review

Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials

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Background: The results of the recently published large European randomised study in rectal cancer (European Organisation for Research and Treatment of Cancer 22921 trial) do not support current guidelines recommending postoperative chemotherapy for patients who have previously undergone preoperative radiochemotherapy or radiotherapy [radio(chemo)therapy]. To evaluate this discrepancy further, a systematic review of relevant randomised trials was undertaken.

Materials and methods: A systematic literature search was carried out in order to identify randomised studies exploring adjuvant chemotherapy against observation in patients with rectal cancer previously treated with preoperative radio(chemo)therapy.

Results: A statistically significant benefit of adjuvant chemotherapy was not found in any of the four relevant randomised trials. Non-protocolised subgroup analysis of one study indicated a beneficial effect of adjuvant chemotherapy for high rectal tumours and for patients downstaged to ypT0-2N0 but no effect for low-lying rectal tumours. However, the body of evidence indicates that patients downstaged after radio(chemo)therapy to ypT0-2N0 disease are not candidates for testing adjuvant chemotherapy in future trials due to the considerable over-treatment anticipated by this manoeuvre.

Conclusions: To resolve the issue in question, a meta-analysis of relevant studies is required, and new trials should be launched to explore new drug combinations against observation. Currently, delivery of adjuvant chemotherapy in patients undergoing preoperative radio(chemo)therapy is not evidence based.

Key words: adjuvant chemotherapy, neoadjuvant radiation, rectal cancer

introduction

Primary colonic and rectal tumours are anatomically in continuity; appear similar both macroscopically and in terms of histology. When metastatic, they show similar responsiveness to cytotoxic chemotherapy. Although it is therefore assumed that the effects of postoperative adjuvant chemotherapy are similar in rectal cancer to results achieved in colon cancer, there is little direct randomised evidence to support this in patients who have received preoperative radiochemotherapy or radiotherapy [radio(chemo)therapy]. In the postoperative setting, the combination of radiotherapy with simultaneous chemotherapy has made the assessment of the impact of adjuvant chemotherapy per se more difficult.

Randomised trials have shown better local control, lower toxicity (both acute and late), and higher compliance if preoperative short-course radiotherapy or conventionally fractionated chemoradiation is administered rather than postoperative conventionally fractionated radiotherapy [1, 2]. Hence, preoperative chemoradiation or short-course radiation (5 × 5 Gy) is now the current standard of care in Europe for locally advanced resectable rectal cancer.

Two meta-analyses of Japanese trials have shown a survival benefit of postoperative adjuvant chemotherapy in patients with rectal cancer treated with surgery alone [3, 4]. It is questionable whether these results can be generalised to the Western population, as the standard treatment is different. In Japan, adjuvant chemotherapy is usually based on oral fluoropyrimidines given for 1 year; pelvic preoperative or postoperative radiation is rarely given and the surgical technique differs—lateral lymph nodes are dissected in patients...
with low-lying tumours and abdominoperineal resection is more radical [5]. The large Quick and Simple and Reliable (QUASAR) randomised trial conducted mostly in low-risk patients from Western countries showed survival benefit of adjuvant chemotherapy [6]. This benefit was similar in colon and rectal cancers. However, in majority of patients with rectal cancer, perioperative radiation was not given. For these reasons, there is uncertainty regarding the utility of postoperative adjuvant chemotherapy for those receiving preoperative radio(chemo)therapy.

National Comprehensive Cancer Network guidelines recommended postoperative chemotherapy for all patients undergoing preoperative chemoradiation regardless of the surgical pathology results [7]. European Society for Medical Oncology recommendations stated that “similar to the situation in colon cancer stages III (and ‘high-risk’ stage II), adjuvant chemotherapy can be provided, even if the scientific support for sufficient effect is less” [8]. In contrast, experts of recent European Rectal Cancer Conference acknowledged that there is insufficient evidence on the benefit of adjuvant chemotherapy after preoperative chemoradiation [9]. Many oncologists will have difficulty accepting guideline recommending the use of adjuvant chemotherapy since the recently published large European Organisation for Research and Treatment of Cancer (EORTC) 22921 randomised trial failed to confirm a benefit of postoperative chemotherapy in terms of disease-free or overall survival [10], even in node-positive patients [11]. Due to this discrepancy, a systematic review of relevant randomised trials was undertaken.

materials and methods

The studies qualified for this review if they met the following criteria: (i) eligibility included patients with curatively resected rectal adenocarcinoma; (ii) only postoperative chemotherapy (intravenous, oral, intraportal, or intraluminal) against observation was randomly allocated, and not chemoradiotherapy; and (iii) long-term results were provided. Any trials that included rectal or colorectal cancer were eligible if the results were provided separately for patients with rectal cancer. We have focused on the trials in which preoperative radio(chemo)therapy had been delivered. The other adjuvant trials were searched for comparison and discussion purposes.

The titles and abstracts from PubMed and Cochrane databases were electronically searched through August 2009 independently by two authors without any language and time restrictions with a limit ‘randomised controlled trials’ using keywords rectal cancer chemotherapy or colorectal cancer chemotherapy. The computerised search was supplemented with hand searches of reference lists of all available review articles, meta-analyses, original studies, and handbooks. We also searched electronically abstracts from the American Society of Clinical Oncology meetings, European Cancer Conferences, and European Society for Medical Oncology congresses (2005 to August 2009). To avoid publication bias, both published and unpublished studies were included. The authors were contacted by email when necessary. Full text copies of all studies were obtained and relevant data independently extracted by two investigators using a data collecting form.

In addition to the basic patient characteristics and trial design, the following data were extracted: long-term overall survival, disease-free survival or progression-free interval (preferably 5 years), and corresponding hazard ratios (HRs) with 95% confidence intervals (CIs) and P values. If the 5-year survival or HR had not been provided in the text, the relevant figures were extrapolated from the survival curves or forest plots. If P values were not provided for subgroup analysis, the difference was considered statistically significant when 95% CI of HR seen of forest plot had not included 1.0 value. For trials that included both patients with rectal and patients with colon cancer, the information was extracted as to whether the effect of chemotherapy differs in both groups. Disagreements were resolved by consensus.

results

Of 1914 citations, screening of the titles and abstracts resulted in the exclusion of 1871 publications. The hand searches of reference lists resulted in the identification of one additional relevant trial published in the abstract. Thus, 44 publications including 50 randomised trials of possible relevance were found. Due to linguistic problems, the data from three articles written in Chinese or Japanese were retrieved from the English abstracts [12–14]. Three additional abstracts from meetings’ proceedings were used because full-text articles had not followed. The data from nine Japanese studies were retrieved from three meta-analyses written in English [3, 4, 15]. Data from the remaining 35 trials were retrieved from the original articles. In total, 46 trials were excluded because they did not meet the entry criteria.

excluded trials

Of the 46 excluded trials, 16 studies explored adjuvant chemotherapy in colorectal cancer but did not report results for rectal cancer separately from colon cancer. In the remaining 30 trials, the long-term outcomes for rectal cancer were provided. The latter trials were divided into four following groups.

adjuvant chemotherapy—surgery alone. In 18 trials, preoperative or postoperative radio(chemo)therapy was not given. Of these 18 trials, 9 Japanese studies exploring oral fluoropyrimidines were summarised in three meta-analyses. Most recent meta-analysis involving a total of 2091 patients with rectal cancer from five modern studies with the use of uracil/tegafur demonstrated a statistically significant improvement of both overall survival and disease-free survival with adjuvant chemotherapy [4]. The second meta-analysis involving 2385 patients with rectal cancer from three modern studies (two of these studies were also included in the most recent meta-analysis) also demonstrated a statistically significant benefit of postoperative adjuvant chemotherapy for disease-free survival but not for overall survival [15]. The third meta-analysis involving 2310 patients with rectal cancer from three historical studies demonstrated statistically significant benefit of adjuvant chemotherapy for both overall survival and disease-free survival [3]. An additional Japanese trial involving ~800 patients showed a benefit in overall survival in the adjuvant chemotherapy group [14]. One historical USA study of 371 patients demonstrated an improvement in overall survival with postoperative chemotherapy compared with surgery alone (P = 0.05) [16]. The remaining seven small trials (numbers, N, of patients in both arms ranged from 58 to 185) did not show any advantage with chemotherapy in terms of either disease-free survival or overall survival [17–23].
adjuvant chemotherapy—uncertainty whether preoperative treatment given or not. There was no information of whether preoperative radio(chemo)therapy was given in the publications of five small trials. Three of these trials (N = 106–203) did not demonstrate any survival improvement with adjuvant chemotherapy [24–26]. The remaining two trials showed a statistically significant survival benefit with chemotherapy; in one trial in the total group of rectal cancer patients (N = 64) [27], and in the remaining study a survival benefit was observed only in the subgroup with stage III disease (N = 48) [28].

adjuvant chemotherapy—insufficient details of preoperative treatment group. In three trials (N = 132–691), preoperative radiotherapy or postoperative radiotherapy was administered in some patients, but the results have not been provided in sufficient detail, such that the preoperative radio(chemo)therapy groups could be analyzed separately [29–31]. In all three trials, the benefit of adjuvant chemotherapy was not demonstrated for patients with rectal cancer.

adjuvant chemotherapy—in combination with postoperative radiotherapy. In four trials (N = 218–299), all patients or a substantial number of patients received postoperative radio(chemo)therapy [32–35]. The statistically significant benefit in the overall survival or in the disease-free survival after postoperative chemotherapy was not shown in any of those trials.

The remaining four relevant trials, which evaluated postoperative adjuvant chemotherapy in patients given preoperative radio(chemo)therapy constitute the main material for this review (see Table 1).

relevant trials

EORTC 22921. In the EORTC 22921 trial [10, 11], patients were randomly allocated in 2 × 2 factorial design between preoperative radiotherapy versus preoperative radiochemotherapy and between postoperative chemotherapy versus observation alone. Thus, in this trial the value of postoperative chemotherapy was explored in a population of patients of whom half had received preoperative chemoradiation and the other half preoperative radiotherapy alone. The benefit of postoperative chemotherapy in terms of the long-term disease-free survival and overall survival was not demonstrated regardless as to whether concurrent chemotherapy had been added to the preoperative radiation or not (Table 1).

the Italian study. In the Italian trial, reported only in abstract (L. Cionini personal communication) [36], all patients received long-course preoperative 5-fluorouracil (5-FU)-based chemoradiation. Postoperative chemotherapy was then randomly allocated against observation. The benefit of postoperative chemotherapy in terms of the long-term overall survival and the number of recurrences was not demonstrated (Table 1).

the QUASAR study—uncertain indications. The QUASAR study explored the value of adjuvant chemotherapy using 5-FU and folinic acid in patients with colorectal cancer, where the benefit of chemotherapy was considered uncertain by the clinician [6, 37]. Of 3239 patients, 71% had colon cancer and 29% rectal cancer. For the total group of patients with rectal cancer (N = 984), a survival benefit from adjuvant chemotherapy was demonstrated (P = 0.05). This benefit was similar to that seen in the patients with colon cancer. However, in the rectal cancer group only 20% of patients received preoperative radiation and 28% were intended for postoperative chemoradiotherapy (Table 1).

the Chinese study. The fourth small study reported higher rate of 5-year survival in the postoperative chemotherapy group compared with the control group [13]. However, the methodological problems do not allow accurate estimation of the treatment effect (Table 1).

differences in an effect of adjuvant chemotherapy between colon and rectal cancer location

The trials provided inconsistent information on whether the effect of adjuvant chemotherapy differs between rectal cancer and colon cancer. There were 13 trials and three meta-analyses in which both patients with colon cancer and patients with rectal cancer were included. In four of those trials and in one meta-analysis, all or substantial percentage of patients received preoperative or postoperative chemoradiation or radiation. In three of these four trials, differences in the effectiveness of chemotherapy between colon and rectal cancer location were not found [6, 29, 30]. In one remaining trial, chemotherapy was found effective in colon cancer but not in rectal cancer when these two groups were analyzed separately [34]; however, the test for heterogeneity did not confirm significant difference. Only one meta-analysis was published in which the issue in question was explored in patients receiving radiation [31]. In this meta-analysis (N = 1786) of randomised trials testing adjuvant portal venous 5-FU infusion, the test for interaction showed difference of chemotherapy effect in colon cancer compared with rectal cancer (P = 0.024). The HR of death for colon cancer in chemotherapy group compared with control group was 0.82, 95% CI 0.74–0.91. In contrast, for rectal cancer no effect was found, HR = 1.00, 95% CI 0.87–1.15.

In the remaining nine studies and two meta-analyses, perioperative radiation was not given, or there was no information as to whether perioperative radiation was given. Of these, in six studies and one meta-analysis, the effectiveness of adjuvant chemotherapy appears to be similar in both colon and rectal cancer (14, 15, 19, 22, 23, 25, 26], in two trials chemotherapy was found effective in colon cancer but not in rectal cancer [18, 20], and in the remaining one study and one meta-analysis chemotherapy was found effective in rectal cancer but not in colon cancer [3, 27]. The difference in response to adjuvant chemotherapy between colon and rectal cancer location was not confirmed in any of those studies when tested for heterogeneity.

discussion

A statistically significant survival benefit of adjuvant chemotherapy was not found in any of the four randomised trials in patients given neoadjuvant radio(chemo)therapy (Table 1). In addition, a statistically significant survival benefit
Table 1. Randomised trials in which adjuvant chemotherapy has been explored in patients with resectable rectal cancer receiving preoperative radiochemotherapy or radiotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Design</th>
<th>Results</th>
<th>Comments</th>
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<tr>
<td>EORTC 22921</td>
<td>1011 patients younger than 81 years with clinically staged T3–4 tumours within 15 cm from the anal verge; accrual 1993–2003</td>
<td>2 × 2 factorial randomisation to preoperative radiotherapy alone versus preoperative radiochemotherapy (radiation with bolus 5-FU and leucovorin) and postoperative chemotherapy (four courses of 5-FU and leucovorin every 21 days) versus no postoperative chemotherapy; stratification with respect to the distance from the tumour to the anal verge</td>
<td>Median follow-up was 5.4 years; 5-year overall survival was 67% in the postoperative chemotherapy group and 63% in the control group, HR = 0.85 (95% CI 0.68–1.04), P = 0.12; 5-year disease-free survival was 58% in the postoperative chemotherapy group and 52% in the control group, HR = 0.87 (95% CI 0.72–1.04), P = 0.13; due to the 2 × 2 factorial design, half of the patients received preoperative chemoradiation and the other half preoperative radiotherapy alone; in the former patients, the HR of death in the adjuvant chemotherapy group was 0.97 (95% CI 0.70–1.20) and in the latter patients 0.85 (95% CI 0.62–1.28)</td>
<td>This trial did not show statistically significant benefit of adjuvant chemotherapy regardless of whether patients had been given preoperative chemoradiation or preoperative radiotherapy alone</td>
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<tr>
<td>Italian trial</td>
<td>635 patients younger than 76 years with clinically staged T3–4 tumours within 12 cm from anal verge; all patients had preoperative chemoradiation (radiation with bolus 5-FU and leucovorin)</td>
<td>Randomisation to postoperative chemotherapy (six courses of bolus 5-FU and leucovorin every 28 days) versus no postoperative chemotherapy</td>
<td>Preliminary results after the median follow-up of 25 months were reported on 536 patients with available data; there was no statistically significant difference in respect to either the number of recurrences (71 versus 71) or the overall survival (5 years: 68% versus 64% in the postoperative chemotherapy group and in the control group, respectively); the final data confirmed the absence of advantage of adjuvant chemotherapy</td>
<td>This trial did not show statistically significant benefit of adjuvant chemotherapy in patients who had been given preoperative radiation; the trial was reported only in the abstract form</td>
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<tr>
<td>QUASAR study</td>
<td>Ascertain indication for chemotherapy (mostly stage II); colon (2291 patients) and rectal (948 patients) cancer; accrual 1993–2003; of the rectal cancer patients, 203 had preoperative radiotherapy and 264 had postoperative radiotherapy; stratification was carried out with respect to tumour site, preoperative radiotherapy or not and planned postoperative radiotherapy or not; for patients receiving preoperative radiation, the schedule of radiation and whether chemotherapy was simultaneously added to radiation as well clinical and pathological stages were not given</td>
<td>Randomisation to postoperative chemotherapy (5-FU and leucovorin for 6 months, some patients also received levamisol) versus no postoperative chemotherapy</td>
<td>Median follow-up was 5.5 years; results for all rectal cancer patients: 5-year overall survival was 78% in the postoperative chemotherapy group and 74% in the control group, HR of death 0.77 (95% CI 0.54–1.00), P = 0.05, and HR for recurrence 0.68 (95% CI 0.52–0.88), P = 0.004; the benefit of chemotherapy in terms of overall survival or reduction of incidence of recurrence was much the same irrespective of whether patients were given preoperative radiation, postoperative radiation, or no radiation; heterogeneity between groups: P = 0.30 and P = 0.76, respectively; for the preoperative radiation subgroup the benefit was statistically insignificant; the HR of death was 0.44 (95% CI 0.25–1.10) and the HR of recurrence was 0.55 (95% CI 0.23–1.20)</td>
<td>This trial did not show statistically significant benefit of adjuvant chemotherapy in patients who had been given preoperative radiation; small sample size of preoperative radiation group (N = 203); the benefit of chemotherapy was similar in rectal cancer group and colon cancer group</td>
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after postoperative chemotherapy was not shown in rectal cancer in all seven trials in which all patients were given postoperative radio(chemo)therapy or a substantial number of patients were given preoperative or postoperative radiation [29–35].

No single relevant trial was large enough to detect a 5% improvement in 5-year survival. In all four evaluated trials, overall survival tended to be slightly better in the adjuvant chemotherapy groups, although the differences were not statistically significant (Table 1). For this reason, a meta-analysis using individual patient’s data is needed to resolve the issue of whether adjuvant 5FU-based chemotherapy produces worthwhile benefit (outweighing toxicity, cost, and inconvenience) in patients with rectal cancer receiving preoperative radio(chemo)therapy.

It is often claimed that the results demonstrating survival benefit of postoperative chemotherapy in colon cancer can be generalised to rectal cancer. However, the results shown in the table indicate that, for patients receiving preoperative radiation, the available evidence does not support this assumption. Furthermore, the meta-analysis of patients receiving radiation showed benefit of adjuvant chemotherapy in colon cancer but no effect in rectal cancer [31]. Rectal and colon cancers have different gene expression profiles, different cytokeratin profiles, different levels of microsatellite instability-high, and mutations in Kras and BRAF [38–41]. Despite those molecular differences, colon and rectum cancers respond to chemotherapy similarly when metastatic. However, the chemotherapy effect may differ in the adjuvant setting.

It should be highlighted that the consistent improvement in local control resulting from neoadjuvant radio(chemo)therapy in rectal cancer for all randomised trials conducted in the total mesorectal excision era has not translated into a benefit in overall survival [2, 10]. Thus, further efforts to improve local control in patients who receive preoperative radiotherapy are unlikely to produce meaningful survival benefits unless eradication of occult systemic disease can be achieved. The rate of distant metastases is consistently shown to be ~35% for clinically staged T3 disease [2, 10]. Hence, effective systemic treatment is crucial to improve survival in advanced rectal cancer.

The Gastrointestinal Tumor Study Group 7175 study [21] and the North Central Cancer Treatment Group study [42] are cited as supporting the use of adjuvant chemotherapy in patients receiving perioperative radiation. Those trials did not meet our eligibility criteria. Although in those trials the postoperative chemotherapy was randomly assigned, part of it was given alone and another part was given simultaneously with postoperative radiation. Interpretation of the results of these trials is hampered as it is impossible to evaluate separately whether a survival benefit has resulted from postoperative chemotherapy or from improved local control achieved by the synergistic effect of the combination of chemotherapy with radiation.

### ongoing trials

Only one ongoing randomised study, the Dutch simply capecitabine in rectal cancer after irradiation plus TME (SCRIPT) trial, tests adjuvant chemotherapy (capecitabine) against...
observation in patients who have received preoperative radiation (5 × 5 Gy) [9]. Because of poor accrual, the protocol has been amended to include patients who have received chemoradiotherapy. The UK Chronicle trial used a similar design. On the basis that oxaliplatin when added to 5-FU/leucovorin improved survival in patients with colon cancer in the adjuvant setting [43], the study evaluated whether for locally advanced rectal cancer six adjuvant courses of capecitabine and oxaliplatin are more effective than surgery alone in terms of disease-free survival and overall survival in patients previously treated with chemoradiotherapy. Unfortunately, this trial has been closed in March 2008 due to poor accrual after only 113 of an intended 750 patients had been randomised. A major reason for the inability to recruit into Chronicle was the lack of equipoise in many UK medical oncologists.

There are five other ongoing or recently closed phase III trials registered in the http://clinicaltrials.gov Web site (accessed in October 2009): CAO/ARO/AIO-04 in Germany, PETACC 6 in Europe, AERO-R98 in France, NSABP R-04 with complementary Eastern Cooperative Oncology Group (ECOG) E5204 and ECOG E3201 both in the USA. In these studies, different schedules of adjuvant chemotherapy are evaluated in all of the treatment-assigned groups in patients receiving preoperative chemoradiation. Thus, disappointingly, the basic question whether postoperative chemotherapy is effective at all is sidestepped. In addition, three of those trials test intensification of chemotherapy, both as part of the chemoradiotherapy and as adjuvant chemotherapy given postoperatively. This design will not allow us to evaluate separately whether any benefit is due to an intensification of preoperative chemoradiation or due to an intensification of postoperative chemotherapy. Furthermore, in the event of ‘negative’ results, it will be not known whether the tested chemotherapy schedules are equally effective or equally ineffective.

are there any subgroups of patients who are more likely to gain from postoperative chemotherapy?

The authors of the negative EORTC 22921 study observed that progression-free survival and overall survival curves started to diverge at ~2 and 5 years after randomisation, respectively [10]. Their interpretation hypothesised that the subset of patients with a more favourable prognosis might benefit from adjuvant treatment in the long term [11]. Their exploratory non-protocol subgroup analyses proposed that only those achieving pathological complete response (pCR) or were downstaged to ypT1-2 category after preoperative radiation, benefited from adjuvant chemotherapy, whereas those with residual ypT3-4 disease did not [11]. However, there are sources of potential bias. The intention-to-treat principle was not followed as 22% patients were excluded from the analysis. Furthermore, the numbers of patients in whom the benefit of chemotherapy was found, namely those with ypT0-2 disease, were imbalanced in the adjuvant chemotherapy group versus the control group (198 versus 225, respectively). Also, the beneficial effect of adjuvant chemotherapy was confined only to ypT0-2 patients receiving conventionally fractionated preoperative radiation and not those receiving the current standard, namely preoperative chemoradiation [44]. In addition, the suggestion of the EORTC 22921 study that the benefit of adjuvant chemotherapy is observed 2 years after treatment is in contrast to the large QUASAR randomised study, which showed that the disease-free survival benefit from adjuvant chemotherapy had already been manifested within the first 2 years following randomisation, with no benefit thereafter [6]. A similar finding was reported in the pooled analysis of all the randomised trials in patients with colon cancer [45]. Moreover, other data did not confirm results of subgroup analysis of the EORTC study [46, 47]. A pooled retrospective analysis reported 566 patients with advanced rectal cancer with pCR after neoadjuvant radiotherapy or radiochemotherapy [46]. Unexpectedly, a tendency towards worse disease-free survival was noted in the 22% of patients given adjuvant chemotherapy, compared with those not receiving this treatment; Cox multivariate analysis showed that HR of death or recurrence was 1.52 (95% CI 0.90–2.57) in the postoperative chemotherapy group compared with the control group. For all of the aforementioned reasons, the concept of the EORTC trial subgroup analysis that adjuvant chemotherapy provides a benefit in patients staged down after radio(chemo)therapy is dubious.

In the aforementioned subgroup analyses of the EORTC trial, the effect of chemotherapy was observed neither in the ypT0 patients nor in the ypN-positive patients [12]. In addition, no benefit of adjuvant chemotherapy for tumours located in the low rectum was shown, whereas it was beneficial for tumours located higher up in the rectum [12]. We could not find any evidence in the literature supporting or contradicting the latter observation. However, the biology and treatment of a low rectal cancer compared with an upper rectal cancer differ. First, a higher incidence of a positive circumferential resection margin and local recurrence is observed in patients with low-lying rectal cancer undergoing abdominoperineal resection, compared with patients with higher located tumours undergoing anterior resection [48]. Second, all regional lymph nodes at risk for metastases are removed at surgery, when high rectal cancer is resected. Whereas if surgery of low-lying rectal cancer is carried out in Western countries, internal iliac and obturator lymph nodes, which are at risk of involvement [5], are left behind. Third, venous blood flow is directed via portal vein in the high rectal cancers, whereas in the low-lying cancers via both portal vein and vena cava inferior vein. This anatomical difference makes metastases to both liver and lungs more likely in low-lying cancers compared with high rectal cancers [49]. Fourth, the risk of intracelomic spread is much higher for tumours arising above the peritoneal reflection [50], especially if exposed on the serosal surface (i.e. T4). Fifth, low rectal cancers pose a higher T-stage, a higher percentage of poorly differentiated histology, and behave more aggressively compared with high rectal cancer [49, 51]. After treatment of extraperitoneal rectal cancer, disease-free survival is lower compared with intraperitoneal cancer due to higher incidence of both distant and local recurrences [49]. High rectal cancers seem to behave more like colon cancers [32]. For all of the aforementioned reasons, it is possible that the biology and response to adjuvant chemotherapy of high rectal tumours might be similar to colon cancer but different in low-lying rectal tumours. This hypothesis is worth exploring in future studies.
Another clinically relevant question is whether the indication for postoperative chemotherapy should be determined by clinical staging (cTNM (tumour–node–metastasis)) or by the definitive pathological surgical staging (ypTNM) following chemoradiotherapy. Several reports have shown that the postoperative pathological staging after chemoradiation is more discriminative for prognosis than the pretreatment clinical staging [46, 53, 54]. For example, in the series of patients with pCR after radio(chemo)therapy [46], the rate of local recurrence for subgroup of patients with clinically diagnosed nodal disease before therapy was 2.4% and the rate of distant metastases was only 11.1%. These data suggest that for patients achieving pCR, the prognosis is favourable even in those patients initially with clinical stage III disease. Other indirect data from randomised trial also support the view that a favourable response to radiation in terms of nodal disease is associated with a low risk of local and distant recurrence [55]. Conversely, patients with persistent nodal disease after chemoradiation fare very badly [53–55]. For the aforementioned reasons, it seems that pathological staging using the postsurgical specimen instead of the pretreatment clinical staging should guide decisions as to who might be a candidate for adjuvant chemotherapy. Patients downstaged to ypT0-2N0 disease after chemoradiation or after radiation alone have a favourable prognosis [46, 47, 53–55]. For these reasons, the gain in absolute percentages from adjuvant chemotherapy in those groups is expected to be very small. Thus, overtreatment is considerable. Therefore, it seems that those patients are not appropriate candidates for adjuvant chemotherapy. It should be also noted that in the QUASAR study, no benefit from adjuvant chemotherapy was observed in the age group older than 70 years [6].

conclusions

A meta-analysis using individual patient’s data would allow sufficient numbers of patients to be incorporated and is needed to resolve the issue of whether adjuvant 5-FU-based chemotherapy produces worthwhile benefit (outweighing toxicity, cost, and inconvenience). Alternatively, trials in patients younger than 70 years who did not achieve histopathological downstaging and at high risk of relapse could be carried out comparing 5-FU and oxaliplatin against observation.

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references


