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# Is adjuvant chemotherapy justified in rectal cancer patients after radio-chemotherapy and radical resection?

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Recommendations for the application of post-operative adjuvant chemotherapy in patients who received preoperative radio-chemotherapy are not consistent. Some of them advise post-operative chemotherapy, whilst others follow-up without any adjuvant treatment. The objective of this paper is to undertake an overview of the randomised studies evaluating whether the administration of adjuvant chemotherapy can be justified with clinical evidence. A systematic overview of the publications shows 5 randomised trials in which only the patients after pre-operative radio-chemotherapy were enrolled, whilst randomisation concerned adjuvant therapy vs follow-up without adjuvant therapy. None of the studies showed any improvement after post-operative chemotherapy with regards to both the overall survival and disease-free survival rate. Moreover, 3 randomised studies were found in which post-operative chemotherapy with fluoropyrimidine was compared with post-operative chemotherapy with fluoropyrimidine with the addition of oxaliplatin. One of these studies showed an improvement in the overall survival rate after the use of post-operative chemotherapy, whereas in two others the difference was statistically insignificant. Two studies showed a slight improvement after chemotherapy with regards to disease-free survival rates, whilst no such effect was observed in the third. A meta-analysis of the studies comparing the results after the administration of post-operative chemotherapy with the results after the chemotherapy-free follow-up did not demonstrate any positive effect of the chemotherapy on the overall and disease-free survival rate. A meta-analysis of randomised studies in which post-operative chemotherapy with fluoropyrimidine was compared with post-operative chemotherapy with fluoropyrimidine with the addition of oxaliplatin did not show any improvement in disease-free survival rates in patients receiving oxaliplatin. The overall survival was not analysed because of the lack of appropriate data at the moment the meta-analysis was made. The above overview of the randomised trials points to a lack of any strong evidence justifying the administration of post-operative chemotherapy.

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**Key words:** rectal cancer, post-operative chemotherapy, preoperative chemotherapy

## Introduction

This paper deals solely with patients diagnosed with advanced rectal cancer who received pre-operative radio-chemotherapy. Recommendations concerning the administration of post-operative adjuvant chemotherapy in these patients are not consistent. The guidelines of the National Comprehensive Cancer Network recommend administration in the patients with clinical stage II–III of the disease, irrespectively of the tumour's response to irradiation [1]. The guidelines of the Medical Society for Medical Oncology restrict the administration of adjuvant chemotherapy to patients with pathological stage III of the disease, and to the patients with stage II if the recurrence of risk is very high [2]. In contrast to the above guidelines, Dutch and Norwegian recommendations do not advise the administration of chemotherapy [3]. The difference of opinion concerning the advisability of the administration of post-operative chemotherapy is also observed among European experts [4]. The differences are also seen in routine practice: for example a Swedish population study showed that, depending on

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the region, among the patients with stage III of the disease, the rate of those receiving adjuvant chemotherapy varied between 13% and 77% [5]. This paper is an overview of randomisation studies with an objective to evaluate whether the administration of adjuvant chemotherapy is justified by clinical evidence.

## The overview of randomised trials comparing post-operative chemotherapy with observation

A systematic overview of publications [6], revealed 5 randomised trials which fulfilled the following criteria:

1. Only patients after pre-operative radio-chemotherapy were included,
2. Patients were randomised for adjuvant chemotherapy or for a observation without adjuvant chemotherapy [7–13].

The total number of patients included in all these 5 studies was 2398. In 4 studies, 5-fu was administered [7–10, 12, 13], whilst in the fifth — oxaliplatin was added to 5-fu [11]. None of these 5 studies saw any improvement after post-operative chemotherapy with regards either to overall survival and to disease-free survival. A detailed discussion of these studies is presented below.

In the EORTC 22921 study (n [number of patients] = 1011) the patients were randomly allocated to 4 study arms, and randomisation was used twice — for pre-operative radio-chemotherapy vs pre-operative radiotherapy and also post-operative chemotherapy vs follow-up [7, 8]. The 10-year overall survival rate was 51.8% in the patient group with post-operative chemotherapy and 48.4% in those patients undergoing a follow-up without post-operative chemotherapy, hazard ratio (HR) 0.91 (95% confidence interval [CI] 0.77–1.09), p = 0.32. The respective values for disease-free survival were 47.0% and 43,7%; HR = 0.91 (95% CI 0.77–1.08), p = 0.29.

An Italian study (n = 643) showed a 5-year overall survival rate of 66.9% in the patient group with post-operative chemotherapy and 67.9% in the control group, p = 0.88 [9]. The respective values for disease-free survival were 63.8% and 60.8%, p = 0.42.

In the PROCTOR/SCRIPT study (n = 437), a 5-year overall survival was observed in 79.2% of patients in the group receiving post-operative chemotherapy and 79.2% in the control group, HR = 0.93 (95% CI 0.62–1.39), p = 0.73 [10]. The respective values for disease-free survival were 62.7% and 55.4%, HR = 0.80 (95% CI 0.02–1.07), p = 0.13.

The CHRONICLE study was discontinued due to a poor accrual after the inclusion of merely 113 patients [11]. The median of the follow-up period was short — 3.6 years. 3-year overall survival amounted to 89% in patients receiving post-operative chemotherapy and 88% in the control group, HR = 1.18 (95% CI 0.43–3.26), p = 0.75. The respective values for disease-free survival were 78% and 71%, HR = 0.80 (95% CI 0.38–1.69), p = 0.56.

The QUASAR study comprised patients with stage II of the disease, with both rectal and colon cancers [12, 13]. In the rectal cancer patients, an improvement of overall survival was observed after 5 years with borderline statistical significance; 78% — in patients with post-operative chemotherapy and 74% in the group with observation only, HR = 0.77 (95% CI 0.54–1.00), p = 0,05. Yet in the subgroup which received pre-operative radiotherapy (n = 203), the difference was not significant, HR = 0.44 (95% CI 0.25–1.10).

## An overview of randomised studies comparing post-operative chemotherapy with fluoropyrimidine with and without oxaliplatin

A systematic overview of publications [6] showed 3 randomised studies in a total number of 2675 patients in whom post-operative chemotherapy with fluoropyrimidine was compared with post-operative chemotherapy with fluoropyrimidine with the addition of oxaliplatin [14–16]. One of these studies showed an improvement of overall survival rates after the administration of post-operative chemotherapy [16]; in the two remaining studies, the difference was not statistically significant. Two studies showed some improvement after chemotherapy with respect to disease-free survival rates [14, 16], whilst in the third one, no effect was seen [15]. In two studies, randomisation was performed before pre-operative radio-chemotherapy in the patients with clinical stage II or III of the disease [14, 15], whereas in the third study the randomisation was carried out after surgery only in patients with pathological stage III [16]. These studies are discussed in detail below.

In the German CAO/ARO/AIO-04 study, (n = 1265) after a median follow-up period of 50 months, the overall survival rates after 3 years were 88.7% in those patients receiving oxaliplatin and 88.0% in the patients treated only with 5-Fu; HR = 0.96 (95% CI 0.72–1.26) [14]. No 'p' value was presented, yet the 95% confidence interval for the hazard ratio (HR) shows that the difference was not statistically significant. The 3-year disease-free survival rate amounted to 75.9% and 71.2% respectively; HR 0.79 (95% CI 0.64–0.98), p = 0.03. A limitation for the interpretation of the results of this study consisted in the difference in the administration of 5-fu between two randomised groups: in patients in the group with the addition of oxaliplatin, this medication was administered in continuous infusion, whilst in the control group — only in a bolus.

In the PETACC-6 study (n = 1090) after a median follow-up period of 68 months, overall survival rates after 5 years was 83.1% in patients receiving capecitabin alone and 80.1% in patients treated with oxaliplatin with capecitabin; H = 1.17 (95% CI 0.89–1.54), p = 0.25 [15]. The respective values for disease-free survivals were 71.3% and 70.5%, HR = 1.02 (95% CI 0.82–1.28) p = 0.84.

In the Korean phase II study (ADORE) with randomisation of the patients (n = 321) with pathological stage II and

III after preoperative radio-chemotherapy with the use of 5-fu and leucovorin and after tumour resection, the subjects were randomised into two regimens of post-operative chemotherapy: FOLFOX and 5-fu in a bolus with leucovorin [16]. The median age was only 54. After a median follow-up period of 38.2 months, better outcomes were observed in patients treated with the addition of oxaliplatin, both in 3-year disease-free survival rates (71.6% vs 62.9%; HR = 0.66, p = 0.047) and in overall survival rates (95.0% and 85.7%; HR = 0.46, p = 0.036). Similarly to the German study, the limitation of the interpretation of the results of the Korean study was the difference in the administration of 5-fu between the two randomised groups: in the group receiving oxaliplatin, the medication was administered in continuous infusion, whilst in the control group only in a bolus.

## Meta-analyses

Breugom et al. [17] published a meta-analysis with the use of individual data of the patients with pathological stage II and III [7–11]. The meta-analysis comprised 4 out of 5 of the above mentioned studies comparing the results after the administration of post-operative chemotherapy with the results of the observation without chemotherapy. The median observation period was 7 years. No improvements in overall survival rates after the administration of chemotherapy in comparison with observation was seen; HR = 0.97 (95% CI 0.81–1.17). No improvement in disease-free survival rates was observed either; HR = 0.91 (95% CI 0.77–1.07). In the subgroup analysis, only in patients with the rectal cancer located 10–15 cm from the edge of the rectum, was there some improvement observed in disease-free survival rates after chemotherapy; HR = 0.59 (95% CI 0.40–0.85), p = 0.005, yet without any improvement of overall survival rates. In other subgroups, such as pathological stage II or III, ypN0, ypN1 or ypN3, patients after an anterior resection or after an abdominoperineal resection (APR), after preoperative irradiation 5 × 5 Gy or traditionally fractionated radiotherapy or radio-chemotherapy, no improvement after chemotherapy was seen both with regards to overall survival rates and disease-free survivals.

Another meta-analysis [6], made on the basis of the published data concerning all the above listed 5 studies, comparing the results after the administration of post-operative chemotherapy with the results after observation only without chemotherapy [7–13], also showed a lack of any improvement after post-operative chemotherapy with respect to overall survivals and disease-free survivals: 0.95 (95% CI 0.82–1.10), p = 0.49 and 0.92 (95% CI 0.80–1.04), p = 0.19. The lack of any improvement after chemotherapy was observed both in the subgroups with ypT0–2 stage and in the subgroup with metastases to the lymph nodes. When the meta-analysis was made separately for the studies in which randomisation was carried out after the surgery and those in which randomisation was carried out before the commencement of preoperative irradiation, it turned out that in the first case, better disease-free survival rates were observed after the administration of post-operative chemotherapy: HR = 0.79 (95% CI 0.62–1.00), p = 0.047, yet without any improvement in the overall survival rates. In the latter type of randomisation, no positive effect from post-operative chemotherapy was observed in the evaluation of overall and disease-free survival rates.

Also a meta-analysis of [6] 3 of the above mentioned randomised studies was carried out; in this meta-analysis, post-operative chemotherapy with fluoropyrimidine only was compared with post-operative chemotherapy with fluoropyrimidine plus the addition of oxaliplatin [14–16]. The addition of oxaliplatin did not cause any improvement of disease-free survival rates; HR = 0.84 (95% CI 0.66–1.06), p = 0.15. Overall survival rates were not analysed because of the lack of appropriate data at the moment the meta-analysis was carried out.

## Discussion

The meta-analyses of the randomised studies did not show any positive effect of post-operative chemotherapy on overall survival rates in patients who previously received pre-operative irradiation. The lack of any improvement was observed both in the cancer subgroup which responded to radiotherapy, i.e., those patients with stage ypT0–2, and in the patients with stage III of the disease where the largest effect could have been expected. Therefore, no strong evidence points to the advisability of post-operative chemotherapy.

It is worth pointing out, however, that an improvement of disease-free survival rates (yet without any improvement in overall survival rates) was observed in the meta-analysis of the studies in which randomisation was carried out after surgery [6]. The moment of randomisation overlaps with the moment when routinely the decision whether to administer chemotherapy or not is taken. In the studies in which randomisation was carried out before surgery, many patients did not begin previously planned post-operative chemotherapy as a result of post-operative complications, lack of further consent of the patient, or disease progression. These patients had to be included into the analysis with regards to the intention-to-treat principle. However, with regards to the poor prognoses of these patients, chances for observing treatment benefits decreased. That is why randomisation before surgery is suboptimal. The improvement of disease-free survival rates (yet with a lack of improvement in overall survival rates) after surgery in the randomised studies points to the minor influence of post-operative chemotherapy. Thus a question arises whether this benefit outweighs the toxicity of chemotherapy.

The toxicity of chemotherapy lessens the quality of life of patients during treatment [18]. Post-operative chemothe-

rapy with fluoropyridines leads to acute toxicity consisting of diarrhoeas, nausea, vomiting and fatigue as well as pain resulting from stomatitis and loss of appetite [18]. In rare cases, complications may be life-threatening or might require hospitalisation. Toxic deaths occur in about 1% of patients, affecting mainly the elderly [19]. The rate of III+ complications was observed in 36–40% of patients receiving chemotherapy with oxaliplatin [11, 16]. Closure of the colostomy is deferred till the moment chemotherapy is completed. The administration of post-operative chemotherapy is connected with the larger costs of treatment. Post-operative chemotherapy causes not only acute complications, but also delayed ones.

The above mentioned EORTC randomised study after a median observation period of 4.6 years showed that statistically more patients reported pain, diarrhoea, weaker physical activity and difficulties in everyday activities after the administration of post-operative chemotherapy than in the control group [20, 21]. Oxaliplatin causes chronic neuropathy, the intensification of which can lead to a lower quality of life [22].

The controversies concerning the administration of post-operative chemotherapy described in this paper point to the fact that a patient should be informed about its doubtful efficacy and possible complications. An evaluation as to whether the benefits from the use of chemotherapy exceed its toxic side-effects is subjective and should be left to the patient who must be adequately informed about the arguments for and against. It was observed that many patients prefer observation without chemotherapy when its beneficial effect is only minor [23].

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