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VALUE OF ADJUVANT CHEMOTHERAPY FOR COLON AND RECTAL CANCER FROM A SURGEON'S POINT OF VIEW

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Survival of patients with colon and rectal cancer is constantly increasing. In order to further improve prognosis the development of distant metastases after primary tumor resection has to be further reduced. Adjuvant chemotherapy is standard for UICC III colon cancer using fluoropyrimidines or intensified regimens including oxaliplatin. However, many patients receive adjuvant treatment without benefit but suffer from toxicity, in case of oxaliplatin even from life-long chronic neurotoxicity. The aim of this overview is to summarize data for adjuvant treatment of colon and rectal cancer with special focus on UICC substage and age and to discuss points of criticism from a surgical point of view. Adjuvant chemotherapy with 5-fluorouracil (5-FU) and folinic acid (FA) clearly increases survival in colon cancer UICC stage III. Addition of oxaliplatin is especially beneficial for patients with pT3/4pN2 tumors (UICC IIIc). Older patients (≥ 70 years of age) should receive adjuvant treatment as well, because they benefit to the same extent as younger patients. Overall risk reduction by adjuvant treatment is overestimated due to better pre-operative staging (CT) and quality of surgery and pathology resulting in less local recurrence and stage migration. The effects of adjuvant treatment in rectal cancer are less pronounced compared to colon cancer. Especially after the use of neoadjuvant radiochemotherapy in combination with high quality surgery effects of additional adjuvant treatment still have to be clearly established. In summary, adjuvant treatment for colon cancer is well established and should include old patients as well. To reduce side effects and increase efficacy adjuvant treatment should be individualized on the basis of UICC substaging and clinical risk factors, maybe also including molecular subtyping. These strategies may help to further increase the effectiveness of adjuvant treatment in colon and also rectal cancer.

Keywords: *adjuvant treatment, chemosensitivity, colon cancer, rectal cancer, 5-fluorouracil, oxaliplatin.*

Introduction

Colorectal cancer is the second most common cancer in Europe and North America [1, 2]. Advances in many areas of the management of colon and rectal cancer within the last three decades have improved outcome significantly [1, 3]. Cure is often achieved in localized cases (UICC stage I and II) with 5-year overall survival rates reaching 90% and more [2]. The prognosis however is already less favourable in locally lymph node positive disease (UICC stage III) with 5-years survival rates about 70% [2]. Long-term survival reaching

5 years in the presence of distant metastases (UICC stage IV) is still way below 20% among all patients in this subgroup [2]. In order to further improve the prognosis of patients with colon and rectal cancer it is important to further reduce the occurrence of distant metastases after removal of the primary cancer.

Systemic adjuvant therapy of colon cancer was established more than 30 years ago demonstrating an effective reduction in recurrence rates in colon cancer compared to resection alone in the landmark study of Moertel and colleagues [4]. Initially treatment was carried out with 5-fluorouracil (5-FU) monotherapy [3]. Subsequent trials in many countries demonstrated that modulation of 5-FU by addition of folinic acid (FA) further increased the benefit of adjuvant treatment in colon cancer [3, 5, 6]. More recent studies revealed a further reduction of recurrence combining 5-FU/FA with oxaliplatin [7, 8].

In contrast to colon cancer an obvious benefit of adjuvant treatment in rectal cancer is still nowadays hard to determine especially in an area of increasing use of neoadjuvant radiochemotherapy for locally advanced cases (UICC II and III) [3]. It is even possible that colon and rectal cancers might have different sensitivity to chemotherapy [3]. The aim of this critical review is to summarize results of adjuvant treatment for colon and rectal cancer with special focus on UICC substage and age and to discuss points of criticism from a surgical point of view.

Adjuvant treatment of colon cancer

Establishment and modulation of adjuvant treatment

The first study to reveal a benefit for adjuvant 5-FU chemotherapy in colon cancer patients with UICC stage III (pTxpN+) showed a reduction of the 3-year recurrence rate from 53% for surgery alone to 37% using weekly 5-FU and the oral anthelminthicum levamisole after surgery for 12 months [4]. In addition 3-year overall survival increased from 55% to 71% using adjuvant treatment [4]. Many other trials confirmed this benefit with an estimated increase of 5-year overall survival of about 10% comparing 5-FU alone versus resection alone for node positive cases (UICC stage III) [5].

As mentioned earlier subsequent studies even revealed an additional effect of 5-FU modulation by folinic acid (FA) [5]. Our study group (research group of gastrointestinal cancer, called FOGT) conducted thus far the largest German adjuvant trial to investigate the possible additional benefit of either FA or interferon-α (IFN-α) (FOGT-1) [6]. Patients (n=855) either received 5-FU (450 mg/m^2 as a 60 min infusion) alone or in combination with FA (200 mg/m^2) or with interferon-α (IFN-α, 6x10^6 IU) for 12 months (Figure 1). IFN-α was without additional benefit. Modulation of 5-FU by FA increased 5-year overall survival from 60,5% to 72,0% [6]. The 12% benefit adding FA to 5-FU remained constant in the long-term follow-up. The 8-year overall survival rates were 52,6% (95% CI 44,6-59,9) and 65,4% (57,6-72,1) for 5-FU and 5-FU + FA, respectively [10].

Intensified adjuvant treatment of colon cancer

After establishment of 5-FU/FA as standard intensified protocols using additional chemotherapeutic drugs were investigated. Most convincing results were obtained by the combination of 5-FU/FA and oxaliplatin. Two large phase-III trials demonstrated a superiority of the drug combination compared to 5-FU/FA in patients with lymph node positive colon cancer (UICC stage III) [7, 8]. Subgroup analysis of both trials revealed that the effect of oxaliplatin on overall survival are relevant in UICC stage III and especially younger patients. A recent evaluation of the long-term outcome revealed an increase in the 10-year overall survival rate from 59,0% to 67,1% for UICC stage III patients after addition of oxaliplatin confirming its potential benefit [11].

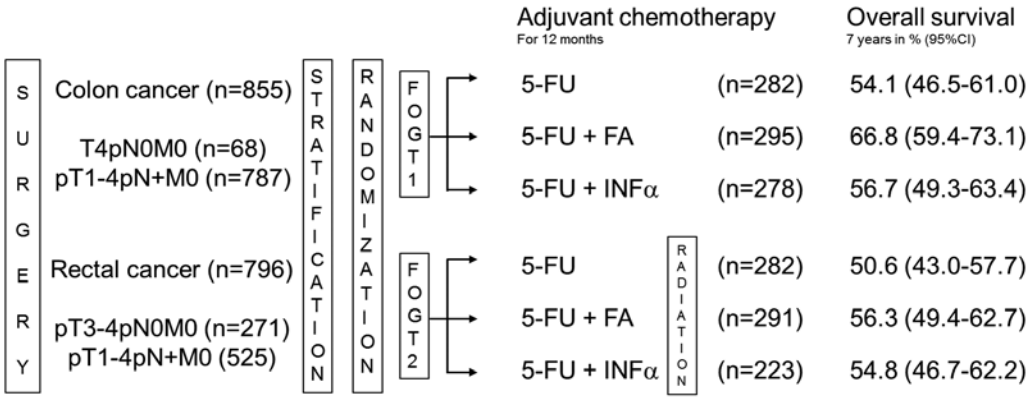

Figure 1. *Flow-chart of the adjuvant colon cancer (FOGT1) and adjuvant rectal cancer (FOGT2) trials. After quality controlled surgery patients with colon (FOGT1) or rectal (FOGT2) cancer were stratified according to center, pT, and pN classification and randomized to receive adjuvant chemotherapy with 5-FU alone, 5-FU + folinic acid (FA), or 5-FU + interferon-alpha (IFNα) for 12 months. All patients received oral levamisol. All rectal cancer patients (FOGT2) received adjuvant radiotherapy. During radiotherapy 5-FU therapy was reduced by 20%. Seven year overall all survival for each treatment group is shown* ***[9]****.*

The oral fluoropyrimidine analogous capecitabine was shown to be as effective as 5-FU/FA for adjuvant treatment of colon cancer although slightly more toxic [12]. Recent results also demonstrated that capecitabine in combination with oxaliplatin improved disease-free survival compared to 5-FU/FA [13] suggesting equivalent effects for fluoropyrimidines combined with oxaliplatin in adjuvant treatment of colon cancer.

Limitations of adjuvant treatment

Most of the patients receiving adjuvant treatment do not benefit because they will never develop a recurrence or develop a recurrence despite treatment. This unnecessary treatment is moreover associated with toxicity and costs especially using intensified protocols. Paresthesia occurred in 92%, neutropenia and thrombocytopenia in 78%, and vomiting in 47 of patients receiving 5-FU/FA and oxaliplatin [14]. Especially long-term neurotoxicity using oxaliplatin cannot be neglected affecting more than 10% of all patients [15, 16].

Besides these inevitable problems the benefit of adjuvant treatment was established in the last millennium. For example the pre-operative staging was of low intensity and quality (no CT-scan) to detect distant metastases in the above mentioned trial of Moertel and colleagues [4]. Moreover at that time patients in the control arm (surgery only) were not followed-up to the same extent as patients in the chemotherapy group. Patients receiving chemotherapy had contact to nurses and doctors on a weekly basis discussing problems and receiving help also in case of other problems. This was not the case for surgery only patients, but might influence the outcome. In addition, the quality of surgery and pathological examination did by far not reach today´s standards. Therefore the real benefit of present adjuvant chemotherapy is probably overestimated [17].

Table 1. *Reasons for the decline of stage specific risk of recurrence*

- More acurate pre-operative staging (CT) – detection of synchronous metastases ↑
- Better quality of surgery (e.g. CME, D3) – local recurrence rate ↓
- Better quality of pathology – stage migration

➢ Stage specific risk of recurrence ↓

First of all a much more accurate pre-operative staging is performed often including a computer tomography (CT) of abdomen and chest. Consequently more frequently synchronous distant disease is diagnosed (UICC stage IV). However in parallel the number of patients who will develop early distant metastases within 3–6 months after primary tumor resection are going to decline and thus early recurrence – i.e. not detected synchronous disease - is becoming a rare event. Second, the technical resection of colon cancer was refined, has become less invasive, and more standardized within the last three decades including complete mesocolic excision in European countries and D3 lymphadenectomy in Asian countries [18–20]. By introducing these techniques it is also estimated that local recurrence rates will further decline. Third, the quality of the pathological workup

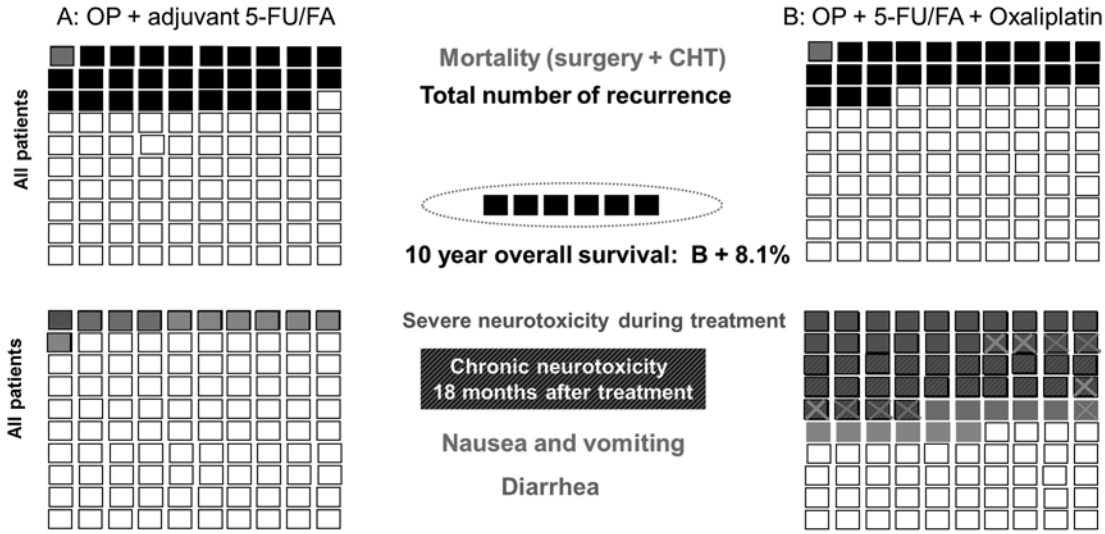

Figure 2. *Graphical illustration of recurrence rates and toxicities for adjuvant treatment options as reported [23]. In each quadrant 100 patients are depicted as open squares. In case of events the squares are filled with respective colours to show the frequency of each event. The upper quadrants show adjuvant treatment for colon cancer UICC stage III assuming a recurrence rate for surgery alone of 40% [17]. In the left upper quadrant the recurrence and mortalities are shown for 5-FU/FA treatment, in the right upper quadrant for the combination with oxaliplatin. The respective lower left and right quadrants show important severe toxicities as reported [14] for both treatment options. In case of overlapping toxicities patients are marked by crosses or lines as described [23]. In the centre the overall benefit for 10 year survival [11] and the number of patients not developing recurrence are summarized.*

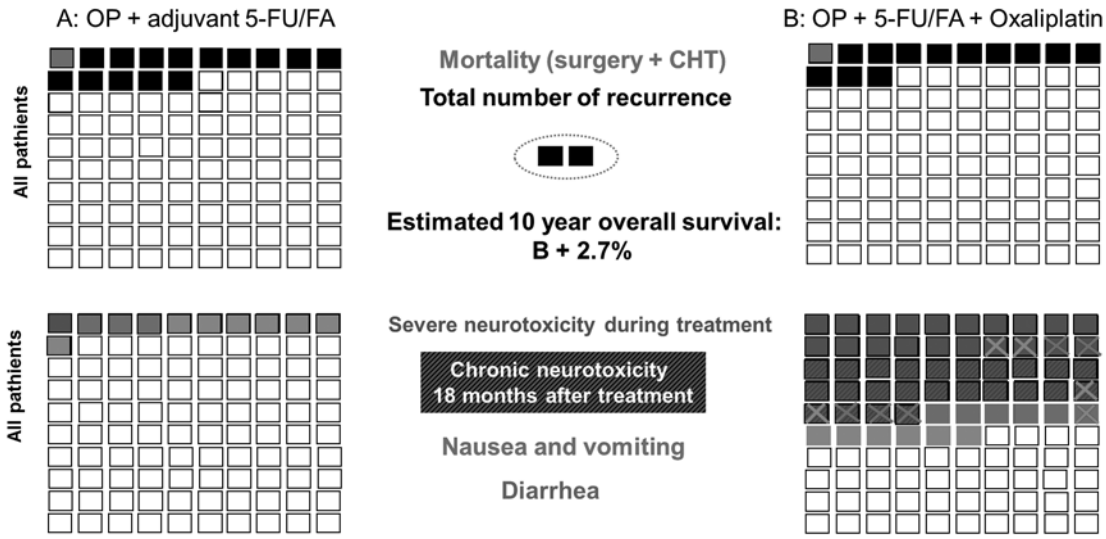

Figure 3. *Hypothetical graphical illustration of recurrence rates and toxicities for adjuvant treatment options based on the assumption that not 40%, but only 20% of UICC stage III patients may recur after high quality staging, surgery and pathological examination [17]. As shown in figure 2 each quadrant represents 100 patients. The upper quadrants show the effects of adjuvant treatment for 5-FU/FA (left) and the combination with oxaliplatin (right). The respective lower left and right quadrants show important severe toxicities based on the reported trial [14]. For both treatment options patients with overlapping toxicities are marked by crosses or lines as described [23]. In the centre the estimated overall benefit for 10 year survival based on reference [11] and the number of patients not developing recurrence are summarized.*

has also been increased and more standardized [21, 22]. This higher quality of pathological processing results for example in a more precise lymph node sampling followed by stage migration (UICC I and II to UICC III). Consequently the stage specific risk of recurrence is reduced. The reasons why stage specific recurrence rates and effect of adjuvant treatment in colon cancer may be overestimated are summarized in table 1.

For UICC stage III colon cancer a recurrence rate for surgery alone of 40% is estimated based on the old results [17]. Adjuvant fluoropyrimidine treatment can reduce that risk by 30%, addition of oxaliplatin by additional 18–20% [17]. In figure 2 the estimated number of patients with recurrence is shown for 5-FU/FA and intensified treatment using oxaliplatin. In addition respective severe side effects are shown as well using an easy to understand graphical illustration as reported [23]. Hypothesizing that under optimal conditions as summarized in figure 2 recurrence risk for surgery alone in UICC stage III may only be 20% [17] the number of patients taking benefit from adjuvant treatment is decreasing. This hypothetical scenario including side effects is shown in figure 3.

Stage and adjuvant treatment

In the treatment guidelines of most countries adjuvant treatment is recommended for all patients with UICC stage III colon cancer and for stage II in case of risk factors like tumor obstruction, emergency resection, or less than 12 sampled notes. However, the prognosis of patients among each UICC stage is quite different according to the respective TNM category and the UICC substage [24]. For example, independent of the final UICC stage, a pT2-4a tumor (perforation of serosa) has a 5-year overall survival 15 points of percentage higher than that of a pT2-4b tumor (infiltration of neighboring organs) [24]. In table 2 5-year overall survival for colon cancer patients from the surveillance, epidemiology, and end results (SEER) population based data base including 109.953 patients from 1992 to 2004 [24] and the FOGT adjuvant colon cancer trial recruiting 855 patients from 1992 to 1999 [6] according to TNM category and UICC stages are summarized. The data indicate that in each UICC stage subgroups exist with large differences in prognosis. For example patients with a UICC IIIa (pT1/2pN1M0) cancer receiving adjuvant 5-FU treatment had an excellent 5-year overall survival of 87% [25] much better than that of all UICC II patients (Table 2).

Similar to these observations the analysis of the long-term outcome of the MOSAIC trial revealed that the best effect of addition of oxaliplatin to 5-FU/FA was seen in UICC stage IIIc (pTxpN2M0) patients (HR, 0,705; 95% CI, 0,535 to 0,928) [11]. There was no benefit for low risk stage II and a minimal risk reduction for high risk stage II (HR, 0,895; 95% CI, 0,606 to 1,323) and stage IIIa/b (HR, 0,864; 95% CI, 0,673 to 1,108) [11]. With regard to side effects an adjustment of the intensity of adjuvant treatment according to TNM categories and UICC substages is mandatory.

Age and adjuvant treatment

The estimated age-adjusted incidence for colon and rectal cancer in Germany for 2002 revealed that only 20% of all patients are younger than 70 years [26]. Analyzing the age of participants in large adjuvant trials reveals

Table 2. 5-year survival according to TNM and UICC stage for colon cancer patients of the SEER data base [24] and the adjuvant FOGT-1 phase III trial [6]

TNM	UICC stage#	SEER data*		FOGT-1*	
		n	5-year-survival	n	5-year-survival (95% CI)
T3 pN0 M0	II A	40.338	66,7%		
pT4a pN0 M0	II B	5.020	60,1%	68	71.4% (60.5-82.3)
pT4b pN0 M0	II B	3.088	45,7%		
pT1/2 pN1 M0	III A	3.134	71,1%	72	87.2% (79.2-95.6)
pT3 pN1 M0	III B	17.966	54,9%		
pT4a pN1 M0	III B	2.771	47,0%	424	70.3% (65.5-75.1)
pT4b pN1 M0	III B	1.774	27,9%		
pT1/2 pN2 M0	III C	499	61,5%	27	75.6% (58.4-92.7)
pT3 pN2 M0	III C	8.566	38,1%		
pT4a pN2 M0	III C	1.653	26,6%	264	48.2% (41.7-54.7)
pT4b pN2 M0	III C	1.383	15,8%		

* Data are shown as 5-year overall survival according to the references [24, 6]. All patients of the FOGT-1 trial received adjuvant 5-FU based chemotherapy.

UICC stage, 6th edition.

that a greater amount of young patients are recruited. For example the median age of patients in the MOSAIC trial was 61 years and 65% of all patients were younger than 65 [14]. However, 80% of the patients are older in daily practice. One problem therefore is to estimate the benefit of adjuvant treatment for older patients.

A first pooled analysis of 7 studies and 3,351 patients comparing surgery alone versus adjuvant 5-FU in colon cancer UICC III included a total of 15% of patients (n=506) ≥ 70 years of age [27]. A similar but more recent analysis of 18 studies and 14,528 patients enrolled between 1998 and 2004 included 18% of patients (n=2575) ≥ 70 years of age [28]. Both investigations came to the same conclusion that old patients benefit to the same extent as younger patients except a slightly higher toxicity.

Due to the fact that age was not an exclusion criterion in the FOGT-1 trial 24% (202 of 855) of the enrolled patients were ≥ 70 years of age [6]. In order to better quantify the benefit a quotient of observed survival time and residual life expectancy (QSL) for each patient was calculated. Data for the residual life expectancy for each individual patient were obtained from the German Statistical Federal Office [10]. In theory, a QSL > 1 means that the observed life expectancy was longer than expected. Vice versa, a QSL < 1 means that the observed life expectancy is more and more limited if the value approximates to zero. In this trial the median QSL values ranged from 0,164 to 0,178 for younger patients < 70 years and from 0,338 and 0,371 for older patients (≥ 70 years), respectively [10] indicating that older patients more often reach their expected life time despite colon cancer. 5-FU/FA seemed to also be very active in older patients. The risk reduction using 5-FU/FA in comparison to 5-FU alone was similar to that in younger patients (Table 3).

Table 3. Risk reduction dependent on treatment and age in the FOGT-1 trial [10]

Patient age	Treatment comparison	Hazard ratio (HR)*	95% confidence interval	p
Age < 70 years	5-FU/FA versus 5-FU	0,571	0,374–0,873	0,010
Age ≥ 70 years	5-FU/FA versus 5-FU	0,657	0,495–0,870	0,004

* Hazard ratios of multivariate Cox regression for overall survival [10].

A recent pooled evaluation (4 trials) of the impact of age and medical comorbidity on the adjuvant treatment benefit of oxaliplatin for stage III colon cancer was performed including a total of 4,819 patients, of which 480 were ≥ 70 years and received oxaliplatin [29]. Fluoropyrimidine-based monotherapy and the combination with oxaliplatin were evaluated. The authors came to the conclusion that also patients ≥ 70 years of age may benefit from oxaliplatin [29]. If used in older patients special care has to be taken due to its potential higher rate of life threatening toxicity. The German treatment guidelines presently do not recommend the general use of oxaliplatin for older patients.

Adjuvant treatment of rectal cancer

Establishment and modulation of adjuvant treatment

In parallel to the establishment of adjuvant treatment in colon cancer [4] an adjuvant trial performed at that time pointed to a benefit in rectal cancer [30]. In addition other studies showed benefits for adjuvant chemoradiotherapy in comparison to resection alone or resection plus radiation [31–33]. The EORTC22921 trial could demonstrate that addition of 5-FU and FA in form of neoadjuvant, adjuvant or combined chemotherapy to preoperative radiation could reduce local recurrence from 17% to about 9% [34]. Addition of chemotherapy however did neither influence distant recurrence nor survival. So far, only a pooled analysis of 5 large European trials and a Cochrane metaanalysis pointed to a significant benefit of adjuvant chemotherapy in terms of survival in rectal cancer [35, 36].

The clear beneficial effect of modulating 5-FU with FA in adjuvant systemic treatment of colon cancer with a reduction of the frequency of distant metastases and improvement of survival could not be reproduced in rectal cancer [37–40]. Our group conducted in parallel to the above mentioned FOGT1 trial in colon cancer [6] an identical trial in rectal cancer (called FOGT2) using exactly the similar chemotherapy protocol however with additional adjuvant chemoradiotherapy (Figure 1) [39]. The rate of distant recurrence in patients with lymph node positive colon cancer (UICC stage III) receiving adjuvant 5-FU/FA was about 35% [6]. In contrast the frequency of distant metastases seems still higher in rectal cancer. Distant metastases occurred in 40% of patients with completely resected rectal cancer (UICC II-III) despite the inclusion of a great portion of earlier stages and using similar chemotherapy protocols (Figure 1) [39]. The comparison of the FOGT-1 and the FOGT-2 trials support the finding that 5-FU modulation by FA is not so effective in rectal than in colon cancer. As a consequence 5-FU was established as standard of adjuvant chemotherapy of rectal cancer in many countries [3]. In comparison to colon cancer the overall effects seem however more decent.

Limitations of adjuvant treatment in rectal cancer

Surgical treatment of rectal cancer in the 1980s and 1990s was associated with very high local recurrence rates up to 50% and local recurrence often determined prognosis [3]. Reducing its frequency from about 30% after resection alone to 20% with neoadjuvant or adjuvant treatment had an influence on outcome [30, 41]. However, the introduction of total mesorectal excision (TME) surgery for rectal cancer resulted in a dramatic decrease of local recurrence rates. Nowadays, local recurrence rates of about 10% in all R0-resectable cases are standard [3]. Therefore, only vague hints about the effects of adjuvant treatment in rectal cancer can be drawn from rectal cancer trials before the introduction of TME surgery.

Adjuvant treatment after neoadjuvant chemoradiotherapy in rectal cancer

Comparing short-term pre-operative radiation versus surgery alone revealed a clear reduction of local recurrence by more than half from 11% for surgery alone to 5% for short-term radiotherapy [42]. In addition short-term radiotherapy increased cancer-specific survival in subpopulations with negative circumferential resection margins however without increase of 10-year overall survival due to other causes of death [42] pointing to an obvious effect of neoadjuvant radio-/chemoradio-therapy in rectal cancer even in the TME era. Although no TME required the EORTC22921 trial could demonstrate that addition of 5-FU/FA in form of neoadjuvant, adjuvant or combined chemotherapy to preoperative radiation could reduce local recurrence from 17% to about 9% [34]. The effect of addition of chemotherapy to preoperative radiation was confirmed by a recent metaanalysis including 6 trials [43].

However, the effect of adjuvant chemotherapy after neoadjuvant chemoradiotherapy has to be proven. The addition of adjuvant chemotherapy in the trial of Bosset and coworkers did neither influence distant recurrence nor survival [34]. A recent pooled analysis of 5 large European trials [35] and a Cochrane metaanalysis of 9785 patients with non-metastatic rectal cancer from 21 randomized controlled trials from 1975 to 2011 [36] pointed to a benefit of adjuvant 5-FU based chemotherapy also in terms of overall survival in rectal cancer. These results point out that neoadjuvant and adjuvant treatment strategies in rectal cancer using fluoropyrimidine-based chemotherapy can minimize local recurrence even in the TME era, but that the effects on disease-free and overall survival are relatively small especially when applying quality controlled TME surgery.

Effect of intensified adjuvant treatment including oxaliplatin

Based on the effectiveness of oxaliplatin in first line metastatic regimens of colorectal cancer and in the adjuvant treatment of colon cancer several trials were

launched summarized recently [3]. An effect is seen on the rate of pathological complete response rates in several studies. However, the effect of addition of oxaliplatin on distant metastases, disease-free and overall survival has to be determined.

Summary and conclusions

The efficacy of adjuvant chemotherapy in colon cancer UICC stage III is unequivocally established. The stage specific risk is decreasing due to better quality of staging, surgery, and pathological work-up. Infusional 5-FU/FA or oral fluoropyrimidines are standard of care for most patients. Intensified treatment using oxaliplatin is especially beneficial for pT3/4pN2 cancers. Due to the high frequency of side effects of intensified treatment the choices of therapy should be adjusted to UICC substages and individual risk factors. Age is not an exclusion criterion and old patients oncologically benefit at least to the same extent than younger patients from adjuvant treatment. Infusional 5-FU/FA [6] is a recommendable protocol due to its efficacy and very low toxicity profile also compared to oral treatment.

In contrast to colon cancer adjuvant treatment in rectal cancer is also effective, but the benefit is less pronounced. Conclusions of the beneficial effects were drawn from older studies with higher rates of local and distant recurrence rates. Nowadays local recurrence rates for all stages are approximately 10%. In addition many patients already receive chemotherapy in combination with radiation before surgery. Therefore, the benefit of adjuvant chemotherapy in rectal cancer after high quality TME surgery and neoadjuvant chemoradiotherapy needs to be established in our opinion. Compared to colon cancer several anatomic, surgical, genetic, epigenetic, and micro-environmental factors may influence chemosensitivity of rectal cancer overall resulting in an ineffectiveness of the drugs used for colon cancer in adjuvant treatment of rectal cancer.

In the future, adjuvant treatment for colon and rectal cancer has to be further individualized on the basis of UICC substaging and clinical risk factors and should probably also include molecular subtyping [44]. These strategies may help to further reduce side effects and costs and at the same time increase the effectiveness of adjuvant treatment in colon and rectal cancer.

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