

Supplemental Online Content

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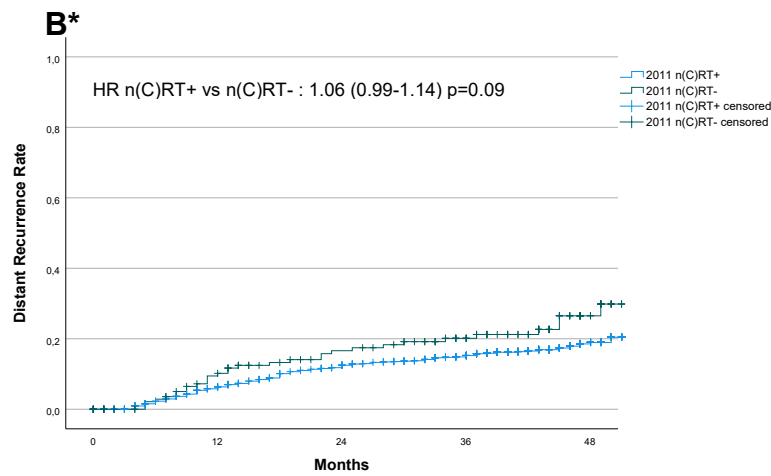
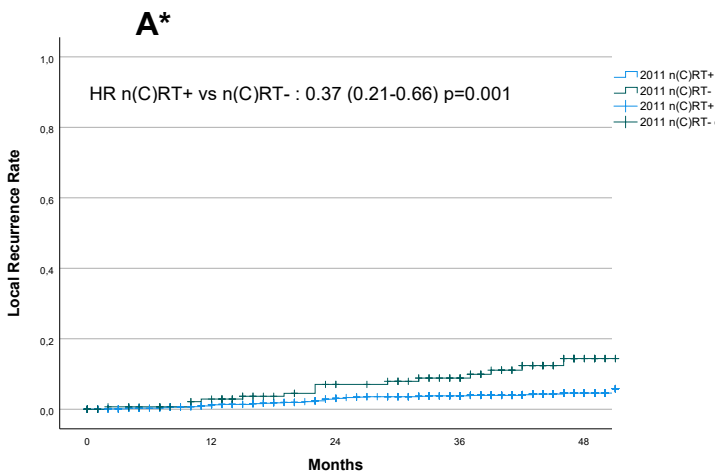
This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1 Overview of guideline differences

	Guideline 2011 (version 2·1 2008)	Guideline 2016 (version 3·0 2014)
Treatment		
Surgery only	cT1N0 (cT2N0 proximal tumors)	cT1-3bN0(MRF-)
5x5 Gy	cT2-cT4N0-1	cT3c-d(MRF-)N0 or cT1-3 (MRF-)N1
Chemoradiation	Expected CRM+ or cN2	cT4 or MRF+ or cN2 or LLN
Diagnostics		
Definition suspicious mesorectal lymph node	Diameter ≥ 5 mm	Diameter ≥ 9 mm or diameter 5-9 cm and 2 or 3 malignant characteristics or diameter < 5 mm and 3 malignant characteristics or diameter, i.e. round shape, heterogeneous aspect or irregular margin
Safe margin to the mesorectal fascia	≥5mm	> 1 mm

MRF: mesorectal fascial; LLN: lateral lymph node

eFigure 1 (A) Local Recurrence Rate, (B) Distant Recurrence Rate, (C) Disease-Free Survival, (D) Overall Survival for cohort 2011, stratified for neoadjuvant (chemo)radiotherapy

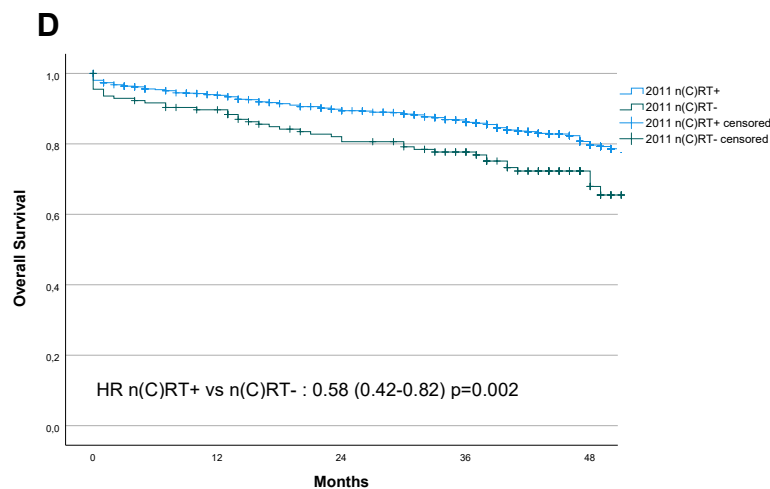
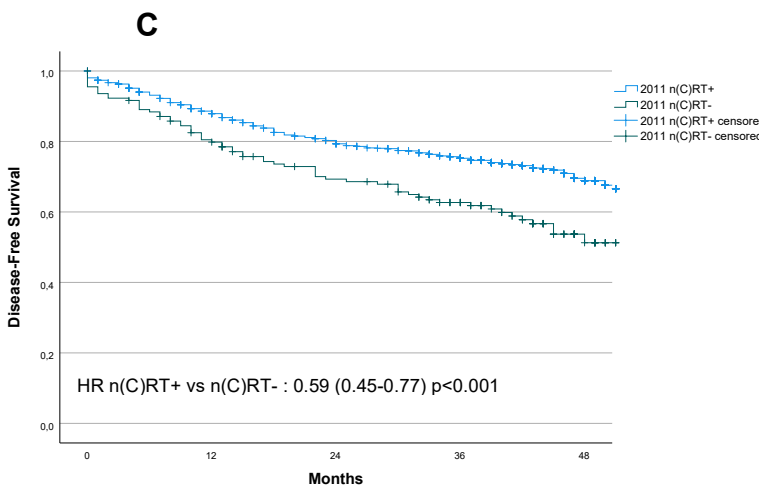


No. At risk:

2011 n(C)RT+	1026 ^a	920	834	751	236
2011 n(C)RT-	156 ^b	131	109	89	27

No. At risk:

2011 n(C)RT+	1023 ^c	872	770	678	210
2011 n(C)RT-	156 ^d	122	99	78	24



No. At risk:

2011 n(C)RT+	1028 ^e	875	766	673	208
2011 n(C)RT-	156 ^f	121	97	76	22

No. At risk:

2011 n(C)RT+	1027 ^g	924	848	761	243
2011 n(C)RT-	156 ^h	135	115	99	33

* The presented hazard ratio is the adjusted hazard ratio after competing risk analyses, with death as competing risk

^aData were missing in 8 patients in the 2011 n(C)RT+ group for the endpoint local recurrence

^bData were missing in 5 patients in the 2011 n(C)RT- for the endpoint local recurrence

^cData were missing in 15 patient in the 2011 n(C)RT+ group for the endpoint distant recurrence

^dData were missing in 5 patients in the 2011 n(C)RT- cohort for the endpoint distant recurrence

^eData were missing in 10 patients in the 2011 n(C)RT+ group for the endpoint disease free survival

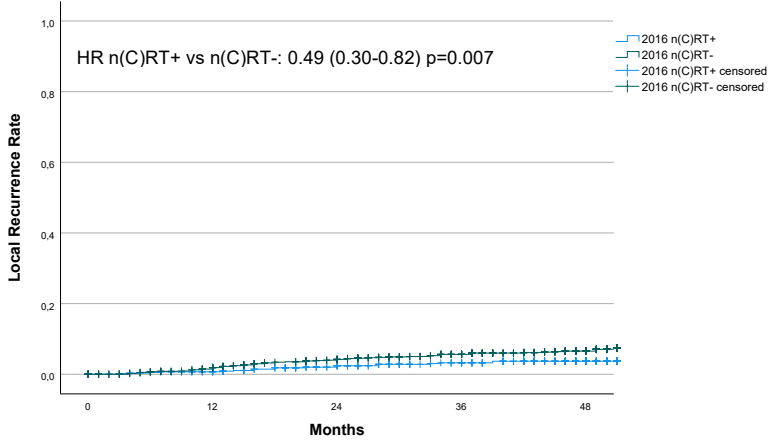
^fData were missing in 5 patients in the 2011 n(C)RT- group for the endpoint disease free survival

^gData were missing in 11 patients in the 2011 n(C)RT+ for the endpoint overall survival

^hData were missing in 5 patient in the 2011 n(C)RT- group for the endpoint overall survival

eFigure 2 (A) Local Recurrence Rate, (B) Distant Recurrence Rate, (C) Disease-Free Survival, (D) Overall Survival for cohort 2016, stratified for neoadjuvant (chemo)radiotherapy

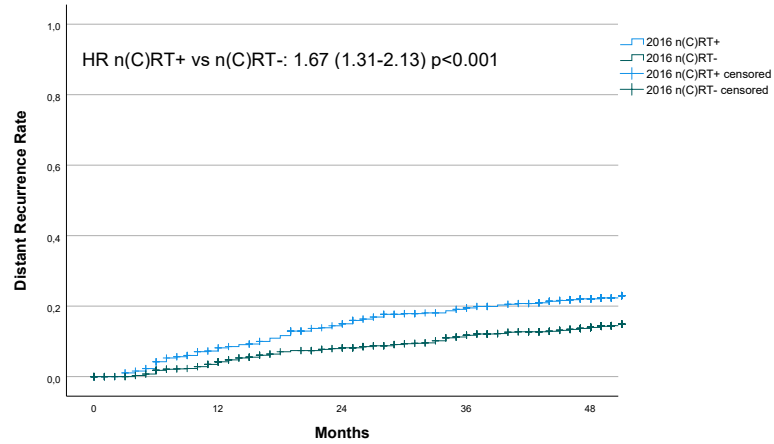
A*



No. At risk:

2016 n(C)RT+	582	544	499	449	365
2016 n(C)RT-	994	925	848	765	620

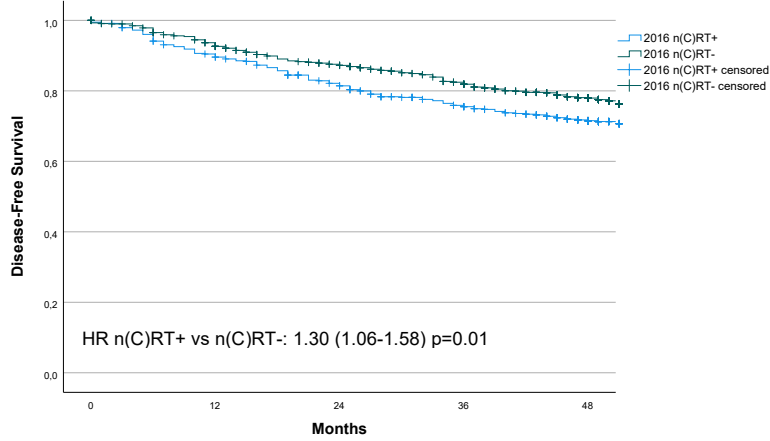
B*



No. At risk:

2016 n(C)RT+	581 ^a	513	454	399	322
2016 n(C)RT-	994	905	817	735	604

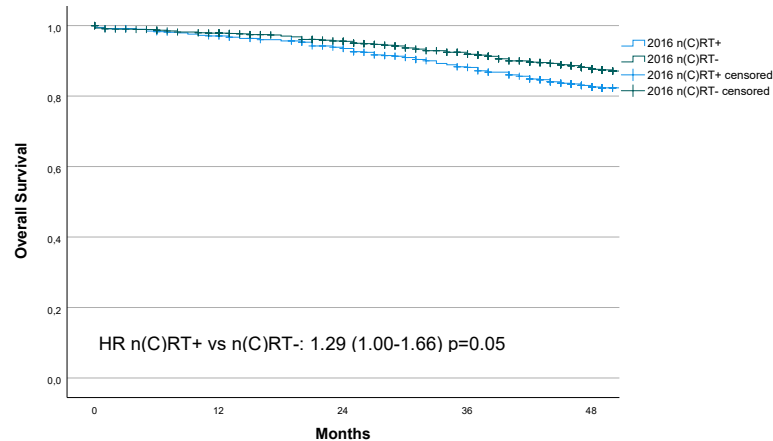
C



No. At risk:

2016 n(C)RT+	582	518	457	401	324
2016 n(C)RT-	994	906	814	729	594

D



No. At risk:

2016 n(C)RT+	582	556	521	467	377
2016 n(C)RT-	994	947	890	813	656

*The presented hazard ratio is the adjusted hazard ratio after competing risk analyses, with death as competing risk

^aData was missing in 1 patient in the 2016 n(C)RT+ group for the endpoint distant recurrence

eTable 2 Univariate and multivariable analyses for Locoregional Recurrence and Overall Survival in cohort 2011

Variable	No	Local Recurrence					Overall Survival				
		Univariable analysis		Multivariable analysis			Univariable analysis		Multivariable analysis		
		HR	95% CI	HR	95% CI	P	HR	95% CI	HR	95% CI	P
Sex											
Male	758	1					1				
Female	423	0.674	0.371-1.222				0.644	0.477-0.870			
Age	1140	1.003	0.978-1.030				1.074	1.058-1.091	1.074	1.053-1.096	<0.001
ASA score											
I/II	948	1					1		1		<0.001
III/IV	206	1.110	0.522-2.359				3.984	3.026-5.244	3.435	2.388-4.943	
Distance from ARJ	821	1.047	0.965-1.137				0.961	0.920-1.004	0.948	0.905-0.994	0.03
Neoadjuvant radiotherapy											
No	156	1		1		0.01	1				
Yes	1026	0.350	0.193-0.635	0.427	0.218-0.839		0.584	0.417-0.818			
Type of resection											
(L)AR	649	1		1		0.002	1				
APR	288	2.040	1.049-3.968	2.744	1.360-5.535		1.555	2.204-2.190			
HP	228	3.372	1.768-6.429	3.047	1.546-6.002		2.920	2.126-4.011			
Approach											
Open	636	1					1				
Minimal invasive	514	0.833	0.479-1.450				0.893	0.680-1.173			

Variable	No	Local Recurrence					Overall Survival				
		Univariable analysis		Multivariable analysis			Univariable analysis		Multivariable analysis		
		HR	95% CI	HR	95% CI	P	HR	95% CI	HR	95% CI	P
Adjuvant chemotherapy											
No	1062	1					1				
Yes	119	2.114	1.090-4.099				0.763	0.471-1.236			
(y)pT-stage											
(y)pT0	52	1		1		<0.001	1		1		0.004
(y)pT1	110	0.328	0.055-1.966	0.342	0.056-2.078		0.715	0.272-1.879	0.758	0.194-2.960	
(y)pT2	452	0.408	0.112-1.481	0.415	0.113-1.518		1.122	0.514-2.450	1.167	0.359-3.797	
(y)pT3	489	1.202	0.367-3.940	1.107	0.332-3.693		2.075	0.969-4.447	2.025	0.632-6.490	
(y)pT4	21	8.582	2.136-34.481	4.665	1.016-21.420		4.913	1.868-12.924	4.189	0.940-18.675	
(y)pN-stage											
(y)pN0	756	1					1		1		<0.001
(y)pN1	292	1.858	1.003-3.442				1.667	1.234-2.252	1.618	1.092-2.398	
(y)pN2	80	3.708	1.672-8.226				2.851	1.883-4.318	2.801	1.602-4.896	
Resection margin											
R0	1106	1		1		0.004	1				
R1	28	9.250	4.162-20.559	3.604	1.513-8.587		2.797	1.523-5.136			
Pelvic sepsis											
No	92	1					1				
Yes	203	1.015	0.493-2.088				1.322	0.946-1.848			

eTable 3 Univariate and multivariable analyses for Locoregional Recurrence and Overall Survival in cohort 2016

Variable	No	Local Recurrence				P	Overall Survival				
		Univariable analysis		Multivariable analysis			Univariable analysis		Multivariable analysis		
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI	P
Sex											
Male	1029	1		1		0.04	1				
Female	547	0.590	0.357-0.976	0.566	0.329-0.973		0.906	0.690-1.188			
Age	1541	1.011	0.987-1.034				1.073	1.057-1.089	1.061	1.044-1.077	<0.001
ASA score											
I/II	1296	1					1		1		<0.001
III/IV	261	0.701	0.351-1.401				2.762	2.101-3.632	1.906	1.086-1.852	
Distance from ARJ	1371	0.845	0.784-0.911	0.816	0.757-0.880	<0.001	0.987	0.948-1.027			
Neoadjuvant radiotherapy											
No	994	1		0.409	0.240-0.698	0.001	1		1		0.01
Yes	582	0.534	0.323-0.883				1.287	0.996-1.563	1.418	1.086-1.852	
Type of resection											
(L)AR	1120	1					1				
APR	267	2.404	1.462-3.954				1.817	1.323-2.493			
HP	181	2.562	1.425-4.605				2.891	2.092-3.995			
Approach											
Open	167	1		1		0.02	1				
Minimal invasive	1409	0.546	0.307-0.970	0.487	0.266-0.892		0.625	0.440-0.887			

Variable	No	Local Recurrence					Overall Survival				
		Univariable analysis		Multivariable analysis			Univariable analysis		Multivariable analysis		
		HR	95% CI	HR	95% CI	P	HR	95% CI	HR	95% CI	P
Adjuvant chemotherapy											
No	1536	1						1			
Yes	40	0.441	0.061-3.168				0.484	0.155-1.512			
(y)pT-stage											
(y)pT0	47	1		1		0.004	1		1		<0.001
(y)pT1	274	1.418	0.177-11.339	1.023	0.116-9.034		1.514	0.457-5.016	1.817	0.542-6.094	
(y)pT2	610	1.830	0.248-13.504	1.364	0.179-10.530		1.525	0.479-4.856	1.738	0.508-5.282	
(y)pT3	618	3.509	0.484-25.461	2.721	0.358-20.648		3.548	1.130-11.141	2.819	0.882-9.009	
(y)pT4	25	11.250	1.256-100.754	10.874	1.030-114.840		10.633	2.965-38.146	6.952	1.882-25.683	
(y)pN-stage											
(y)pN0	1084	1		1		<0.001	1		1		<0.001
(y)pN1	365	2.211	1.360-3.592	1.870	1.091-3.206		1.773	1.321-2.379	1.256	0.919-1.715	
(y)pN2	125	4.176	2.333-7.478	3.779	2.013-7.095		3.886	2.774-5.444	2.424	1.665-3.528	
Resection margin											
R0	1516	1					1		1		<0.001
R1	58	4.969	2.633-9.377				3.997	2.659-6.010	2.595	1.694-3.977	
Pelvic sepsis											
No	1346	1					1				
Yes	222	1.668	0.990-2.812				1.027	0.717-1.470			

eTable 4 Causes of death per cohort and use of n(C)RT

	Cohort 2011 (C)RT- (n=43)	Cohort 2011 (C)RT+ (n=174)	Cohort 2016 (C)RT- (n=135)	Cohort 2016 (C)RT+ (n=103)
	n (%)	n (%)	n (%)	n (%)
Rectal cancer	13 (30)	56 (32)	73 (54)	57 (55)
Surgical complications	4 (9)	14 (8)	1 (1)	1 (1)
Secondary malignancy	4 (9)	15 (9)	17 (13)	9 (9)
Cardiovascular cause	6 (14)	17 (10)	13 (1)	9 (9)
Pulmonary cause	3 (7)	18 (10)	6 (4)	3 (3)
Infectious cause	0 (0)	1 (1)	2 (2)	3 (3)
Neurological cause	2 (5)	3 (2)	5 (4)	2 (2)
Ileus	0 (0)	2 (1)	1 (1)	1 (1)
Other	1 (2)	4 (2)	4 (3)	1 (1)
Unknown	10 (23)	44 (25)	13 (10)	17 (17)