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Quality of surgery in T3-4 rectal cancer: Involvement of circumferential resection margin not influenced by preoperative treatment. Results from EORTC trial 22921 ☆

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ABSTRACT

Purpose: The present analyses aimed to determine risk factors for rectal cancer patients associated with circumferential resection margin (CRM) and number of examined lymph nodes (LN) and to correlate these parameters of surgical quality with local recurrence (LR), disease-free and overall survival (DFS and OS).

Materials and methods: Data of 884 eligible patients, who underwent a resection and had no metastases at time of surgery, were analysed.

Results: Age, period of treatment, distance and pT-stage were associated with surgical quality. CRM involvement, but not the number of examined LN, was associated with a higher risk of an LR, reduced DFS and OS. An abdomino-perineal resection (APR) was a risk factor for adverse outcome.

Conclusion: Surgical quality is an important predictor of outcome, also for patients treated with conventional RT or chemoradiotherapy (CRT). Preoperative CRT results in downstaging and downsizing of the tumour, but not in less CRM involvement.

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1. Introduction

Surgery is the cornerstone of the curative treatment of rectal cancer. However, in 1991, McArdle and Hole reported that surgical variability could influence outcome to a large extent.[1] Afterwards, several groups reported that the surgeon is an important prognostic factor for outcome in patients with rectal cancer.[2–4] Havenga and colleagues studied cohorts of patients treated with different surgical techniques.[5] Standardised surgery resulted in 30% survival and 25% local control benefit. Quality assurance aims to reduce this variability and can be defined as the systematic measures required to achieve a treatment result that meets a certain standard.

From the end of the eighties, surgeons and pathologists started to be interested in the lateral spread of rectal cancer.[6,7] Quirke and colleagues observed that the amount of excised tissue varied from surgeon to surgeon and found that circumferential resection margin (CRM) involvement was an important predictor for local recurrence (LR) and described a method to study CRM.[6,7] Also in the standardised TME trial, CRM was found to be an important predictor of outcome.[8] Consequently, CRM can be considered as a determinant of surgical quality. Another prognostic factor for outcome of rectal cancer is the number of examined lymph nodes (LN).[9–11] Although the pathologist also influences the number of reported LN,[12] the number of removed and examined LN could be considered as a measure of the extent of surgery. Recently, Quirke and colleagues found that CRM and the number of examined LN were related, and therefore number of examined LN can be regarded as a measurement of quality of surgery as well (P. Quirke, St James's University Hospital, Leeds).

The EORTC 22921 trial studied the addition of pre- and/or postoperative chemotherapy (CT) to preoperative radiotherapy (RT) followed by surgery in T3 or resectable T4 rectal cancer.[13] The present analyses aimed to determine risk factors associated with quality of surgery in EORTC 22921 trial, defined by CRM and the number of examined LN, and to correlate these parameters of surgical quality with LR, disease-free and overall survival (DFS and OS) in RT or chemoradiotherapy (CRT) treated patients.

2. Patients and methods

2.1. Trial design

The trial design and eligibility criteria are reported previously[13] and therefore only the main features are summarised. Patients were randomised between preoperative RT or CRT and to either postoperative CT or no further treatment (Fig. 1). Inclusion criteria were T3 or resectable T4 M0 adenocarcinoma of the rectum located within 15 cm from the anal verge, aged 80 years or less and a WHO performance status of 0 or 1. The study was approved by the ethics committees of the participating centres. Informed consent was obtained from all patients before their inclusion. The present analyses were restricted to eligible patients who underwent a resection and had no distant metastases at the time of surgery. Patients treated with a Hartmann procedure ($n = 22$) were excluded from some analyses due to small patient numbers.

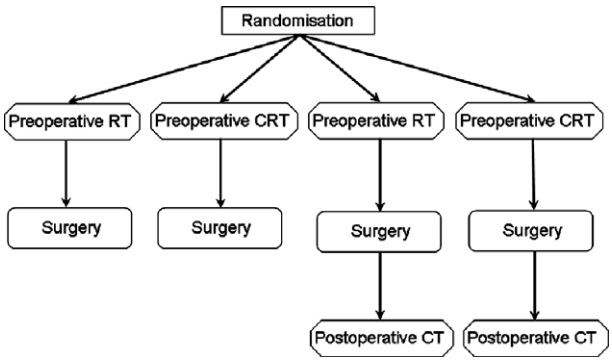

Fig. 1 – Treatment groups in the trial. RT = radiotherapy; CT = chemotherapy; CRT = chemoradiotherapy.

RT consisted of 45 Gy delivered in 25 fractions of 1.8 Gy to the posterior pelvis.[14] Variability of the treated volume and dose homogeneities have previously been studied and reported.[15] Preoperative CT (fluorouracil, 350 mg/m^2/d and leucovorin, 20 mg/m^2/d) was administered in two 5-day courses. Surgery was planned 3–10 weeks after the end of the preoperative treatment. It was recommended to maintain the surgical technique that was planned upfront (low anterior resection (LAR) or abdominoperineal resection (APR)), to perform a total mesorectal excision (TME; included in the recommendations in 1999), to create a protective colostomy in the case of a low-lying anastomosis and to primarily close the perineum after an APR. When allocated, four courses of postoperative CT had to be delivered starting between 3 and 10 weeks after surgery.

2.2. Pathology procedures

Macroscopic and microscopic characteristics of the resected specimen were prospectively recorded by the local pathologists on a standard case report form. Macroscopic examination was performed on the fixed specimen. The total number of LN examined and total number of LN involved were registered. Tumour staging was performed according to TNM classification 4 (UICC, 1987).[16] For pathological (p)T3-4 tumours (beyond the muscularis propria), the status of the CRM was determined according to the recommendations of Quirke and colleagues.[6] In this study, CRM was considered positive only if the tumour was microscopically abutting the resection margin.

2.3. Endpoints studied and variables considered

All recurrences were confirmed with radiological or histological examination. DFS is defined as the time from the day of surgery to the first event of loco-regional or distant recurrence or death of any cause, or to the date of the most recent follow-up for censored cases. Local control was calculated from the day of surgery to the day of LR, defined as tumour regrowth within the pelvis or perineum. OS is calculated from the day of surgery to the day of death of any cause or the day of most recent information if alive. The endpoints and variables studied are shown in Table 1. In the analysis for the number of examined LN as endpoint, this variable was analysed as a

Table 1 – Relationships that were assessed during the analyses

Endpoints	Variables									
	Randomised treatment	Sex	Age	Distance tumour to anal verge	Period of treatment	Type of surgery	CRM	Pathological T-stage	Pathological N-stage	Number of examined lymph nodes (categorical)
Type of surgery (LAR versus APR)	Yes	Yes	Yes	Yes	Yes	n.a.	No	No	No	No
CRM	Yes	Yes	Yes	Yes	Yes	Yes	n.a.	No	No	No
Number of examined lymph nodes (numerical)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	n.a.
Local recurrence	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Disease-free survival	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall survival	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

LAR = low anterior resection; APR = abdominoperineal resection; CRM = circumferential resection margin; n.a. = not applicable.

numerical variable, whereas in analyses where the number of examined LN was used as covariate, this variable was analysed as a categorical variable.

2.4. Statistics

Data were analysed with Statistical Analysis Software (SAS®, Cary, NC, USA). A multivariate backward selection model was used for all analyses whereby all variables were initially in the model and then the least significant variables were sequentially removed from the model until all remaining variables were significant at the 0.05 level. All models were adjusted for allocated treatment. Local control, DFS and OS were studied by Cox regression models. Logistic regression was used to study the probability of APR surgical procedure and CRM, whereas rank ANOVA was used to study the number of examined LN. The two-sided 0.05 significance level was used for all analyses.

3. Results

3.1. Patients

From April 1993 to March 2003, 1011 patients entered the trial, of whom 884 were included in the present analyses. The reasons for excluding patients were distant metastases at surgery ($n = 46$), unknown status of distant metastases ($n = 62$), no resection ($n = 11$) and ineligibility ($n = 8$). The characteristics of the 884 patients are shown in Table 2. The median follow-up at the time of analysis was 5.0 years (range 0.3–10.6 years). The 22 cases with a Hartmann resection were excluded from all further analyses.

3.2. Type of surgery

An APR was performed in 363 patients (41%), whereas 499 (56%) and 22 (2%) were treated with an LAR and a Hartmann procedure, respectively. To evaluate prognostic factors determining the type of surgery, preoperative treatment (RT or CRT), age, sex, distance between tumour and anal verge, and period of treatment were included in the initial step of the multivariate analysis. Preoperative treatment was kept in the model to adjust for trial design. All variables but age were retained in the final model (Table 3). Compared to LAR, APR was more frequently applied in males, in patients treated in the period 1993–1996 and in tumours located within 3 cm from the anal verge.

3.3. Circumferential resection margin (for pT3-4 tumours)

CRM involvement was studied pathologically only in pT3-4 tumours, whereas patients with a pT0-2 tumour were assumed to have a negative CRM. Information on the status of the resection margin was unknown for 115 patients (14%) who were treated with an LAR or APR. In total, 778 patients could be analysed, of whom 42 patients (5.4%) had a positive CRM; 6.5% for patients treated with preoperative RT and 4.9% for patients treated with preoperative CRT ($p = 0.35$). In the multivariate analysis, treatment after 1999 was associated with a

Table 2 – Patient characteristics

	Preoperative RT		Preoperative CRT		Preoperative RT and postoperative CT		Preoperative CRT and postoperative CT		Total	
	N = 221 (%)		n = 224 (%)		N = 221 (%)		N = 218 (%)		N = 884 (%)	
Sex										
Male	162	(73)	163	(73)	159	(72)	161	(74)	645	(73)
Female	59	(27)	61	(27)	62	(28)	57	(26)	239	(27)
Age										
Median	63.0		62.0		63.0		62.0		62.0	
Range	23.0–79.0		36.0–79.0		31.0–78.0		22.0–78.0		22.0–79.0	
pT-stage										
T0	15	(7)	32	(14)	10	(5)	28	(13)	85	(10)
T1	16	(7)	24	(11)	17	(8)	25	(12)	82	(9)
T2	69	(31)	80	(36)	66	(30)	71	(33)	286	(32)
T3	107	(48)	77	(34)	116	(53)	84	(39)	384	(43)
T4	13	(6)	7	(3)	9	(4)	6	(3)	35	(4)
Tx	1	(1)	4	(2)	3	(1)	4	(2)	12	(1)
pN-stage										
N0	144	(65)	157	(70)	143	(65)	165	(76)	609	(69)
N+	73	(33)	61	(27)	74	(34)	46	(21)	254	(29)
Nx	4	(2)	6	(3)	4	(2)	7	(3)	21	(2)
Distance tumour to anal verge										
⩽3 cm	51	(23)	58	(26)	52	(24)	55	(25)	216	(24)
3–6 cm	88	(40)	79	(35)	79	(36)	83	(38)	329	(37)
6–9 cm	46	(21)	48	(21)	57	(26)	46	(21)	197	(22)
>9 cm	36	(16)	39	(17)	33	(15)	34	(16)	142	(16)
Surgical procedure										
APR	93	(42)	94	(42)	92	(42)	84	(39)	363	(41)
LAR	122	(55)	125	(56)	122	(55)	130	(60)	499	(56)
Hartmann	6	(3)	5	(2)	7	(3)	4	(2)	22	(2)

Percentages may not sum to 100 because of rounding. T-stage and N-stage are pathological stages. RT = radiotherapy; CT = chemotherapy; CRT = chemoradiotherapy; APR = abdominoperineal resection; LAR = low anterior resection.

Table 3 – Final model of multivariate logistic regression analysis for the probability of an abdominoperineal resection (APR) compared to a low anterior resection (LAR)

Variable	OR	95% CI	*p*-Value
Preoperative treatment			0.28
RT*	1.00		
CRT	0.83	0.60–1.16	
Sex			0.03
Male*	1.00		
Female	0.67	0.46–0.98	
Period of treatment			0.008
1993–1995*	1.00		
1996–1999	0.51	0.33–0.79	0.003
2000–2003	0.54	0.33–0.86	0.010
Distance			<0.001
⩽3 cm*	1.00		
3–6 cm	0.21	0.14–0.32	<0.001
6–9 cm	0.05	0.03–0.08	<0.001
>9 cm	0.01	0.01–0.03	<0.001

* Reference groups, RT = radiotherapy; CRT = chemoradiotherapy; OR = odds ratio; CI = confidence interval, OR < 1 indicates an increased likelihood of LAR and decreased likelihood of an APR.

significantly lower risk of margin involvement (Table 4). In Fig. 2, the relation between CRM and period of treatment is shown ($p = 0.01$ in univariate analysis, χ^2 for trends).

3.4. *Number of examined lymph nodes*

The LN status was known for 831 patients treated with an LAR or APR. The median number of examined LN was 8 (range 0–45). The results of the multivariate analysis are displayed in Table 5. Younger age, treatment after 1995, proximal tumour location and advanced tumour stage (pT3-4) were independently associated with a larger number of examined LN.

3.5. *Prognostic factors for outcome*

Most LR were found in the group treated with preoperative RT alone[13] and were located in the presacral area (42%). LR occurred in 99 (12%) of the 862 patients with a LAR or APR. The local recurrence rate per period is shown in Fig. 2 ($p = 0.14$). The results of the multivariate analysis are presented in Table 6: younger age, APR surgery, advanced pT-stage and positive CRM were independent predictors of an increased risk of LR. Of the 862 patients treated with an LAR or an APR, 346 (40%) had a local or distant recurrence

Table 4 – Final model of multivariate logistic regression analysis for the probability of a positive CRM in patients with LAR or APR

Variable	OR	95% CI	*p*-Value
Preoperative treatment			0.33
RT*	1.00		
CRT	0.73	0.39–1.37	
Period of treatment			0.04
1993–1995*	1.00		
1996–1999	0.81	0.40–1.71	0.56
2000–2003	0.29	0.10–0.75	0.01

* Reference group, RT = radiotherapy; CRT = chemoradiotherapy; OR=odds ratio; CI=confidence interval, OR < 1 indicates a decreased risk of positive circumferential resection margin compared to the reference level.

or died during follow-up. The results of the multivariate analysis stratified for treatment are presented in Table 6 and show that an APR procedure, advanced pT-stage, positive LN status and positive CRM are independent prognostic factors for a shorter DFS. During follow-up, 247 patients treated with an APR or an LAR died (29%). The final multivariate model for OS is presented in Table 6. The same variables as for DFS were independent prognostic factors for OS.

4. Discussion

In this analysis, we investigated risk factors associated with quality of surgery in EORTC 22921 trial, which assessed the efficacy of adding pre- and/or postoperative CT to a conventional schedule of preoperative RT for T3 and resectable T4 rectal cancer. In the present analyses, it was found that the period of treatment was associated with CRM and the number of examined LN. Besides, preoperative treatment was not found to be associated with CRM involvement.

The results indicate that the quality of the surgical resections improved during the trial. In the second half of the eighties, both surgeons and pathologists became interested in the lateral spread of rectal cancer and consequently CRM.[6,7] In addition, results from the TME trial demonstrate that RT is even beneficial for tumours located >1 cm from the CRM, indicating that lateral tumour spread is present in these tumors.[17] In the mid- 1990s, after the start of EORTC 22921 trial, it became evident that excision of the total mesorectum should be considered as the gold standard.[18] In EORTC 22921 trial, CRM involvement decreased in the period 2000–2003 compared to the period 1993–1999, which correlates with the addition of the recommendation to perform a TME procedure in the protocol in 1999. A limitation of the present analyses was that CRM status was determined only for pT3-4 tumours; all tumours that were downstaged to pT0-2 were considered to have a negative margin. Although patients with T0-2 tumours in general will have a negative CRM, a few patients might have had a positive CRM similar to findings in the Dutch trial (18% overall margin involvement; 2% margin involvement for T1-2 tumours).[8] Another parameter of surgical quality also improved: over time more LN were examined. However, in the period 2000–2003, 8.4 LN were on average examined, whereas in the 5th TNM-classification (UICC, 1999), it was recommended to remove at least 12 LN.[19] Part of this difference could be explained by the use of preoperative (chemo)radiotherapy, which might have resulted in a reduced number of examined LN.[20] In daily clinical practice, patients in whom no sufficient lymph nodes are removed are often considered as high risk stage II patients and consequently treated with postoperative chemotherapy. However, by examining an adequate number of LN, a number of these patients could be considered as low risk patients, without the need to be treated with chemotherapy.

Surgical quality has been shown to be an important predictor of outcome in TME operated patients.[21,22] For patients in the TME trial, an incomplete mesorectum at pathological

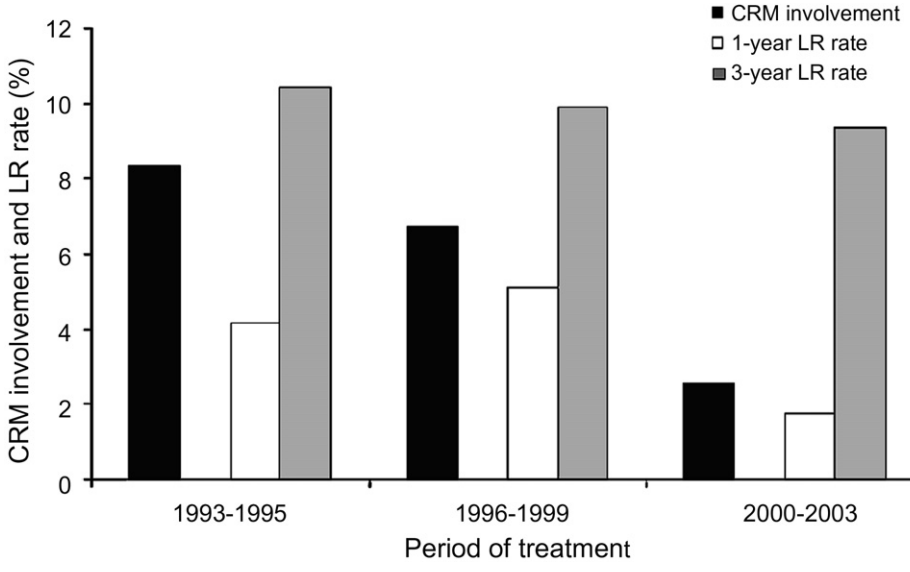

Fig. 2 – CRM involvement, 1-year and 3-year local recurrence (LR) rate shown per period of treatment. *P*-value for CRM involvement is 0.01 (χ^2-test), for LR 0.79 (log-rank test).

Table 5 – Final model of multivariate rank ANOVA analysis for the number of examined lymph nodes (LN)

Variable	Difference in number of examined LN	95% CI	*p*-Value
Preoperative treatment			0.41
RT*	0.00		
CRT	−0.38	−1.28 to 0.51	
Age			0.04
⩽50 years*	0.00		
51–60 years	−0.87	−2.29 to 0.55	
61–70 years	−1.77	−3.11 to −0.43	
>70 years	−1.73	−3.31 to −0.14	
Period of treatment			<0.001
1993–1995*	0.00		
1996–1999	2.65	1.47 to 3.83	
2000–2003	3.58	2.31 to 4.85	
Distance			0.02
⩽3 cm*	0.00		
3–6 cm	0.87	−0.39 to 2.13	
6–9 cm	1.18	0.06 to 2.30	
>9 cm	0.99	0.98 to 4.87	
Pathological T-stage			<0.001
T0–T2*	0.00		
T3–T4	1.90	0.99 to 2.80	

* RT = radiotherapy; CRT = chemoradiotherapy; CI = confidence interval. The average number of examined LN for a reference patient aged ⩽50 years, treated with preoperative RT, year of entry before 1996 and a pT1-2 tumour located within 3 cm from the anal verge was 4.86.

examination was associated with an increased risk of local and distant recurrence.[21] These results were confirmed in the MRC CR07 trial: an incomplete mesorectum was associated with more CRM involvement and subsequently with decreased local control.[22] However, in the present trial, recommendations to perform a TME were included in the protocol halfway through the trial in 1999. Consequently, in many patients, no TME surgery was performed. Compared to before 2000, CRM involvement decreased in the period 2000–2003. Patients in this trial were treated with preoperative 45 Gy RT with or without pre- and/or postoperative CT. Several studies have investigated CRM involvement after CRT,[23–25] whereas only few studies report on the association between CRM involvement and outcome after preoperative CRT.[23] As far as we know, the association between CRM and outcome for curatively treated patients in whom postoperative chemotherapy has been administered in addition to preoperative RT or CRT, has not been reported before. Our analyses for LR, DFS and OS, which were stratified for the four treatment arms, indicated that CRM involvement was still an independent predictor of outcome, even though patients were treated with RT and/or pre- or postoperative CT. Moreover, the highest hazard ratio for OS was found for CRM, indicating that CRM was the most important prognostic factor for survival.

The type of surgical resection was found to be a prospective factor for LR, DFS and OS. Factors which increased the likelihood to undergo an APR were male sex, inclusion in the trial in the period 1993–1995 and tumour location within 3 cm from the anal verge. In the nineties, it was shown that a tumour free distal margin of 5 cm was unnecessary, and that a clear margin of at least 1 cm was sufficient in TME operated patients.[26] Consequently, less patients were treated with an APR and more with an LAR since the introduction of TME surgery.[27] In addition, an APR was associated with a higher risk of CRM involvement and reduced local control and DFS.[28,29] Therefore, it is often advised to treat patients preoperatively with CRT before an APR. Significant more downstaging and downsizing was observed after CRT compared with RT.[14] Despite this downstaging, no significant difference for CRM status could be found when comparing CRT with RT in the present multivariate analysis. Apparently, increased downstaging and downsizing after

Table 6 – Final multivariate Cox models for local recurrence (LR), disease-free survival (DFS) and overall survival (OS), stratified for the four treatment arms

Variable	LR			DFS			OS		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age			0.02			–			–
⩽50 years* versus 51–60 years versus 61–70 years versus >70 years (linear trend)	0.75	0.60–0.95							
Surgical procedure			0.007			0.008			0.001
APR* versus LAR	0.54	0.34–0.85		0.72	0.57–0.92		0.60	0.45–0.81	
pT-stage			<0.001			<0.001			0.002
T0–T2* versus T3/T4	3.08	1.84–5.16		1.90	1.46–2.46		1.64	1.20–2.25	
pN-stage			–			<0.001			0.02
N0* versus N+				1.71	1.31–2.23		1.48	1.07–2.04	
CRM			<0.001			0.02			<0.001
Negative* versus positive	3.81	2.12–6.86		1.67	1.09–2.57		2.40	1.50–3.84	

CI = confidence interval; APR = abdominoperineal resection; LAR = low anterior resection; CRM = circumferential resection margin. A hazard ratio (HR) < 1 indicates a decreased and an HR >1 indicates an increased risk of an event compared to the reference category (*).

CRT did not result in more radical resections. To reduce CRM involvement, the surgical procedure should change, especially for APR. For this procedure, it could be an option to perform a so-called cylindrical resection by widening the resection near the sphincter, an area were the resection is often incomplete.[29]

In the early 1990s, endo-rectal ultrasound was commonly used for rectal cancer. Consequently, endo-rectal ultrasound was advised in the EORTC trial protocol. In the same time period, the importance of a negative CRM became clear. However, it is found that CRM involvement cannot be appropriately assessed with ultrasound.[30] Nowadays, it is possible to predict CRM involvement preoperatively with a MRI-scan.[30] In patients who are found to have an involved or threatened CRM on a MRI scan, treatment could be adapted. CRT, for example, could be administered to downstage and downsize the tumour and subsequently the resection should be widened to obtain a negative CRM. In that way, individualisation of treatment with preoperative imaging could improve surgical resection quality.

In conclusion, important surgical parameters improved over time: less APR procedures were performed, the rate of CRM involvement decreased and the number of examined LN increased. However, an APR procedure was still a risk factor for an adverse outcome, even though all patients were preoperatively treated with 45 Gy RT (or CRT) followed by delayed surgery after 6 weeks. Although downstaging might be helpful in the treatment of these advanced tumours, the ultimate aim of the treatment should still be to perform a radical operation.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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