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INVITED REVIEW

Role of Neoadjuvant Chemotherapy in Locally Advanced Colon Cancer

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ABSTRACT

Stage II and stage III (T1-4/N1-2/M0) colon cancers are known as locally advanced colon cancer (LACC). About 15% of colon cancers present as LACC without signs of metastasis. Standard treatment of LACC is based on complete oncologic resection followed by adjuvant chemotherapy (AC). In the surgical treatment of LACC, multivisceral resections are applied to obtain R0 resection. Despite such aggressive resections, the rate of obtaining R0 in LACC varies between 40% and 90%, and 5-year survival is between 28% and 73%. Neoadjuvant chemotherapy (NAC) is widely used in the treatment of gastrointestinal system malignancies, such as locally advanced gastric, esophageal and rectal cancers and locally advanced breast cancer. In the literature, there has been an increase in studies on the use of NAC in LACC. These show that NAC appears to be safe and provides similar overall survival compared to adjuvant CT in LACC, that the R0 resection rate is increased in patients who have undergone NAC, that there is no significant increase in postoperative complications or mortality, and that there is also significant downstaging of tumor and lymph node stages in patients who have undergone NAC.

Keywords: Locally advanced, colon cancer, neoadjuvant therapy

Introduction

Stage II and Stage III (T1-4/N1-2/M0) colon cancers are known as locally advanced colon cancer (LACC). Approximately 15% of colon cancers present as LACC without signs of metastasis.[1] Standard treatment for LACC is based on complete oncologic resection followed by adjuvant chemotherapy (AC).[2,3] Current European guidelines suggest surgery of the primary tumor in high-risk stage II or III tumors.[4] This recommendation has been shown to be effective in adenocarcinoma, and similarly improved survival has been demonstrated in both mucinous and signet-ring cell tumors.[1]

In this context, multivisceral resections are applied to obtain complete resection (R0) in the surgical treatment of LACC. Despite such aggressive resections, the rate of obtaining R0 in LACC is variable, ranging from 40% to 90%, and 5-year survival ranges from 28% to 73%. Having a 20-30% risk of local or distant recurrence, this treatment strategy has been shown to fail to prevent the risk of locoregional spread of the tumor.[5,6] A number of factors have been suggested for this failure. These include delayed onset of chemotherapy (later than four months after the initial diagnosis), accelerated duplication of colorectal metastases during this chemotherapy-free period, stimulation of growth factors causing tumor progression with surgery, and the growth and advance of micrometastases at the surgical site because of induced immunosuppression in the postoperative period. Therefore, initiating neoadjuvant chemotherapy (NAC) in these patients provides an improvement in prognosis by eliminating the circulating micrometases through control of the putative failure factors mentioned above, and improving the integrity and quality of tumor surgery with local downstaging. The response of the primary tumor to chemotherapy and the preoperative imaging of these patients should be carefully evaluated, the tumor stage should be performed correctly, and NAC should be well tolerated and should not increase the risk of complications before and after surgery.[6] Computed tomography (CT) is the generally preferred method in the staging of colon cancer. With CT,

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the depth of tumor spread along the colon wall (T-stage) can be measured, and metastatic spread to regional lymph nodes (stage-N) and distant metastases (stage-M) can be detected. The quality of CT used for colon cancer depends on the quality of bowel preparation, oral and rectal administration of contrast agent, amount of air in the colon, and intravenous (i.v.) contrast administration. Combining the venous and arterial phases during CT scanning provides a better evaluation of the T and N-phases.[7] Dighe et al.[8] compared CT and pathological staging in 94 patients and reported a sensitivity of 87% and specificity of 49% for high-risk tumors. The sensitivity to predict any tumor suitable for chemotherapy (T3 or T4) was 95% and specificity was 50%. For node-positive disease, the sensitivity was 68% and the specificity was 42.8%. The management of LACC requires expertise. In CT, T-stage can be reported more accurately than N-stage. Thus, it is difficult to distinguish stage II patients from stage III patients in the preoperative period.

NAC is widely used for the treatment of gastrointestinal system malignancies, such as locally advanced gastric, esophageal and rectal cancers, and locally advanced breast cancer.[1,9] There has been an increase in the number of studies published about the use of NAC in LACC. The first of the potential benefits of NAC is downstaging. That is, it induces tumor regression with a decrease in tumor volume/mass, seen on both imaging and pathological examinations. Since the tissues are intact, preoperative chemotherapy reduces the number and viability of tumor cells that have spread to lymph and blood vessels, thereby reducing the possible rate of micrometastasis.[10] NAC can reduce the risk of distant relapse and increase overall survival. It can help facilitate a laparoscopic procedure and so minimizing the delay in starting AC. In addition, NAC reduces the rate of multivisceral resection and the rate of tumor cell shedding during surgery, and increases the rate of R0 resection.[10,11] The failure of the tumor to respond to NAC can provide valuable information about the biology of the tumor. In patients who respond well to NAC, the effect of postoperative AC may be questionable, with a tendency to reduce AC.[10,12] In their study in 2020, de Gooyer et al.[1] achieved R0 in 77.2% of patients in the NAC group (n=115). In 19 (12.8%) patients, the resection margins were macroscopically disease-free but microscopically positive for tumor invasion (R1).[1] Six (4%) patients had macroscopically visible residual disease (R2) in which complete resection of the tumor was not possible. In the control group, 86.2% (n=225) R0 resection rate, 6% (n=18) R1 resection rate, and 1.7% (n=5) R2 resection rate were achieved. Data on complications were available in 92% (n=137) of patients in the NAC group and 93% (n=275) of patients in the control group, with no significant difference between the two groups in terms of surgical complications, such as anastomotic leak and abscess formation (p=0.854).[1] Concerns about tumor growth and inability to perform surgical treatment during NAC, incorrect selection of high-risk patients with incorrect radiological staging, and the possibility of incorrect radiological staging that may lead to overtreatment of low-risk patients have limited the use of NAC in LACC. However, with more effective chemotherapy regimens and advances in radiological staging, NAC is now seen as a promising National Comprehensive Cancer Network (NCCN)-supported option for patients with LACC.[13]

The NCCN Guideline Colon Cancer, version 2.2021, recommends that neoadjuvant treatment with folinic acid, fluorouracil, and oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin (CAPEOX) can be applied before surgery in bulky nodal disease or clinical T4b colon cancer (Figure 1).[3,14] There are small series describing the feasibility of NAC or chemoradiation. These studies demonstrated safety, high R0 resection rates, and excellent local control rates. The most compelling evidence to date was published by the Fluoropyrimidine Oxaliplatin and Targeted Receptor Preoperative Therapy (FOxTROT) Collaborative group. In this study, the results of a pilot phase randomized clinical trial comparing NAC with AC were published.[12] The FOxTROT trial was the first randomized controlled trial to evaluate preoperative chemotherapy in primary colon cancer. The FOxTROT trial was designed to evaluate whether an effective 6-week combination chemotherapy regimen given preoperatively to patients with radiologically-staged, locally advanced but potentially resectable colon cancer improved disease-free survival. In this study, patients with locally advanced T4 or colon adenocarcinoma with an extramural depth ≥5 mm were included in the study. In the pilot phase, it provided clear evidence of downstaging with only six weeks of preoperative treatment.[12] In the FOxTROT trial which was performed in 1,052 patients and published in 2019, 59% of patients treated with NAC had histological regression and 4% had pathological complete response. It was reported that NAC was well tolerated, there was no increase in perioperative morbidity and there was a decrease in serious complications. It was also shown that there was a half reduction in histological downstaging and incomplete resection rates. FOxTROT concluded that NAC for colon cancer improved surgical outcomes and that NAC could now be considered as a treatment option, but longer follow-up and further studies were needed to confirm the long-term benefits of NAC, examine its use, and optimize patient selection.[14]

In the 2018 study of Dehal et al.[5], a total of 27,575 patients with non-metastatic and clinically T3 and T4 primary colon cancer were included, with 97% treated with surgery

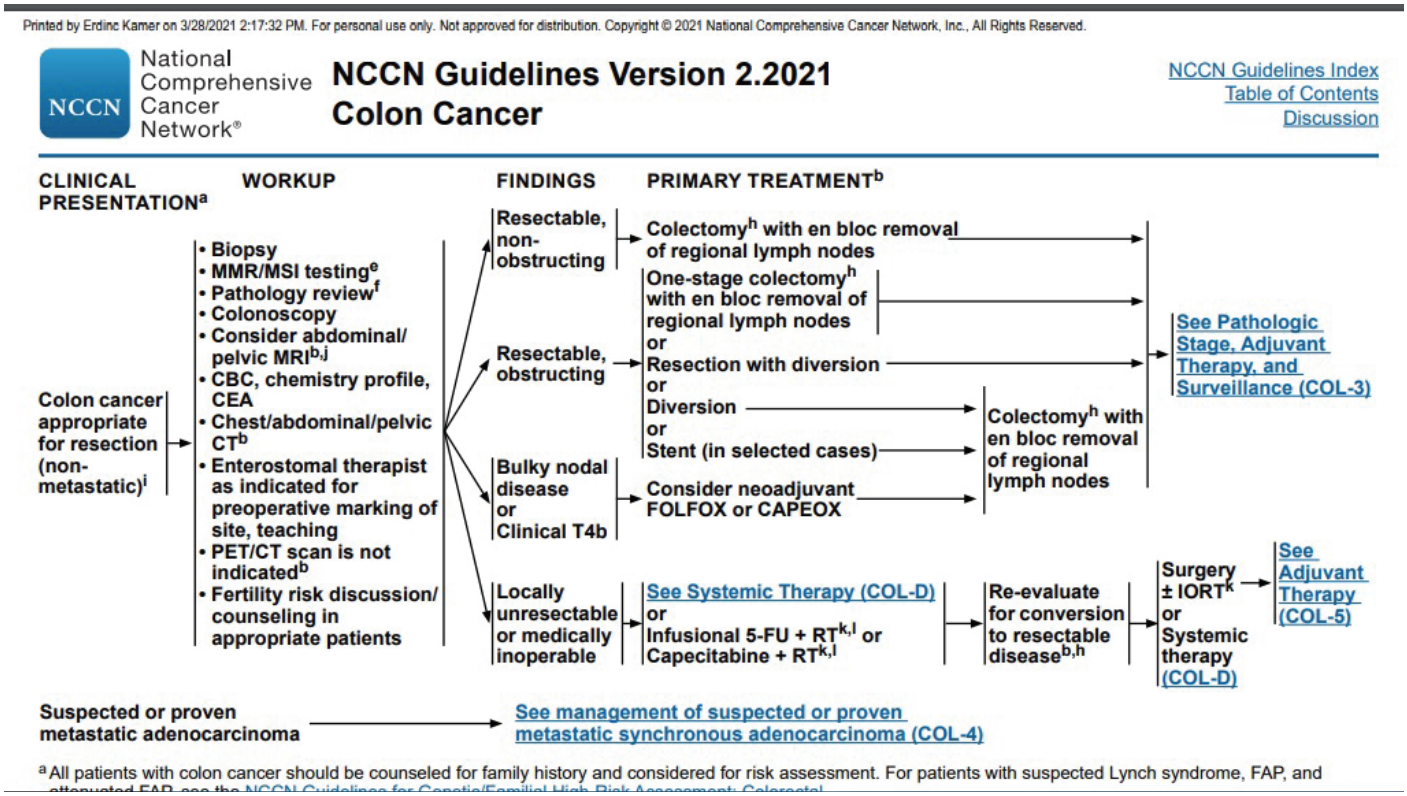

Figure 1. NCCN Guidelines Version 2.2021 Colon Cancer[3]
NCCN: National Comprehensive Cancer Network, MMR: Mismatch repair, MSI: Microsatellite instability, CBC: Complete blood count, CEA: Carcinoembryonic antigen, CT: Computed tomography, PET: Positron emission tomography, 5-FU: 5-Fluorouracil, RT: Radiation therapy, IORT: Intra Operative radiation therapy, FOLFOX: Folinic acid, fluorouracil, and oxaliplatin, CAPEOX: Capecitabine plus oxaliplatin, MRI: Magnetic resonance imaging

followed by AC, and 3% treated with NAC followed by surgery. It was the first study on the long-term outcomes of NAC and reported that patients with T4b colon cancer who underwent NAC and subsequently underwent surgery had a better survival than patients who received AC after surgery. It was also reported that the majority of patients with LACC still underwent surgical resection and subsequently received AC, and that NAC had been used at an increased rate in patients with T4b colon cancer in the last 10 years. In this study, it was shown that the risk of death within 3 years was reduced by 23% in the NAC group.[5] In the study of de Gooyer et al.[1], the median follow-up time was 44 (4-133) months in the NAC group and 44 (0-133) months in the control group. The 5-year overall survival was 67% in the NAC group and 65% in the control group, and the difference between the two groups was not statistically significant (p=0.867). The postoperative 30-day mortality in the NAC group was 0.5%.

Conclusion

Some studies have shown that NAC appears to be safe in LACC and provides similar overall survival compared to AC, the R0 resection rate is increased in patients who have undergone NAC, and there is no significant increase in postoperative complications or mortality. In addition, it has been shown that tumor and lymph node stages exhibit significant downstaging in patients undergoing NAC. In the NCCN Guideline Colon Cancer version 2.2021, the feasibility of NAC with FOLFOX or CAPEOX before surgery in bulky nodal disease or clinical T4b colon cancers is suggested, which means that NAC is now included in the guidelines for the treatment of LACC, but it seems that larger randomized studies are still needed.

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Authorship Contributions

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