Adjuvant chemotherapy

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1. Rectal cancer – less scientific evidence than for colon cancer

In rectal cancer there is much less scientific evidence for clinically relevant gains from postoperative chemotherapy than there is for colon cancer. The large adjuvant trials that revealed the gains in disease-free survival (DFS) and overall survival (OS) included either patients with colon cancer only or a limited number of patients with rectal cancer. In comparison with colon cancer, combination chemotherapy with a fluoropyrimidine and oxaliplatin has not been explored at all in rectal cancer, whereas three large randomised trials in colon cancer all showed improved DFS and possibly OS in patients randomised to combination therapy [1–3].

In colon cancer, the loco-regional therapy has not changed to any major extent during recent decades. This has been the case for rectal cancer, where the quality of surgery has been substantially improved with the introduction of the total mesorectal excision (TME) concept. Furthermore, a great majority of rectal cancer patients now receive preoperative therapy, at least if they belong to the intermediate or locally advanced groups, and postoperative radiotherapy or chemoradiotherapy is seldom given as it often was in recent decades [4–6]. This more complex treatment scenario, and the improvements over time of the loco-regional treatment strategies, have made it difficult to evaluate the effects of adjuvant chemotherapy in rectal cancer.

Two opposing views can be considered when giving recommendations for whether or not to give adjuvant chemotherapy to rectal cancer patients. One is to extrapolate from colon cancer, applying the knowledge achieved from the large trials to rectal cancer under the assumption that they all come from the same organ and all are adenocarcinomas. The other view is to look at the trials in detail, explore what types of loco-regional treatment have been given and then evaluate whether we have randomised evidence for favourable effects in the different clinical situations.

2. Do rectal and colon cancers respond similarly to chemotherapy?

In metastatic disease, the primary location of the colorectal cancer appears to be irrelevant on the basis of numerous studies which have analysed the relevance of the tumour site (colon versus rectum), e.g. Köhne et al [7]. Thus, a possible reason for the apparently greater effect of adjuvant chemotherapy with modulated 5-fluorouracil (5-FU) in colon than in rectum cancer is probably not due to different chemosensitivities. No study has explored the value of capecitabine or a combination regimen with a fluoropyrimidine and oxaliplatin as adjuvant therapy in rectal cancer, whereas these treatments have been extensively used in metastatic disease [8], with no detectable differences according to site.

Detectable metastases do come from tumour cells/cell deposits that once have been subclinical and present at the time of diagnosis. Thus, the lack of difference in the metastatic setting strongly argues against lower chemosensitivity of rectal cancer cells compared with colon cancer cells. However, colon cancer differs in some aspects relevant to tumour biology, and thus potentially chemosensitivity, from rectal cancer [9–11]. The molecular characteristics, however, also differ between parts of both colon and rectum [12]. These differences may not materialise in the metastatic setting, but may be relevant when the disease is only subclinical.

3. Evidence for effects of adjuvant chemotherapy in rectal cancer

A Cochrane report [13], based upon 21 clinical trials including 9221 patients, concluded that significant gains are present in both DFS and OS (Table 1). These patients have been treated over several decades. During this extended time period, both surgery and the use of additional (chemo)radiotherapy have evolved considerably [6]. The hazard ratios (HRs) for gains in

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1359-6349/$ - see front matter

http://dx.doi.org/10.1016/j.ejcsup.2013.07.034

Table 1 – Summary of the cochrane meta-analysis and of the major randomised clinical trials on the role of systemic adjuvant chemotherapy after curative loco-regional treatment of rectal cancer.

Treatment setting	Study/Ref.	No. of pts	Study features	Results	Comments
All	Cochrane analysis [13]	9221 from 21 trials	All stages, all treatments, all settings	HR for OS 0.88 (0.76–0.91), for DFS 0.75 (0.68–0.83)	Trials running during several decades, great heterogeneity between the trials
Adjuvant chemotherapy after surgery alone	Sakamoto/Japanese meta-analysis [41]	2310 from three old trials	Stages I–III, 5FU, UFT or carmofur 6 m, mitoC 6 m added in two trials	HR for OS 0.86 ($P = 0.049$), for DFS 0.77 ($P = 0.0003$)	No gain in colon cancer ($n = 2380$)
	JSCCR/Japanese meta-analysis [42]	2385 from three trials	Stages I–III, UFT or carmofur 12 m, mitoC 6 m	HR for OS 0.92 ($P = 0.04$), for DFS 0.83 (NS)	Two trials probably included in the above study
	Sakamoto/Japanese meta-analysis [43]	2091 from five trials	Stages I–III, UFT or carmofur12–24 m, mitC 6 m added in three trials	HR for OS 0.82 ($P = 0.02$), for DFS 0.73 ($P < 0.0001$) and for LRFS 0.68 ($P = 0.003$)	Some trials overlapping with the above two meta-analyses
	NSAS-CC [44]	274	Stage III, surgery w/wo UFT 12 m	HR for OS 0.60 ($P = 0.034$), for DFS 0.66 ($P = 0.033$)	No gain in colon cancer ($n = 334$), HR 0.82, $P = 0.4$). Included in the above meta-analysis, updated results
	Nordic trials [45]	691	Stages II–III, 5FU 4–12 m	OS at 5 y 73% versus 81% for AC in stage II ($P = 0.09$) and 51% versus 48% for AC in stage III ($P = 0.91$)	Various 5FU regimens. A numerical gain was seen in colon cancer stage III ($n = 708$, OS at 5 y 48 versus 55%, $P = 0.15$), however, dependent upon the time from surgery to start of AC [33]
	NSABP-R01 [46]	371	Stage II–III, 5FU, semustine and vincristine	OS and DFS improved (43% versus 53% for AC at 5 y, $P = 0.05$ and 30% versus 42% for AC, 0.006, respectively	Postop RT alone had no effect on OS or DFS
	QUASAR uncertain [18]	549	Stage II, III. 5FU 6 m	HR for OS approx 0.85 (NS), for DFS approx 0.75 (NS)	Subgroup analysis from the trial. In all 948 RC patients included, HR for OS was 0.77 (95% CI 0.54–1.00), for DFS 0.68 (0.48–0.96). 86% of all pts included had stage II

Continued on next page

Table 1 – continued

Treatment setting	Study/Ref.	No of pts	Study features	Results	Comments
Adjuvant chemotherapy after postop RT/CRT	Hellenic group [47]	220	Stage II, III, postop CRT alone or with 5FUFA 4 cycles	AC NS improved DFS at 5 y from 68 to 70% and OS from 73 to 77%	
	Cafiero et al [48]	218	Stage II, III, postop RT w/wo 5FU/Leva 6 m	HR for OS 1.04 ($P = 0.9$), for DFS 1.12 ($P = 0.6$)	Low compliance with adjuvant chemotherapy, NS improvement in compliant pts
	Dutch group [49]	299	Stage II, III, postop RT w/wo 5FU/Leva 12 m	HR for OS approx 0.95, for DFS approx 0.90 (NS)	Approx 75% of pts had at least 6 m treatment. Significant effect seen in colon cancer in the same trial
	ECOG Est 4276 [50]	237	Stages II–III, postop RT, CT or CRT	5-yr OS RT 46%, CT 47%, CRT, 50% (NS)	Abstract only
	QUASAR uncertain [18]	201	Stage II, III, postop RT w/wo 5FU 6 m	HR for OS approx 0.80 (NS), for DFS approx 0.65 (NS)	See comment on QUASAR above
Adjuvant chemotherapy after preop RT	EORTC 22921 [19]	505	cT3, T4, preop RT w/wo 5FU 3 m postop	HR for OS for AC versus no AC 0.85 (0.68–1.04) and for DFS 0.87 (0.72–1.04). LR at 5 y was 17 and 10% in the RT and RT/AC groups, resp	Represents 2 of the 4 arms in this trial. Results not separated for preop RT and CRT (see below) groups. 27% of pts scheduled for AC never started. Difference in LR between preop RT only and the other 3 groups, $P = 0.002$
	QUASAR uncertain [18]	198	Stage II, III. preop RT w/wo 5FU 6 m	HR for OS and DSF approx 0.55 (NS)	See comment on QUASAR above
Adjuvant chemotherapy after preop CRT	EORTC 22921 [19]	506	cT3, T4, preop CRT w/wo 5FU 3 m postop	See above. LR was 9% and 8% in the CRT and CRT/AC groups, respectively	See above
	Italian Group [51]	635	Fixed/tethered RC. Preop CRT w/wo 5FU 4.5 m postop	OS 64% for CRT only and 68% when AC added (NS). No difference in LR	Preliminary data, median follow-up 25 m. Abstract only
	Fernandez-Martos et al [52]	108	CRT + surg + AC 4 m XELOX versus 4m XELOX + CRT + surg	No difference	Randomised phase 2, preop CT tolerable
Adjuvant chemotherapy before and after preop CRT	Expert-C [53]	164	High risk operable RC, neoadjuvant Cape/Oxali 3 m, CRT, postop Cape/Oxali 3 m or same treatment with cetuximab	HR for OS 0.27 ($P = 0.035$), for DFS 0.81 ($P = 0.668$)	Results for K-ras wild-type pts only

Preop, preoperative; Postop, postoperative; AC, systemic adjuvant chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy; pts, patients; UFT, uracil–tegafur; carmofur, 1-hexylcarmobyl-5-fluorouracil; m, months; HR, hazard ratio; OS, overall survival; DFS, disease-free survival; LRFS, local relapse-free survival; JSCCR, Japanese Society for Cancer of the Colon and Rectum; HCFU, 1-hexylcarbomoyl-5-fluorouracil; NS, not statistically significant; 5FU, 5-fluorouracil[a]; mitoC, mitomycin C; y, year; w/wo, with or without; Leva, levamisole; approx, approximately; CI, confidence interval; Cape, capecitabine, Oxali, oxaliplatin; resp, respectively.

[a]5FU was modulated with folinic acid in most trials.

rectal cancer are, according to the Cochrane report, for stages II + III: 0.75 for DFS and 0.89 for OS. No heterogeneity was seen between stages II and III. These HRs appear rather similar to the ones seen in colon cancer stage II but are less than those seen in colon cancer stage III [14–16]. Whether the relative gains differ between colon cancer stages II and III is uncertain, however, since they are to a large extent based upon inter-trial comparisons. The trials predominantly including stage III patients are generally older than those including stage II patients. Furthermore, the estimates for stage II are from a Cochrane report probably including all trials and patients, whereas no such report has been completed for stage III. The large ACCENT (Adjuvant Colon Cancer Endpoints) (Adjuvant Colon Cancer Endpoints) database gives important information as it includes the majority of the large trials [16] but then also tends to overestimate the gains, since all positive trials were included but not necessarily all negative trials.

It may thus be possible to conclude that adjuvant treatment for rectal cancer should be given as for colon cancer, based upon the Cochrane analyses. Others would argue that the heterogeneity between the trials is so extensive that no firm conclusions can be drawn. An entirely different view was also expressed in a recent systematic review [17] where the different rectal cancer trials were scrutinised according to whether the patients were pretreated, with radiotherapy only or with chemoradiotherapy, or if they received (chemo)radiotherapy postoperatively. These trials are summarised in Table 1.

4. Discussion of selected individual trials and of an analysis of pooled data

4.1. *QUASAR uncertain study*

This trial [18] included 984 rectal cancer patients (and 2345 colon cancer patients) in whom the doctors were uncertain about the value of adjuvant chemotherapy. In the group of rectal cancer patients, 5-year OS was increased from 74% in the control group to 78% (HR 0.77, $P = 0.05$) in the group of patients who were randomised to surgery and adjuvant 5-FU + calcium folinate. This gain was numerically the same in those rectal cancer patients who had surgery alone ($n = 549$) or preoperative ($n = 198$) or postoperative (chemo)radiotherapy, albeit not statistically significant. This is probably due to limited patient numbers in the subgroups. This study provides the strongest individual proof that adjuvant chemotherapy has at least some efficacy in rectal cancer.

4.2. *EORTC 22921/FFCD9203 (Fédération Francophone de la Cancérologie Digestive)*

These two trials [19–21] chiefly tested the value of concomitant chemotherapy and radiotherapy in intermediate rectal cancer, although the European Organisation for Research and Treatment of Cancer (EORTC) trial, having a 2×2 design, also explored the value of adjuvant 5-FU/leucovorin. The trials ($n = 1011$ and 756 patients, respectively) showed that the addition of chemotherapy decreased local recurrence rates (HR 0.54; 0.41–0.78) but not distant progression or OS, even if analysed together to increase power [21]. Although subgroup analyses according to ypT stage indicated that a survival gain was seen in the group of patients whose tumours appeared to respond to the (chemo)radiotherapy [22], the EORTC trial argues against any relevant gain from adjuvant chemotherapy in pretreated rectal cancer patients.

4.3. *PROCTOR/SCRIPT/Chronicle (Preoperative Radiotherapy and/or adjuvant Chemotherapy combined with TME-Surgery in Operable Rectal cancer/Simply Capecitabine in Rectal cancer after Irradiation Plus TME)*

Due to the scientific lack of firm evidence for benefit from adjuvant chemotherapy in rectal cancer properly operated and pretreated with (chemo)radiotherapy, trials with a surgery-alone group were initiated by researchers in the Netherlands, Sweden and the United Kingdom (UK). These trials have unfortunately been prematurely closed for patient inclusion because of poor accrual. The PROCTOR study included patients who had preoperative 5×5 Gy and TME and randomised the patients to surgery alone or 6 months of 5-FU/leucovorin. It was later changed (to SCRIPT) to capecitabine instead of 5-FU/leucovorin. In addition, patients who had received preoperative chemoradiotherapy could be included. In total, over 500 patients were included in these Dutch/Swedish trials until December 31, 2012. The UK Chronicle trial randomised 110 patients who had preoperative chemoradiotherapy to a control group or adjuvant 5-FU/leucovorin and oxaliplatin. There are no mature data from the trials, although an interim report presented at a scientific meeting when 470 patients had been included could not see any gain (van de Velde, personal communication). The trials illustrate the ambitions from scientists to create good scientific evidence and rely on extrapolated data as little as possible [23].

4.4. *Other recent trials*

In a Finish trial, 278 patients in clinical stage II + III were randomised between TME alone or preoperative 5×5 Gy, TME and adjuvant 5-FU/leucovorin [24]. The trial results will again be confounded by radiotherapy, but early and late toxicity of the combined treatment can be properly evaluated against modern surgery alone. No increase in serious surgical complications was seen. Wound infections and perineal wound dehiscence were, as expected, more common after irradiation. If the trial turns out to be negative, it will argue against the value of adjuvant chemotherapy since any survival gains from 5×5 Gy with TME is at best limited [6]. The limited number of patients and inclusion also of patients with early stages may prevent firm conclusions.

In two parallel identically designed German trials in colon ($n = 855$) and rectal ($n = 796$) cancer, respectively, adjuvant 5-FU/leucovorin was superior to 5-FU alone in colon cancer [67% (95% CI 59–73) versus 54% (95%; CI 97–61)] – but not in rectal cancer – [56% (95% CI 99–63) versus 51% (95% CI 43–58)] [25]. The authors speculate that the chemosensitivity of colon and rectal cancer differs.

4.5. *Nomogram*

Valentini et al. [26] collected information from a total of 2795 patients included in five European clinical trials with the aim

of allowing the selection of patients who might benefit from adjuvant chemotherapy. The trials were heterogeneous in many relevant aspects, and only two of them randomised patients between adjuvant chemotherapy or not [19] (Cionini et al, unpublished). The other three trials either planned to give adjuvant chemotherapy to all patients [20,27] or did not specify this in the protocol [28]. Neither of the two individual trials exploring the value of adjuvant chemotherapy revealed any significant gain in recurrence-free survival, whereas a small gain was seen when all trials were pooled together. Pooling of data from different trials may, however, easily introduce bias. Nomograms were developed for prediction of local recurrence, distant metastases and OS. The pathological stage (ypTN) after preoperative treatment (most patients had chemoradiotherapy to 45–50 Gy) was most important, although the use of adjuvant chemotherapy gave some additional value to the models. This added value was numerically smaller for distant metastases [HR ± 95% CI; 0.90 (0.83–0.97)] than for local recurrence [HR ± 95% CI; 0.81 (0.72–0.92)] and OS [HR ± 95% CI; 0.82 (0.76–0.88)]. The proposed nomogram was considered to have reliable concordance indices (0.73 for distant metastases) and could thus be useful for clinical assistance. The nomogram – which did not account for competing risk of death for recurrence prediction, therefore slightly overestimating the risk – indicated that any gains from adjuvant chemotherapy were minimal (1–2%) for responding patients, whereas the gains were larger for those who did not respond well to the preoperative chemoradiotherapy. The opposite conclusion was reached, as described above, when one of the included trials [19] was analysed retrospectively [22].

5. Recommendations

5.1. *High rectal cancers*

It is reasonable to conclude that tumours arising in the upper peritonealised third of the rectum should be treated as if arising from the colon. This means that most stage II patients should not have any adjuvant chemotherapy, some high-risk stage II patients should have adjuvant fluoropyrimidine and a few with several or very high-risk features an oxaliplatin combination. Most stage III patients should have an oxaliplatin combination, although some with low-risk features, particularly if they are older than 70 years, should rather be offered a fluoropyrimidine alone. These patients seldom have had preoperative (chemo)radiotherapy, although this may have been used in locally advanced, ugly tumours [6].

5.2. *Non-irradiated low and medium-high rectal cancer*

Adding 5FU-based adjuvant chemotherapy after surgery alone seems to provide meaningful benefits in terms of OS and DFS and perhaps also local recurrence rates, also in rectal cancers from the lower two-thirds. In practice, this is not often clinically relevant since very few patients with a tumour below about 10 cm from the anal verge with adverse histological features have been treated with surgery alone. Clinical and radiological imaging is not perfect, with a tendency for over-staging being more common than under-staging. What could be discussed in these patients is whether adjuvant chemotherapy then should be given alone or whether they should rather have adjuvant chemotherapy with chemoradiotherapy given either upfront or sometime during the treatment period. There are no data from modern trials to rely upon. If the local recurrence risk is reasonably high, for example if the surgery was non-radical (R1 + R2 or crm+), chemoradiotherapy is probably more relevant than if the risk of local recurrence is limited but the risk of systemic relapse is higher. Extensive lymph-node involvement (N2) and extramural vascular invasion (EMVI+) increase the risk particularly of systemic dissemination but also to some extent of local recurrence. However, it appears as if trial data taken together indicate that adjuvant chemotherapy seems more relevant for most patients than chemoradiotherapy, although this conclusion is controversial due to the lack of good trial data.

5.3. *Pretreated rectal cancer*

The ability to give solid recommendations based upon good evidence is limited when radiotherapy and particularly chemoradiotherapy have been given prior to surgery. Often a time period has been present between the end of chemoradiotherapy and surgery, and during that time period substantial tumour regression may have been seen. Most evidence, although based upon retrospective or pooled data, indicate that the patients then are best treated according to the pathological stage. If a pCR or a good regression is seen the value of adjuvant chemotherapy may be minimal, chiefly because the risk of recurrence is small (<15%). The study which developed the nomogram [26] indicates that patients with poor tumour regression benefit from adjuvant chemotherapy. This author is uncertain about its value, and would have preferred to see a randomised study completed. Still, adjuvant oxaliplatin-based therapy is often given, chiefly because the risk of recurrence is high. In a United States (US) national comprehensive cancer network analysis [29] it was seen that a sizeable minority of the patients (about 20%) who preoperatively received chemoradiotherapy did not receive adjuvant chemotherapy, as recommended. Strategies to facilitate the ability to complete the third and final component of curative treatment were considered necessary.

Adjuvant chemotherapy is also provided in the control group of the ongoing RAPIDO trial (Clin Trials Gov, NCT01558921) where locally advanced, ugly rectal cancers are randomised between chemoradiotherapy, surgery and optional adjuvant capecitabine–oxaliplatin (XELOX) for 6 months or 5×5 Gy, 5 months of XELOX and surgery [30]. Due to the scientific uncertainty, some countries (centres) have chosen not to give adjuvant chemotherapy in the control group.

6. Timing of chemotherapy

Sensitivity of the subclinical tumour cells potentially present after surgery to the given drug(s) is for obvious reasons crucial for an increase in recurrence-free survival, and hence DFS and OS. However, since the currently available drugs in colo-

rectal cancer have rather limited tumour cell kill effects, the number of tumour cells to be killed is also relevant. The tumour cells have left the primary tumour prior to diagnosis, between the diagnosis and the surgery (or start of a treatment that at least temporarily prevents the tumour cells from being clonogenic) and at the latest during the surgery to remove the primary. The number of cells in the deposits to be killed is also influenced by the delay from surgery to initiation of the adjuvant therapy. The relevance of this delay has been the focus of many retrospective studies and meta-analyses of the studies in colon cancer [31–33]. Most studies have reported poorer survival in groups of individuals who started adjuvant therapy later rather than earlier. The start of treatment is not random (a randomised trial comparing different times is not possible for ethical reasons) but may be caused by many factors that negatively influence particularly survival but also risk of and time to recurrence. The analyses may thus be subject to severe bias. All trials that have shown a benefit from adjuvant therapy in colon cancer had a requirement that it should be initiated within 4–6 weeks. In later trials, the maximum allowed time has been much longer, up to 12–13 weeks, actually diminishing the ability to detect a difference between two treatments. Several national guidelines also permit a delay up to 12 weeks (e.g. [34]). In a survey among 679 out of 1151 patients who received chemotherapy, only 72% met the 12-week benchmark. This proportion was lower in rectal cancer (67%) than in colon cancer (79%).

For many reasons, the time from diagnosis to start of adjuvant therapy is longer in rectal cancer than in colon cancer. The surgery is generally more extensive, with more complications and longer postoperative recovery. The preoperative radiotherapy – which probably efficiently decreases the clonogenic capacity of the tumour cells in the primary, but not in the subclinical distant metastases – is another reason for a longer delay during which tumour cell growth occurs. The chemotherapy given concomitantly with the radiotherapy is not very dose-efficient compared with that when it is used alone, and probably has marginal influence on the risk of distant recurrence. The tendency to prolong the interval between the end of (chemo)radiotherapy and surgery to see more pCRs and down-sizing [35] further prolongs the interval and may cause survival to deteriorate. One apparently positive aspect of likely no benefit for the patients (the treatment has already been given) may be counterbalanced by another aspect. This also relates to the increased use of 5×5 Gy with a delay of 6–8 weeks (as explored in the randomised Stockholm III trial [36]) outside of trials in intermediate (bad) rectal cancers (designated by most as locally advanced) [6]. The Stockholm III completed patient accrual in January 31, 2013, so survival data will not be available for many years.

7. Conclusions

In many countries the use of adjuvant chemotherapy for rectal cancer is not an issue, meaning that it is recommended and given as for colon cancer. There are no good studies describing how often it is an issue, but several centres in several countries have expressed concerns about the value of adjuvant chemotherapy in rectal cancer [37]. This is not the case for colon cancer, where treatment recommendations are probably very similar to the guidelines presented by the European Society for Medical Oncology (ESMO) [38]. These recommendations are based upon firm evidence when they relate to the entire group of patients with colon cancer, but must be questioned in the different substages. The surgery performed today for colon cancer is of higher quality than it was when the trials were run. Furthermore, and possibly even more relevant, is higher quality of the pathology investigations. This has caused stage migration. The extent of this has not been quantified. However, if we follow the recommendations [38], we treat groups of patients with very low risks of recurrence (even less than 10% with an oxaliplatin combination), gaining very few individuals. When analysed, population data indicate that the use in colon cancer follows the present recommendations (e.g. [39]), whereas greater variability has been reported for rectal cancer (e.g. [40]). The available literature-based documentation from the trials has been briefly summarised here. No one can object to the much less scientific evidence for sufficient gains in rectal cancer compared with colon cancer. However, interpretations differ considerably between different researchers and clinicians, particularly when the surgery has been preceded by (chemo)radiotherapy.

Conflict of interest statement

None declared.

REFERENCES

[1] Andre F, Delaloge S, Soria JC. Biology-driven phase II trials: what is the optimal model for molecular selection? J Clin Oncol 2011;29:1236–8.
[2] Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol 2011;29:3768–74.
[3] Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol 2011;29:1465–71.
[4] Valentini V, Aristei C, Glimelius B, et al. Multidisciplinary rectal cancer management. Radiother Oncol 2009;92:148–63.
[5] Valentini V, Glimelius B. Rectal cancer radiotherapy: towards European consensus. Acta Oncol 2010;49:1206–16.
[6] Glimelius B. Multidisciplinary treatment of patients with rectal cancer: development during the past decades and plans for the future. Ups J Med Sci 2012;117:225–36.
[7] Köhne C-H, Cunningham D, Di Costanzo F, et al. Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. Ann Oncol 2002;13:308–17.
[8] Glimelius B, Cavalli Björkman N. Metastatic colorectal cancer: current treatment and future options for improved survival. Medical approach – present status. Scand J Gastroenterol 2012;47:296–314.
[9] Aamodt R, Jonsdottir K, Andersen SN, et al. Differences in protein expression and gene amplification of cyclins between colon and rectal adenocarcinomas. Gastroenterol Res Pract 2009;2009. article ID 285830.

[10] Minoo P, Zlobec I, Peterson M, Terracciano L, Lugli A. Characterization of rectal, proximal and distal colon cancers based on clinicopathological, molecular and protein profiles. Int J Oncol 2010;37:707–18.
[11] Slattery ML, Wolff E, Hoffman MD, et al. MicroRNAs and colon and rectal cancer: differential expression by tumor location and subtype. Genes Chromosom Cancer 2011;50:196–206.
[12] Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012;487:330–7.
[13] Petersen SH, Harling H, Kirkeby LT, Wille-Jorgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev 2012;3:CD004078.
[14] Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004;22:1797–806.
[15] Figueredo A, Coombes ME, Mukherjee S. Adjuvant therapy for completely resected stage II colon cancer. Cochrane Database Syst Rev 2008:CD005390.
[16] Sargent D, Sobrero A, Grothey A, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2009;27:872–7.
[17] Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radio(chemo)therapy? A systematic review of randomized trials. Ann Oncol 2010;21:1743–50.
[18] Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet 2007;370:2020–9.
[19] Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114–23.
[20] Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-P4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24:4620–5.
[21] Bonnetain F, Bosset JF, Gerard JP, et al. What is the clinical benefit of preoperative chemoradiotherapy with 5FU/leucovorin for T3-4 rectal cancer in a pooled analysis of EORTC 22921 and FFCD 9203 trials: surrogacy in question? Eur J Cancer 2012;48:1781–90.
[22] Collette L, Bosset JF, den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? J Clin Oncol 2007;25:4379–86.
[23] Glimelius B. Adjuvant chemotherapy in rectal cancer – an issue or a non-issue? Ann Oncol 2010;21:1739–41.
[24] Salmenkyla S, Kouri M, Osterlund P, et al. Does preoperative radiotherapy with postoperative chemotherapy increase acute side-effects and postoperative complications of total mesorectal excision? Report of the randomized finnish rectal cancer trial. Scand J Surg 2012;101:275–82.
[25] Kornmann M, Staib L, Wiegel T, et al. Long-term results of 2 adjuvant trials reveal differences in chemosensitivity and the pattern of metastases between colon cancer and rectal cancer. Clin Colorectal Cancer 2013;12:54–61.
[26] Valentini V, van Stiphout RG, Lammering G, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol 2011;29:3163–72.
[27] Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–40.
[28] Bujko K, Kepka L, Michalski W, Nowacki MP. Does rectal cancer shrinkage induced by preoperative radio(chemo)therapy increase the likelihood of anterior resection? A systematic review of randomised trials. Radiother Oncol 2006;80:4–12.
[29] Khrizman P, Niland JC, ter Veer A, et al. Postoperative adjuvant chemotherapy use in patients with stage II/III rectal cancer treated with neoadjuvant therapy: a national comprehensive cancer network analysis. J Clin Oncol 2013;31:30–8.
[30] Nilsson PJ, van Etten B, Hospers GAP, et al. Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer – the RAPIDO trial. BMC Cancer 2013;13:279.
[31] Des Guetz G, Nicolas P, Perret GY, Morere JF, Uzzan B. Does delaying adjuvant chemotherapy after curative surgery for colorectal cancer impair survival? A meta-analysis. Eur J Cancer 2010;46:1049–55.
[32] Biagi JJ, Raphael MJ, Mackillop WJ, et al. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA 2011;305:2335–42.
[33] Berglund A, Cedermark B, Glimelius B. Is it deleterious to delay the start of adjuvant chemotherapy in colon cancer stage III? Ann Oncol 2008;19:400–2.
[34] Rayson D, Urquhart R, Cox M, Grunfeld E, Porter G. Adherence to clinical practice guidelines for adjuvant chemotherapy for colorectal cancer in a Canadian province: a population-based analysis. J Oncol Pract 2012;8:253–9.
[35] Dhadda AS, Zaitoun AM, Bessell EM. Regression of rectal cancer with radiotherapy with or without concurrent capecitabine – optimising the timing of surgical resection. Clin Oncol (R Coll Radiol) 2009;21:23–31.
[36] Pettersson D, Cedermark B, Holm T, et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg 2010;97:580–7.
[37] Glimelius B. Adjuvant chemotherapy in rectal cancer – an issue or a nonissue? Ann Oncol 2010;21:1739–41.
[38] Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO consensus guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol 2012;23:2479–516.
[39] Abrams TA, Brightly R, Mao J, et al. Patterns of adjuvant chemotherapy use in a population-based cohort of patients with resected stage II or III colon cancer. J Clin Oncol 2011;29:3255–62.
[40] Tiselius C, Gunnarsson U, Smedh K, Glimelius B, Pahlman L. Patients with rectal cancer receiving adjuvant chemotherapy have an increased survival: a population-based longitudinal study. Ann Oncol 2013;24:160–5.
[41] Sakamoto J, Hamada C, Kodaira S, Nakazato H, Ohashi Y. Adjuvant therapy with oral fluoropyrimidines as main chemotherapeutic agents after curative resection for colorectal cancer: individual patient data meta-analysis of randomized trials. Jpn J Clin Oncol 1999;29:78–86.
[42] Meta-Analysis Group of the Japanese Society for cancer of the colon and rectum and the Meta-Analysis Group in cancer. Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials. *J Clin Oncol* 2004;**22**:484–492.
[43] Sakamoto J, Hamada C, Yoshida S, et al. An individual patient data meta-analysis of adjuvant therapy with uracil-

tegafur (UFT) in patients with curatively resected rectal cancer. Br J Cancer 2007;96:1170–7.
[44] Hamaguchi T, Shirao K, Moriya Y, et al. Final results of randomized trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC). Cancer Chemother Pharmacol 2011;67:587–96.
[45] Glimelius B, Dahl O, Cedermark B, et al. Adjuvant chemotherapy in colorectal cancer: a joint analysis of randomised trials by the Nordic Gastrointestinal Tumour Adjuvant Therapy Group. Acta Oncol 2005;44:904–12.
[46] Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP Protocol R-01. J Natl Cancer Inst 1988;80:21–9.
[47] Fountzilas G, Zisiadis A, Dafni U, et al. Postoperative radiation and concomitant bolus fluorouracil with or without additional chemotherapy with fluorouracil and high-dose leucovorin in patients with high-risk rectal cancer: a randomized phase III study conducted by the Hellenic Cooperative Oncology Group. Ann Oncol 1999;10:671–6.
[48] Cafiero F, Gipponi M, Peressini A, Bertoglio S, Lionetto R. Preliminary analysis of a randomized clinical trial of adjuvant postoperative RT vs. postoperative RT plus 5-FU and levamisole in patients with TNM stage II–III resectable rectal cancer. J Surg Oncol 2000;75:80–8.
[49] Taal BG, Van Tinteren H, Zoetmulder FA. Adjuvant 5FU plus levamisole in colonic or rectal cancer: improved survival in stage II and III. Br J Cancer 2001;85:1437–43.
[50] Mansour EG, Lefkopoulou M, Johnson R, Douglass H. A comparison of postoperative adjuvant chemotherapy, radiotherapy or combination therapy in potentially curable resectable rectal carcinoma. Proc Am Soc Clin Oncol 1991;10:154 (abstr).
[51] Cionini L, Manfredi B, Sainato A, et al. Randomized study of postoperative chemotherapy after preoperative chemoradiation in locally advanced rectal cancer. Preliminary results. Eur J Cancer 2001;37:S300 (abstr).
[52] Fernandez-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859–65.
[53] Dewdney A, Cunningham D, Tabernero J, et al. Multicenter Randomized Phase II Clinical Trial Comparing Neoadjuvant Oxaliplatin, Capecitabine, and Preoperative Radiotherapy With or Without Cetuximab Followed by Total Mesorectal Excision in Patients With High-Risk Rectal Cancer (EXPERT-C). J Clin Oncol 2012;30:1620–7.