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Review

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Postoperative Chemotherapy After Surgical Resection of Metachronous Metastases of Colorectal Cancer: A Systematic Review

Sevindzh Evdokimova[a, e], Anna Kornietskaya[b], Larisa Bolotina[b], Dmitriy Sidorov[c], Andrey Kaprin[a, d]

Abstract

Currently, 6 months of perioperative or adjuvant chemotherapy (ACT) is a standard treatment option after radical surgical removal of metachronous metastases in patients with metastatic colorectal cancer (CRC). Data show that ACT improves relapse-free survival in such patients, although no difference in overall survival rate was observed. We perform a systematic review to evaluate the efficacy of adjuvant chemotherapy after radical resection of metachronous metastases in CRC.

Keywords: Colorectal cancer; Metachronous metastases; Adjuvant chemotherapy; Radical resection; Liver metastases

Introduction

The incidence of colorectal cancer (CRC) is steadily increasing worldwide, so in 2020 more than 1.93 million cases were newly identified. Despite advances in screening programs and treatment of precancerous conditions, 20-30% of all patients with CRC have metastatic disease at the time of diagnosis, and 30-40% of patients with cured locally advanced stages of CRC develop metachronous metastases during follow-up [1, 2]. Depending on the stage of the disease, the 5-year overall survival (OS) rate is 90% at stage I, 70-80% at stage II, and 40-65% at stage III. The risk of progression also depends on the stage of the primary tumor: 30% and 50% at stage II and III, respectively, and is higher first 2 years after radical surgery [3]. CRC usually metastasizes to the liver, lungs, lymph nodes of the abdominal cavity, and peritoneum. The study showed that patients with radically resected metastatic foci had significantly improved long-term survival by increasing the overall 5-year survival rate by 60% [4].

Clinical guidelines suggest that patients with metachronous resectable metastases may undergo surgical treatment followed by adjuvant therapy or receive perioperative chemotherapy for 6 months if adjuvant chemotherapy (ACT) has not been performed previously or after 12 months' period after they finished ACT. However, trials that studied the efficacy of ACT have controversial results with some limitations such as inappropriate study design, chemotherapy regimen, a small number of patients, and retrospective analysis.

Thus, the rationale and duration of adjuvant treatment after removal of solitary metachronous metastases still remain unclear, especially in patients with certain prognostic factors. Purpose of this study is to review the necessity of adjuvant chemotherapy after radical resection of metachronous metastases in patients with CRC.

Review

Surgical treatment of metachronous metastases of CRC has been proven to improve the OS of patients, which was confirmed by the RAXO study [4]. This multicenter study included 1,086 patients, who were divided into three groups: resectable, potentially resectable, and unresectable. The median OS of those who underwent radical removal of metastases was 82.8 months compared to 20.8 months in patients who received only systemic chemotherapy. It is worth noting that in patients with initially unresectable or potentially resectable metastatic foci, preoperative chemotherapy with subsequent surgical treatment improved the OS of these patients comparable to that in patients with initially resectable foci (82.8 months and 80.4 months, respectively).

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[a]P. Hertsen Moscow Oncology Research Institute - Branch of the National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation, Moscow125284, Russia
[b]Department of Chemotherapy, P. Hertsen Moscow Oncology Research Institute - Branch of the National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation, Moscow, Russia
[c]Abdominal Oncology, City Clinical Oncological Hospital No. 1, Moscow 105005, Russia
[d]Urology Department, Peoples' Friendship University of Russia, Moscow117198, Russia
[e]Corresponding Author: Sevindzh Evdokimova, P. Hertsen Moscow Oncology Research Institute - Branch of the National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation, Moscow125284, Russia. Email: evdokimova.sevindzh@gmail.com

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Nowadays, three main cytostatic drugs are used in the treatment of metastatic CRC after radical metastasectomy: oxaliplatin, leucovorin, and fluoropyrimidines. Previously, irinotecan was used in adjuvant chemotherapy regimens; however, three randomized studies CALGB-89803 [5], PETACC-3 [6], FFCD9802 [7] demonstrated no benefit for irinotecan-containing regimens compared with 5-fluorouracil (5-FU) and leucovorin in long-term outcomes [8]. For patients with a good performance status and no comorbidity, systemic chemotherapy with oxaliplatin and fluoropyrimidines is recommended, while in elderly patients with significant comorbidity fluoropyrimidine monotherapy is usually preferred.

Also, the use of targeted drugs in the adjuvant setting had a negative impact on survival, this was demonstrated in studies of NCCTG NO147 [9], PETACC-8 [10], in which cetuximab was used in combination with oxaliplatin, leucovorin and 5-FU (FOLFOX6). Similarly, the adding of bevacizumab in the NSABP C-08 study, which included 2,710 patients, showed no benefit compared with chemotherapy [11]. Thus, the use of irinotecan and targeted drugs in adjuvant therapy of CRC should not be recommended.

The management of patients with initially resectable metastases after radical surgical treatment is still subject of discussion. In NCCN guidelines, surgical resection of metastases followed by ACT or observation in case of previous oxaliplatin-containing chemotherapy is preferred strategy in treatment of metachronous metastases in CRC patients [12]. However, ESMO recommendations note that in patients with resectable metastases and favorable prognosis, perioperative Chemotherapy is not required, and upfront surgery is usually recommended, as well as in patients with favorable criteria who have not received perioperative chemotherapy, there is insufficient evidence to support the use of systemic chemotherapy [13].

Currently, limited data exist as to whether ACT significantly improves OS and relapse-free survival (RFS) in patients with CRC metachronous metastases.

In 2015 Park et al presented the results of study evaluating the efficacy of ACT after radical resection of lung metastases in patients with CRC [14]. The study was conducted in South Korea that randomly assigned 221 patients with metastasectomy to postoperative chemotherapy versus observation alone. The first group included 176 (79.6%) patients who received ACT using one of the following options: FOLFOX (41.5%); irinotecan, leucovorin, fluorouracil (FOLFIRI) (31.8%) and fluoropyrimidine monotherapy (25.0%) (Table 1) [14-21]. The duration of ACT was 6 months. The second group included 45 (20.4%) patients. ACT showed significant benefit in terms of RFS compared with observation alone, the median RFS (mRFS) was 32.7 versus 11.20 months, respectively, (P = 0.076) regardless of the chemotherapy regimen. However, there were no significant differences between the groups when assessing the OS (89.6 vs. 86.8 months, respectively, P = 0.833).

In another Japanese retrospective study, a total of 384 patients with CRC after radical resection of synchronous and metachronous lung metastases were included and divided into two groups [15]. The first group included patients who received postoperative chemotherapy with either fluoropyrimidine monotherapy (71% of 136 patients), fluoropyrimidines with oxaliplatin (44 patients) or irinotecan-containing regimen (12 patients). In the second group patients underwent only radical resection of metastatic foci. The groups were well balanced without significant differences, both in demographic indicators and in the nature of metastatic lesions (80% of patients in both groups had solitary metastases). The median OS (mOS) in the observation arm was not achieved compared with 8 years in the adjuvant treatment group (hazard ratio (HR): 1.00; 95% confidence interval (CI): 0.69 - 1.45; P = 1.00). No statistically significant difference in mRFS was observed between study groups (2.1 and 2.2 years, HR: 1.07; 95% CI: 0.82 - 1.39; P = 0.62).

A meta-analysis that included 18 cohort studies with 3,885 European and Asian patients was published in 2019, which assessed the impact of ACT after previous resection of lung metastases [16]. The fluoropyrimidine-containing regimens with oxaliplatin, irinotecan, and fluoropyrimidine monotherapy were used. ACT did not affect OS (HR = 0.78; 95% CI: 0.60 - 1.03; P = 0.077) and progression-free survival (PFS) (HR = 0.91; 95% CI: 0.74 - 1.11; P = 0.339).

Similarly, the results of the meta-analysis of adjuvant therapy using monotherapy with fluoropyrimidines after radical resection of liver metastases were reported at ESMO congress in 2018. No benefit in terms of OS was observed in adjuvant therapy group (HR = 0.781, 95% CI: 0.593 - 1.030, P = 0.080) [17].

The only one study with prospective design was the JCOG0603 study, which was presented at ASCO congress in 2021 [18]. A total of 300 patients with metastatic colorectal cancer (mCRC) with liver metastases were included between 2007 and 2019. Patients were randomized with an allocation ratio 1:1 into two groups: the first group received postoperative modified FOLFOX6 (mFOLFOX6), the second group was observed after surgery. One of the key points of this study was that patients did not receive oxaliplatin-containing regimen as part of adjuvant treatment for the primary disease, and about 73% of patients did not receive any postoperative systemic therapy after primary tumor resection. Despite the fact that the study was terminated prematurely due to the discovery of a statistically significant difference in mRFS between the groups: 3-year RFS was 52.1% in the ACT group and 41.5% in the surgery-only group, P = 0.002; the subsequent evaluation of the results of the OS led the researchers to conclude that postoperative FOLFOX6 improves RFS, but worsens OS (5-year OS 71.2% in the ACT group and 83.1% in the surgery-only group, HR = 1.25; 95% CI: 0.78 - 2.00; two-sided P = 0.42).

In the subgroup analysis, patients who received ACT after resection of the primary tumor and metachronous metastases did not benefit from postoperative therapy. On the contrary, those who received ACT only after primary tumor resection and were just observed after subsequent surgery of metachronous metastases had better survival rates.

If we turn to the sources on the basis of which the decision was made to conduct the ACT, a statistically significant difference was achieved only in relation to RFS, while no benefit was achieved in relation to OS [19, 20]. One of the only weighty arguments in favor of ACT was meta-analysis, which included three randomized and two objective compara-

Table 1. Characteristics of Studies Included in Systematic Review

Author/year	Country	Chemotherapy regimen	Number of patients	RFS (ACT vs. surgery only)	OS (ACT vs. surgery only)
Park et al, 2015 [14]	Korea	1) Monofluoropyrimidines (5-FU, TS-1, or capecitabine) 2) FOLFOX 3) FOLFIRI	221	32.7 vs. 11.20 months, P = 0.076	89.6 vs. 86.8 months, P = 0.833
Imanishi et al, 2019 [15]	Japan	1) Monofluoropyrimidines 2) FOLFOX 3) FOLFIRI	384	2.1 vs. 2.2 years (HR: 1.07; 95% CI: 0.82 - 1.39; P = 0.62)	8 years and not reached in the surgery alone group (HR: 1.00; 95% CI: 0.69 - 1.45; P = 1.00)
Zhang et al, 2019 [16]	China	1) Monofluoropyrimidines 2) Fluoropyrimidine with leucovorin 3) FOLFOX 4) FOLFIRI	3,885	HR: 0.91; 95% CI: 0.74 - 1.11; P = 0.339	HR: 0.78; 95% CI: 0.60 - 1.03; P = 0.077
Mauri et al, 2018 [17]	Greece	Monofluoropyrimidines	482	HR: 0.645, 95% CI: 0.509 - 0.818, P = 0.001	HR: 0.781, 95% CI: 0.593 - 1.030, P = 0.080
Kanemitsu et al, 2021 [18]	Japan	FOLFOX	300	5-year RFS 49.8% vs. 38.7%, P = 0.006	5-year OS 71.2% vs. 83.1% (HR: 1.25; 95% CI: 0.78 - 2.00; two-sided P = 0.42)
Ciliberto et al, 2012 [19]	Italy	FOLFOX, FOLFIRI	642	HR: 0.75; 95% CI: 0.620 - 0.910; P = 0.003	HR: 0.743; 95% CI: 0.527 - 1.045; P = 0.088
Wang et al, 2015 [20]	China	5-FU, FOLFOX, hepatic arterial infusion, regional Chemotherapy in combination with systemic Chemotherapy	1,896	HR: 0.81; 95% CI: 0.72 - 0.91; P = 0.0007	HR: 0.88; 95% CI: 0.77 - 1.01; P = 0.07
Araujo et al, 2015 [21]	Brazil	5-FU, FOLFOX	2,475	HR: 0.71; 95% CI: 0.61 - 0.83; P < 0.001	HR: 0.77; 95% CI: 0.67 - 0.88; P < 0.001

ACT: adjuvant chemotherapy; 5-FU: 5-fluorouracil; FOLFOX: oxaliplatin, leucovorin, fluorouracil; OS: overall survival; RFS: relapse-free survival; FOLFIRI: irinotecan, leucovorin, fluorouracil; HR: hazard ratio; CI: confidence interval.

tive studies. A total of 2,475 patients were included, of which 1,024 (41.4%) were in the combined treatment group (ACT plus surgery) and 1,451 (58.6%) were in surgery group alone. Combined treatment increased OS rate by 23% compared with surgery alone (HR = 0.77; 95% CI: 0.67 - 0.88; P < 0.001), also RFS by 29%, (HR = 0.71; 95% CI: 0.61 - 0.83; P < 0.001) [21].

Discussion

The need for postoperative chemotherapy after radical resection of metachronous metastases in patients with CRC is still controversial due to the lack of convincing evidence regarding the differences in OS. In this review, we evaluated the studies with the highest reliability.

However, they have a number of disadvantages, so Park et al in the study of some patients performed chemotherapy based on irinotecan, which is ineffective in adjuvant treatment, and also included only the Asian population of patients [14]. It is also important that the study was retrospective and had a non-randomized design, as well as 26.1% of patients were unable to complete the full cycles of systemic cytotoxic treatment.

The study of our Japanese colleagues has similar limiting factors, and among other things, there is no data on patients' adherence to treatment and the duration of the performed ACT is unknown [14].

If we consider the JCOG0603 study, the authors did not provide data on the patient population, and the molecular genetic features of the tumor were also not noted. As is known, patients with microsatellite instability do not benefit from prescribing chemotherapy regimens containing fluoropyrimidines in an adjuvant regimen [22]. The duration of the recurrence-free interval and the ratio of R0 and R1 resections between the groups is also unknown.

Chemotherapy is associated with a number of potential risks associated with the possibility of developing steatohepatitis and sinusoidal liver damage, the development of peripheral sensory neuropathy and other adverse reactions [23, 24].

Recent studies have studied the possibility of shortening the duration of chemotherapy. Thus, patients with localized forms of the disease may be prescribed adjuvant drug treatment for 3 months in the absence of risk factors without a negative impact on long-term oncological results [25]. Therefore, currently many researchers are wondering whether all patients with metachronous metastatic process, in the case of radical surgical treatment, require systemic therapy. Perhaps the answer to this question lies in the assessment of prognostic factors, so in a study conducted in China, patients were assigned to a low- and high-risk group among those who underwent ACT or were left under dynamic observation using the Memorial Sloan-Kettering Cancer Center Clinical Risk Scale (MSKCC-CRS) [26]. The prognostic scale was based on five clinical factors: lymph node lesion in the primary tumor, the size of the largest metachronous metastatic focus more than 5 cm, the presence of multiple liver metastases, preoperative carcinoembryonic antigen (CEA) level > 200 ng/mL, relapse-free interval from the moment of resection of the primary tumor to the realization of distant metastases less than 12 months. According to the results, 3-year RFS and OS did not differ significantly between the groups of ACT and dynamic observation and was not statistically significant (RFS: 56.1% compared to 52.0%, P = 0.747; OS: 79.5% compared to 63.8%, P = 0.265). In turn, when assessing patients by risk groups, in patients with low levels, the 3-year RFS and OS were comparable between the groups (RFS: 50.5% compared to 55.8%, P = 0.709; OS: 72.2% compared to 78.6% P = 0.834). Among high-risk patients, there was also no significant difference in the 3-year RFS (25.4% vs. 21.2%, P = 0.978); however, 3-year OS was significantly higher in the ACT group (68.2% vs. 33.8%, P = 0.015).

In a similar design study, which was conducted by Rahbari et al, it has been demonstrated that ACT significantly improved survival in high-risk patients on the MSKCC-CRS scale (HR: 0.40; 95% CI: 0.23 - 0.69, P = 0.001), but did not bring any benefit to low-risk patients (HR: 0.90; 95% CI: 0.57 - 1.43, P = 0.670) [27]. Similarly, ACT did not affect on the 5-year RFS (55.7% vs. 62.7%, P = 0.93) and OS (81.1% vs. 71.7%, P = 0.460) in low-risk patients in the study by Nakai et al [28]. These results justify the importance of a differential approach in assessing the indications for the appointment of postoperative chemotherapy in patients with metachronous mCRC.

Thus, ACT after radical removal of metastatic foci is more preferred treatment option for patients with negative prognostic risk factors. Moreover, it is necessary to assess the effect of microsatellite instability and molecular genetic mutation profile on the results of ACT.

This statement also was confirmed in the Dynamic study, which were reported at the ASCO in June 2022 [29]. This is the first randomized study of using circulating tumor DNA (ctDNA) in stage II CRC to determining the possibility of avoiding ACT. A total of 302 patients were assigned to ctDNA-guided management and 153 to standard treatment group. A lower percentage of patients in the ctDNA-guided group received ACT compared with in the standard group (15% vs. 28%; relative risk, 1.82; 95% CI: 1.25 - 2.65). The using of ctDNA was noninferior to standard management (93.5% and 92.4%, respectively; absolute difference, 1.1 percentage points; 95% CI: -4.1 to 6.2 (noninferiority margin, -8.5 percentage points)) in assessing of 2-year RFS. Among ctDNA-positive patients who received ACT, 3-year RFS was 86.4% and 92.5% among ctDNA-negative patients, who did not. Therefore, the use of ctDNA for stage II CRC reduced ACT without compromising outcomes.

Also, Federica Marmorino et al analyzed ctDNA as a prognostic marker in patients after radical resection of colorectal liver metastases [30]. It was a retrospective trial and included 76 patients. The ctDNA was found in 39 (51%) of 76 patients, among which the disease progression was identified in 33 patients. Patients with positive ctDNA had significantly shorter RFS compared to those who had negative ctDNA (mRFS 12.7 vs. 27.4 months, HR = 2.09, P = 0.008).

So, the realization of ctDNA in clinical practice could become a reliable method when deciding prescribe ACT also for patients after radical resection of metachronous metastasis in CRC.

However, there is also many limitations in assessing ctDNA. First, there could be false negative results, when a very small number of mutant genes is contained and as a result, this method does not detect them, or false positive results associated with clonal hematopoiesis, that is, mutations that are not characteristic of the tumor are detected [31]. Secondly, detection rate varies across metastatic tumor types and not all types of cancers are sensitive to ctDNA; the level of ctDNA depends on disease site, and the timing of blood sampling in relation to treatment is important too [32]. Moreover, tumor cell type also influences on the level and efficacy of revealing ctDNA. For example, squamous and adenocarcinoma are more detectable than mucinous cancer. Thirdly, nowadays this method is still quite expensive and not yet established into routine clinical practice.

Conclusions

This review has demonstrated the lack of ACT efficacy in patients with metastatic CRC after radical resection of metachronous metastases. However, it is worth stratifying patients by the presence of risk factors to determine further treatment strategy, because patients belonging to the high-risk group have advantages from the appointment of systemic chemotherapy. Further prospective studies are needed to determine the indications for prescribing ACT after radical metastasectomy.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

Sevindzh F. Evdokimova: manuscript writing, overview of the previously published works on a topic. Anna Kornietskaya: manuscript review, critical revision of manuscript for important intellectual content. Larisa Bolotina: manuscript preparation and editing. Dmitriy Sidorov: data collection, manuscript preparation and editing content. Andrey Kaprin: drafting and approval of final version.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

ACT: adjuvant chemotherapy; CRC: colorectal cancer; 5-FU: 5-fluorouracil; FOLFOX6: oxaliplatin, leucovorin, fluorouracil; OS: overall survival; RFS: relapse-free survival; FOLFIRI: irinotecan, leucovorin, fluorouracil; mRFS: median RFS; mOS: median OS; HR: hazard ratio; PFS: progression-free survival; mCRC: metastatic colorectal cancer; MSKCC-CRS: Memorial Sloan-Kettering Cancer Center Clinical Risk Scale; CEA: carcinoembryonic antigen; ctDNA: circulating tumor DNA

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