Adjuvant chemotherapy may improve disease-free survival in patients with mrEMVI-positive rectal cancer following chemoradiation

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Abstract

Aim: MRI-detected extramural venous invasion (mrEMVI) is a poor prognostic factor in rectal cancer. Pre-operative chemoradiotherapy (CRT) can cause regression in the severity of EMVI and subsequently improve survival whereas mrEMVI persisting after CRT confers an increased risk of recurrence. The effect of adjuvant chemotherapy (AC) following CRT on survival in rectal cancer remains unclear. The aim of this study was to determine whether there is a survival advantage for AC given to patients with mrEMVI persisting after CRT.

Method: A prospective analysis was conducted of consecutive patients with locally-advanced rectal cancer between 2006-2013. All patients underwent CRT followed by surgery. AC was given to selected patients based on the presence of specific 'high-risk' features. Comparison was made between patients offered AC with observation alone. The primary outcome was three -year disease-free survival (DFS).

Results: 227 (36.0%) of 631 patients demonstrated persistent mrEMVI following CRT. Patients were grouped on the basis of AC or observation and were matched for age, performance status and final histopathological staging. Three-year DFS in

the AC group was 74.6% compared with 53.7% in the observation only group. AC had a survival benefit on multivariate analysis (HR 0.458; 95%CI 0.271-0.775 p=0.004).

Conclusion: Patients with persistent mrEMVI following CRT who receive AC may have a decreased risk of recurrence and an improved three-year DFS compared with patients not receiving AC, irrespective of age and performance status.

What does this paper add to the literature?

The paper provides further evidence that MRI-detected EMVI in rectal cancer after preoperative chemoradiotherapy is associated with a poor prognosis. It should be an indication for adjuvant chemotherapy despite the current lack of consensus.

Introduction

MRI-detected extramural venous invasion (mrEMVI) is a poor prognostic factor in rectal cancer associated with poor survival (1, 2). Persistent mrEMVI following pre-operative chemoradiotherapy (CRT) is associated with an increased risk of recurrence (3-5) (Figure 1). Conversely, when there is MRI evidence of fibrosis in the extramural veins and regression of venous disease, survival is improved (6) suggesting that patients with persistent mrEMVI are a 'high-risk' group for treatment failujre. Stage II tumours with EMVI have been shown to have a similar survival as stage III tumours following CRT (7).

The role and timing of adjuvant chemotherapy in rectal cancer is contentious and the evidence-base is lacking compared with colon cancer (8). The QUASAR trial (9) still provides the only robust evidence for adjuvant chemotherapy in rectal cancer.

Furthermore, the effect of adjuvant chemotherapy for patients who have already undergone CRT is even less clear.

Adjuvant chemotherapy is the main oncological treatment to improve long-term survival although its optimal timing and patient selection are still not clear. The aim of the present study was to determine whether there is a survival advantage from adjuvant chemotherapy in patients with persistent mrEMVI following CRT.

Method

Patients

The study was carried out following internal review of the study proposal by the Department of Clinical Research and Development at The Royal Marsden Hospital.

Patients were identified from a prospectively maintained database. Data were extracted on consecutive patients undergoing curative treatment for locally advanced rectal cancer between January 2006 and January 2013. Treatment included long-course neoadjuvant chemoradiotherapy followed by surgery. Adjuvant chemotherapy was offered to selected patients an informed discussion based on the presence or absence of specific adverse or 'high-risk' features including nodal disease, increasing tumour penetration into the mesorectum, threat of involvement of the circumferential resection margin. Patients with synchronous tumours, undergoing local excision and those treated by palliative surgery were excluded. There was a central review of all pathology and radiology by specialised gastrointestinal pathologists and radiologists.

Staging and neoadjuvant therapy

All patients were staged by clinical rectal examination, colonoscopy, high-resolution magnetic resonance imaging (MRI) of the rectum and computed tomography (CT) of the thorax, abdomen and pelvis. All treatment decisions were made during a multidisciplinary team meeting. Our policy has been to offer long-course pre-operative chemoradiotherapy (54Gy in 2 Gy fractions with concominant 5-fluorouracil based chemotherapy) to patients with any of the following features: tumour within 1 millimetre (mm) of the mesorectal fascia or bordering the intersphincteric plane (potential circumferential resection margin involvement), MRI-detected EMVI, extramural tumour spread of more than 5mm, and N2 nodal disease (metastasis in four or more regional lymph nodes). Patients were fully restaged with MRI following completion of preoperative chemoradiotherapy. Restaging MRI was used to determine the presence of persisting EMVI and formed the basis of the patient group for the study.

Adjuvant chemotherapy regime

The decision to advise chemotherapy following surgery was made during the multidisciplinary meeting. Not all patients were offered the same regime which was determined following informed discussion. No regime lasted longer than six months unless there was progression of disease with a view towards palliation. The regimes can be divided into i) Capecitabine; ii) Capecitabine and Oxaliplatin; iii) 5-FU based; iv) Folinic acid, 5-FU and Oxaliplatin; v) Other. All adjuvant treatment was started within six weeks of surgery.

Outcome

The primary outcome was 3-year disease-free survival from the date of surgery. The main secondary outcome was recurrence which was defined by radiological or histological evidence of disease and confirmed on multidisciplinary discussion.

Definitions

Performance status was defined according to the Eastern Cooperative Oncology Group (ECOG) classification. Evidence of mrEMVI was confirmed on T2-weighted images and seen as a serpiginous or tortuous linear structure. Assessment of mrEMVI included the following: pattern of tumour margin (extension into small veins may produce a nodular border), location of tumour relative to major vessels, vessel calibre (tumour causes vessel expansion and increase in tumour signal in the lumen) and vessel border. Smaller venules can be seen perforating the outer rectal wall and produce a low to intermediate signal intensity in tubular structures on T2-weighted images. Venous invasion into these can be seen recognised by their enlargement and irregularity adjacent to the tumour due to contiguous tumour extension.

A positive resection margin was defined as tumour within 1mm of the circumferential resection margin in the surgical specimen. Staging was performed according the 5th Edition of the Tumour, Node, Metastasis (TNM) system from the American Joint Committee on Cancer and was based on the final pathological findings. Stage II disease is classified as T1-4, N0, M0 and stage III as T1-4, N1-2, M0. Disease free survival (DFS) was the time from the date of surgery to the date of pelvic recurrence and/or distant disease or death due to pelvic recurrence and/or distant disease.

Statistical analysis

Differences between groups were assessed using Pearson's chi-squared test or Fisher's Exact test as appropriate. Survival estimates of the disease free survival (DFS) were obtained using the Kaplan-Meier product limit method. Patients were censored at the last point of known contact or if they died during follow-up without experiencing the outcome of interest.

Cox's proportional hazard models were built to test the impact of confounding variables on survival such as age, gender, performance status, pathological T-stage and N stage and CRM involvement. These models allowed the effect of predictive factors on outcome to be assessed, accounting for censored outcome, differing time of follow-up and the interval between surgery and the adverse event of interest. Hazard ratios (HR) and 95% confidence intervals (CI) were generated. In order to provide clinically and meaningful risk adjustment, a fully adjusted model was used. All predictive risk factors that were judged to be clinically relevant were entered into a fixed model to adjust the impact of adjuvant chemotherapy on survival. Data were analysed using SPSS 21 (SPSS Inc, Chicago, Illinois) and Excel 2013.

Results

Demographics and treatment

Of 631 patients, 227 (36.0%) had evidence of persistent mrEMVI following CRT. The median age was 63.5 (IQR: 54.8- 72) years. 158 patients had undergone adjuvant chemotherapy with 69 being observed following surgery. Demographic and tumour characteristics are shown in Table 1.

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Histopathological staging

Most patients had advanced disease, T stages 3 and 4. Involvement of the regional lymph nodes was less common being present in less than third of patients showing histopathological evidence of malignant nodes following CRT. Only 14 (6.2%) patients had a positive CRM after surgery.

Comparison of adjuvant chemotherapy and observation (non-chemotherapy) groups

Patients were grouped according to whether or not they had received adjuvant chemotherapy. Their demographic and tumour characteristics are shown in Table 3. Both groups were matched for age, performance status and final histopathological staging including T- and N-stage, and CRM status. Most (206 [90.7%]) patients in each group were of performance status 0 or 1 with a locally advanced T-stage. Table 4 shows the different chemotherapy regimes offered to patients.

Survival analysis

At a median follow-up of 26 (2-84) months there were 68 recurrences of which 12 (17.6%) were local. These included 10 local and 34 distant recurrences in the AC group and 2 local and 22 distant in the observation group . The three year DFS for patients who received adjuvant chemotherapy was 74.6% and observation only 53.7% (Figure 2). There was a significant difference in disease-free survival using the Mantel Cox Log Rank Test – p=0.02. On multivariate analysis, CRM involvement was a significant factor for a reduced three year DFS (HR 3.891; 95%CI 1.642-9.174).

For the purposes of analysis, patients who received adjuvant chemotherapy were used as reference to test the significance of chemotherapy on recurrence. Adjuvant chemotherapy had a survival benefit on multivariate analysis (HR 0.458; 95%CI 0.271-0.775) (Table 3).

Discussion

The main finding of the present study was that patients with persistent mrEMVI who receive adjuvant chemotherapy following neoadjuvant chemoradiation had a reduced risk of developing disease recurrence. This was independent of age, performance status and nodal disease. The patients also had a significantly improved disease-free survival at three years compared with those undergoing clinical follow-up alone (74.6% versus 53.7%). Although most patients had adjuvant chemotherapy, approximately 30% did not, implying that there was a significant number of patients who may have benefited from additional treatment but were currently being denied optimal treatment. It is notable that nodal disease was not an independent factor for recurrence in matched patients who had previously undergone neo-adjuvant treatment and oncologically successful surgery. CRM status was also shown to be a significant factor for disease relapse.

There is a lack of consensus on the use of adjuvant chemotherapy following neo-adjuvant chemoradiation (8, 10). The current European and North American guidelines recommend that all patients with stage III and 'high-risk' stage II rectal cancers are offered adjuvant chemotherapy although this is not based on robust evidence. The survival benefit of further treatment with up to six months of 5-FU-based chemotherapy in patients who may have already had a significant response from pre-operative treatment is unknown and further confuses the issue. The

literature shows that patients who have had a minimal response to neoadjuvant treatment have no survival benefit following adjuvant chemotherapy (11-13). The PROCTOR/SCRIPT trial is a Dutch-Swedish collaborative phase III study of patients with stage II or III rectal cancer who have undergone pre-operative CRT and surgery. Comparison was made between those patients having adjuvant chemotherapy and those under observation only. A total of 437 patients were eligible for analysis with a median follow-up of five years. There was no difference in DFS, overall survival (OS) or recurrence (14). Bosset et al have recently published the long-term results from the well-known EORTC Trial 22921. In this, patients with T3 or T4 disease were assigned to chemotherapy or observation following pre-operative radiotherapy with or without sensitising chemotherapy. Again, there was no difference in DFS or OS at a median follow-up of 10.4 years. A recent meta-analysis also showed no survival benefit in patients with stage II and III disease following CRT (15) which would suggest that the results of the present study are at odds with the literature. The present study is, however, not directly comparable and highlights the difficulty in conducting trials involving adjuvant chemotherapy.

This study investigated a specific high-risk factor rather than analysing the outcome of all patients who had undergone pre-operative treatment. The DFS of the observation group was much lower than in those studies which have looked at more general endpoints but this simply may demonstrate the high likelihood of recurrent or metastatic disease in patients with persistent EMVI. Previous studies have shown the increased risk of recurrence with EMVI (4, 7, 16) so it is not surprising that patients with persistent mrEMVI under observation only have a significant risk of developing metastases.

Risk stratification has evolved in recent years with increasing use of MRI in this area. There are, however, only limited reports of using MRI to specifically determine prognosis (16, 17). This is an area which requires further study and robust randomised trial evidence to determine which patients will most benefit from adjuvant chemotherapy as increasing numbers are undergoing 'successful' pre-operative treatment. A 'blanket' approach whereby all patients are routinely given adjuvant therapy may lead to substantial over-treatment with perhaps no survival benefit. The use of MRI in selecting high-risk patients may further improve future trial design allowing for treatment decisions to be made in conjunction with the pathology.

This uncertainty has led to differences in practise with regard to the recommendation for adjuvant chemotherapy (18). Khrizman et al have explored the reasons behind the variability in adjuvant chemotherapy and whether this is related to patient or tumour characteristics (19). They found that age, co-morbidity, performance status, operative complications and a complete pathologic response were significant factors for not receiving adjuvant chemotherapy. Age is most commonly cited as a reason for not recommending adjuvant treatment (20-22) but there is good evidence for comparable results for elderly patients who are given such treatment in both colonic and rectal cancer (23, 24). With an increasingly elderly population and a drive towards improving the outcome for this group of patients, there is very likely in the future to be a rise in the number of elderly patients being offered adjuvant treatment. Another interesting point is that comorbidity or performance status are often used as reasons why eligible patients did not receive adjuvant chemotherapy (25).

The design of the present study and the subsequent analysis attempted to address some of these points which have previously explained the variability in practise with regard to adjuvant chemotherapy. mrEMVI is a 'high-risk' factor and patients should

be offered adjuvant treatment to reduce the risk of recurrence. While there are many reasons for patients to be offered or declined chemotherapy, those in the present study were matched for age, performance status and final staging which means the results of the multivariate analysis show a true independence for recurrence. All patients were of similar staging and received the same treatment apart from subtle variations in the specific adjuvant chemotherapy regime.

mrEMVI is being increasingly recognised as a prognostic factor in rectal cancer(4, 7, 26). It has been shown to be affected by neoadjuvant treatment and in those patients having a significant response there is an associated improvement in survival. MRI is thus being increasingly used as an imaging biomarker in rectal cancer, as demonstrated in initial small-scale study (6). There has been recent concern of the reliability of routine pathological analysis to detect EMVI accurately particularly after CRT when much of the architectural features which form the basis of its identification are lost by the fibrosing effect of CRT (27). Using the MRI characteristics to guide and inform adjuvant treatment decision-making is becoming more prevalent and is already universally done with regard to neoadjuvant treatment. Extending this to adjuvant treatment seems a natural progression particularly if there is difficulty in interpreting the routine pathological analysis following CRT and there is the potential for patients who may benefit from further treatment to miss this opportunity.

Limitations of the study include a lack of information regarding the decision-making process for chemotherapy following surgery. Knowledge of whether treatment was not recommended or whether it was not offered would have given further understanding of any variability in practise. There was was no information on the severity or extent of any surgical complications. These are known to be a factor in delaying or withholding adjuvant treatment and may have played a role in the

present study. Understandably, if a patient has endured difficult complex treatment, he or she is less likely to consider further therapy particularly if there is a risk of morbidity. Furthermore, to quantify the effect of adjuvant chemotherapy most accurately the ideal study design would be a randomized prospective study with a larger number of patients. The present retrospective study will inherently contain some degree of selection bias on which patients were offered chemotherapy although the matching of the two group goes some way to diminish for this. A further limitation is the primary outcome measure of using DFS which does not account for death from other causes. This confounding factor has the potential to bias the results although in these numbers this is unlikely and 3-year DFS is widely considered a good measure of survival.

The present study has provided further evidence that there may be certain patients who will benefit from adjuvant treatment. It is also the first study to use MRI to select patients deemed to be at 'high-risk' meaning that decisions to intensify treatment can be tailored before surgery when compliance may be improved, although the numbers are too small to make definitive recommendations on chemotherapy in such patients.

Acknowledgement

Figure 1 – MRI sections showing extramural venous invasion (EMVI) following treatment with chemoradiation. The red arrows show the precise location of the extramural veins containing tumour signal.
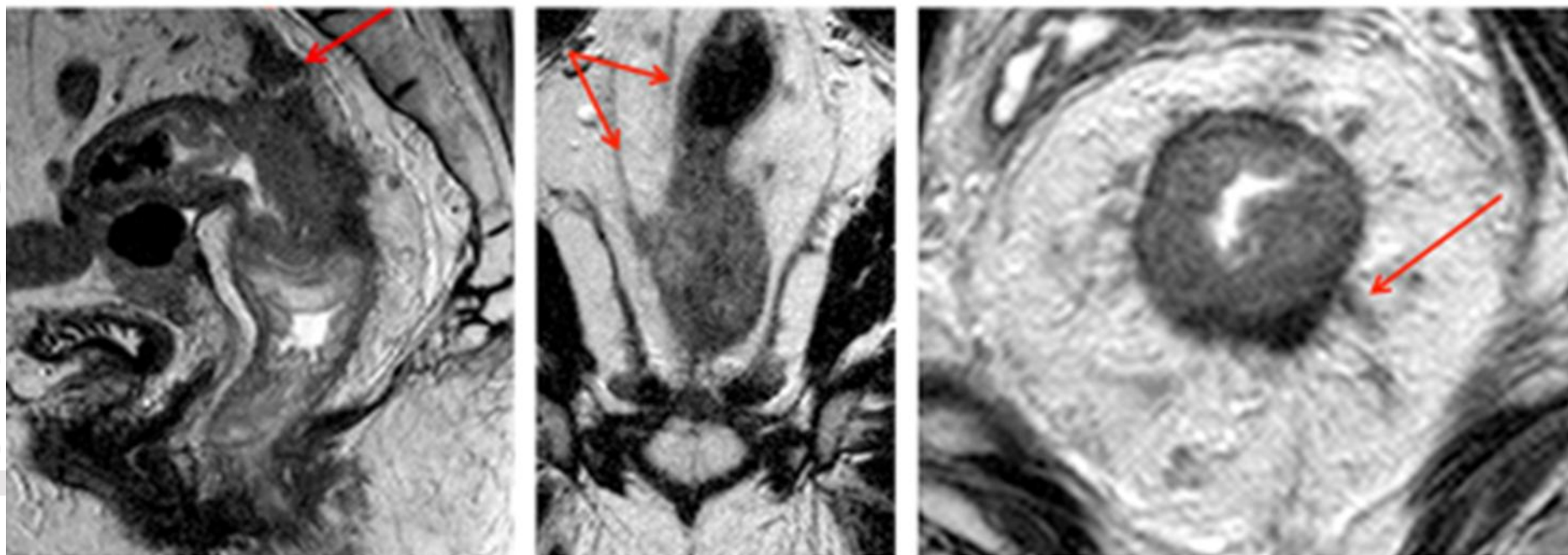
Table 1 - Cohort characteristics in patients receiving and not receiving adjuvant chemotherapy

		Adjuvant chemotherapy N (%)	Observation n (%)	Total	P-value
Age	<70	98 (62)	48 (70)	146	
	>70	60 (38)	21 (30)	81	0.30
Performance status	0-1	144 (91)	62 (90)	206	
	2-3	14 (9)	7 (10)	21	0.14
Gender	Female	45 (28)	28 (41)	73	
	Male	113 (72)	41 (59)	154	0.09
Pathological T-stage	pT0-2	32 (20)	19 (28)	51	
	pT3-4	126 (80)	50 (72)	176	0.34
Nodal status	Negative	110 (70)	48 (70)	158	
	Positive	48 (30)	21 (30)	69	0.95

Table 2 – Drugs used in Adjuvant chemotherapy

No of patients	Capecitabine	Capecitabine and Oxaloplatin	5-FU only	FOLFOX	Other
Total (n=144)	47	34	6	45	12

Figure 2 – Kaplin Meier Curves showing Disease-Free Survival in patients receiving (green) and not receiving (blue) chemotherapy
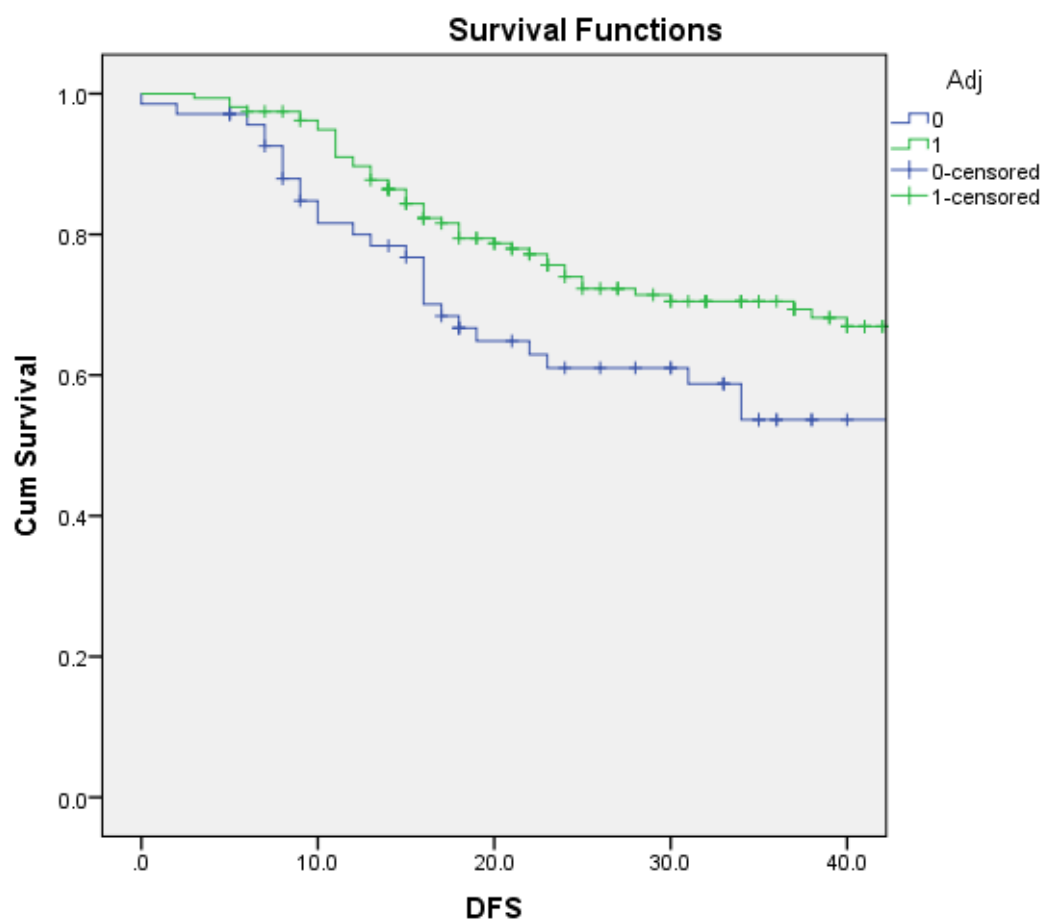
Table 3 Fully adjusted multivariable Cox's proportional hazard model for 3 year disease free survival (DFS)

		HR	95% CI lower	95% CI upper	p value
Gender	Female	Ref			
	Male	1.125	0.668	1.895	0.657
Pathological T-stage	T0	Ref			
	T1	1.633	.234	5.048	.914
	T2	.822	.217	18.302	.543
	T3	2.571	.210	3.508	.831
	T4	1.270	.940	6.951	.066
Pathological N-stage	Negative	Ref			
	Positive	1.372	0.799	2.353	.252
CRM	Negative	Ref			
	Positive	3.891	1.642	9.174	0.02
Performance status	0	Ref			
	1	1.837	.518	.146	.309
	2	1.376	.393	.112	.144
	3	2.085	.488	.114	.333
Adjuvant chemotherapy	No	Ref			
	Yes	0.458	0.271	0.775	.004
pEMVI	Negative	Ref			
	Positive	2.041	1.168	3.559	.012
Age	Below 70	Ref			
	Above 70	0.997	0.975	1.019	.765

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