Tailored treatment for colon and rectal cancer

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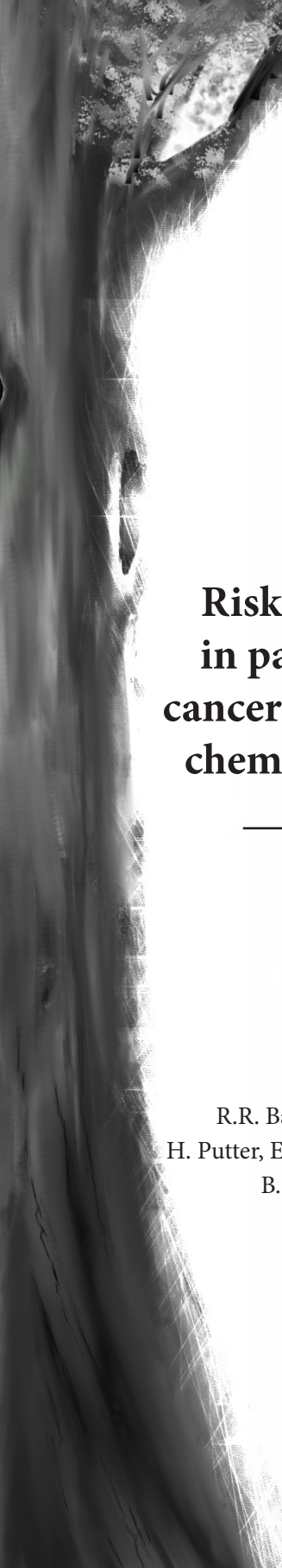

Risk and location of distant metastases in patients with locally advanced rectal cancer after total neoadjuvant treatment or chemoradiotherapy in the RAPIDO trial

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Abstract

Introduction: Although optimising rectal cancer treatment has reduced local recurrence rates, many patients develop distant metastases (DM). The current study investigated whether a total neoadjuvant treatment strategy influences the development, location, and timing of metastases in patients diagnosed with high-risk locally advanced rectal cancer included in the RAPIDO trial.

Material and methods: Patients were randomly assigned to short-course radiotherapy followed by 18 weeks of CAPOX or FOLFOX4 before surgery (EXP), or long-course chemoradiotherapy with optional postoperative chemotherapy (STD). Assessments for metastatic disease were performed pre- and post-treatment, during surgery, and 6, 12, 24, 36, and 60 months postoperatively. From randomisation, differences in the occurrence of DM and first site of metastasis were evaluated.

Results: In total, 462 patients were evaluated in the EXP and 450 patients in the STD groups. Cumulative probability of DM at 5 years after randomization was 23% [95%CI 19-27] and 30% [95%CI26-35] (HR 0.72 [95%CI 0.56-0.93];P=0.011) in the EXP and STD, respectively. Median time to DM was 1.4 (EXP) and 1.3 years (STD). After diagnosis of DM, median survival was 2.6 years [95%CI 2.0-3.1] in the EXP and 3.2 years [95%CI 2.3-4.1] in the STD groups (HR 1.39 [95%CI 1.01-1.92];P=0.04). First occurrence of DM was most often in the lungs (60/462 (13%) EXP and 55/450 (12%) STD) or the liver (40/462 (9%) EXP and 69/450 (15%) STD). A hospital policy of postoperative chemotherapy did not influence the development of distant metastases.

Conclusions: Compared to long-course chemoradiotherapy, total neoadjuvant treatment with short-course radiotherapy and chemotherapy significantly decreased the occurrence of metastases, particularly liver metastases.

Trial registration: EudraCT, 2010-023957-12, and ClinicalTrials.gov, NCT01558921

Keywords: rectal cancer, total neoadjuvant therapy, distant metastases, metastatic pattern

Introduction

Treatment of locally advanced rectal cancer (LARC) has evolved during the past decades. Irradiation has shifted from postoperative to preoperative, leading to fewer local recurrences. (1, 2) The effectiveness of short-course radiotherapy has been demonstrated next to long-course radiotherapy.(3-5) Moreover, the addition of chemotherapy to radiotherapy has proven to be effective in further reducing local recurrence rates in more advanced tumours but it has not improved survival except possibly in the most LARCs.(6-8) Improved preoperative imaging has contributed in selecting patients for neoadjuvant treatment. Moreover, due to improvements in surgical technique, local recurrence is no longer a major problem after treatment of LARC. In contrast, up to 30-40% of the patients still develop distant metastases (DM).(9, 10)

The RAPIDO trial enrolled patients diagnosed with LARC including at least one high-risk criterion. A decrease in the probability of disease-related treatment failure at 3 years from 30% to 24% after treatment with preoperative short-course radiotherapy followed by chemotherapy compared to preoperative long-course chemoradiotherapy and optional postoperative chemotherapy was demonstrated.(11) Although this difference could mainly be attributed to fewer DM in the experimental group, no improvement in overall survival was observed after a median follow-up of 4.6 years.

The current study aims to investigate whether a total neoadjuvant treatment strategy influences the development, location and timing of DM and the prognosis thereafter in patients diagnosed with high-risk LARC included in the RAPIDO trial after a median follow-up of 5.6 years.

Material and methods

Study population and design

The RAPIDO trial is an investigator-driven, international, open-label, phase III, randomized trial. The design, inclusion and exclusion criteria and results of the primary endpoint were published previously. (11) Eligible patients had non-metastasized locally advanced rectal cancer fulfilling at least one high-risk criteria on pelvic MRI (clinical tumour stage T4, clinical nodal stage N2, extramural vascular invasion (EMVI+), involved mesorectal fascia (MRF+),

or enlarged lateral lymph nodes) indicating high risk of failing locally and/or systemically. Between June 21, 2011, and June 2, 2016, 920 patients were assigned to either short-course radiotherapy (5x5 Gy), followed by six cycles of CAPOX or nine cycles of FOLFOX4 and surgery after a recovery period of two to four weeks (n=462, experimental group) or long-course radiotherapy (28-25 x 1.8-2.0 Gy) with concurrent capecitabine, followed by surgery after eight ± two weeks (n=450, standard-care group). Administration of postoperative chemotherapy in the standard-care group was allowed when recommended by the hospitals' local policy. The RAPIDO trial was carried out in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. After central evaluation and approval by the medical ethics committee of University Medical Center Groningen, the boards of directors or local ethics committees of all participating centres approved the protocol. The RAPIDO trial is registered with EudraCT (2010-023957-12) and ClinicalTrials.gov (NCT01558921).

Evaluation of the primary tumour and during follow-up

Pre-treatment screening included CEA, CT thorax-abdomen-pelvis and an MRI of the pelvis. Re-staging before surgery was mandatory (in the experimental group 1-2 weeks after the last chemotherapy cycle; in the standard-care group 2-3 weeks prior to planned surgery). After surgery, a standardised, minimal follow-up schedule was defined, with clinical assessments at 6, 12, 24, 36, and 60 months postoperatively, including CEA measurement. A chest x-ray and liver ultrasound or CT of thorax and abdomen were required at least at 12 and 36 months. Evidence of recurrent disease was accepted in case of positive histology or cytology, or with metastases on ultrasound, X-ray, (PET)CT, bone-scintigraphy and/or pelvic pathology on PET. Distant metastses were defined as relapse of the tumour outside the pelvic region. Analyses were based on information from the case report forms and corresponding copies of imaging and/or pathology reports in which the first occurrence of DM was documented. Type of imaging modality used all involved subsites at that assessment, and treatment of the metastases were recorded.

Statistical analyses

The reverse Kaplan-Meier method was used for the calculation of median follow-up.

Proportions were compared with chi-square tests. Survival analyses were performed on an intention-to-treat basis. For calculation of the cumulative incidence of DM, competing risks analyses were performed with death as competing risk. For calculation of the cumulative incidence of different sites of DM competing risks analyses were also performed, with time as the time of the first occurrence of distant metastasis, death or last follow-up, and the different sites of DM (liver-only, lung-only, liver+lung, other), and death as competing risks. Patients alive and DM-free at last follow-up were censored. A Cox proportional hazards regression, with the time-interval of DM after randomization as a continuous variable (in years), was performed to investigate the influence of time of first occurrence of DM on subsequent survival. Patients with locoregional failure prior to the diagnosis of DM were excluded when calculating the risk of developing locoregional failure after the diagnosis of DM. Locoregional failure and DM diagnosed within 90 days of each other were considered to occur synchronously. HRs and 95% confidence intervals (CI) were computed using Cox regression (for competing risks analyses based on the cause-specific hazards). Violation of the proportional hazards assumption was checked by visual inspection. P-values were calculated based on (cause-specific) log-rank tests.(12, 13) Univariate Cox regressions were performed to investigate the influence of baseline characteristics on the development of DM. Variables with a p-value <0.10 were included in a multivariate Cox regression, with the exception of 'number of high-risk criteria' as the high-risk criteria were already included in the multivariate analyses. Subgroup analyses of the effect of treatment on associations between prognostic factors of DM and the development thereof were performed and presented in a forest plot. The significance threshold for all P-values was 0.05. All analyses were performed using IBM SPSS Statistics version 25.0 or 'R' version 4.0.1.

Results

Clinical characteristics of eligible patients are demonstrated in table 1. At the time of analyses (data lock: 11March, 2022), median follow-up was 5.6 years (IQR 5.4-7.5).

Distant metastases

At 5 years after randomization the cumulative probability of DM was 23% [95%CI 19-27]

Table 1 Clinical characteristics

	All eligible patients			
	Experimental (n = 462)		Standard-care (n = 450)	
Gender				
Male	300	(65%)	312	(69%)
Female	162	(35%)	138	(31%)
Age at randomization (years)				
(median, range)	62	31-83	62	23-84
High-risk criteria *				
cT4	149	(32%)	139	(31%)
cN2	318	(69%)	314	(70%)
enlarged lateral nodes	70	(15%)	74	(16%)
EMVI +	166	(36%)	151	(34%)
MRF +	311	(67%)	312	(69%)
Number of high-risk criteria per patient *				
None	2	(<1%)	-	-
1	132	(29%)	136	(30%)
2	166	(36%)	155	(34%)
3	107	(23%)	106	(24%)
4	46	(10%)	39	(9%)
5	9	(2%)	14	(3%)
Distance from anal verge on endoscopy				
< 5 cm	103	(22%)	114	(25%)
5 – 10 cm	181	(39%)	153	(34%)
≥ 10 cm	146	(32%)	152	(34%)
Unknown	32	(7%)	31	(7%)
Treated in a hospital with a policy for postoperative chemotherapy (standard-care group)				
Yes	-	-	265	(59%)
No	-	-	185	(41%)

Continuation Table 1 Clinical characteristics

	All eligible patients	
	Experimental (n = 462)	Standard-care (n = 450)
Number of postoperative chemotherapy courses (standard-care group)		
None, no hospital policy		183 (41%)
None, despite hospital policy	- -	80 (18%)
1-3	- -	65 (14%)
≥ 4	- -	122 (27%) ‡

Data are n (%), unless otherwise indicated. Percentages might not equal 100% due to rounding. * MRI defined, according to radiology reports. ‡ Two patients without a hospital policy are also included.

and 30% [95%CI 26-35] in the experimental and standard-care groups, respectively (HR 0.72 [95%CI 0.56-0.93];P=0.011, figure 1A). Median time from randomization to the diagnosis of DM was 1.4 years (IQR 0.9-2.5) in the experimental group and 1.3 years (IQR 0.5-2.2) in the standard-care group. The moment of diagnosis of the first appearance of DM is described in table 2. From diagnosis of DM, patients in the experimental group had a worse prognosis than those in the standard-care group (HR 1.39 [95%CI 1.01-1.92];P=0.04) with a median survival of 2.6 years [95%CI 2.0-3.1] and 3.2 years [95%CI 2.3-4.1], respectively, figure 1B. A hospital policy of postoperative chemotherapy in the standard-care group did not influence the development of DM (Supplementary Figure A). Table 3 describes the occurrence of DM and locoregional failure in relation to each other. Supplementary Figure B contains additional information on the timing of development of DM and/or locoregional failure. At 5 years the cumulative probability of developing locoregional failure synchronously or after being diagnosed with DM was 25% [95%CI 15-35] in the experimental group and 13% [95%CI 7-19] in the standard-care group (HR 2.02 [95%CI 1.07-3.81];P=0.03). The cumulative probability of disease-related treatment failure at five years was 28% [95%CI 24–32] in the experimental group and 34% [95%CI 30–38) in the standard-care group (HR 0.79 [95%CI 0.63–1.00];P=0.048. Overall survival of all eligible patients in the RAPIDO trial at 5 years was 82% [95%CI 78-85] for the experimental group and 80% [95%CI 77-84] for the standard-care group (HR 0.91 [95%CI 0.70-1.19];P=0.50). For all analyses, visual inspection showed no evidence of violation of the proportional hazards assumption.

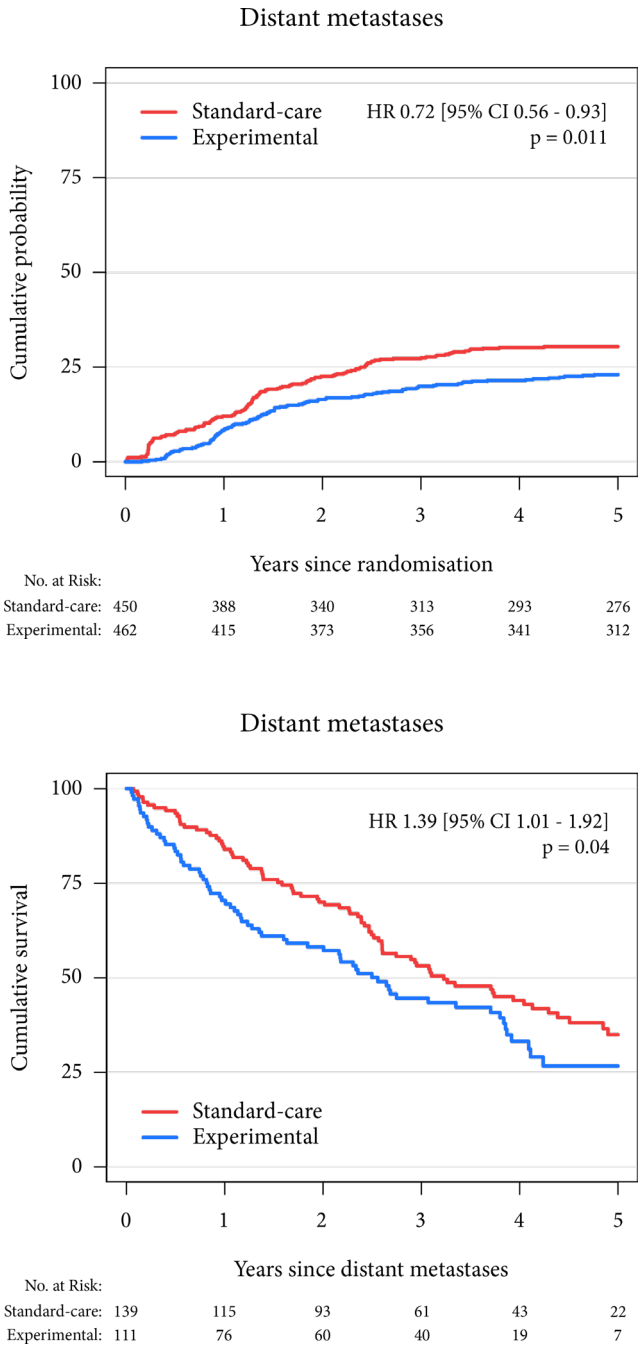

Figure 1 The risk of distant metastases (A) and survival after diagnosis of metastases (B).

First metastasized organ-site

In the experimental and standard-care groups, 73% (81/111) and 78% (109/139) of patients were initially diagnosed with DM in one organ-site, 22% (24/111) and 17% (23/139) had DM in two organ-sites, and 5% (6/111) and 5% (7/139) in 3-6 organ-sites, respectively (P=0.58). DM were most often located in the liver or the lungs (figure 2,3). In the experimental group, 9% (40/462) of patients were diagnosed with liver metastases compared to 15% (69/450) of patients in the standard-care group (P=0.002). Lung metastases were equally common in both groups, 13% (60/462) in the experimental group and 12% (55/450) in the standard-care group (P=0.73). Survival after lung-only versus liver-only metastases was not statistically significantly different, stratified for treatment group or for the treatment groups combined (Supplementary Figure C). Tumour level did not influence first metastatic organ-site (Supplementary Table A).

Treatment of distant metasases

Of the patients with DM, 46% (51/111) and 52% (72/139) underwent surgery for metastatic disease (P=0.36), 14% (15/111) and 16% (22/139) received radiotherapy (P=0.61), 45% (50/111) and 58% (81/139) received chemotherapy (P=0.037), and 6% (7/111) and 9% (12/139) received other or no treatment (P=0.49) in the experimental and standard-care groups, respectively. Treatment according to the location of DM is displayed in table 4 (in more detail, Supplementary Table B).

Prognostic factors for the development of distant metastases

Treatment group, all high-risk criteria except cT4, and the total number of high-risk criteria were associated with the development of DM. In the multivariate analyses, treatment group, EMVI+, cN2 and MRF+ were statistically significant (table 5). No interaction between risk factors and treatment groups could be demonstrated (figure 4).

Discussion

The RAPIDO trial demonstrates that short-course radiotherapy followed by chemotherapy before surgery decreases the cumulative probability of DM at five years to 23% compared to

30% after chemoradiotherapy before surgery and optional postoperative chemotherapy in patients with LARC who are considered to have a high risk of systemic recurrence. Median time to appearance of DM was the same and median survival after DM was six months longer in the standard-care group than in the experimental group (3.1 vs 2.6 years, p=0.04).The decrease in DM is mainly caused by a reduction in liver-only metastases.

The appearance of distant metastases

As reported earlier from the RAPIDO trial, compliance with systemic chemotherapy was increased when this was delivered pre-operatively.(14) With the TNT approach, the intended dose of chemotherapy could be given to more patients resulting in a lower DM rate. In colon cancer, an early start of adjuvant chemotherapy is more effective than starting more than 10 weeks after surgery, the latter negatively impacts disease-free survival.(15) By bringing forward chemotherapy as part of a TNT in rectal cancer, micrometastases, when susceptible to chemotherapy, can be combatted earlier in the treatment process, preventing development of detectable metastases. This is supported by our finding that DM were more often diagnosed during re-staging in the standard-care group than in the experimental group, where restaging was after a longer interval. The follow-up schedule after surgery was standardised leading to clear increases of DM at set times. Merely postponement of DM does not seem to be the case as median time to DM is comparable between treatment groups.

Decrease in liver metastases

It is unknown why neoadjuvant chemotherapy appears more effective in decreasing liver metastases than lung metastases in the RAPIDO trial. The literature is not unequivocal regarding the most common metastasised organ in rectal cancer. Some studies have reported the liver as most common metastasized organ(16), other retrospective and prospective single-centre studies have reported the lungs as the most common metastasized organ-site.(17, 18) However, this finding may be explained by the inclusion of mostly mid-, and lower rectal cancers in those studies.(17, 19-21) Tumour height did not influence first-metastasised organ-site in the RAPIDO trial as distance from the anal verge was equal between the treatment groups (supplementary table A).

Table 2 Moment for the diagnosis of the first appearance of distant metastases

	All patients		
	Experimental (n = 462)	Standard-care (n = 450)	P-value
			0.040
Before start of treatment *	0 (0%)	5 (1%)	
At restaging after the end of the neoadjuvant treatment	8 (2%)	20 (4%)	
During surgery	6 (1%)	4 (1%)	
After surgery or sustained cCR	97 (21%)	110 (24%)	

* At planning CT-scan for radiotherapy. Data are presented as n (absolute %).

Table 3 Events of disease-related treatment failure

	All patients	
	Experimental (n = 462)	Standard-care (n = 450)
DM only	74 (16%)	106 (24%)
LRF only	15 (3%)	6 (1%)
DM + LRF synchronously *	15 (3%)	11 (2%)
DM before LRF	11 (2%)	8 (2%)
DM after LRF	9 (2%)	5 (1%)
New primary tumor (without DM or LRF)	21 (5%)	28 (6%)
Treatment-related death	4 (1%)	4 (1%)

* Locoregional failure and distant metastases diagnosed within 90 days of each other.
Data are presented as n (absolute %).

Prognosis after distant metastases

In the experimental group, 84% (387 of 462) of patients received at least 75% of the prescribed courses of systemic chemotherapy before the diagnosis of DM compared to 24% (108 of 450) of patients in the standard-care group.(14) As a consequence, patients in the experimental group with metastatic disease who progressed after this systemic treatment had already received a nearly cumulative maximum dose of oxaliplatin, hampering administration of oxaliplatin-

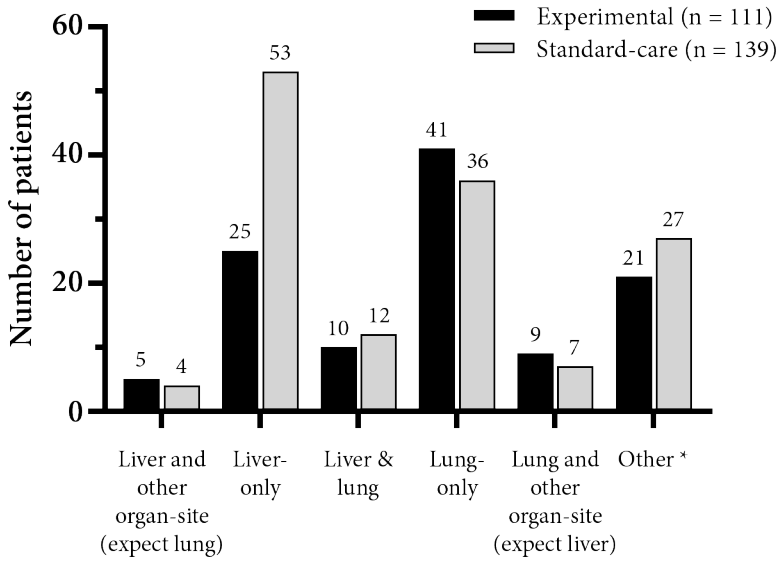

Figure 2 First metastasized organ-site.

**Other includes bone, brain, peritoneum, distant lymph nodes, and pleura.*

containing chemotherapy in the metastatic setting. These patients often received second-line chemotherapy, known to be less effective in the palliative setting, as tumour cells that cause relapse after treatment with systemic chemotherapy can have a worse biological profile and could therefore be partly responsible for a poorer prognosis.(22) In contrast, patients developing metastatic disease in the standard-care group who had not received adjuvant chemotherapy could be treated with first-line oxaliplatin-containing chemotherapy. The gain in fewer DM from preoperative chemotherapy may be counterbalanced by shortening of survival after recurrence, as recently stressed in a systematic review.(23)

Also, a more aggressive treatment with multiple interventions creates survival advantages for chemo-resistant tumour cells after each successful intervention. A combined treatment as the RAPIDO schedule (radiotherapy and chemotherapy) is more effective than only one local intervention (chemoradiotherapy in the standard-care group) resulting in a higher pCR rate. (11) However, the most aggressive and invasive cancer cells will survive after each intervention if not eliminated.(24) This selection effect was observed in the experimental group with

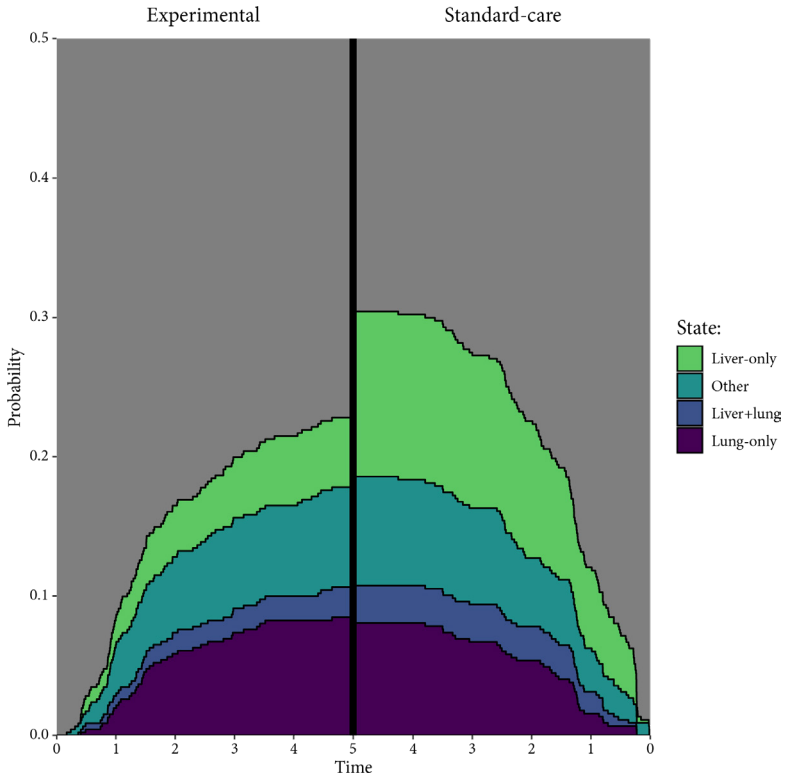

Figure 3 First diagnosis of distant metastases over time, based on cumulative probabilities according to the first metastasized organ-site. Other includes liver and another organ-site, lung, and another organ-site.

worse survival and a higher probability of developing locoregional failure synchronously or after the diagnosis of DM.

The experimental treatment possibly prevented the DM with very little tumour burden, which was still present in the standard-care group. These patients may be the ones cured by local treatment being another reason for the better survival after DM in the standard-care group. Metastases with the worst prognosis (non-resectable, non-responsive to chemotherapy etc) were the ones remaining in both treatment groups influencing overall survival. Possibly explaining why overall survival of the whole group is comparable at 5 years. However, another

		Experimental Events/patients		Standard-care Events/patients		HR [95% CI]	*P*interaction
mr cT4	yes	39/149	(26%)	50/139	(36%)	0.68 [0.44-1.03]	0.68
	no	72/313	(23%)	89/311	(29%)	0.75 [0.55-1.02]	
mr cN2	yes	86/318	(27%)	103/314	(33%)	0.77 [0.58-1.03]	0.44
	no	25/144	(17%)	36/136	(26%)	0.60 [0.36-1.00]	
mr lat LN +	yes	22/70	(31%)	28/74	(38%)	0.82 [0.47-1.43]	0.66
	no	89/392	(23%)	111/376	(30%)	0.71 [0.54-0.94]	
mr EMVI +	yes	50/166	(30%)	60/151	(40%)	0.68 [0.47-1.00]	0.76
	no	61/296	(21%)	79/299	(26%)	0.73 [0.52-1.02]	
mr MRF +	yes	82/311	(26%)	105/312	(34%)	0.73 [0.55-0.98]	0.94
	no	29/151	(19%)	34/138	(25%)	0.72 [0.44-1.18]	
High-risk criteria per patient	1	20/132	(15%)	29/136	(21%)	0.67 [0.38-1.19]	0.89
	2	37/166	(22%)	48/155	(31%)	0.64 [0.42-0.99]	
	3	30/107	(28%)	34/106	(32%)	0.78 [0.45-1.35]	
	4-5	23/55	(42%)	28/53	(53%)	0.77 [0.45-1.35]	
Overall estimate							

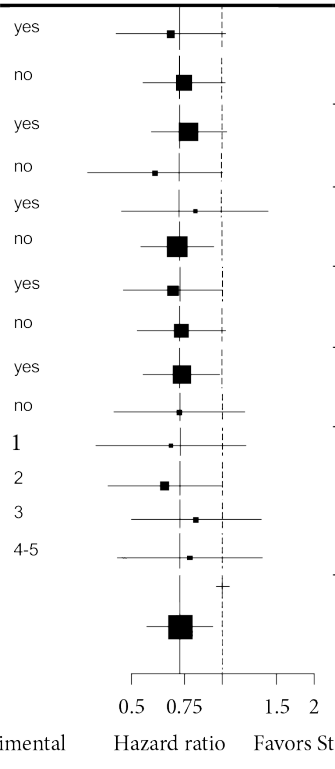

Figure 4 Forest plot of the effect of high-risk factors present at abseline MRI on the development of distant metastases.

Table 4 Treatment according to location of distant metastases

	Liver-only		Lung-only	
	EXP (n=25)	STD (n=53)	EXP (n=41)	STD (n=36)
No treatment	3 (12%)	3 (6%)	3 (7%)	5 (14%)
Surgery only	8 (32%)	18 (34%)	17 (41%)	9 (25%)
Surgery + CT	7 (28%)	17 (32%)	2 (5%)	2 (6%)
Surgery + RT	- -	2 (4%)	2 (5%)	- -
CT only	4 (16%)	4 (8%)	10 (24%)	13 (36%)
RT only	- -	1 (2%)	5 (12%)	5 (14%)
CT + RT	- -	- -	1 (2%)	2 (6%)
Other treatment*	3 (12%)	8 (15%)	1 (2%)	- -

	Liver + lung		Other	
	EXP (n=10)	STD (n=12)	EXP (n=21)	STD (n=27)
No treatment	4 (40%)	1 (8%)	3 (14%)	2 (7%)
Surgery only	1 (10%)	- -	3 (14%)	3 (11%)
Surgery + CT	2 (20%)	1 (8%)	3 (14%)	6 (22%)
Surgery + RT	- -	1 (8%)	1 (5%)	1 (4%)
CT only	2 (20%)	7 (58%)	7 (33%)	10 (37%)
RT only	- -	- -	1 (5%)	1 (4%)
CT + RT	1 (10%)	1 (8%)	- -	1 (4%)
Other treatment*	- -	1 (8%)	3 (14%)	3 (11%)

EXP = experimental group; STD = standard-care group; CT = chemotherapy;
RT = radiotherapy.
*Other treatment also includes: (a combined treatment using) microwave ablation, radiofrequency ablation, HIPEC, electrochemotherapy.

possible explanation is that the RAPIDO trial was not powered to address overall survival. The gain in DM rate (7%-unites) may be too small to detect a difference in overall survival with the number of patients included.

Table 5 Univariate and multivariate cox regression analyses for distant metastases

Variable	Number of patients at risk	Univariate		Multivariate	
		Hazard ratio (CI 95%)	P-value	Hazard ratio (CI 95%)	P-value
Treatment			0.011		0.011
Experimental	462	1.00		1.00	
Standard-care	450	1.39 (1.08-1.78)		1.39 (1.08-1.78)	
Gender			0.138		
Male	612	1.00		-	
Female	300	0.81 (0.62-1.07)		-	
Age			0.703		
	912	1.00 (0.99-1.02)		-	
Distance from anal verge (endoscopy)			0.689		
≤ 5cm	217	1.00		-	
5-10 cm	334	0.92 (0.66-1.27)		-	
≥10 cm	298	1.05 (0.75-1.45)		-	
High risk factors					
mr cT4			0.060		0.285
No	624	1.00		1.00	
Yes	288	1.28 (0.99-1.66)		1.16 (0.88-1.53)	
mr cN2			0.008		0.005
No	280	1.00		1.00	
Yes	632	1.48 (1.11-1.98)		1.53 (1.14-2.06)	
mr Lat LN +			0.025		0.081
No	768	1.00		1.00	
Yes	144	1.43 (1.05-1.94)		1.32 (0.97-1.81)	

Continuation Table 5 Univariate and multivariate cox regression analyses for distant metastases

Variable	Number of patients at risk	Univariate		Multivariate	
		Hazard ratio (CI 95%)	P-value	Hazard ratio (CI 95%)	P-value
mr EMVI +			<0.001		<0.001
No	595	1.00		1.00	
Yes	317	1.66 (1.29-2.13)		1.64 (1.28-2.12)	
mr MRF +			0.007		0.013
No	289	1.00		1.00	
Yes	623	1.48 (1.11-1.97)		1.46 (1.08-1.97)	
Number of high-risk criteria			<0.001		
	912	1.41 (1.26-1.57)			

Strengths and limitations

To our knowledge, this study is the first to compare the first metastatic organ-site in LARC while comparing TNT to conventional chemoradiotherapy and to report a changed metastatic pattern with the different treatment regimens. A limitation of the current study is that further diagnostics of the occurrence of DM were not always fully performed after an LRF had been established and vice versa. This has not been checked and corrected for in the analyses as this differs per hospital and country. In addition, comparisons with regard to systemic chemotherapy were more challenging as the standard-care group was not evenly distributed because adjuvant chemotherapy was allowed according to the hospital protocol. Although the results of the RAPIDO trial are promising with respect to a decrease in DM, a higher pCR rate, and therewith a possible organ-saving strategy, an important clinical dilemma still concerns the selection of LARC patients who will most likely benefit from this new treatment schedule. Recently our study group published that enlarged lateral lymph nodes, a positive circumferential resection margin, tumour deposits, node positivity at pathology and experimental treatment were significant predictors for developing locoregional recurrence. No statistically significant association was found in the multivariate analysis regarding distance from the anal verge. (25) In the current manuscript, we demonstrated that EMVI,

cN2, MRF and standard-care treatment are prognostic factors for the development of DM, yet, identification of patients who would benefit the most from the RAPIDO schedule or other TNT schedules is not yet possible. Although health-related quality of life and bowel function were not compromised and no increase in grade ≥ 3 toxicity was observed,(26) the benefits and harms of a total neoadjuvant treatment should be carefully balanced, as some patients are overtreated.

Further research is needed to predict clinical response, for example, via biomarkers and to define the optimal selection criteria for total neoadjuvant treatment. In addition, standardised follow-up schedules should be applied to future studies to provide comparable results.

Conclusion

In summary, compared to standard care with long-course chemoradiotherapy, short-course radiotherapy in combination with systemic chemotherapy effectively decreases liver metastases in patients with high-risk LARC without influencing the time of diagnosis of DM. With the experimental TNT, an effective dose of chemotherapy can be given to eliminate more micrometastases, when susceptible to chemotherapy, early in the treatment process, preventing development into detectable metastases. Why this effect mainly occurs in liver metastases cannot be fully explained based on the current data.

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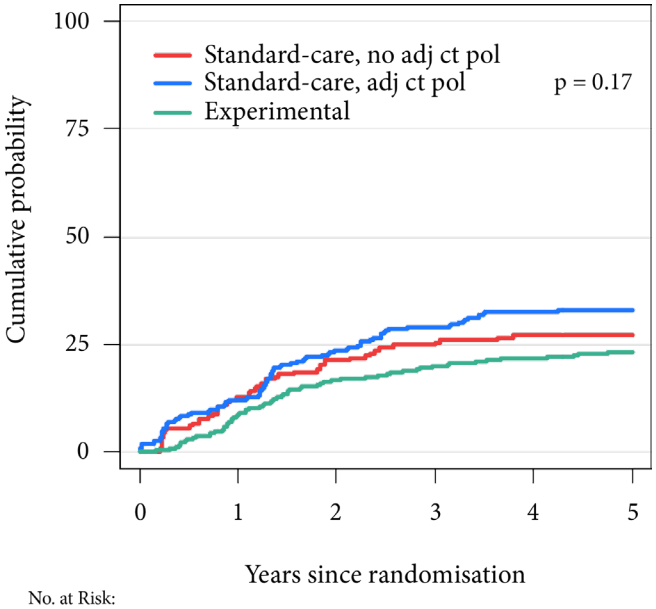
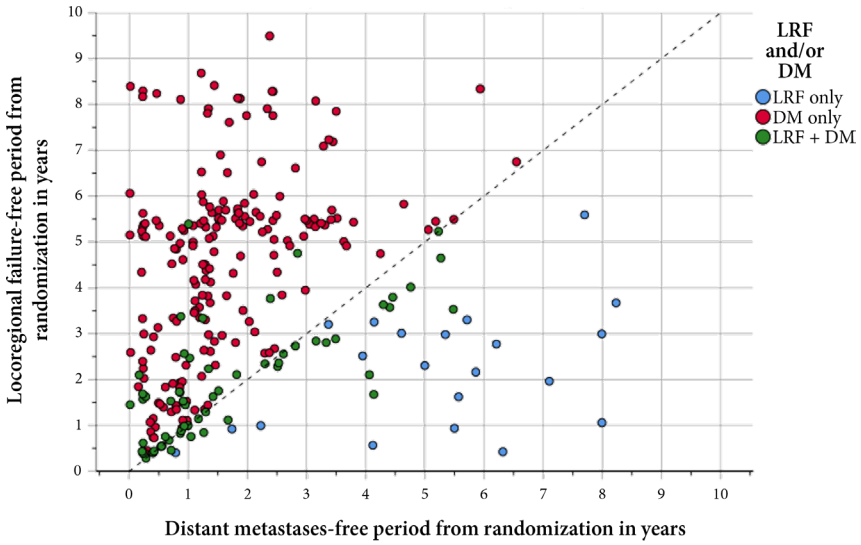
Supplementary Appendix Chapter 5



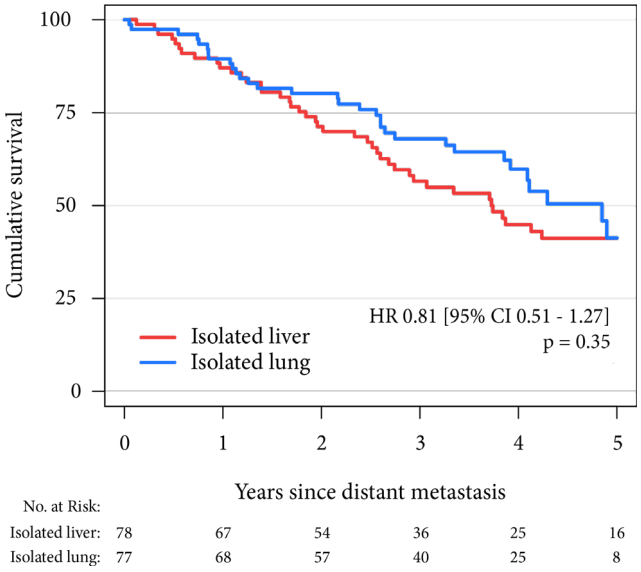
No. at Risk:						
Standard-care, no adj ct pol:	185	158	141	133	124	117
Standard-care, adj ct pol:	265	230	199	180	169	159
Experimental:	462	415	373	356	341	312

Supplementary Figure A The development of distant metastases stratified for the experimental group and the standard-care group with or without a hospital policy for postoperative chemotherapy.

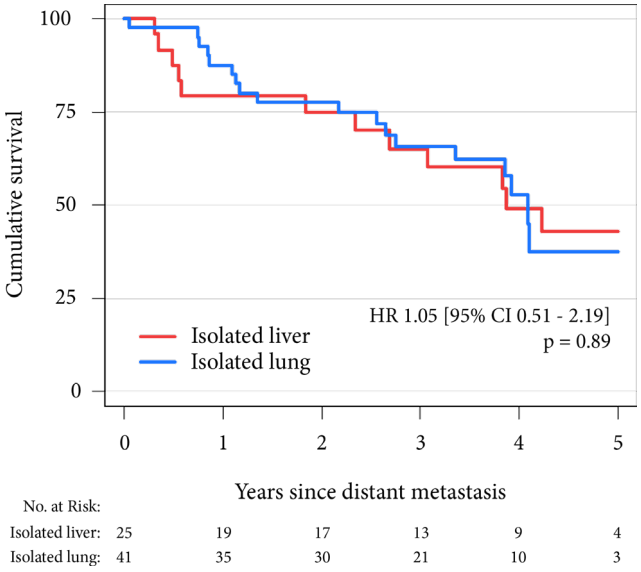
Cumulative probabilities at five years after randomization were 33% [95% CI 27-38] and 27% [95% CI 21-34] with or without hospital policy, respectively (HR 1.22 [95% CI 0.86-1.72]; P=0.019). In total, 187 patients started adjuvant chemotherapy in the standard-care group; two patients were from the group without a hospital policy for adjuvant chemotherapy.



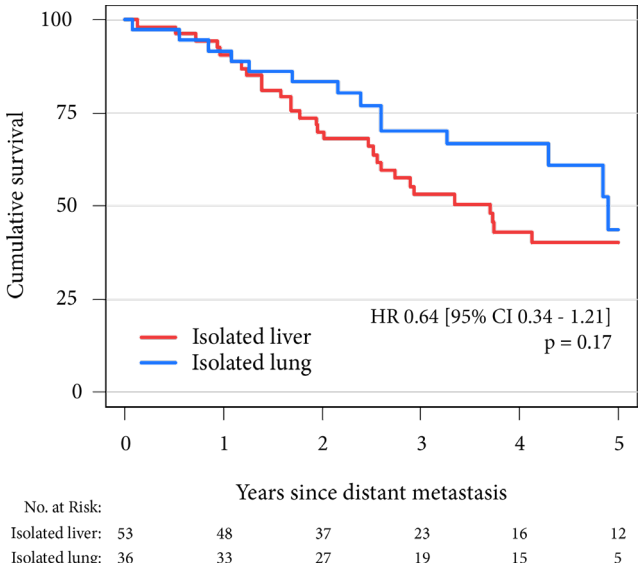
Supplementary Figure B Timing of distant metastases and/or locoregional failure.
LRF = locoregional failure DM = distant metastases.



Supplementary Figure C.1 Survival after isolated lung metastases versus after isolated liver metastases (both treatment groups).



Supplementary Figure C.2 Survival after isolated lung metastases versus after isolated liver metastases (experimental group).



Supplementary Figure C.3 Survival after isolated lung metastases versus after isolated liver metastases (standard-care group).

Supplementary Table A First metastatic organ-sites according distance from anal verge.

	Whole group				Whole group			
	Experimental		Standard		Experimental		Standard	
	< 5cm				5-10 cm			
No metastases	154	(71%)			247	(74%)		
	75	(73%)	79	(71%)	139	(77%)	108	(71%)
Isolated liver	14	(22%)			31	(36%)		
	4	(4%)	10	(9%)	11	(6%)	20	(13%)
Liver and other organ-site (except lung)	1	(1%)			3	(1%)		
	1	(1%)	-	-	1	(1%)	2	(1%)
Isolated lung	24	(11%)			29	(9%)		
	13	(13%)	11	(10%)	17	(9%)	12	(8%)
Lung and other organ-site (except liver)	6	(3%)			5	(2%)		
	2	(2%)	4	(4%)	4	(2%)	1	(1%)
Other	13	(6%)			13	(4%)		
	5	(5%)	8	(7%)	7	(4%)	6	(4%)
Liver + lung	5	(2%)			6	(2%)		
	3	(3%)	2	(2%)	2	(1%)	4	(3%)

None of the differences are statistically significant

Continuation

Supplementary Table A First metastatic organ-sites according distance from anal verge.

	Whole group				Whole group			
	Experimental		Standard		Experimental		Standard	
	≥ 10 cm				unknown			
No metastases	212	(71%)			49	78%)		
	111	(76%)	101	(66%)	26	(81%)	23	(74%)
Isolated liver	32	(37%)			1	(7%)		
	10	(7%)	22	(15%)	-	-	1	(3%)
Liver and other organ-site (except lung)	4	(1%)			1	(2%)		
	2	(1%)	2	(1%)	1	(3%)	-	-
Isolated lung	21	(7%)			3	(5%)		
	10	(7%)	11	(7%)	1	(3%)	2	(7%)
Lung and other organ-site (except liver)	2	(1%)			3	(5%)		
	1	(1%)	1	(1%)	2	(6%)	1	(3%)
Other	18	(6%)			4	(6%)		
	8	(6%)	10	(7%)	1	(3%)	3	(10%)
Liver + lung	9	(3%)			2	(3%)		
	4	(3%)	5	(3%)	1	(3%)	1	(3%)

None of the differences are statistically significant

Supplementary Table B Treatment according to location of distant metastases

	Liver-only		Lung-only		Liver + lung		Other	
	EXP (n=25)	STD (n=53)	EXP (n=41)	STD (n=36)	EXP (n=10)	STD (n=12)	EXP (n=21)	STD (n=27)
No treatment	3 (12%)	3 (6%)	3 (7%)	5 (14%)	4 (40%)	1 (8%)	3 (14%)	2 (7%)
Surgery only	8 (32%)	18 (34%)	17 (41%)	9 (25%)	1 (10%)	- -	3 (14%)	3 (11%)
Surgery + CT	7 (28%)	17 (32%)	2 (5%)	2 (6%)	2 (20%)	1 (8%)	3 (14%)	6 (22%)
Surgery + RT	- -	2 (4%)	2 (5%)	- -	- -	1 (8%)	1 (5%)	1 (4%)
CT only	4 (16%)	4 (8%)	10 (24%)	13 (36%)	2 (20%)	7 (58%)	7 (33%)	10 (37%)
RT only	- -	1 (2%)	5 (12%)	5 (14%)	- -	- -	1 (5%)	1 (4%)
CT + RT	- -	- -	1 (2%)	2 (6%)	1 (10%)	1 (8%)	- -	1 (4%)
Other treatment*	3 (12%)	8 (15%)	1 (2%)	- -	- -	1 (8%)	3 (14%)	3 (11%)

EXP = experimental group; STD = standard-care group; CT = chemotherapy; RT = radiotherapy.

Continuation Supplementary Table B Treatment according to location of distant metastases

Other treatment*

Experimental liver only:1x MWA, 1x surgery + RFA, 1x surgery + CT + RT

Standard-care liver only:1x electrochemotherapy, 3x surgery + RFA, 2x CT + RFA, 1x surgery + CT + RFA, 1x surgery + RT + chemo + RFA

Experimental lung only: 1x microwave ablation

Standard-care liver + lung: 1x RT + CT + RFA

Experimental other: 2x surgery, including HIPEC, 1x RT + pain relief,

Standard-care other: 1x surgery, including HIPEC, 1x surgery + RT + CT + HIPEC, 1x surgery + CT + RT

Treatment liver + other

Experimental: 1x surgery + CT, 4x only CT

Standard-care: 1x CT + RT, 2x surgery + CT, 1x surgery + CT + RT

Treatment lung + other

Experimental: 3x no treatment, 4x only CT, 1x only RT, 1x CT + RT

Standard-care: 1x no treatment, 4x only CT, 1x CT + RT, 1x surgery + CT + HIPEC