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Does delaying adjuvant chemotherapy after curative surgery for colorectal cancer impair survival? A meta-analysis

Gaetan Des Guetz [a,*], *Patrick Nicolas* [b], *Gérard-Yves Perret* [b], *Jean-François Morere* [a], *Bernard Uzzan* [b]

[a] *AP-HP, Department of Oncology, Avicenne Hospital, 125 route de Stalingrad, 93009 Bobigny, France*
[b] *AP-HP, Department of Pharmacology, Avicenne Hospital, 125 route de Stalingrad, 93009 Bobigny, France*

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ABSTRACT

Background: In stage III colorectal cancer (CRC), adjuvant chemotherapy (CT) is usually prescribed within two months after curative surgery. Whether or not delaying initiation of CT affects survival is still debated.

Material and methods: We performed a meta-analysis (MA) of all published studies (full papers or abstracts) comparing delayed CT with standard care. Studies were obtained from a PubMed query (keywords: CRC, adjuvant treatment, delay of CT), a review (Chau et al., 2006), cross-checking references and abstracts from the proceedings of ASCO, ASCO GI and WCGI annual meetings. We chose a cutoff delay of 8 weeks. Risk Ratios (RRs) were calculated from the recorded events (deaths, relapses). We used EasyMA software (fixed-effect model).

Results: Fourteen studies (including four abstracts) were identified (17,645 patients; 5952 males, 5151 females, mean age 70 years). Of these, three could not be statistically analysed and three used another cutoff (4, 5 or 6 weeks), leaving 8 studies for main MA (13,158 patients; 3932 males, 3644 females, 5942 missing data; 5576 colon cancers, 6677 rectal, 1265 missing data). Delaying CT more than 8 weeks was associated to worse Overall Survival (OS) (RR: 1.20; 95% Confidence Interval (CI) 1.15–1.26). In the MA including all studies whatever their cutoff, longer delay was similarly associated to a worse OS but not a worse Relapse-Free Survival (RFS) (five studies).

Conclusion: Adjuvant chemotherapy should be started within 8 weeks after surgery. Delaying the initiation of adjuvant CT for more than 8 weeks after surgery significantly decreased OS but not RFS. This discrepancy might be due to factors not directly related to cancer (post-operative complications, social status) or to a more accurate appraisal of death.

1. Introduction

After curative surgery, treatment of localised colorectal cancer (CRC) usually consists of adjuvant chemotherapy (CT) for stage III disease and for stage II disease with elements of poor prognosis (T4 lesions, bowel perforation and inadequately sampled lymph nodes ($n < 13$)).[1,2] It is usually accepted that this CT should begin within two months after surgery.[2] However, several reasons may delay the initiation of adjuvant CT: post-operative complications such as wound infection for patients experiencing major surgery or operated in emergency situations; lack of compliance of some patients. When delayed, does adjuvant CT bring the same benefit in terms of Overall Survival (OS) or Relapse-Free Survival

* *Corresponding author:* Tel.: +33 (0)1 48 95 50 31; fax: +33 (0)1 48 95 50 35.
E-mail address: gaetan.des-guetz@wanadoo.fr (G. Des Guetz).
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(RFS)? It should be reminded that adjuvant CT can cure patients by treating micrometastatic disease. On the other hand, it seems illogical to expose patients to CT-induced toxicities if its benefit wanes progressively as time to initiation of CT increases, for instance in patients who experienced post-operative complications. From a practical point of view, the pertinence of beginning an adjuvant CT more than two or three months after surgery is questionable. The greater the time lapse between surgery and CT, the greater the need for a thorough search of metastasis. Several retrospective studies have been published to assess the effect on survival of delaying adjuvant CT. Some derived from randomised controlled trials which compared the benefits of adjuvant CT (mainly 5FU-based) to surgery alone in the 90s.[3] These trials led to a consensus around the year 2000 to treat all stage III CRC patients with adjuvant CT. This situation led to the constitution of registries, useful to describe real life and which have subsequently been divided into two subgroups, one with the usual delay from surgery to CT, the other with prolonged delay (*post hoc* analyses).[4]

The results of these various studies were contradictory. The two largest studies came from SEER (Surveillance Epidemiology and End Results) database, one older study on more than 4000 stage III colon cancers[4] and the other recent study on more than 6000 rectal cancers.[5] Both studies found that delaying adjuvant CT resulted in a statistically significant decrease in survival. However, other studies concluded to the absence of detrimental effect of delaying CT. Therefore, we performed a MA of all published studies to give a more precise insight into this crucial issue. The main goal of our MA was to assess the effect on survival of delaying adjuvant CT for more than 8 weeks. We chose this cutoff because it was the most frequently used among studies. An ancillary goal was to assess the effect on survival (Overall Survival was much more assessed than Relapse-Free Survival) of all studies which compared a shorter and a longer delay of initiation of CT, whatever the individual delays. Delays between surgery and initiation of CT ranged from 5[6] to 12 weeks.[4,5]

2. Material and methods

2.1. Publication selection

We performed our MA according to a predefined written protocol. To be eligible, studies had to deal with stage II/II colon or rectal cancer, and to assess the relationships between shorter or longer delay to CT and OS and RFS.

Publications were identified by an electronic search using online PubMed, updated on 15th August 2009 with the following keywords simultaneously: 'delay of chemotherapy, adjuvant treatment, colorectal cancer'. Only three references out of 42 provided by PubMed were thought to correspond to our inclusion criteria.[3–5] Another paper corresponded to a review about the treatment in adjuvant setting[2] and provided one additional reference.[7] Abstracts from the proceedings of American Society of Clinical Oncology (ASCO) and ASCO Gastro-Intestinal meetings (1998–2009) and World Congress of Gastro-Intestinal Cancer (WCGI) were reviewed. From ASCO proceedings, six abstracts were selected: one in 2009,[8] two in 2007[9,10], two from ASCO GI 2007[11,12] and one in 2008[5] recently published as a full article.[5] We also found one abstract in WCGI proceedings (2006–2009).[13] Three papers were obtained by cross-checking of references: QUASAR from the review by Chau and Cunningham,[2] Arkenau from the correspondences to the SEER study,[4] Taal from the study by Berglund et al.[3] Information was requested from several authors.[3,4,9,10,12–15] Only one author answered in a way that allowed inclusion of his study into our MA.[14] The different steps of the article selection are given on the flow chart (Fig. 1).

We used a predefined data sheet to collect key information in each study. G. Des Guetz, oncologist, wrote the protocol and read the selected articles, putting the emphasis on clinical and oncological aspects. B. Uzzan, methodologist and pharmacologist, read the articles, putting the emphasis on clinical and methodological aspects. Disagreements between the two authors were resolved by consensus. P. Nicolas, pharmacologist and statistician, gathered and controlled the numerical data needed for statistical calculations and participated with G.D.G. and B.U. in the decisions of inclusion or rejection of the studies. J.F. Morere and G.Y. Perret provided supervision to this work.

2.2. Statistical analysis

In each study, the relationship between survival and delay of adjuvant CT was considered significant when the *p*-value for the statistical test comparing survival distributions was below 0.05 (two-tailed test). For each study, the Relative Risk (RR) was estimated by a method depending on the data provided in the publication. The simplest method consisted of the direct collection of RRs with their 95% Confidence Intervals (CIs) when mentioned in the original publication. If not available, we looked at the total number of events (deaths, relapses) and at the number of patients at risk in each group to calculate the RR. Calculations of HRs and their 95% CIs were done according to Morris and Gardner.[16] When the data were only available as graphical survival plots, the calculations were made only if the number of steps on the curves equalled the number of events given in the publication, assuming that the rate of censored patients was constant during the study follow-up. By convention, in each study, we chose as reference the shorter delay, and RRs higher than 1 meant that survival was worse among patients with the longer delay.

We could include in our meta-analytic calculations only 11 studies,[3–9,12–14,17] four of which in abstract form.[8,9,12,13] Our main MA relied upon the eight studies, for which we could stratify the data according to a common cutoff delay of 8 weeks from surgery to CT.[3–5,7–9,12,13] Only three studies used a different cutoff for delay from surgery to adjuvant CT: 4 weeks in one study,[14] 5 weeks in another study[6] and 6 weeks in the third one QUASAR.[17] We also performed a global MA of the 11 studies for which a stratification of data according to a cutoff delay from surgery to CT was possible, whatever the delay.

We calculated a pooled random RR estimate and its 95% CI by using a fixed-effect model (Mantel Haenszel) due to the absence of heterogeneity between studies. The statistical calculations used EasyMA. Net (http://www.spc.univ-lyon1.fr/easyma.net/), a software available online (Department of Clinical Pharmacology, Cardiology hospital, Lyon, France).

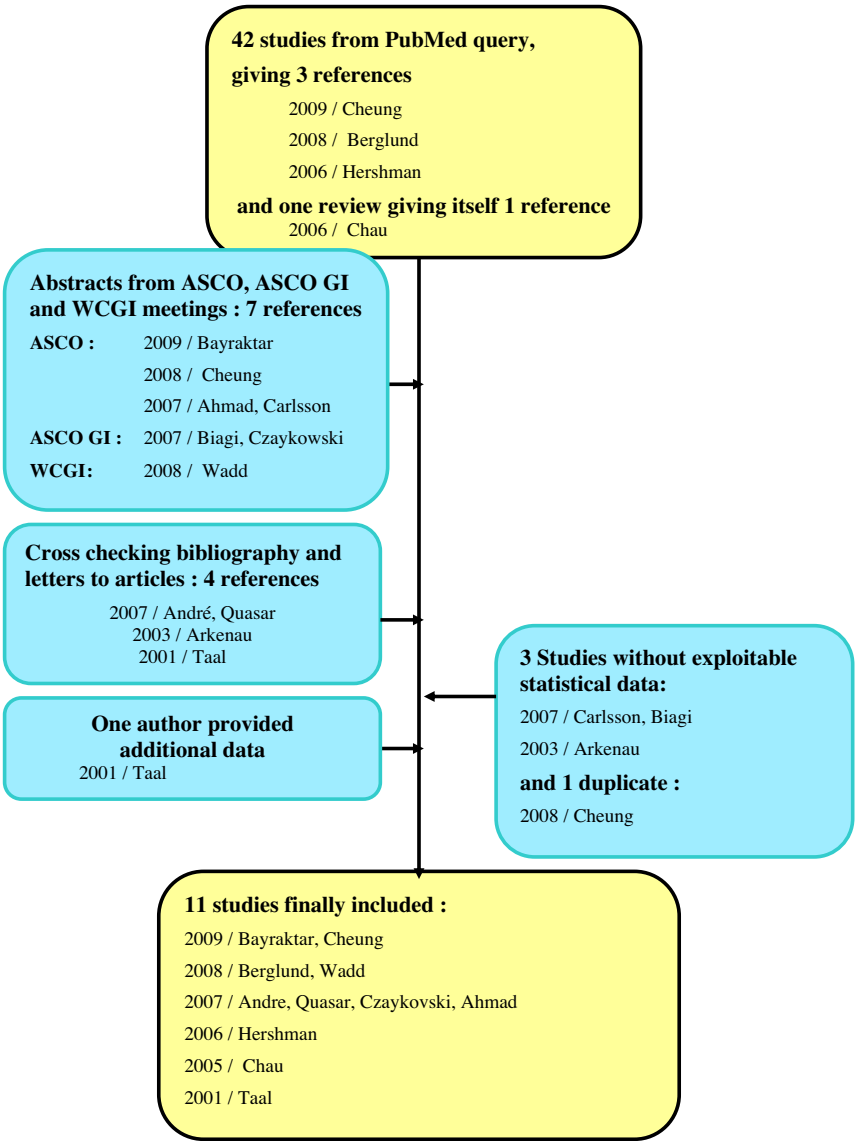

Fig. 1 – Flow-chart of the different steps of the meta-analysis.

3. Results

3.1. *Study and patient characteristics*

Our literature search found a total of 14 studies (of which six were only published in abstract form) meeting our inclusion criteria. These studies corresponded to *post hoc* stratifications of randomised controlled trials or cohorts or to retrospective studies. The oldest study was published in 2001.[14] These 14 studies included a total of 17,645 patients (5952 males and 5151 females, 6542 missing data). Mean age of the patients was 69.8 years. Only two studies including 1038 patients did not specify age.[11,13] There were 8908 colon cancers (60%), 7005 rectal cancers (1732 missing data) and 4504 stage II, 11,740 stage III colorectal cancers (1401 missing data).

Table 1 shows the main characteristics of the studies. Three studies could not be included in our MA,[10,11,15] leaving 11 studies that could be assessed. The 11 studies[3–9,12–14,17] in which statistical calculations could be done included 16,552 patients (94% of the overall population). The eight studies included in the main MA[3–5,7–9,12,13] represented a total of 13,158 patients (3932 males, 3644 females, 5942 missing data; 5576 colon cancers, 6677 rectal cancers, 1265 missing data) and 2998 stage II, 10718 stage III colorectal cancers (701 missing data).

3.2. *Effect on survival of delaying CT*

The main MA relied upon the eight studies for which data could be stratified according to a common cutoff delay of 8 weeks between surgery and adjuvant CT. Delaying the initiation of CT for more than 8 weeks after surgery was associated to a worse Overall Survival (OS) (RR: 1.20; 95% Confidence Interval or CI 1.15–1.26; $p = 0.001$) (Fig. 2). In only two studies was Relapse-Free Survival (RFS) available. We also performed a second MA including all 11 studies for which statistical calculations could be done, whatever their cutoff delay. Results for OS were very similar to those of the main meta-analysis

Table 1 – Main characteristics of the 11 studies included in the overall meta-analysis. Eight studies share a common cutoff of 8 weeks to discriminate between the shorter and the longer delays between surgery and adjuvant chemotherapy. ND: not determined. 5FU: 5 fluoro-uracile.

Author [reference] year of publication	N (M/F)	Age (median)	Primary tumour, colon/rectum	Differentiation well + moderately/poor	Stage, II/III	Delay (Weeks after surgery): Nb patients delayed	Chemotherapy (CT) protocols	Total number of relapses		Total number of deaths		Causes of delay
								Delay	Standard	Delay	Standard	
Bayraktar [8] 2009	190	57	190/0	ND	35/155	+8 W: 56	5FU based CT	23	46	22	33	
Cheung [5] 2009	6059 (3147/2912)	73	0/6059	340 + 4420/1105	2249/3810	+8 W: 1583	5FU based CT			725	1790	Advanced age, black race and postoperative recovery +
Berglund [3] 2008	231 (125/106)	65	231/0	0/231	0/231	+8 W: 82	5FU/levamisole, 5FU/leucovorin (LV) or 5FU/LV + levamisole			39	60	
Wadd [13] 2008	859	ND	0/859	ND	0/859	+8 W: 359	5FU based CT			142	171	
Quasar [16] 2007	1622 (1006/616)	63	1148/474	ND	1483/131	+6 W: 799	5FU + high dose folinic acid ± levamisol 5FU + low dose folinic acid ± levamisol	145	146	154	155	
Ahmad [9] 2007	701 (ND)	66	701 (ND)	ND	ND	+8 W: 248	5FU based CT	156	276			
Czaykowski [12] 2007	295 (155/140)	66	295/0	ND	0/295	+8 W: 69	5FU based CT			34	88	
Andre [6] 2007	905 (489/416)	60	905/0	ND	389/516	+5 W: 302	LV/5FU2 FU + Lv	106	206	72	137	
Herschman [4] 2006	4382 (ND)	74	4382/0	2975/1235	0/4382	+8 W: 869				476	1510	Older age, increased comorbid conditions, well/moderately differentiated grade, and being unmarried
Chau [7] 2005	801 (431/370)	62.5	478/323	685/84	325/470	+8 W: ND	5FU/LV 5FU(continuous)	ND	ND	ND	ND	
Taal [14] 2001	514 (301/213)	62	365/149	ND	233/281	+4 W: 201	5FU levamisol	127	89	93	69	

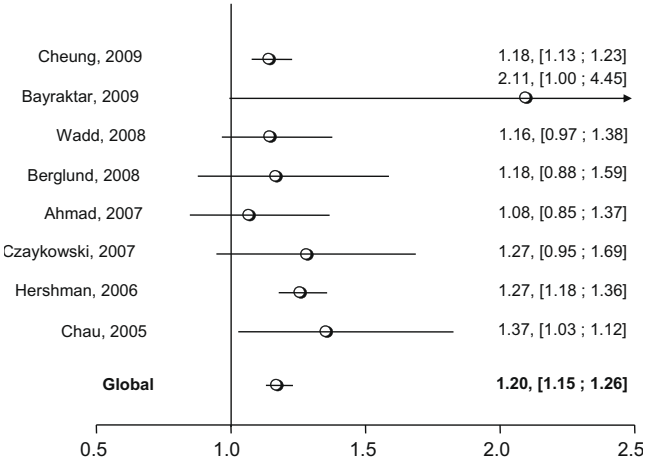

Fig. 2 – Forest plot of the eight studies including 13,518 patients assessing Overall Survival and sharing a common cutoff delay between surgery and adjuvant chemotherapy of 8 weeks. By convention, we chose for reference the shorter delay. A Hazard Ratio > 1 corresponds to a worse survival. Due to the absence of heterogeneity between studies, we chose a fixed-effect model.

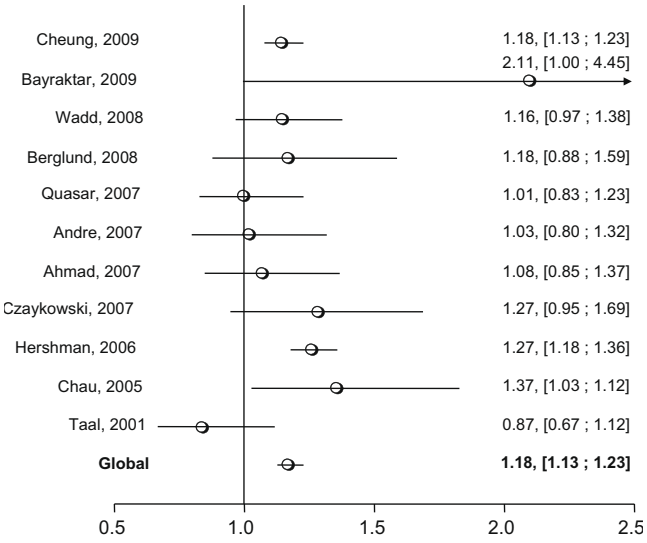

Fig. 3 – Forest plot of the 11 studies including 16,552 patients assessing Overall Survival with various cutoff delays between surgery and adjuvant chemotherapy. By convention, we chose for reference the shorter delay. A Hazard Ratio > 1 corresponds to a worse survival. Due to the absence of heterogeneity between studies, we chose a fixed-effect model.

(MA). Delaying initiation of CT was associated with a worse OS (RR: 1.18; 95% CI 1.13–1.23; $p = 0.001$) but not with a worse RFS (RR: 0.98; 95% CI 0.89–1.08) (five studies including 3925 patients) (Figs. 3 and 4). The addition of the study by Taal et al.[14] altered the test for heterogeneity from a non-statistically significant to a borderline significant result ($p = 0.06$). This fact may be explained by the very short cutoff delay

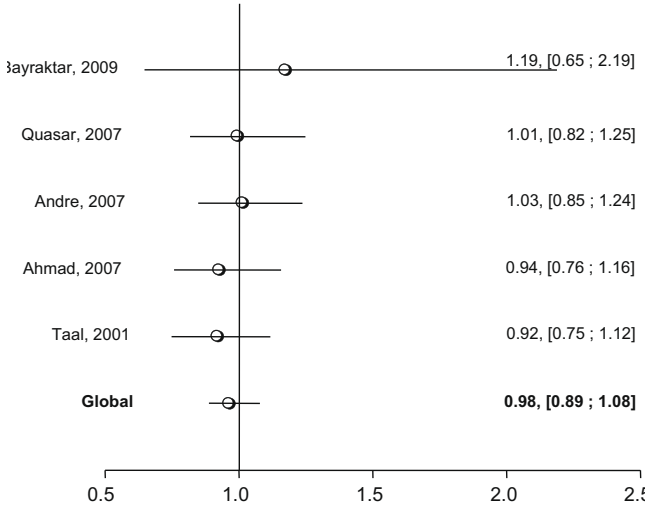

Fig. 4 – Forest plot of the five studies with various cutoff delays between surgery and adjuvant chemotherapy including 3925 patients assessing Relapse-Free Survival. A Hazard Ratio > 1 corresponds to a worse survival.

between surgery and CT in that study. We performed a MA specifically dealing with only colon cancer[3,4,8,12,18] (five studies; 5579 patients) and found a HR OS of 1.25 (95% CI 1.17–1.34) very close to the HR of Hershman et al.[4] which is not surprising due to the important weight of this study. The same held true when performing a MA specifically on stage III cancers[3,4,12,13] (HR 1.25, 95% CI: 1.18–1.33). The same results were found when pooling the three studies dealing with stage III colon cancer.

We performed a sensitivity analysis by excluding from the MA the two studies which included by far the greatest number of patients, both deriving from the SEER database, one dealing with colon cancers (4382 patients),[4] the other with rectal cancers (6059 patients).[5] This sensitivity analysis included only 5597 patients from nine studies and found similarly that a longer delay was associated to a worse OS (RR: 1.14; 95% CI 1.04–1.25; $p = 0.01$).

4. Discussion

According to our meta-analysis, delaying initiation of adjuvant CT after curative surgery for CRC for more than 8 weeks was associated with a statistically significant decrease in Overall Survival (RR: 1.20; 95% CI 1.15–1.26). To our knowledge, it is the first time that this result, although intuitive, is established from an overview of the literature with a high level of evidence. In the MA including all 11 studies for which statistical calculations could be done, whatever the cutoff delay from surgery to CT, a longer delay was similarly significantly associated with worse OS (RR: 1.18; 95% CI 1.13–1.23; $p = 0.001$) but not with worse Relapse-Free Survival (RR: 0.98; 95% CI 0.89–1.08; five studies). This discrepancy between the association of longer delay to decreased OS but unchanged RFS might be interpreted as a major contribution of non-cancer specific factors to this worse survival. Another plausible explanation would be that death is much easier to capture

accurately from various sources than relapses. However, this last result should be interpreted cautiously since it relied upon only five studies including 3925 patients. The main limitation of the overall is the fact that a shorter delay in a study with a cutoff of 8 weeks could be considered as a longer delay in a study with a cutoff value of 5 or 6 weeks. Our results mainly apply to colon cancer and to stage III disease. The impact of CT has generally been demonstrated in this subgroup. No study assessed specifically the effect of delaying CT in stage II cancers. The conclusions of our subgroup analyses are limited by the small numbers of studies included and the major weight of the SEER studies[4,5] (more than 4000 patients for colon and more than 6000 patients for rectal cancer). A sensitivity analysis excluding the two largest studies confirmed that a longer delay to CT was associated to a worse OS, strengthening the conclusion of our meta-analysis. The persistence of a statistically significant reduction in OS with a longer delay despite exclusion of the two studies with the highest numbers of patients strengthens the conclusion of our MA, confirming the absence of heterogeneity between studies. The validity of our decision is still reinforced by the fact that these two studies had several drawbacks, in that they included only patients aged 65 years or more and that it cannot be discerned accurately whether the treatment was prescribed as adjuvant therapy.

For obvious ethical reasons, a randomised controlled trial comparing the effect on survival of two different delays of initiation of adjuvant CT after surgery would not be feasible. Therefore, the question of timing to CT cannot be answered prospectively. Our MA did not answer the question as to whether it is still valuable to begin CT in a patient seen for the first time more than 8 weeks after surgery. To answer to this question, would be needed a comparison between the risk-to-benefit ratio of delayed adjuvant CT and no CT, by means of a randomised controlled trial. This trial would raise ethical but also practical issues (limited accrual). No definite cutoff delay can be drawn from the literature, but it should be reminded that with time, the positive but rather small advantage of adjuvant CT wanes. In both studies coming from the SEER database,[4,5] the large number of patients included allowed for evaluation of different cutoff delays from 1 to 3 months: both studies showed that survival was significantly affected by a delay longer than 3 months between surgery and adjuvant CT. In breast cancer, a large single institution cohort concluded similarly that survival was decreased when CT was delayed more than 12 weeks after curative surgery.[19] In the SEER database, 5003 women received adjuvant CT: 47% initiated CT within 1 month, 37% between 1 and 2 months, 6% between 2 and 3 months and 10% more than 3 months (decreased survival). Delay was associated with older age, rural residence, being unmarried, earlier tumour stage, hormone receptor positivity, mastectomy and no radiation therapy.[20]

There is no agreement as to the choice of a precise time for the initiation of adjuvant CT after surgery for CRC, although a 8-week cutoff is generally accepted This results from various cutoff time delays after surgery among the studies, ranging from 4 to 12 weeks. These delays were retrospectively set up. The reason why delaying adjuvant CT is associated with worse survival is not known. The longer the interval between surgery and adjuvant CT, the higher the risk of proliferation of micrometastases. Adjuvant CT is started only after recovery from surgery. Surgery and wound healing after surgery create a favourable environment for metastatic clones to grow.[21] From a theoretical point of view, adjuvant CT should be initiated as early as possible after curative surgery. On the contrary, the study by Lohrisch concerning breast cancer seems to indicate that starting adjuvant CT too early (<4 weeks) may not be associated with better outcomes than starting a bit later.[19]

In published studies, adjuvant CT was usually begun within 8 weeks after surgery. In real life, however, this time interval may be longer. Several reasons can explain why in some patients the beginning of adjuvant CT after curative surgery is delayed: firstly, the occurrence of post-operative complications, but also, more generally, longer recovery from surgery, which can be related to cancer complication (perforation, occlusion) or decreased pre-operative performance status, which can be seen in more advanced stages or in patients with important co-morbidities or in the elderly. Delays related to slow pathology reporting, delayed referrals, wait-times for oncology consultations and CT room availability could be shortened. Another reason would be the poor compliance of some patients to their treatment schedule. Among CRC patients, compliance would be expected to be higher among patients receiving neo-adjuvant CT than among those who began CT after surgery. Good compliance is associated to personality traits and behaviours favouring good health. In the Beta Blocker Heart Attack Trial, mortality is more than doubled among both beta blocker users and placebo non-compliant users.[22] A MA has been recently published to assess the association between adherence to drug therapy and mortality.[23] These findings have been summarised under the name of 'healthy user effect'.

To conclude, the time interval between curative surgery for CRC and adjuvant CT should be kept within 8 weeks whenever it is possible. A time interval longer than 12 weeks would put into question the utility of adjuvant CT.

Conflicts of interest statement

None declared.

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