Review Article

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Update on Diagnosis and Treatment of Colorectal Cancer

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The rate of colorectal cancer (CRC) has altered. Early-onset CRC patients are increasing, and it is one of the main causes of cancer-related death. Based on epidemiologic change, the CRC screening program needs to be changed. To increase compliance, non-invasive screening techniques are developed. Although CRC survival has increased, the oncologic prognosis of metastatic CRC is remains poor. Even in metastatic CRC, which is the most difficult to treat, attempts are being made to increase the survival rate by active surgical therapy with the creation of chemotherapeutic regimens and targeted treatment based on genomic information. Due to the introduction of aggressive chemotherapy regimens, targeted therapy based on genomic features, and improvements in surgical technique, the role of surgical treatment in metastatic CRC has expanded. Metastatic CRC surgery was indicated for liver, lung, and even peritoneal seeding. Local ablation therapy was also effectively used for liver and lung metastasis. Cytoreductive surgery and intraperitoneal chemotherapy were tried for peritoneal seeding and demonstrated good results in a subgroup of patients, although the right indication was carefully assessed. At the same time, one of the key goals of treatment for CRC was to maintain functional outcomes. Neoadjuvant treatment, in particular, helped rectal cancer patients preserve functional results while maintaining oncologic safety. Rectal cancer organ preservation techniques are now being researched heavily in a variety of neoadjuvant treatment settings, including immunotherapy and whole neoadjuvant therapy. Precision medicine based on patient and disease characteristics is currently being used for the diagnosis and treatment of CRC.

Introduction

In 2019, cancer is the leading cause of death in Korea, and colorectal cancer (CRC) is one of the most prevalent malignancies worldwide [1,2]. CRC is the second leading cause of cancer-related death and the third most prevalent malignancy globally [2]. Thyroid, lung, stomach, colorectal, and breast cancer were the five most frequently diagnosed malignancies in Korea in 2019 according to statistics from the National Cancer Registration Project of the Central Cancer Registry of Korea. After stomach and lung cancer in males and breast and thyroid cancer in women, CRC is the third most frequent malignancy in both sexes [1]. Since 1999, the incidence of CRC has been consistently rising; however, it has been slowly declining since about 2011. Both rectal and colon cancers exhibit the same incidence trend (Fig. 1). Although adenocarcinoma makes up the majority of CRC cases, neuroendocrine tumors are the most common non-adenocarcinoma [3]. A feature worth observing is the lowering of the age of onset, and it has

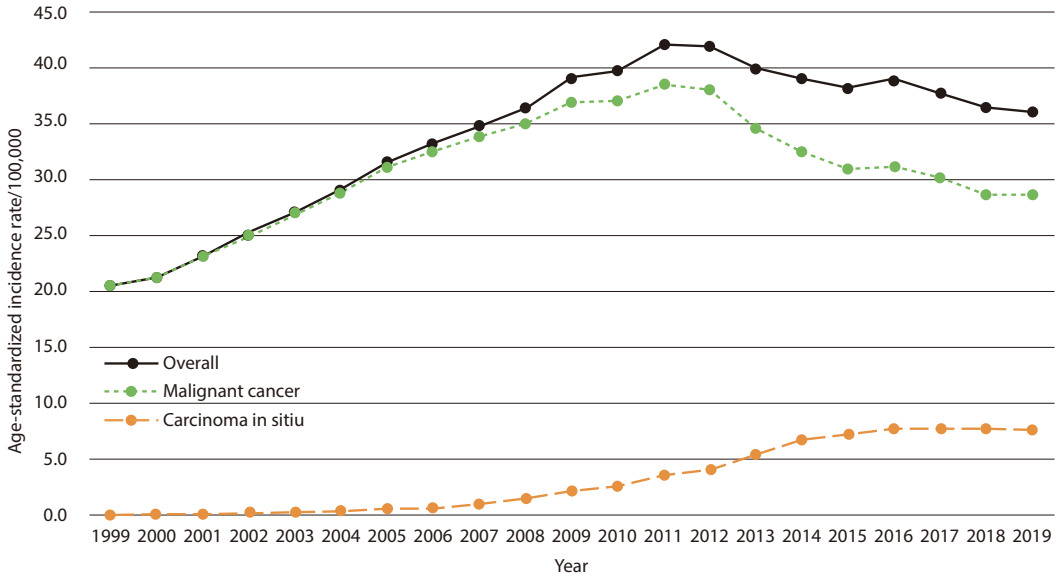

Fig. 1. Age-standardized incidence rates of colorectal cancer in Korea, 1999–2019. Adapted from Kang et al. [1] with CC-BY-NC.

been observed that in industrialized nations, the prevalence of early-onset CRC in those under 50 is rising, increasing social awareness It is very obvious that CRC incidence is rising among the elderly. The growing older population in good health appears to be the cause. A national investigation on the treatment strategy for advanced CRC seems necessary given the current trend toward an aging society [1,2,4].

Overall survival (OS) rates for CRC patients in Korea are extremely high, and the relative OS rate for CRC patients is reported to be 74.3% of patients diagnosed between 2015 and 2019 [1]. In Korea, the OS rate of CRC varies by gender, with men having a greater rate than women. The increased survival rate in men is thought to be due to the average age of CRC diagnosis being older in women than in men and the presence of more right-sided CRC in women, despite the fact that the precise mechanism is unknown [1,2,5]. Although the survival rate for CRC in stages I-III is increasing, there is still an issue because the increase in the OS rate for CRC with metastatic disease is not significant.

Advances in Colorectal Cancer Screening and Diagnosis

The cost, compliance, sensitivity, and specificity of the test, as well as other factors, are taken into account while choosing the screening test to be used. Fecal occult blood test, an immunochemical test method, is now employed in Korea as the first line screening test for national health screening. Although there is still debate regarding the accuracy of the diagnosis of polyps or CRC, the non-invasive test has the significant advantage of high compliance. There will not be any debate on the importance of colonoscopy in the timely diagnosis and treatment of precancerous lesions and early CRC. Due to the invasiveness and low compliance of the colonoscopy as a primary screening test, it is crucial to weigh this option [6,7]. Fecal occult blood testing every one to two years for asymptomatic persons aged 45 to 80 is the current CRC screening prescription in Korea, and colonoscopies are only occasionally conducted according on individual risk. The question of whether colonoscopy can be used as a primary screening test

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is being investigated in Korea as a pilot project, but it is still necessary to make decisions about potential complications and costs, whether the examination can be restricted based on bowel preparation, and how to assess the operator's skill. In particular, the screening test may only be used and assessed for effectiveness after extensive research and development on how to improve patient compliance.

More accurate non-invasive screening methods have been developed in an effort to replace the fecal occult blood test, which is the current screening method [8–10] (Table 1). The test that seeks to identify tumor epithelial DNA in feces in order to diagnose CRC is now coming the closest to clinical application. An assay for mutant *KRAS*, methylation *BMP3*, methylated *NDRG4*, and a fecal immunochemical test for hemoglobin were all included in the FDA-approved multi-target fecal DNA test [8]. In a research involving 9,989 average-risk people having colonoscopy, the multi-target fecal DNA test demonstrated better sensitivity for the diagnosis of CRC (92% vs. 74%) and advanced adenoma (42% vs. 24%) when compared with fecal immunochemical test test. In 2018, the Ministry of Food and Drug Safety in Korea approved the EarlyTect fecal DNA test (Genomic Tree, Daejun, Korea), which only examines the methylation of one gene, the syndecan-2 gene [10]. The findings are significant since we are carrying out a prospective multicenter study with a focus on the asymptomatic general population over 60 or in the high-risk category. Due to its excellent disease prediction, non-invasiveness, and high compliance, this fecal DNA detection test is projected to be used as a screening tool. The poor identification rate of pre-cancerous lesions is a challenge; thus it is important to watch with greater skepticism what kind of outcomes will be seen in the long-term impact of CRC prevention in the future.

Changes to CRC screening are required in light of the rising incidence of CRC in people under the age of 50 [1,2,11] and the growing elderly population. Although the US Preventive Services Task Force and the Multi-Specialty Task Force currently recommend starting screening at age 50, the American Cancer Society published guidelines in 2018 with a qualified recommendation to lower the starting age for CRC screening from 50 to 45 years of age in the average-risk adult population [12]. Few empirical studies have been conducted on the effectiveness of screening in younger, average-risk persons [13,14], and it is unknown which screening method is best for this age group.

According to the US Preventive Services Task Force's most recent CRC screening recommendation for individuals aged 76 to 85, the choice to test for CRC should be made individually, taking into account the patient's general health and screening history [15]. According to the recommendation, screening is best recommended for people who have never been screened, are healthy enough to get treatment if CRC is found, and do not have significantly shortened life expectancies. Due to conflicting sources of death, screening is not advised for persons 86 years of age and older. Although further research is needed, healthcare professionals should participate in shared decision-making when evaluating people over 75 years old and take into account factors like life expectancy, patient risk, values, and preferences.

Table 1. Clinically available non-invasive screening method with stool DNA detection for colorectal cancer diagnosis

Product name	Target	Sensitivity, cancer	Specificity, cancer	Sensitivity, advanced adenoma detection
Cologuard [8]	*NDRG4*, *BMP3* DNA methylation, KRAS mutation, hemoglobin	92.3%	89.8%	42.4%
EarlyTect [10]	*SDT2* methylation, hemoglobin	90.2%	90.2%	66.7%

NDRG4, N-myc downstream-regulated gene 4; *BMP3*, bone morphogenetic protein 3; *KRAS*, Kirsten rat sarcoma virus; *SDT2*, synthecan 2.

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It is crucial to advise when to halt screening in future research.

Development Surgical Treatment of Metastatic Colorectal Cancer

Despite a significant improvement in treatment outcomes for CRC, metastatic CRC therapy outcomes remain remarkably poor [1,2]. Therefore, we have worked hard to actively treat patients with metastatic disease in an effort to increase the OS of CRC patients.

Chemotherapy is the major treatment for CRC that has spread to other organs, and surgery is only occasionally employed. However, with advancements in systemic therapy, increased use of genetic information, and the development of surgical techniques, more individuals with metastatic CRC can benefit from curative-intent surgical surgery [16–18].

Liver metastasis, common metastasis of CRC, is known as metastatic CRC that can improve the prognosis with surgery. Liver resection with or without local ablation therapy, such as radiofrequency ablation and stereotatic radiation (SBRT), can be used for curative treatment in CRC patients with liver metastases [19–21]. Numerous prognostic factors and key drivers of resectability have included the size and location of liver metastases, as well as their distribution throughout the liver and the existence of extrahepatic metastatic lesions [20,22,23]. However, today, even in situations with multiple liver metastases, surgery is used when the likelihood of resection is verified through earlier chemotherapy, and in some instances, secondary resection is carried out in specific patients [23–25]. In metastatic CRC patients with bi-lobar liver metastases and limited functional liver remnants, portal vein embolization can be used with CRC surgery to assure tumor regression and hepatic hypertrophy (FLR). The two-stage hepatectomy would also enable the total removal of bi-lobar liver metastases and FLR regulation. To get around the drawback of liver resection in CRC patients with a small FLR and numerous liver metastases, associating liver partition and portal vein ligation for phased hepatectomy (ALPPS) was created. According to reports, there was no discernible difference between ALPPS and two-stage hepatectomy in terms of postoperative morbidities and fatalities, although ALPPS had improved survival outcomes in randomized controlled trials [25,26].

Different strategies would be taken into consideration for individuals with synchronous liver metastases depending on their general health, the likelihood of curative resection, and extra-hepatic metastasis. There have been recommendations for simultaneous resection, liver-first strategy, and bowel first approach. Although a simultaneous liver and colon resection has advantages over a liver-first/bowel-first approach in terms of avoiding two surgeries, expediting the start of chemotherapy, and lowering the risk of cancer dissemination, postoperative complications and increased surgical stress are still a concern [27–29].

Surgical treatment for lung metastases and peritoneal metastases is developing in addition to liver metastases. Surgery can be beneficial for pulmonary metastasis, a metastatic lesion that is similar to liver metastasis in terms of how well it responds to treatment [30,31]. A five-year OS rate of more than 50% was observed after pulmonary metastasectomy in a systematic analysis of surgical removal of pulmonary metastases in CRC patients [31]. Now, pulmonary oligo-metastasis and solitary lesions are frequently treated with video-assisted thoracoscopic surgery. In a recent meta-analysis, there was no discernible difference in the rates of OS and recurrence-free survival between open thoracotomy and video-assisted thoracoscopic surgery for pulmonary metastasectomy [32]. Additionally, SBRT is beginning to show promise in the management of lung metastases. The examination of a sizable multi-center database revealed that OS was enhanced by SBRT for oligo-metastatic CRC. Retrospective analysis of 381 oligo-

metastatic CRC lesions in 235 CRC patients revealed that those who underwent SBRT had two-year OS rates of 76.1% and five-year OS rates of 35.9% [21,33]. The advancement of non-surgical local therapy benefits the active management of lung metastases as well.

It is known that peritoneal metastasis occurs in about 5%–15% of CRC patients, and the metastasis of CRC is known to have the worst prognosis [16]. Surgery has a very small part in the management of peritoneal metastases; the primary therapy is palliative chemotherapy. However, the role of surgery has been consistently examined in patients with limited peritoneal metastases, and efforts to increase the survival rate have persisted through active treatment with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) [16,34–36] (Fig. 2). In some patients with peritoneal metastases, CRS/HIPEC may enhance oncological outcomes, according to long-term randomized controlled trials and meta-analyses [35,36]. Effectiveness of HIPEC has been questioned, though, with the advent of systemic chemotherapy [37], and it is thought that this is due to resistance to the anticancer medications that are currently being employed. As a result, progress in treating metastatic CRC, particularly in raising the survival rate, has stalled. Instead, doctors are still choosing anticancer drugs that are sensitive to the disease and using precision medicine when it is necessary. It appears to be a solution for the treatment of peritoneal metastasis [38]. In order to effectively treat metastatic CRC in the future, new medications will need to be created and used, with treatment decisions based on more precise genetic data. In addition, the role of sophisticated multidisciplinary treatment involving professionals will be critical for improving oncological outcomes in order to increase the potential of curing as well as controlling the disease by performing surgical treatment and other local treatments at the right moment.

Paradigm Shift of Rectal Cancer Treatment

Neoadjuvant chemoradiotherapy (nCRT) altered the idea of surgical excision in the treatment

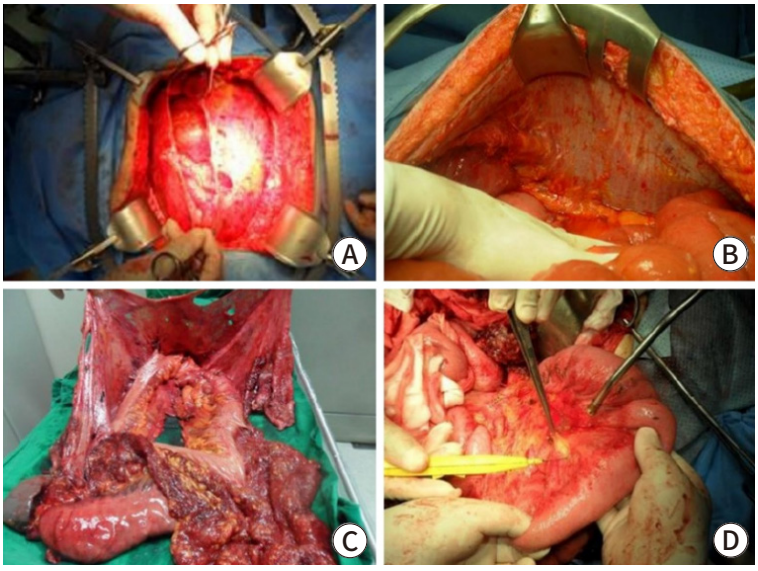

Fig. 2. Cytoreductive surgery for patients with peritoneal carcinomatosis from colorectal cancer. Peritoectomy process at (A) pelvic cavity, (B) left upper quadrant, (C) intestinal organs, (D) and small bowel mesentery. Adapted from Kim and Kim 2021 [16] with CC-BY-NC.

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of rectal cancer. Surgery has always been and continues to be regarded as the most crucial and necessary step for cure of CRC [39]. Although it is known that there is no change in the OS or recurrence-free survival rates when compared to postoperative radiation therapy or surgical resection alone, radiation therapy prior to rectal cancer surgery boosts the full resection rate of rectal cancer and lowers the local recurrence rate [40]. Despite this drawback, finding total or nearly complete rectal cancer regression to nCRT allowed even individuals with early-stage advanced rectal cancer to use an organ-preserving method. Although radical resection of rectal cancer has improved functional outcomes and greater sphincter preservation due to technical advancements [41,42], organ preservation strategies have grown in popularity due to its obvious functional benefits when compared to oncologic outcomes [43–45]. When the results of representative trials, which showed good oncologic outcomes following organ preservation [44,45], were compared to the outcomes of radical resection for patients who respond well to nCRT, interest in organ preservation of rectal cancer has sharply increased. Many initiatives have been made in an effort to increase the number of patients who fully respond to nCRT. The greatest barrier to incorporating organ preservation techniques into actual clinical practice, meanwhile, continues to be the poor accuracy of response evaluation to nCRT. It also has to do with the diagnosis of local regrowth, a rare variation of local recurrence in rectal cancer treated with organ preservation techniques. However, the salvage percentage for these patients was observed to vary [46,47]. Local regrowth occurred in 20%–30% of patients who undergo organ preservation [44–46]. In this context, we must be careful not to reduce the likelihood of a cure by improperly implementing an organ preservation strategy.

In the era of advanced rectal cancer treatment, trials to enhance distant metastasis control are ongoing, along with enhancing quality of life by including comprehensive neoadjuvant treatment (TNT) [48,49]. TNT, however, has not yet demonstrated any advantages in terms of controlling distant metastases, although showing a rise in clinical near-complete responders. After nCRT, distant metastasis is still a significant oncologic issue, therefore we need to wait and critically examine long-term results [50]. The emphasis on striking a balance between quality of life and oncologic outcomes for the treatment of rectal cancer will continue.

Conclusion

A significant cancer subtype that continues to endanger public health is CRC. Although the screening program is now run well, there is ongoing concern about how to increase compliance and practically apply non-invasive tests. The screening program must be revised to reflect epidemiologic shift as the prevalence of young-age CRC grew and, on the other hand, elderly CRC patients increased due to an increase in life expectancy. Physicians and patients are more interested in finding ways to balance quality of life and oncologic outcomes, and surveillance is more crucial to find cancer as early as feasible in order to preserve function without impairing oncologic results.

Active treatment for metastatic CRC has been carried out to break the CRC survival plateau. The role of surgical treatment has increased for metastatic CRC along with systemic treatment and targeted treatment based on genomic features of individuals. On the other hand, one of the most significant changes in the period of surgical therapy of CRC is the judicious deferral of surgical treatment, including nCRT/TNT.

The overall trend in CRC treatment is toward precision medicine, which protects the patient's quality of life while also ensuring the best oncological treatment outcomes by taking into

account the patient's unique traits, way of life, and genetic characteristics. As a result, the trend in treatment showed development at both ends: for rectal cancer, which responds well to neoadjuvant therapy, efforts are rising in the direction of organ preservation, and for metastatic CRC, which had previously undergone rather harsh treatment. It will be able to offer a new development direction for CRC treatment when the financial support to move from the current standard, which concentrated on standard treatment to enhance the overall treatment outcome, to precision treatment and the improvement of the system come together.

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Conflict of Interest

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

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Author Contribution

The article is prepared by a single author.

Ethics Approval and Consent to Participate

Not applicable.

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