symptoms such as fever or pharyngitis [9]. A recent systematic review found an overall prevalence of adverse effects of 17.6% in children with GD, with major side effects occurring in only 1.1% of cases [15]. Most adverse effects appear within the first three months of ATD therapy, although some may arise later [14]. The adverse effects associated with MMZ seem to be dose-dependent, which necessitates careful monitoring, particularly in children on higher initial doses [13].

2) Long-term antithyroid drug treatment

When ATD therapy is initiated as the first-line treatment for pediatric GD, the 2016 ATA guidelines recommend a duration of 1–2 years of ATD therapy [8]. However, remission rates in children are lower, ranging from 20% to 30%, compared to 40%–60% in adults, and a significant number of children experience a relapse after a median duration of 2 years on ATD therapy [16]. In clinical practice, it is common for children with GD to be treated with ATDs for extended periods, if hyperthyroidism remains well-controlled with the medication and no adverse events occur.

Several studies over the past few decades have explored the efficacy and safety of long-term ATD therapy in children [14,15,17–19]. A randomized trial comparing long-term (96–120 months) MMI treatment with short-term treatment (18–24 months) in pediatric GD found significantly higher remission rates in the long-term group: 92% at 1 year and 88% at 4 years post-MMI withdrawal, versus 46% and 33% in the short-term group, respectively [18]. A recent systematic review, which included 3,057 patients from 29 articles, reported an overall remission rate of 28.8% in children with GD treated with ATDs. The pooled remission rate increased with the duration of ATD therapy: 23.7%, 31.0%, 43.7%, and 75% after 1.5–2.5, 2.5–5, 5–6, and 9 years of

treatment, respectively [15]. In light of the latest research, the ETA has updated its guidelines to recommend a minimum treatment duration of 3 years for children with GD, extending to 5 years or more in cases with a low likelihood of remission [9].

3) Strategies for antithyroid drug treatment: dose titration vs. block-and-replacement

Given the potential for long-term ATD treatment in children with GD to increase the likelihood of remission [16], selecting an appropriate ATD treatment regimen is crucial. There are two main approaches: dose titration (DT) and block-and-replace (BR) methods. In the DT method, MMI doses are adjusted following the normalization of thyroid hormone levels to prevent hypothyroidism. In contrast, the BR method involves maintaining higher ATD doses to suppress endogenous thyroid hormone production, which is then supplemented with levothyroxine [9,10].

A previous meta-analysis reported that a higher incidence of adverse effects was associated with BR regimens than with DT, which was attributed to the higher doses of MMZ involved [20]. Although the 2016 ATA guidelines recommended against the use of BR regimens based on these findings [8], they continue to be utilized in clinical practice, particularly for patients who experience fluctuations in thyroid function with only minimal changes in MMZ dosage. A 2018 survey in the UK revealed that BR regimens were still commonly used among pediatric endocrinologists, with 29% favoring BR compared to 65% using DT [21].

Several studies have assessed the effects of DT and BR regimens in treating childhood GD [22–24]. An Italian retrospective study demonstrated favorable outcomes with the BR regimen, indicating improved control of thyroid function without an increase in adverse effects [23]. In a recent multicenter randomized trial by a British group comparing DT and BR regimens, the DT group achieved faster normalization of free thyroxine levels than the BR group within the first 6 months [24]. Over a period of 3 years, there were no significant differences in the proportion of patients with thyroid hormone levels within the reference range between the two groups, and the remission rates did not prove to be superior in the BR group [22]. The 2022 ETA guidelines suggest that while DT is generally preferred, BR may be considered in selected cases for biochemical stability, particularly for patients who frequently experience biochemical relapse during the DT method [9].

4) Outcomes of antithyroid drug treatment and predictors for remission

Recent systematic reviews have reported that the remission rate following ATD treatment ranged from 28.8% (829 out of 2,880 patients) [15] to 34.4% (850 out of 2,466 patients), while the relapse rate was 26% (551 out of 2,124 patients) [25]. Although these reviews included a few studies from Asian countries, specifically Japan and Taiwan, they did not investigate the effects of ethnicity on treatment outcomes [25].

Table 1 presents the characteristics of studies that have investigated the efficacy of ATD in Korean children with GD. All the studies were retrospective in design and included between 42 and 187 pediatric patients [26–30]. Following 2.9 to 4.5 years of ATD treatment, which consisted of one to three courses, the remission rate varied from 18.3% to 57.8%, while the relapse rate after ATD withdrawal ranged from 17.4% to 60.6%. The broad range of remission and relapse rates may be due to differences in the definition of outcomes, the duration and number of ATD courses, or the length of follow-up.

In addition to the duration of ATD treatment, various clinical factors have been associated with the outcomes of ATD therapy. Younger age at diagnosis, male sex, non-Caucasian ethnicity, large goiter size, and more severe thyrotoxicosis or elevated levels of thyroid receptor antibody

Table 1. Characteristics of studies investigating the effects of antithyroid drugs in Korean children with Graves disease

Reference	No. of patients	Age at diagnosis, years (mean, range)	Duration of ATD therapy, years (mean, range)	Duration of follow-up, years (mean)	ATD discontinuation rate, % (n)	Remission rate, % (n)	Relapse rate (among discontinuation group), % (n)	Predictors for remission
Lee et al., 2009 [26]	64	11.1 (3–16)	ND	8.1	67.2 (43/64)	57.8* (37/64)	37.2 (16/43)	Shorter time for TBII normalization
Song et al., 2010 [27]	113	12.6 (6–18)	4.5 (0.4–14.2)	6.6 (0.8–16.5)	66.4 (75/113)	55.8* (63/113)	20.4 (23/75)	Older age at diagnosis
Kim et al., 2012 [28]	42	11.5	4.3 (1.7–11.0) for remission group; 4.8 (2.0–9.4) for non-remission group	4.5	54.8 (23/42)	52.4* (22/42)	17.4 (4/23)	Lower TSH levels at diagnosis
Song et al., 2021 [29]	187	12.9	4.7	5.9	55.6 (104/187)	33.2* (62/187)	60.6 (63/104)	Lower FT4 at diagnosis
Rho et al., 2021 [30]	98	11.6 (2–16)	2.9 for remission group	All followed for 5 years	24.5 (24/98)	18.3 (18/98)	25.0 (6/24)	Lower TBII at diagnosis and follow-up; Shorter time for TBII normalization

ATD, antithyroid drug; ND, no data; TBII, thyroid-binding inhibitory immunoglobulin; TSH, thyroid-stimulating hormone; FT4, free thyroxine.
*Remission rate after 1–3 courses of antithyroid drug treatment.

titers have all been linked to lower remission rates [10,14,31–34]. These findings are consistent with those reported in Korean studies (Table 1) [26,27,29,30]. Although long-term ATD therapy can be effective in controlling and treating hyperthyroidism, it is not suitable for all patients, as some may ultimately require definitive treatments such as RAI therapy or surgery. Identifying children at a higher risk of relapse after long-term ATD therapy is crucial, and this can be done by evaluating their initial and follow-up clinical characteristics [19].

2. Radioactive iodine therapy

In children who do not achieve remission after ATD therapy or experience adverse events associated with ATD, RAI therapy can be chosen as the definitive treatment for GD. The goal of RAI therapy is to induce hypothyroidism through ablation because residual irradiated thyroid tissue carries an elevated risk for thyroid neoplasms [8,9].

RAI can be administered in either capsule or liquid form. There are various methods for determining the appropriate dosage. Some physicians opt for a fixed dose, while others base the calculation on the size of the thyroid gland [8,35]. Although it has not been conclusively shown which method is superior, recent guidelines recommend personalized RAI dosing that takes into account the size of the thyroid gland as estimated by ultrasound [9]. Prior to RAI treatment, ATD should be discontinued for 3 to 5 days. Thyroid hormone levels typically start to decline approximately 7 days following RAI administration, and it generally takes 2 to 3 months to reach a state of euthyroidism or hypothyroidism [8,12].

A recent systematic review, which included 1,283 pediatric patients with GD treated with RAI across 23 studies, found that the efficacy of achieving hypothyroidism after the first RAI treatment varied widely, ranging from 42.8% to 97.5% [36]. Adverse effects, both short-term and long-term, were infrequently reported, with only 1 to 6 cases for each event. Short-term side

effects included vomiting, local inflammation, and palpitations, while long-term complications encompassed benign nodules, hyperparathyroidism, multinodular benign goiter, and papillary thyroid cancer [36]. Additionally, another meta-analysis reported an RAI remission rate of 86% (164 out of 190) in children with GD [25].

In adults, RAI is contraindicated during pregnancy and lactation, in the presence of coexisting or suspected thyroid cancer, and is not recommended for patients with active Graves' ophthalmopathy or a large goiter. RAI therapy should also be avoided in very young children under the age of 5 due to the theoretical risks of later malignancy [8,9]. For children aged 5–10 years, RAI should be considered only when surgery is not a viable option [9]. While RAI is a safe and definitive treatment for older children with GD, there are still concerns among some clinicians regarding the long-term risk of malignancy. A retrospective study that followed 116 patients treated with RAI at a pediatric age (ranging from 3.6 to 19.8 years, with a mean age of 15) found that none of the patients developed thyroid cancer or leukemia after a follow-up period of up to 36 years [37].

3. Surgery: Thyroidectomy

Thyroidectomy is a definitive and effective treatment for children with GD, particularly when performed by high-volume surgeons. In some instances, it is preferred over RAI. To prevent recurrent hyperthyroidism, a total or near-total thyroidectomy is recommended rather than a subtotal thyroidectomy [8,9]. Prior to surgery, patients should be treated with ATD to normalize thyroid hormone levels. Additionally, a potassium iodide solution may be administered for 1–2 weeks preoperatively. After thyroidectomy, patients should commence levothyroxine treatment [9].

Complications of thyroidectomy can include transient or permanent hypoparathyroidism, injury to the recurrent laryngeal nerve (RLN), or bleeding. Studies have shown that young children experience a higher rate of complications following thyroidectomy compared to adolescents or adults [8,38,39]. GD is the most prevalent cause of thyroidectomy in children with benign thyroid conditions, yet the rates of complications are similar to those associated with thyroid cancers [40]. A recent systematic review, which encompassed 1,424 pediatric patients with GD across 21 retrospective cohort studies, examined the frequency of postoperative complications in this group [41]. The review found that while transient hypocalcemia and transient RLN injury were relatively common, occurring in 6.5%–50.0% and 0.0%–10.0% of cases respectively, the incidences of permanent hypocalcemia and RLN injury were much lower, at 2.5% and 0.4% respectively. Other complications, such as infections, hemorrhage, or keloid formation, were reported infrequently [41]. The review also highlighted that better outcomes, characterized by fewer postoperative complications, were linked to operations performed by high-volume thyroid surgeons. Therefore, it is recommended that thyroidectomies in pediatric patients with GD be performed by surgeons with extensive experience in the field [8–10].

4. Comparison of each treatment modality

While numerous studies have individually examined the outcomes of ATD, RAI, and surgery in treating GD, direct comparisons of these three strategies are limited, particularly in adult populations. A multicenter study in Sweden has provided comprehensive long-term outcome data for various treatments of GD in adults [42]. This study included 1,186 patients diagnosed with GD between 2003 and 2005. After 6–10 years of follow-up, the remission rates were 45.3% (351/774) with ATD, 81.5% (264/324) with RAI, and 96.3% (52/54) with surgery. Post-remission,

hypothyroidism developed in 23%, 77.3%, and 96.2% of patients in each respective group, highlighting that only 35.7% of patients maintained normal thyroid function without the need for levothyroxine treatment. In addition, a separate review article has compiled comprehensive data on the outcomes of long-term ATD use compared to RAI and surgery. This review took into account not only thyroid status but also patient-centered outcomes such as quality of life, psychiatric morbidity, and treatment costs [43]. Long-term ATD treatment (lasting at least 24 months in adults) was found to achieve and maintain euthyroidism comparably to RAI or surgery, with the added benefits of lower financial costs and improved quality of life profiles. Currently, there are no comprehensive studies that investigate all three treatment modalities in children with GD. Further research is needed to directly compare the long-term outcomes of each treatment modality in pediatric populations.

5. Novel therapies for Graves disease

Since conventional therapeutic options for GD, including ATD, RAI, and surgery, have limited efficacy in controlling the disease, novel therapies that target the direct cause of hyperthyroidism are under investigation [44]. GD is an autoimmune disease that results from the loss of immunologic tolerance to the TSHR, and it also involves interactions between B and T lymphocytes [45]. In this context, new treatment options that target B-cells or modulate TSHR using small molecule antagonists, monoclonal antibodies, or TSHR peptides are being investigated [44].

Several therapies targeting B-cells are currently under investigation in clinical trials to determine their effectiveness in treating GD (Table 2). Rituximab, an anti-CD20 monoclonal antibody, is pivotal in the management of various autoimmune disorders due to its B-cell-depleting action. A recent phase 2 study assessed the efficacy of Rituximab as an adjunctive treatment in young patients with GD aged 12–20 years. The study reported a remission rate of approximately 50% at 24 months following a single dose of Rituximab in combination with 12 months of ATD therapy [46]. Iscalimab, another monoclonal antibody that targets CD40, works by inhibiting B-cell activation via blocking the CD40-CD154 co-stimulatory pathway [45]. In a recent phase 2 trial, 47% of adult patients with GD (7 out of 15) achieved normal thyroid hormone levels without the need for ATDs during the 24-week period after receiving five doses of iscalimab over 12 weeks [47]. Furthermore, clinical trials are in progress to assess the potential of other therapies that either block immunoglobulin recycling or inhibit B-cell proliferation and differentiation [48].

Treatments that directly target TSHR signaling, including small molecules, TSHR-blocking antibodies, and TSHR-specific immunotherapy, are currently under development (Table 2). These approaches offer a more specific form of intervention compared to the B-cell targeted therapies mentioned earlier and, theoretically, do not result in global immunosuppression [44]. A recent phase 1 trial of the monoclonal TSHR-blocking antibody K1-70 has demonstrated a safe and tolerable profile, as well as clinical improvement in symptoms of hyperthyroidism [49]. In the context of other autoimmune diseases, immunotherapy strategies have been devised that involve administering small and gradually increasing doses of antigens to elicit a tolerogenic immune response. An example of this in GD is the TSHR peptide mixture ATX-GD-59 [44]. A recent phase 1 study has shown that 50% of adult patients with GD (5 out of 10) achieved normalization of hyperthyroidism, and 70% (7 out of 10) experienced improvements in free thyroid hormone levels [50]. For these emerging therapies, randomized clinical trials of extended duration are necessary to evaluate their potential impact on long-term outcomes.

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Table 2. Novel therapeutic approaches for Graves disease under investigation in clinical trials

	Mechanism	Drug	Stage of development	Outcome
B-cell target	B-cell depletion	Rituximab (anti-CD20 monoclonal antibody)	Phase 2 trial in young patients (12–20 years old) [46]	13/27 (48%) in remission at 24 months after a single dose of rituximab and 12 months of ATD
	Blocking CD40 receptor interactions (attenuating B-cell activation)	Iscalimab (anti-CD40 monoclonal antibody)	Phase 2 trial [47]	7/15 (47%) showed normal free T4 and free T3 levels without ATD at 24-week after 5 doses of iscalimab over a 12-week period
	Blocking immunoglobulin recycling (targeting FcRn)	RVT-1401 (rozanolixizumab, Efgartigimod), IMVT-1401 (batoclimab)	Phase 2 trial for thyroid eye disease (batoclimab) [48]	3/7 showed responses in both ptosis and clinical activity score
	Inhibition of B-cell proliferation and differentiation (blocking BAFF)	Belimumab (anti-BAFF monoclonal antibody)	Ongoing phase 2 trial (EudraCT 2015-002127-26)	ND
TSHR target	TSHR-blocking antibodies	K1-70 (anti-TSHR monoclonal antibody)	Phase 1 trial [49]	Tolerable pharmacodynamics effects (decrease in free T4 and T3) and safety profile
	TSHR-specific immunotherapy	ATX-GD-59 (TSHR peptide)	Phase 1 trial [50]	After 10 doses in treatment-naïve patients over an 18-week period, 5/10 showed normalization of hyperthyroidism; 7/10 showed improvement in hyperthyroidism

ATD, antithyroid drug; T4, thyroxine; T3, triiodothyronine; TSHR, thyroid-stimulating hormone receptor; FcRn, neonatal immunoglobulin Fc receptor; BAFF, B-cell activating factor; ND, no data.
Modified from Lane et al. [44] with CC-BY.

Conclusion

The management of GD in children presents some challenges, including a lower rate of spontaneous remission with ATD therapy and an increased risk of complications from treatment options compared to adults. It is crucial to educate patients and their families about the disease trajectory, the effectiveness of treatment options, and potential drawbacks, as well as the long-term outlook. While recent guidelines advocate for extended ATD therapy in pediatric GD management, some patients may still need definitive therapy. Ongoing research is necessary to pinpoint risk factors. Emerging treatment strategies that target the root causes of GD are in development and expected to become part of future clinical practice, though their role in treating pediatric GD requires more research.

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

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Management of Hyperphagia and Obesity in Prader–Willi Syndrome

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Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by the absence of paternally expressed imprinted genes on chromosome 15q11–13. Individuals with PWS typically experience feeding difficulties and a lack of appetite in infancy, followed by weight gain, uncontrolled appetite, and a lack of satiety. Hyperphagia in PWS is exacerbated by impaired satiety, low energy expenditure, and intellectual difficulties, including obsessive-compulsive disorder and/or autistic behaviors. Without rigorous external management of their eating behaviors, patients with PWS become severely obese and are at a higher risk of obesity-related morbidities, such as type 2 diabetes, obstructive sleep apnea, and hypertension. Moreover, the main causes of death for PWS are obesity-related comorbidities, such as renal failure, pulmonary embolism, and respiratory and heart failure. Clinical experiences with different supplements, diets, and other methods have not been encouraging. However, therapeutic options for patients with PWS may be improving, based on recent clinical trials for a number of medications. This report reviews the causes and management of hyperphagia, as well as previous and recent clinical trials aimed at treating hyperplasia in PWS. We are optimistic that the novel treatments currently in development will help alleviate the complex metabolic issues associated with PWS.

Introduction

Prader-Willi syndrome (PWS) is a genetic disorder caused by loss of function of paternal chromosome 15 q11–q13. The paternally expressed PWS region contains genes that encode polypeptides and small nucleolar RNAs, such as *MKRN3*, *MAGEL2*, and *NECDIN* [1]. The clinical manifestations of PWS include hypotonia, early childhood-onset hyperphagia, a characteristic facial appearance, hypogonadism, growth hormone (GH) deficiency, mild-to-severe intellectual delays, and behavioral disturbances [2]. With advancements in genetic testing, PWS can now be diagnosed very early, during the neonatal period. Early diagnosis and comprehensive therapy can significantly improve the natural progression of PWS [3]. However, without rigorous management of dietary habits, individuals with PWS are prone to developing severe obesity and its associated health risks, such as type 2 diabetes (T2DM), obstructive sleep apnea, and hypertension. Complications related to obesity, including respiratory and cardiac failure, pulmonary embolism, and renal failure, are the primary causes of mortality in PWS patients. The clinical management of PWS typically involves strict dietary control and vigilant monitoring of food consumption. Currently, there are no definitive pharmacological treatments for the hyperphagia or obesity

that affect individuals with PWS. Nevertheless, clinical trials are currently investigating several medications that may offer new therapeutic options for PWS patients in the future. This study reviews the management of hyperphagia, its underlying causes, and both current and past clinical trials aimed at treating hyperphagia in PWS.

Natural Course of Hyperphagia in Prader-Willi Syndrome

The natural course of PWS is characterized by various nutritional phases, each with a distinct and complex progression, as presented in Table 1 [4]. The prenatal characteristics of phase 0 include being small for gestational age, breech presentation, polyhydramnios, decreased fetal movement, and lower birth weight compared to siblings [5]. At birth (phase 1), hypotonia is the defining characteristic. From birth to 9 months (phase 1a), poor sucking and feeding difficulties are common, often leading to failure to thrive. From birth to 24 months (phase 1b), growth typically follows a disease-specific growth chart [6,7]. During phase 2a (2–4.5 years of age), weight gain is observed, although there is no significant change in appetite. In phase 2b (ages 4.5–8), an individual's appetite and interest in food usually increase. By phase 3 (after 8 years of age), hyperphagic behaviors become evident, including aggressive food-seeking and an insatiable desire to eat. Hyperphagia significantly disrupts learning, social interactions, relationships, work productivity, and overall quality of life [8]. Some adults reach phase 4, where the increased appetite subsides; however, most individuals with PWS do not experience this phase. As the nutritional stages advance, various behavioral and endocrine disturbances emerge, leading to a range of comorbidities throughout the individual's lifetime.

Potential Mechanisms of Hyperphagia

Several theoretical models have been proposed to explain why people with PWS tend to overeat. These include issues with satiety rather than hunger; the impact of internal physiological awareness on hunger and satiation; hyperresponsive reward systems that liken food to a drug of abuse; the direct influence of genetics on the hypothalamic feeding pathway; and the significance of the perinatal environment [9]. Table 2 provides a summary of the pertinent findings.

Table 1. Natural course of hyperphagia in Prader-Willi syndrome

Phases	Median ages	Clinical characteristics
0	Prenatal to birth	Less activity during pregnancy and a smaller birth weight than siblings
1	At birth	Hypotonia
1a	0–9 months	Difficulty feeding and decreased appetite
1b	9–24 months	Enhanced appetite and eating; proper growth
2a	2.0–4.5 years	Gaining weight in the absence of an increase in appetite or additional calories
2b	4.5–8.0 years	Heightened interest in and hunger for meals, but feeling full
3	8 years-adulthood	Hyperphagic, rarely feels full
4	Adulthood	Appetite is no longer insatiable

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Table 2. Potential mechanisms causing hyperphagia in Prader-Willi syndrome (PWS)

Factor	Type of abnormality	Function	Reference
Thyroid hormone	Decreased	Regulates whole-body metabolism. In PWS: Altering metabolic rate and energy consumption as a consequence.	[57]
Ghrelin	Elevated	Temporally regulates food intake, heightens appetite, and lessens appetite after eating. In PWS: prolonged elevation of ghrelin levels, even after meals, leads to weight gain.	[58]
Leptin	Elevated	Helps regulate the body's long-term food intake and use.	[59]
Brain-derived neurotrophic factor (BDNF) and leptin	BDNF: decreased Leptin: elevated	Serves as an indicator of fullness. In PWS: local BDNF levels decrease as a result of a disruption in BDNF signaling, which boosts leptin levels and leads to leptin resistance, ultimately resulting in obesity and hyperphagia.	[60]
Insulin	Decreased	Activates melanocortin-4 receptor (MC4R) and cause satiety, stimulates Pro-opiomelanocortin (POMC) and inhibits Neuropeptide Y (NPY) neurons. In PWS: decreased insulin causes MC4R not to be stimulated.	[61]
Peptide YY	Decreased	Induces satiety by decreasing stomach emptying and activating α and β-Melanocyte-stimulating hormone(MSH) through the inhibition of NPY and stimulation of POMC. In PWS: reduced PYY stops stimulating α- and β-MSH and results in a decrease of stimulating signals to POMC.	[62]
Altered brain structure	Cortical volume: decreased White matter integrity: reduced fractional anisotropy Gray matter volume: decreased	Reduced cortical volume in the bilateral frontal, medial prefrontal cortex, and anterior cingulate causes imbalances in cognitive and emotional processing, which in turn causes appetite management dysfunctions, elevated self-reported hunger, and an increased risk of overeating. White matter function decreases in proportion to the fractional anisotropy decrease. The PWS brain areas linked to food consumption showed abnormalities in both the white and gray matter.	[63]
Orexin A	Elevated	Boosts food consumption and stimulates appetite. In PWS: the hypothalamus overstimulates orexin signaling, which exacerbates food addiction and leads to hyperphagia.	[64]

Obesity and Related Comorbidities in Prader-Willi Syndrome

In individuals with PWS, obesity is a primary contributor to early morbidity and mortality [10]. The rate of obesity varies among PWS patients, with different age groups showing different prevalence rates. In children and adolescents, the prevalence of obesity has been reported to be 40% [11]. This prevalence increases to between 82% and 98% in adult PWS patients, depending on the cohort studied [12]. Reduced sleep duration and longer sitting times are strongly linked to a higher risk of overweight or obesity [13].

Pulmonary embolism, respiratory failure, pulmonary hypertension, obstructive sleep apnea, right heart malfunction, steatohepatitis, gallstones, deep venous thrombosis, and chronic leg edema are among the comorbidities frequently linked to obesity in PWS [10,14–16]. These comorbidities can lead to potentially fatal conditions. For example, a case study reported a 21-year-old man with PWS who became severely obese and developed obstructive sleep apnea, which led to cor pulmonale—a potentially life-threatening outcome [17]. Respiratory and cardiac disorders account for 38% and 16% of deaths in PWS, respectively [16].

Obesity is linked to a markedly higher prevalence of metabolic syndrome (MS) and cardiometabolic risk factors [18]. Studies indicate that hyperlipidemia is present in approximately one-third of individuals with PWS [19]. Low high-density lipoprotein cholesterol levels and abdominal obesity, which are components of MS, were found to be strongly associated with high-sensitivity

C-reactive protein levels in Korean children and adolescents [20]. MS not only potentially contributes to the high mortality rate in PWS but is also a major risk factor for T2DM and atherosclerotic cardiovascular disease. The general guidelines for managing obese adolescents are similar to those for diagnosing, treating, and screening T2DM and MS. First-line treatments include intensive dietary counseling and regular physical activity. Metformin may be used as an adjunct therapy [21]. Regular insulin administration is also necessary, depending on the hemoglobin A1c level [22]. Pediatric endocrinologists often face challenges in providing transitional care for patients with T2DM [23].

Current Standard Therapies

GH treatment is currently part of the routine care for people with PWS during their youth. [24]. GH treatment may reduce insulin sensitivity regardless of obesity status; however, short-term trials have not demonstrated changes in hemoglobin A1c levels [25]. Although patients with PWS who receive GH treatment remain obese, long-term observational studies have shown improvements in body composition and body mass index [26].

Nutritional counseling plays a crucial role in preventing excessive weight gain, and studies show that with early nutritional management, children can attain a normal body mass [27]. Infants and children with PWS typically require only 60% to 80% of the standard daily caloric intake because of their reduced resting energy expenditure, which helps maintain a stable body weight [28,29].

An energy-restricted, well-balanced diet consisting of 30% fat, 45% carbohydrates, 25% protein, and at least 20 g of fiber daily can help prevent excessive weight gain and fat accumulation in children with PWS, typically starting at 2 years of age [30]. From an early age, children should be accustomed to drinking plain water, and parents should avoid offering sweetened beverages. Reducing sugar intake early in life can decrease the propensity to overeat. Additionally, individuals with PWS are advised to adhere to a Mediterranean diet, which is rich in complex carbohydrates, fruits, vegetables, legumes, nuts, and oils, while being low in meat and predominantly plant-based [31]. Portion sizes should be carefully regulated in relation to the individual's physical activity level and weight management goals.

Regular weighing, portion control, implementing barriers to food access (such as locking cabinets, refrigerators, and/or kitchens to deter food theft), along with dietary and financial restrictions, are additional weight-management strategies. Locking pantries, refrigerators, and food cabinets should be considered only when there is clear evidence of someone searching for food. For individuals with PWS, knowing that food is secure and not a source of temptation can be incredibly beneficial, even though such measures may appear unfair and archaic. Children with PWS need the support of educators, grandparents, caregivers, and family friends to adhere to recommended diets, eating schedules, healthy eating practices, and regular physical activity. Exercise should be considered a daily requirement beginning at a young age. The relationship between individuals with PWS and their coaches, therapists, dietitians, or doctors is a critical factor in determining the success of adherence to and maintenance of various activities, such as exercise and dietary modifications [32].

Potential Pharmaceutical Treatments for Reducing Hyperphagia

Several pharmaceutical companies have attempted to develop drugs to target the mecha-

nisms of PWS (Table 3).

1. Oxytocin

The neuropeptide hormone oxytocin is involved in social interactions, eating habits, anxiety, energy expenditure, maternal behaviors, and controlling body weight [33,34], all of which are negatively impacted by PWS. PWS patients have fewer oxytocin-producing neurons in the hypothalamic periventricular nuclei [35]. Therefore, multiple clinical studies have investigated the use of oxytocin to treat PWS (Table 3).

Intranasal oxytocin was found to be ineffective in treating hyperphagia and body weight in a group of 92 individuals with PWS, according to a comprehensive review and meta-analysis. The outcomes were comparable to those observed with a placebo [36]. The lack of positive results from oxytocin treatment in the analyzed trials may be attributed to variations in dosage and administration methods. However, this does not conclusively indicate that oxytocin is ineffective

Table 3. Potential treatments to reduce hyperphagia in Prader-Willi syndrome (PWS)

Mechanism of action	Reason for treatment selection	Studies
Oxytocin The brain produces the neuropeptide hormone oxytocin, which is involved in eating behavior, anxiety, energy expenditure, controlling body weight, and social interactions.	It has been noted that PWS patients have fewer neurons that produce oxytocin. Their inability to control their emotions, bad eating habits, and poor social integration may all be related to this deficiency.	[65–72]
Diazoxide choline-controlled release (DCCR) DCCR, a benzothiadiazine, is used to treat hyperinsulinemia-related hypoglycemia in newborns, children, and adults by increasing ion flow through ATP-sensitive K^+ channels.	The dysregulation of neuropeptide Y/Agouti-related protein/gamma-aminobutyric acid (NAG) neurons, which are regulated by leptin by decreasing their excitability, is linked to hyperphagia in Parkinson's disease. The most powerful endogenous neuropeptide, Neuropeptide Y (NPY), is produced and secreted in significant amounts as a result of this imbalance. The hyperpolarization of the resting membrane potential caused by leptin's activation of ATP-sensitive K^+ channels (KATP) via phosphoinositide-3-kinase (PI3-K) limits the release of NPY by these neurons, thereby attenuating the hyperphagia signal.	[39]
Glucagon-like peptide-1 agonist During meals, the pancreas secretes more insulin in response to food consumption, which aids in controlling postprandial glucose levels. The synthesis of glucagon-like peptide-1 (GLP-1) aids in this process.	Studies have investigated how GLP-1 receptor agonists, which delay stomach emptying and decrease appetite, impact weight loss.	[42–44]
Setmelanotide Setmelanotide, an agonist of the melanocortin (MC)-4 receptor, influences feeding and satiety to decrease eating.	Patients with PWS show strong food desire and hyperphagia from an early age, and eventually develop excessive obesity if their condition is not treated externally.	[45–47]
Livoletide Livoletide is an inactive analog of ghrelin that works by lowering the amount of the active form of ghrelin in the brain. The stomach produces a neuropeptide known as ghrelin, which triggers the human hypothalamus to directly stimulate appetite.	PWS patients have higher ghrelin levels.	[48–50,69]
Cannabinoids The control of appetitive behavior is significantly influenced by the cannabinoid-1 receptor (CB1R).	Cannabinoids have an anti-obesity effect because of their antagonistic impact on CB1R.	[51]
Beloranib In animal models, beloranib inhibits methionine aminopeptidase 2 (MetAP2) by removing methionine residues from proteins, thereby impacting adipocyte development and fat metabolism.	It has been discovered that MetAP2 inhibitors lower food intake, impact adipose tissue, and decrease fat production during weight reduction in people.	[73]
Transcranial direct-current stimulation (tDCS) tDCS is a method of modifying neural and cognitive performance in specific brain regions to help control food cravings. It is painless, safe, and non-invasive.	The dorsolateral prefrontal cortex is a brain region that mediates the processing and regulation of human food appetites and motivation.	[53–55]

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in treating hyperphagia and behavioral abnormalities, which are two symptoms of PWS. To determine the efficacy of oxytocin in PWS patients more conclusively, further large-scale prospective randomized controlled trials are necessary.

2. Carbetocin

An analog of oxytocin, intranasal carbetocin, has been explored as a targeted therapy for oxytocin replacement and has shown promising effects on hyperphagia [37]. A phase III trial, which was randomized, double-blind, placebo-controlled, and included long-term follow-up, involved 130 patients with PWS aged 7 to 18. These participants were recruited from 24 outpatient clinics at academic medical centers [38]. They were randomized to receive either 9.6 mg/dose of carbetocin, 3.2 mg/dose of carbetocin, or a placebo three times daily for 8 weeks. During the subsequent 56-week long-term follow-up, those initially on placebo were reassigned to either the 9.6 mg or 3.2 mg carbetocin dose. The onset of the coronavirus disease 2019 (COVID-19) pandemic led to the early termination of enrollment. The Hyperphagia Questionnaire for Clinical Trials (HQ-CT) and the Children's Yale-Brown Obsessive-Compulsive Scale showed numerical improvements in the 9.6-mg group, but these did not reach statistical significance. In contrast, the 3.2-mg group showed marginally significant improvements compared to placebo on the HQ-CT, the PWS Anxiousness and Distress Behaviors Questionnaire, and the Clinical Global Impression of Change. The most common adverse effect was flushing, ranging from mild to severe. Consequently, carbetocin was well-tolerated, and a 3.2-mg dose was associated with clinically meaningful improvements in hyperphagia, anxiety, and distress behaviors in patients with PWS.

3. Diazoxide choline controlled-release

Diazoxide choline, a benzothiadiazine, activates ion flow through ATP-sensitive K^+ channels (KATP). It is currently used to treat hypoglycemia and hyperinsulinemia. In the adipocytes of patients with PWS, diazoxide may exert a therapeutic effect by stimulating KATP channels, modulating hypothalamic neuropeptide Y, and affecting insulin secretion from pancreatic β-cells [39]. An oral, once-daily, extended-release tablet of diazoxide choline controlled-release (DCCR) has been developed. A 12-week course of oral DCCR treatment has been shown to reduce blood glucose levels, decrease fat mass, and improve endurance [40]. A phase 3 trial involving 127 PWS patients aged 4 years and older with hyperphagia, was conducted over 13 weeks. This double-blind, placebo-controlled study randomly assigned participants in a 2:1 ratio to receive either DCCR or a placebo [41]. The primary outcome measure was the change in hyperphagia from baseline, as assessed by the HQ-CT. Secondary endpoints included the Clinical Global Impression of Change score and changes in behavior, hormones, and body composition. In the pre-COVID-19 analysis, and particularly among subjects with severe baseline hyperphagia, DCCR treatment significantly improved hyperphagia. However, the primary analysis did not show a significant improvement in hyperphagia overall.

4. Glucagon-like peptide-1 agonists

The hormone glucagon-like peptide-1 (GLP-1) is produced by the L-cells of the colon and ileum. It is released in response to food intake and enhances the pancreas's ability to secrete insulin during meals, aiding in the regulation of postprandial glucose levels. Research on the effects of GLP-1 receptor agonists on weight loss has shown that they can lead to delayed gastric emptying and a reduction in appetite [42]. A comprehensive review indicates that GLP-1

receptor agonists are generally safe for individuals with PWS and may offer benefits in managing weight, blood glucose, and satiety. However, given the inherent risk of gastric rupture in this population and the potential side effect of delayed gastric emptying, careful consideration is required when prescribing GLP-1 receptor agonists [43,44].

5. Setmelanotide

Setmelanotide is a potent and specific agonist of the melanocortin-4 receptor that is used to treat genetic disorders associated with obesity. Effective activation of melanocortin-4 receptor may help reduce the hyperphagia associated with PWS [45]. A phase II trial investigated the effects of once-daily subcutaneous injections of setmelanotide in 40 individuals with PWS (19 males and 21 females; mean age, 26.4 years) [46]. There was no significant difference in the mean weight change between the setmelanotide and placebo groups at 4 weeks. At the two highest doses of setmelanotide, there was a slight, but not statistically significant, reduction from baseline in the mean hyperphagia questionnaire score. Adverse effects included occasional mild-to-moderate injection site reactions, darkening of the skin and nevi, and sporadic, spontaneous penile erections. Although the results in PWS were not promising, subsequent studies on the effects of setmelanotide in other rare monogenic forms of obesity, such as in individuals with POMC mutations or Bardet-Biedl syndrome—a group of genetic disorders affecting ciliary proteins—were successful [47].

6. Livoletide

In PWS, hyperphagia is associated with the ratio of acylated ghrelin (AG) to unacylated ghrelin (UAG) [48]. It has been theorized that a decrease in UAG levels leads to an increased AG/UAG ratio, which may contribute to the development of hyperphagia [49]. Therefore, one potential treatment approach for hyperphagia is to pharmacologically increase UAG levels. Livoletide, also known as AZP-531, is a peptide analogue of UAG [49]. In a pivotal phase 2b/3 study, which was double-blind and placebo-controlled, 158 PWS patients were randomly assigned to receive either livoletide at a dose of 60 μg/kg or a placebo at a dose of 120 μg/kg [50]. Livoletide was generally well-tolerated throughout the study period. The most common adverse effect reported was a mild reaction at the injection site. However, livoletide did not significantly impact body weight, waist circumference, or fat mass as measured by dual-energy X-ray absorptiometry. It also failed to significantly reduce hyperphagia or food-related behaviors. Consequently, the company announced that it would discontinue the development of livoletide as a potential therapeutic option for PWS.

7. Cannabinoids

The cannabinoid-1 receptor (CB1R) plays a crucial role in regulating appetitive behavior. It is most abundantly expressed in the hypothalamus and other brain regions associated with appetite control. Cannabidiol, a non-psychotropic constituent of cannabis plants, exerts an anti-obesity effect through its antagonistic action on CB1R [51]. The CB1R blocker JD5037 interacts with cannabinoid receptors to diminish appetite and enhance satiety. Although JD5037 reached the stage of enrolling participants for an early clinical trial as a potential treatment for hyperphagia in PWS, unforeseen complications resulted in the trial's discontinuation.

8. Beloranib

Beloranib removes methionine residues from proteins, thereby inhibiting methionine amino-

peptidase 2 and influencing fat metabolism. In the United States, a large group of adults and adolescents with PWS participated in a phase III randomized, placebo-controlled, double-blind study of beloranib. Over the 26-week treatment period, the groups receiving beloranib experienced a significant decrease in fat mass compared to the placebo group, with participants achieving a weight loss of 5% or more. Additionally, those treated with beloranib demonstrated improvements in eight of the nine HQ-CT item scores. Unfortunately, the occurrence of venous thromboembolic events, including two deaths, among participants in the beloranib group necessitated the premature discontinuation of the trial.

9. Transcutaneous vagus nerve stimulation

Recently, Holland et al. [52] showed that transcutaneous vagus nerve stimulation can be an effective treatment for temper tantrums and associated behaviors in individuals with PWS and hyperphagia. Four of the five participants with PWS exhibited a significant reduction in the frequency of their outbursts. Additionally, improvements were noted in emotional regulation, responses to treatments, and the ability to manage and cope with situations that typically precipitate outbursts. However, there was no observed decrease in hyperphagia [52].

10. Transcranial direct-current stimulation

Transcranial direct-current stimulation (tDCS) is a safe, painless, and non-invasive technique that can modify neuronal and cognitive functions in targeted areas of the brain [53]. For instance, tDCS activates the dorsolateral prefrontal cortex, which is important in processing and controlling food urges [53–55]. A few studies have provided evidence that tDCS is beneficial for hyperphagic behavior in PWS patients [53]; however, further testing is required.

Surgical Management of Obesity in Prader-Willi Syndrome

Bariatric surgery remains a contentious treatment option for obesity in individuals with PWS. Scheimann et al. [56] conducted a retrospective analysis of 60 documented cases of bariatric surgery in patients with PWS, identifying a range of postoperative complications. Individuals with PWS are highly susceptible to developing gastric dilatation or necrosis due to prevalent medical issues such as hyperlipidemia, GH deficiency, increased insulin sensitivity, a reduced ability to vomit, and an atypical eating pattern characterized by hyperphagia. Consequently, compared to obese individuals without PWS, those with PWS may face a higher risk of complications from bariatric surgery. Severe incidents reported include the death of one patient following gastric and jejunoileal bypass, deep vein thrombosis and wound infection in another, and the necessity for splenectomy during bariatric surgery in two patients. Although the majority of PWS patients who undergo gastroplasty initially lose weight, they tend to regain it over time. Given the limited evidence from a few case series, it appears there is little justification for subjecting individuals with PWS to the significant potential risks associated with bariatric surgery [56].

Conclusion

Safe and effective treatment is necessary for managing both hyperphagia and obesity in patients with PWS, as the majority of affected individuals display significant food-seeking behavior and hyperphagia from early childhood. Without intervention, they often develop severe obesity over time. A variety of medications have been explored or are currently undergoing

clinical trials to address hyperphagia and obesity in PWS patients. Research has shown that several medications can ameliorate hormonal imbalances, body composition issues, and eating behaviors. However, there is scant evidence supporting the long-term safety and effectiveness of these treatments in the PWS population, highlighting the need for further study. Additionally, there is a need for more rigorous research to develop objective measures of hyperphagia, beyond the subjective questionnaires currently used in clinical trials. Through these treatments, we aim to mitigate the complex metabolic challenges associated with PWS.

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Conflict of Interest

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

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Review Article

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Updates on Obesity in Prader-Willi Syndrome: From Genetics to Management

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Prader-Willi syndrome; Genomic imprinting; Hyperphagia, obesity

Prader-Willi syndrome (PWS), which is considered the most common genetic form of obesity, results from the absence of imprinted genes in the paternally derived PWS critical region located on chromosome 15q11.2–13. Infants with PWS exhibit poor sucking, neonatal hypotonia, and delayed motor milestones. These patients begin to experience hyperphagia and obesity from 2 to 3 years of age. PWS is a multisystemic disorder, and its clinical manifestations include developmental delay/intellectual disability, behavioral problems, dysmorphic facial features, short stature, scoliosis, and endocrine abnormalities such as hypogonadism, growth hormone deficiency, hypothyroidism, and central adrenal insufficiency. Although the underlying mechanism of hyperphagia is not completely understood, hypothalamic and endocrine dysregulation is believed to be responsible for the lack of satiety and abnormal food-seeking behaviors that lead to severe obesity. The management of PWS requires a multidisciplinary team approach. Early diagnosis and comprehensive early intervention are essential to prevent the development of obesity-related morbidities, including metabolic syndrome, diabetes mellitus, obstructive sleep apnea, respiratory failure, pulmonary hypertension, and cardiovascular complications. Although several clinical trials have been conducted on the pharmacologic treatment of obesity in PWS, no drugs have demonstrated a consistently beneficial effect to date. Nevertheless, ongoing research efforts should be directed toward understanding the mechanism of the unique obesity phenotype of PWS and developing pharmacological therapies.

Introduction

Prader-Willi syndrome (PWS) is a rare multisystem genetic disorder that is recognized as the most common genetic cause of obesity [1]. Its incidence ranges from 1 in 10,000 to 1 in 30,000 births [2]. PWS results from the absence of imprinted genes in the paternally derived PWS/Angelman syndrome region of chromosome 15q11.2–13.

Clinical manifestations of PWS include poor sucking and swallowing difficulties accompanied by infantile hypotonia, followed by delayed motor milestones. Patients with the condition begin to experience hyperphagia and obesity in early childhood, along with reduced physical activity. They also exhibit abnormal body composition characterized by increased fat mass and reduced lean body mass, as well as a low metabolic rate potentially leading to severe obesity [1,3,4]. Developmental delay/intellectual disability, learning difficulties, behavioral problems, and autistic features are common [5,6]. Characteristic facial features of PWS include narrowing of the

forehead, almond-shaped eyes, small chin, and high-arched palate [3]. Endocrine abnormalities, such as growth hormone deficiency, hypopituitarism, hypothyroidism, and hypogonadism, may also be present [3]. The PWS phenotype is currently believed to result from the complex dysregulation of hypothalamic control [7].

The management of PWS necessitates a multidisciplinary team approach that includes a neonatologist, medical geneticist, pediatric endocrinologist, dietitian, orthopedist, and rehabilitation therapist [6,8]. Early diagnosis and intervention are crucial for preventing morbid obesity, which is key to managing patients with PWS. Due to morbid obesity, individuals with PWS may experience numerous complications, such as type 2 diabetes mellitus (T2DM), metabolic syndrome, obstructive sleep apnea, respiratory failure, thromboembolism, pulmonary hypertension, and right heart failure. These complications contribute to a high mortality rate relative to the general population [7,9–12]. In this context, the present review covers the genetic and endocrine mechanisms of obesity and the current therapeutic strategies for managing obesity in PWS.

Hyperphagia and Obesity Phenotype in Prader-Willi Syndrome

Patients with PWS experience poor sucking and feeding difficulties during infancy, followed by uncontrolled hyperphagia and a lack of satiety. This can lead to rapid weight gain and obesity beginning at 2 to 3 years of age. Progressive food-seeking behavior and hyperphagia are observed in association with constant and inexorable hunger, which can lead to life-threatening obesity in adults with PWS [10]. Individuals with PWS often exhibit behavioral problems related to aggressive and obsessive food-seeking, including hoarding food, foraging, and stealing food or money to purchase food [7]. These abnormal behaviors can cause lifelong distress for patients and their families and may negatively impact social adaptation, occupational performance, and quality of life.

The obesity phenotype in PWS is distinguishable from other common forms of obesity [6]. Patients with PWS typically have lower muscle mass than individuals with simple obesity, which results in lower resting energy expenditure [13]. In contrast, patients with PWS have higher fat mass than body mass index (BMI)-matched individuals with common obesity [13,14]. Typically, individuals with PWS exhibit an excessive accumulation of subcutaneous fat in the trunk and proximal extremities in conjunction with relatively low visceral adiposity, which is responsible for higher insulin sensitivity compared to BMI-matched populations with common obesity [14].

Genetics of Prader-Willi Syndrome

Three distinct genetic mechanisms are responsible for PWS: approximately 65% to 70% of cases result from paternal deletion of 15q11.2–13, 20% to 30% are caused by maternal uniparental disomy of chromosome 15, and the remaining 2% to 5% of cases result from imprinting center defects or chromosome 15 rearrangement [15–19]. The paternally expressed PWS region contains several genes, including *MKRN3*, *MAGEL2*, *NECDIN*, and small nucleolar RNA genes [6,20]. *SNORD116*, a small nucleolar RNA gene, is known to be the critical gene for most PWS phenotypes [21,22]. Depletion of *SNORD116* has been demonstrated to cause an imbalance in the neuromodulatory systems of the hypothalamus, leading to abnormal food intake behavior and sleep problems in a mouse model that mimics the clinical manifestations of PWS [21].

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Hypothalamic Abnormalities in Prader-Willi Syndrome

Structural brain alterations, including a scarcity of oxytocin neurons in the hypothalamus and reduced fractional anisotropy in neuron fibers, have been linked to uncontrollable hyperphagia and a lack of satiety [7,23,24]. Mouse models with disrupted *SNORD116* expression in the mediobasal hypothalamus have mimicked the hyperphagic behavior observed in PWS [25]. Furthermore, imaging studies have shown an increased hypothalamic response to food stimuli and diminished coupling between the ventral striatum and limbic structures [26,27]. These findings suggest that structural or functional dysregulation of the hypothalamus plays a critical role in the hyperphagia and obesity associated with PWS.

Endocrine Alterations in Prader-Willi Syndrome

The mechanism underlying abnormal hyperphagia in PWS is not fully understood. However, several studies have demonstrated alterations in anorexigenic and orexigenic hormones in patients with PWS relative to obese individuals (Fig. 1).

Elevated serum leptin, an anorexigenic hormone, has been reported [28]. However, leptin levels have not been shown to differ significantly between individuals with PWS and those with simple obesity [28,29]. Patients with PWS have lower circulating levels of brain-derived neurotrophic factor than individuals with simple obesity [30]. Since brain-derived neurotrophic factor acts as a satiety signal and regulates energy homeostasis, its reduced presence may contribute to the persistent hunger observed in patients with PWS [30]. Oxytocin, another anorexigenic hormone, inhibits food intake. Low levels of this hormone have also been observed in patients with PWS, suggesting a potential causal relationship with PWS-associated hyperphagia [31]. Glucagon-like peptide 1 (GLP-1) and peptide YY are secreted in response to food intake and exert anorexigenic effects. Research has found no significant difference in GLP-1 levels between individuals with PWS and those with simple obesity [32]; however, data on peptide YY levels in PWS are conflicting [7,32]. Adiponectin, released from adipose tissue, is involved in appetite modulation, energy homeostasis, and lipid and glucose metabolism, as well as insulin sensitivity and inflammation. This hormone stimulates food intake in the fasting

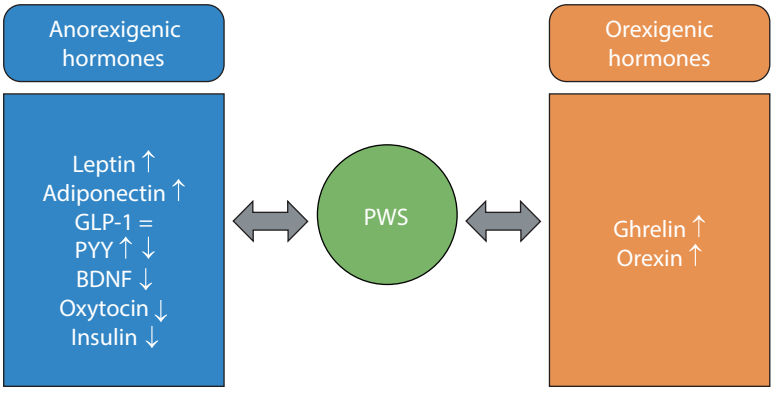

Fig. 1. Endocrine changes in Prader-Willi syndrome. Changes in orexigenic and anorexigenic hormone levels in PWS. ↑, increased; ↓, decreased; =, unchanged; GLP-1, glucagon-like peptide 1; PYY, peptide YY; BDNF, brain-derived neurotrophic factor; PWS, Prader-Willi syndrome.

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state, and higher levels have been reported in patients with PWS compared to obese controls [33]. A well-known endocrine characteristic of PWS is relative hypoinsulinemia and low insulin resistance, despite severe obesity. This fasting and/or postprandial hypoinsulinemia may also play a role in the hyperphagia seen in PWS [7].

Among the orexigenic hormones, an elevated level of ghrelin has been observed in children and adults with PWS [34]. Two forms of ghrelin are found in circulation: acylated ghrelin (AG) and unacylated ghrelin (UAG) [19]. AG is known to stimulate hunger, and studies have shown that a high AG/UAG ratio is associated with hyperphagia and obesity in individuals with PWS [35,36]. Orexin, another orexigenic hormone, interacts with other neuropeptides to stimulate food intake. One study suggests that dysregulation of orexin may contribute to the abnormal eating behaviors observed in PWS [37].

Pharmacological Treatments for Obesity in Prader-Willi Syndrome

Pharmacological therapeutic options for patients with PWS are extremely limited. Unfortunately, no medications have yet demonstrated long-term efficacy in managing hyperphagia associated with PWS [7].

1. Orlistat

Orlistat is a pancreatic lipase inhibitor that reduces the absorption of ingested fats. This medication acts peripherally, and the resulting presence of undigested fats can alter stool consistency, potentially reducing long-term compliance [7]. A trial of orlistat in patients with PWS demonstrated modest efficacy, but poor compliance and gastrointestinal side effects were noted [38].

2. Metformin

Metformin is commonly prescribed for patients with PWS who also exhibit insulin resistance or T2DM. A pilot study has indicated that metformin may enhance feelings of satiety and decrease food-related anxiety in certain individuals with PWS, potentially through the mechanism of improved insulin sensitivity [39].

3. Serotonin receptor agonists

Serotonin plays a role in reducing food intake, and serotonin receptor agonists are therefore utilized in the management of obesity. Sibutramine, a non-selective serotonin and norepinephrine reuptake inhibitor, has been considered for patients with PWS due to its promising results in those with hypothalamic obesity [40]. However, sibutramine was withdrawn from the market because of its association with adverse cardiovascular events. Lorcaserin, a selective serotonin 2C receptor agonist with high affinity, has been demonstrated effective in promoting weight loss in individuals with obesity. Moreover, it has been shown to reduce blood pressure, along with levels of total and low-density lipoprotein cholesterol, fasting glucose, insulin, and inflammatory markers [41,42]. Unfortunately, lorcaserin was also withdrawn from the market due to an increased risk of pancreatic, lung, and colorectal cancers.

4. Growth hormone

Almost all children with PWS and some adults with the condition exhibit growth hormone

deficiency. Growth hormone therapy is beneficial in reducing body fat, increasing lean body mass, and increasing height, which leads to improved body composition [43,44]. Several studies have demonstrated the efficacy of growth hormone therapy in addressing developmental and behavioral problems, particularly when initiated at a young age [44–46]. However, growth hormone therapy has limited effects on reducing appetite and food-seeking behavior [7].

5. Octreotide

Octreotide is a long-acting somatostatin analogue that can significantly reduce fasting ghrelin concentrations in both acylated and unacylated forms. Considering that individuals with PWS display increased serum ghrelin levels, octreotide therapy has been attempted. However, this therapy has not demonstrated significant effects on weight, appetite, or food-seeking behaviors in patients with PWS [47,48].

6. Topiramate

Topiramate acts as a modulator on sodium ion channels, gamma-aminobutyric acid (GABA) receptors, and AMPA/kainate receptors, which affects food-seeking behavior [7]. Additionally, topiramate reduces messenger RNA levels for neuropeptide Y, which stimulates food intake, increases appetite, and delays satiety [19]. In a double-blind, randomized, placebo-controlled clinical trial involving 62 adults with PWS, topiramate therapy was well tolerated and exerted a beneficial effect on eating behaviors in a dose-dependent manner, although no significant reduction in BMI was observed [49].

Emerging Treatments for Hyperphagia

Recent years have seen ongoing development of new pharmacological therapies for the management of hyperphagia and obesity in PWS.

1. Glucagon-like peptide 1 agonists

Research has shown that GLP-1 agonist therapy is effective in managing obesity, satiety issues, and elevated blood glucose levels in patients with PWS [8,50–53]. A 6-month course of GLP-1 agonist therapy led to reduced appetite scores and lower levels of glycosylated hemoglobin (HbA1c) in a group of 10 patients with the condition, although no significant changes were observed in body weight, BMI, adiposity, or ghrelin levels [51]. In a separate study, 24 months of subcutaneous GLP-1 agonist therapy yielded reductions in BMI, waist circumference, and serum HbA1c levels in adult patients with PWS and T2DM, without serious adverse events [53].

2. Ghrelin

In patients with PWS, UAG levels tend to be low, while the ratio of AG to UAG is high. Administering a pharmacologically stable amino acid form of a UAG analogue can normalize this ratio and may treat the hyperphagia associated with the condition [19,35]. In a mouse model, while no significant weight changes were observed, this treatment approach led to a reduction in waist circumference and fat mass, with no serious side effects reported [54]. A phase 2 clinical trial involving 47 patients with PWS revealed that UAG analogue therapy significantly improved food-related behaviors and showed promising metabolic outcomes [55].

Another approach involves inhibiting ghrelin O-acyltransferase, the enzyme responsible for the

octanoylation of ghrelin. Inhibiting ghrelin O-acyltransferase reduces the production of AG and could lead to a decreased AG/UAG ratio, thereby helping to control hyperphagia [56,57].

3. Melanocortin 4 receptor agonist

An melanocortin 4 receptor (MC4R) agonist, a synthetic peptide, binds to human MC4R, leading to decreased food intake and substantial weight loss [4]. In 2020, the US Food and Drug Administration approved setmelanotide for the treatment of obesity in adults and children aged 6 years and older with monogenic obesity due to Pro-opiomelanocortin, proprotein convertase subtilisin/kexin type 1, or leptin receptor deficiency [58]. Additionally, setmelanotide is under evaluation for its effectiveness in patients with syndromic obesity, such as Bardet–Biedl syndrome and Alström syndrome, as well as those with chromosomal rearrangements at the 16p11.2 locus [59–61]. However, in a phase II clinical trial (ClinicalTrials.gov: NCT02311673), setmelanotide therapy did not significantly reduce hyperphagia or body weight in obese patients with PWS [7].

4. Diazoxide

Diazoxide is an adenosine triphosphate-sensitive potassium (K_{ATP}) channel agonist used in the treatment of hyperinsulinemic hypoglycemia. It has been shown to help manage obesity in PWS by downregulating insulin secretion, reducing the synthesis and secretion of hypothalamic appetite-stimulating neuropeptides such as neuropeptide Y and Agouti-related protein, increasing GABAergic neuronal excitability, and activating K_{ATP} channels in adipocytes [19]. One study reported that 14 weeks of oral diazoxide administration was associated with significant reductions in hyperphagia and aggressive behaviors [62]. Additionally, diazoxide treatment in adolescent and adult patients with PWS was associated with decreased fat mass, waist circumference, and improvements in lipid profiles and insulin resistance, although these changes did not reach statistical significance [62]. While the mechanism by which diazoxide affects hyperphagia in PWS is not fully understood, current observations suggest that diazoxide may be a potential therapeutic option, warranting further research.

5. Oxytocin and carbetocin

Oxytocin, a hormone produced in the hypothalamic paraventricular nucleus and supraoptic nucleus, plays a role in regulating food intake and satiety [63]. Patients with PWS exhibit abnormalities in the oxytocin system [7]. Intranasal administration of carbetocin, an oxytocin analogue, has been tested in individuals with PWS and has shown a beneficial effect in reducing hyperphagia [64].

6. Beloranib

Beloranib inhibits methionine aminopeptidase 2 (MetAP2), leading to hormonal changes that decrease fat biosynthesis, enhance fat oxidation, and increase lipolysis. This compound also influences satiety in the hypothalamus. In a phase 3 clinical trial involving patients with PWS, beloranib significantly reduced food intake and promoted weight loss [65]. However, the development of beloranib was halted following the deaths of two patients from pulmonary embolism during the trial. In a preclinical study, another MetAP2 inhibitor was assessed for safety and efficacy in the treatment of diabetes mellitus and obesity; the results indicated improved safety with regard to endothelial cell proliferation and coagulation [66].

Conclusion

Once established, managing obesity in individuals with PWS is challenging due to the complex interplay of contributors to hyperphagia and obesity, including metabolic, hormonal, behavioral, and neurological factors. Consequently, early diagnosis and a comprehensive, multidisciplinary approach that includes parental education are crucial for preventing the early onset of obesity and maintaining a child's weight within a healthy range. This involves implementing rigorous structures to limit food intake and encourage physical activity. However, sustaining lifestyle interventions over the long term often proves difficult for patients with PWS. Although no medications have consistently demonstrated effectiveness in managing obesity in PWS to date, ongoing research efforts are essential for the development of potential pharmacological therapies.

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Conflict of Interest

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

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