

Perioperative therapy of locally advanced adenocarcinoma in the upper third of the rectum – long-term results of different therapeutic approaches

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Background

The German S3-guideline's recommendations for the perioperative treatment of stage II and III rectal cancer in the upper third of the rectum have recently changed. Between 2008 and 2017 it was up to the treating physician whether to follow the guideline's recommendations on rectum- or on colon carcinoma; nowadays, there is a clear statement in favor of the colon line of treatment to refrain from neoadjuvant radiochemotherapy in low risk situations. In high risk situations (e.g. T4 tumor or extensive lymph node involvement) a neoadjuvant radiochemotherapy should be considered according to the guideline's recommendations.

The aim of this study was to compare the two approaches "neoadjuvant radiochemotherapy and adjuvant chemotherapy combined" and "adjuvant chemotherapy only" in locally advanced upper third rectal cancer based on clinical data from 30 German cancer registries.

Literature: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Kolorektales Karzinom, Langversion 2.1, 2019, AWMF Registrierungsnummer: 021/0070L

Patients and Methods

In the nationwide dataset provided by the *Arbeitsgemeinschaft deutscher Tumorzentren (ADT)* we identified 5,312 cases of upper third rectal cancer, gathered by 30 clinical cancer registries in Germany between 2000 and 2016 with the following specifications:

UICC stage II or III adenocarcinoma cases located in the upper third of the rectum (distal tumor margin 12-16 cm from the anal verge) with R0-resection status, preservation of the anal sphincter, and neither occurrence of previous or synchronous colorectal cancer nor death within 30 days after surgery.

For patients undergoing neoadjuvant therapy, the cTNM stage was used, otherwise the pTNM stage.

Based on this cohort we performed a comparison of 462 cases of "neoadjuvant radiochemotherapy and adjuvant chemotherapy combined" and 1,049 cases of "adjuvant chemotherapy only".

Using the Kaplan-Meier method, cumulative rates for overall survival, disease-free survival, local and distant recurrence were calculated; uni- and multivariable Cox-regression analyses yielded the corresponding hazard ratios. Additionally, subgroup analyses stratified by stage (stage II vs. stage III) or risk profile (stage III T1-3 vs. stage III T4 and stage III N1 vs. stage III N2) were performed.

In the multivariable Cox-regression analyses, we adjusted for UICC stage in the joint analyses, and for T-status and N-status in the analyses stratified by stage. Regarding overall survival and disease-free survival, we adjusted additionally for age, sex, grading and the number of resected and examined lymph nodes. Regarding distant recurrence we adjusted additionally for grading and regarding local recurrence for the number of resected and examined lymph nodes.

For patients characteristics see Tab. 1.

Tab. 1: Patients characteristics, n=1511

Variable	category	neoadjuvant RCTX + adjuvant CTX	adjuvant CTX	total	
Age (years)	average (std. deviation)	62.4 (9.8)	65.3 (10.6)	-	
Follow up (years)	average		6.7	6.3	
Sex	male	323	606	929	
	female	69.9%	57.8%	61.5%	
Stadium	II (N0)	139	238	377	
	III (N1/N2)	30.1%	22.7%	25.0%	
	III T1-3	286	729	1015	
	III T4	37	82	119	
	III N1	275	527	802	
	III N2	48	284	332	
	Grading	G1/2	366	826	1192
	G3/4	79.2%	78.7%	78.9%	
Gx / n.a.		53	201	254	
		11.5%	19.2%	16.8%	
total		43	22	65	
		9.3%	1.4%	4.3%	
		462	1049	1511	
		30.6%	69.4%	100%	

Results

Patients in UICC stage II/III receiving "adjuvant chemotherapy only" showed a cumulative 5-year local recurrence rate of 5.6% and patients receiving "neoadjuvant radiochemotherapy and adjuvant chemotherapy combined" a cumulative 5-year local recurrence rate of 4.1% (Log-Rank p=0.227) (see Fig. 1). In the multivariable analyses for stage II/III there were no significant differences concerning overall survival, disease-free survival, local and distant recurrence between the two groups.

In the subgroup analyses for stage II, there were also no significant differences to be found. In contrast, in the analyses for stage III, patients showed a significantly worse overall and disease-free survival when they had obtained "adjuvant chemotherapy only". In the risk profile-based subgroup analyses, the significant disadvantages for "adjuvant chemotherapy only" vanished in the low-risk constellations III T1-3 and III N1 and increased in the high risk constellations III T4 and III N2 (disease free survival: HR=3.225, 95%-CI=1.140-9.123, p=0.027 / HR=2.352, 95%-CI=1.153-4.798, p=0.019). In the high risk constellations, there were also significant disadvantages regarding the risk of distant recurrence for the "adjuvant chemotherapy only" group. All local recurrences recorded in the high risk constellations were found among the patients with "adjuvant chemotherapy only". For detailed results see Tab. 2 and for visualization of the relative risks concerning disease free survival see Fig. 2.

Tab. 2: Results of the comparison of "adjuvant chemotherapy only" with the reference group "neoadjuvant radiochemotherapy and adjuvant chemotherapy combined" (HR=1) using multivariable Cox-regression analyses (95% confidence interval in brackets)

Collective	Overall survival	Disease free survival	Distant recurrence	Locoregional recurrence
Stage II/III	HR=1.161, (0.909-1.483), p=0.232	HR=1.155, (0.909-1.468), p=0.238	HR=0.930, (0.724-1.195), p=0.571	HR=1.447, (0.843-2.420), p=0.180
Stage II	HR=0.986, (0.626-1.553), p=0.950	HR=1.005, (0.646-1.561), p=0.983	HR=0.869, (0.540-1.398), p=0.562	HR=2.117, (0.698-6.425), p=0.185
Stage III	HR=1.358, (1.011-1.823), p=0.042	HR=1.347, (1.009-1.800), p=0.044	HR=1.083, (0.804-1.458), p=0.601	HR=1.411, (0.756-2.632), p=0.280
Stage III T1-3	HR=1.209, (0.866-1.688), p=0.266	HR=1.171, (0.844-1.625), p=0.344	HR=0.951, (0.686-1.318), p=0.761	HR=1.032, (0.526-2.025), p=0.926
Stage III T4	HR=3.049, (1.069-8.697), p=0.037	HR=3.225, (1.140-9.123), p=0.027	HR=2.694, (1.077-6.738), p=0.034	- no value calculated, only 10 incidents, all in group "adjuvant chemotherapy only"
Stage III N1	HR=1.009, (0.691-1.473), p=0.962	HR=0.964, (0.665-1.399), p=0.848	HR=0.679, (0.464-0.994), p=0.047	HR=0.969, (0.448-2.097), p=0.937
Stage III N2	HR=2.161, (1.058-4.412), p=0.034	HR=2.352, (1.153-4.798), p=0.019	HR=2.457, (1.219-4.953), p=0.012	- no value calculated, only 22 incidents, all in group "adjuvant chemotherapy only"

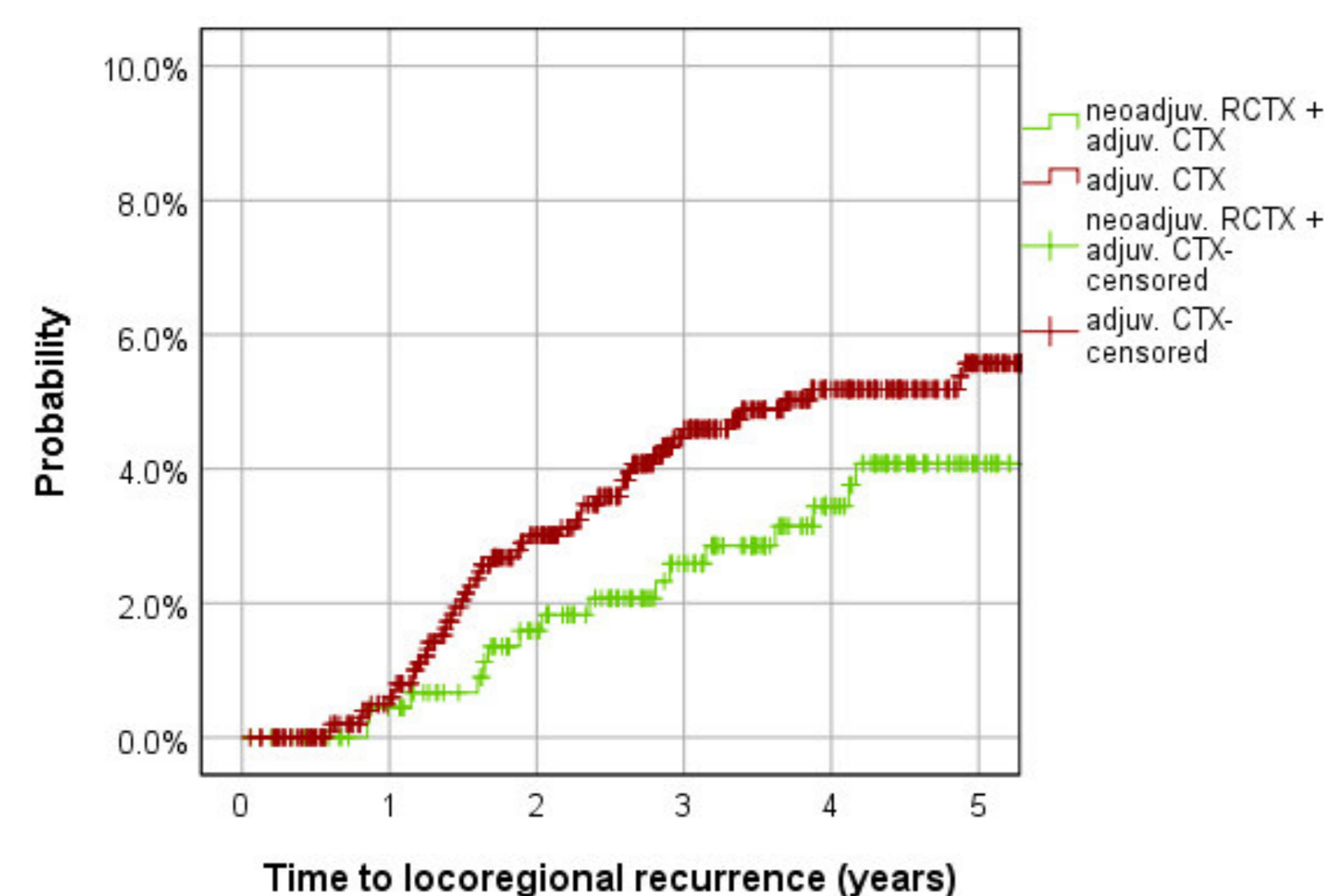


Fig. 1: Local recurrence rates in stage II/III by Kaplan-Meier method; 5-year local recurrence rates 4.1% and 5.6%, Log-Rank p=0.227

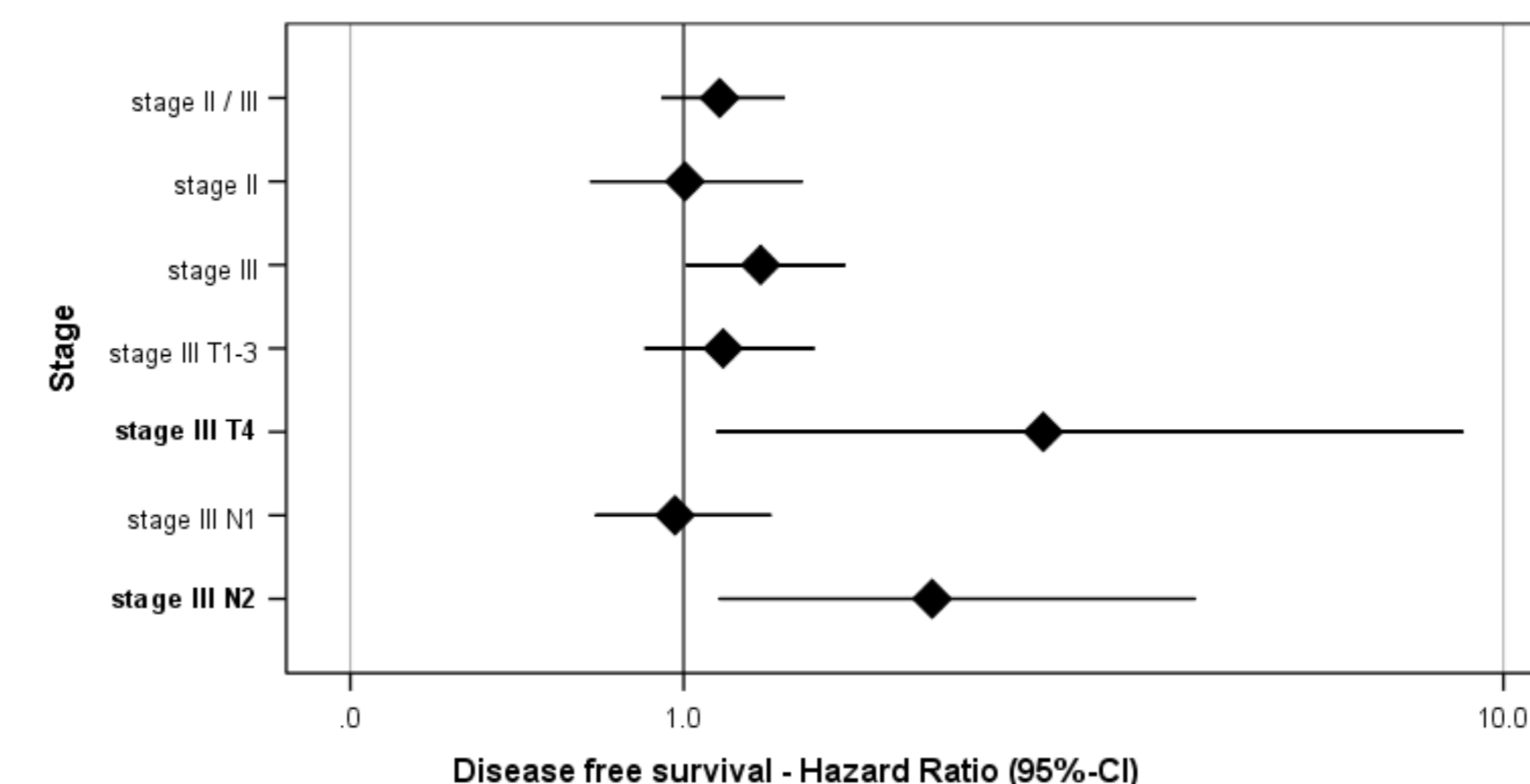


Fig. 2: Forest plot – hazard ratio for disease free survival of "adjuvant chemotherapy only" compared to the reference group "neoadjuvant radiochemotherapy and adjuvant chemotherapy combined" (HR=1.0) using multivariable Cox-regression analyses

Conclusion and Discussion

Combined adjuvant and neoadjuvant radiochemotherapy yields a significant benefit concerning overall and disease-free survival for patients with upper rectal adenocarcinoma in high risk situations, while in low risk situations no significant differences to adjuvant chemotherapy only could be seen. The 5-years local recurrence rates for stage II/III in general were rather low in both groups.

The recommendations of the German S3-guideline of 2019 to refrain from neoadjuvant radiation therapy in low-risk patients with a tumor in the upper third of the rectum, and to consider neoadjuvant radiochemotherapy in high risk situations are therefore supported by the results of this study.

Limitations of the study are caused mainly by its retrospective character and by the necessity to use the cTNM stage for the neoadjuvantly treated patients and the pTNM stage for patients without neoadjuvant treatment, which could have caused contortion of the results.

Contact

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