BJR

Received: 16 October 2016 | Revised: 9 January 2017 | Accepted: 19 January 2017

https://doi.org/10.1259/bjr.20160807

Cite this article as:
Kim Y-J, Kim K, Min SK, Nam EM. Role of adjuvant radiotherapy for localized extrahepatic bile duct cancer. *Br J Radiol* 2017; **90**: 20160807.

FULL PAPER

Role of adjuvant radiotherapy for localized extrahepatic bile duct cancer

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Objective: To evaluate the benefit of adjuvant radiotherapy (RT) after surgical resection for extrahepatic bile duct (EHBD) cancer.
Methods: From 1997 to 2015, 59 patients with EHBD cancer were the subject of this study; 36 patients not undergoing adjuvant treatment after surgery (observation group) and 23 patients receiving adjuvant RT (RT group) were compared. Microscopic residual disease (R1) was in 9 (25%) patients and 5 (22%) patients, and macroscopic residual disease (R2) was in 2 (6%) patients and 6 (26%) patients in the observation and RT groups, respectively. Adjuvant RT was delivered to the tumour bed and regional lymph nodes up to 50.4 Gy (range, 45–61 Gy).
Results: With a median follow-up of 19 months, local recurrence was observed in 10 (28%) patients and 2 (9%) patients in the observation and RT groups, respectively. On univariate analysis, the 5-year local recurrence-free survival (LRFS) rates were 50% in the observation group and 54% in the RT group ($p = 0.401$). The 5-year overall survival (OS) rates were 29.3% in the observation group and 26.3% in the RT group ($p = 0.602$). On multivariable analysis, however, adjuvant RT significantly improved LRFS [hazard ratio (HR), 0.310; 95% confidence interval (CI), 0.100–0.963; $p = 0.043$] and had a trend towards increased OS (HR, 0.491; 95% CI, 0.219–1.102; $p = 0.085$). Resection margin (RM) status was also correlated with LRFS (HR for R1 6.134, 95% CI 2.051–18.344; and HR for R2 18.551, 95% CI 3.680–93.520; $p < 0.001$) and OS (HR for R1 1.816, 95% CI 0.853–3.867; and HR for R2 3.564, 95% CI 1.175–10.809; $p = 0.054$).
Conclusion: RM status was a significant prognosticator of EHBD cancer, and adjuvant RT improved local control rate; thereby, survival rate might be increased.
Advances in knowledge: The benefit of adjuvant RT in EHBD cancer was demonstrated *via* comparison with observation group.

INTRODUCTION

Extrahepatic bile duct (EHBD) cancer is a rare malignancy. However, the biliary tract cancer including gallbladder is the ninth common malignancy in Korea.[1] Prognosis of EHBD cancer is generally poor; the median overall survival (OS) is about 20 months.[2] Surgery provides the only chance for cure with varying resectability rates of 25–91% depending on tumour location.[3–6] However, obtaining a negative resection margin (RM) is a challenge,[7,8] and microscopic (R1) and macroscopic (R2) residual diseases are observed in 20–40% and 4–64%, respectively.[9–15]

Many studies have revealed that positive RM of EHBD cancer is directly associated with high local recurrence (LR) rate.[9,11,15,16] As a result, LR is a major pattern of failure in EHBD cancer.[17] In spite of the high LR rate, the utility of adjuvant radiotherapy (RT) for EHBD cancer has been sparse.[2] Administration of adjuvant RT may increase local control rate, and improved local control might result in survival benefit.[10,18,19] Because of the rarity of the disease, however, no prospective randomized controlled trials comparing adjuvant RT with observation have been performed, and retrospective studies have yielded conflicting results with insufficient evidences supporting the survival benefit of adjuvant RT.[18,20–22]

In this study, we retrospectively analyzed the effect of adjuvant RT on local relapse-free survival and OS for patients with EHBD cancer treated with surgical resection with or without adjuvant RT.

METHODS AND MATERIALS

Study population

This study was approved by the institutional review board (EUMC 2016-05-012). From 1997 to 2015, 59 patients

Table 1. Patient and tumour characteristics

Variables	Number of patients (%)		*p*-value
	Observation ($n = 36$)	RT ($n = 23$)	
Age (years)			
<65	12 (33.3)	16 (69.6)	0.008
≥65	24 (66.7)	7 (30.4)	
Sex			
Male	21 (58.3)	11 (47.8)	0.593
Female	15 (41.7)	12 (52.2)	
Performance status (ECOG)			
0–1	29 (80.6)	21 (91.3)	0.460
2–3	7 (19.4)	2 (8.7)	
Surgery			
Bile duct resection with hepatectomy	6 (16.7)	7 (30.4)	0.136
Bile duct resection	5 (13.9)	6 (26.1)	
Pancreaticoduodenectomy	25 (69.4)	10 (43.5)	
RM			
R0	25 (69.4)	12 (52.2)	0.107
R1	9 (25.0)	5 (21.7)	
R2	2 (5.6)	6 (26.1)	
Tumour location			
Non-hilar	30 (83.3)	12 (52.2)	0.017
Hilar	6 (16.7)	11 (47.8)	
Differentiation			
Well	3 (8.3)	3 (13.0)	0.324
Moderate	22 (61.1)	16 (69.6)	
Poor	11 (30.6)	3 (13.0)	
Unknown	0 (0.0)	1 (4.3)	
T stage			
T1–2	19 (52.8)	14 (60.9)	0.599
T3–4	17 (47.2)	9 (39.1)	
N stage			
N0	21 (58.3)	15 (65.2)	0.785
N1	15 (41.7)	8 (34.8)	
Perineural invasion			
No	5 (13.9)	6 (26.1)	0.730
Yes	20 (55.6)	15 (65.2)	
Unknown	11 (30.6)	2 (8.7)	

ECOG, Eastern Cooperative Oncology Group; RM, resection margin.

who were diagnosed with adenocarcinoma of EHBD and underwent surgical resection followed by adjuvant RT or not were identified.

Treatment

All patients were restaged pathologically, according to American Joint Committee on Cancer 7th edn.[23] There were no patients who received neoadjuvant treatment in this study. Surgeons decided the surgical procedure for patients in accordance with site and extension of the tumour. Referral for adjuvant RT was carried out at the discretion of the attending surgeon; but, RM, age, performance status and patient preference were considered in the decision-making.

Follow-up

Patients were followed up every 3 months for 2 years, and every 6 months thereafter. Routine follow-up methods included physical examination, laboratory screening and simple chest X-ray. Abdominal/pelvic CT scan was performed every 3 months in the initial 1–2 years and repeated every 6 months thereafter. If recurrence was suspected, whole-body positron emission tomography-CT scan and chest CT scan were performed for further evaluations.

Statistical analysis

Exact χ^2 test was performed to compare categorical variables between the observation and RT groups. Cox proportional hazards regression was used to determine univariate and multivariable hazard ratios (HRs) for local recurrence-free survival (LRFS) and OS. LRFS was defined as the time period from the date of surgery to the date of treatment failure in the surgical bed. OS was defined as the time period from the date of surgery to the date of death or last follow-up. Analyses were carried out using the SPSS® Statistics software

Figure 1. Local recurrence-free survival curves according to the resection margin status.

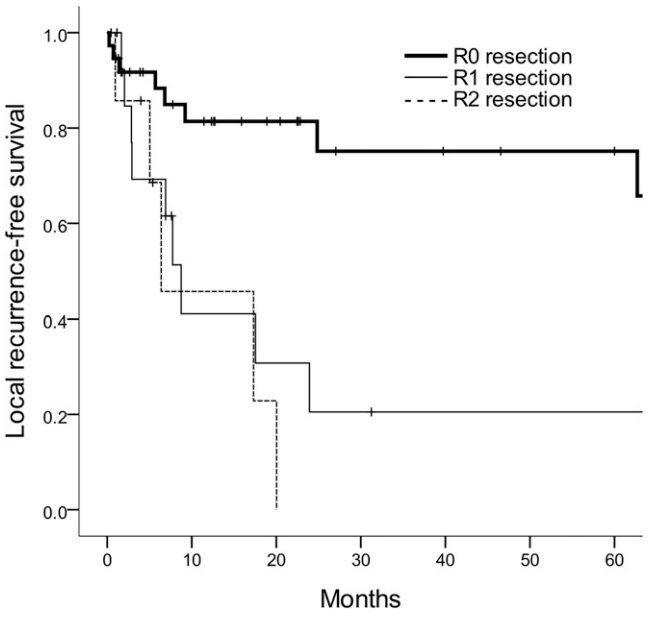


Table 2. Univariable and multivariable analyses for local recurrence-free survival

Variables	Number of patients	5-year rate (%)	Univariable	Multivariable		
			p-value	*p*-value	HR	95% CI
Age (years)						
<65	28	51.8	0.796	0.643	1	
≥65	31	52.1			1.281	0.449–3.657
Sex						
Male	32	56.1	0.377			
Female	27	47.9				
Performance status (ECOG)						
0–1	50	52.7	0.122			
2–3	9	47.6				
Surgery						
Bile duct resection with hepatectomy	13	50.3	0.917			
Bile duct resection	11	49.7				
Pancreaticoduodenectomy	35	53.4				
RM						
R0	37	75.1	0.003	<0.001	1	
R1	14	20.5			6.134	2.051–18.344
R2	8	0.0			18.551	3.680–93.520
Tumour location						
Non-hilar	42	53.0	0.700	0.966	1	
Hilar	17	52.1			1.025	0.329–3.194
Differentiation[a]						
Well	6	100.0	0.502			
Moderate	38	39.1				
Poor	14	63.1				
T stage						
T1–2	33	73.0	0.002	0.029	1	
T3–4	26	24.5			3.079	1.121–8.461
N stage						
N0	36	56.8	0.183	0.039	1	
N1	23	43.5			2.832	1.055–7.607
Perineural invasion[b]						
No	11	69.3	0.445			
Yes	35	35.6				
RT						
No	36	50.0	0.401	0.043	1	
Yes	23	53.7			0.310	0.100–0.963

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; RM, resection margin; RT, radiotherapy.
[a]In one patient, information on differentiation was unavailable.
[b]In 13 patients, information on perineural invasion was unavailable.

v. 18.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Patient and treatment characteristics

Patient and tumour characteristics according to receipt of adjuvant RT are summarized in Table 1. Median age of all patients was 65 years. Patients ≥65 years of age were more common in the observation group (67% *vs* 30%, $p = 0.008$).

13, 11 and 35 patients underwent bile duct resection with hepatectomy, bile duct resection and pancreaticoduodenectomy, respectively. Clear RM (R0) was obtained in 25 (69%) patients in the observation group and 12 (52%) patients in the RT group. R1 resection was observed in 9 (25%) patients and 5 (22%) patients, and R2 resection was observed in 2 (6%) patients and 6 (26%) patients in the observation and RT groups, respectively. Even though RM status was not statistically different, more patients in the RT group underwent R2 resection (26% *vs* 6%).

In the RT group ($n = 23$), RT was delivered to the tumour bed and regional lymph nodes including the porta hepatis, pericholedochal, retrocaval and aortocaval lymph nodes according to the location of the primary tumour. The total dose was from 45 Gy to 61 Gy (median, 50.4 Gy) in 1.8–2.0 Gy/fraction for the tumour bed and 45 Gy in 1.8 Gy/fraction for the regional lymph nodes. 15 (65%) patients in the RT group received 5-fluorouracil- or gemcitabine-based chemotherapy during RT ($n = 7$), during and after RT ($n = 6$) or after RT ($n = 2$). Among eight patients who received adjuvant chemotherapy after RT, enteric-coated tegafur/uracil was given for 1 year after RT or until progression in four patients, 5-fluorouracil for four cycles in three patients and gemcitabine for six cycles in one patient.

Patients with hilar tumour were more likely to receive adjuvant RT than patients with more distally located tumour (65% *vs* 29%, $p = 0.017$). No differences were observed between the groups with respect to sex, T stage and N stage.

Treatment outcome

Median follow-up was 19 months (range, 1–222 months) for all patients and 43 months (range, 11–178 months) for survivors. The median LFRS and 5-year LRFS rate were 63 months and 52%, respectively. On univariate analysis for LRFS, RM status and T stage were significant prognostic factors ($p = 0.003$ and 0.002, respectively). When age, RM status, tumour location, T stage, N stage and RT were incorporated into a multivariable analysis, RM status was still correlated with LRFS; the 5-year LRFS rates of R0, R1 and R2 resection were 75%, 21% and 0%, respectively [HR for R1 6.134, 95% confidence interval (CI) 2.051–18.344; and HR for R2 18.551, 95% CI 3.680–93.520; $p < 0.001$] (Figure 1). Although adjuvant RT did not show significant effect on LFRS on univariate analysis, adjuvant RT revealed a significant association with improved LRFS after adjusting for other prognostic variables on multivariable analysis; the 5-year LRFS rates of the observation and RT groups were 50% and 54%, respectively (HR 0.310, 95% CI 0.100–0.963; $p = 0.043$) (Table 2) (Figure 2).

The median OS of all patients was 21 months and the 5-year OS rate was 29%. High T stage was a poor prognostic factor for OS in univariate analysis ($p = 0.013$). Adjuvant RT (HR 0.491, 95% CI 0.291–1.102; $p = 0.085$), RM status (HR for R1 1.816, 95% CI 0.853–3.867; and HR for R2 3.564, 95% CI 1.175–10.809; $p = 0.054$) and N stage (HR 1.956, 95% CI 0.983–3.892; $p = 0.056$) showed non-significant trends for OS on multivariable analysis incorporating age, RM status, tumour location, T stage, N stage and adjuvant RT (Table 3). The 5-year OS rates of R0, R1 and R2 resection were 42%, 14% and 0%, respectively (Figure 3). The 5-year OS rates were 29% for the observation group and 27% for the RT group (Figure 4).

Treatment failures were observed in 32 patients. As the first site failure, LR with or without distant metastasis was observed in 16 (44%) patients in the observation group and in 4 (17%) patients in the RT group ($p = 0.021$) (Table 4).

Treatment toxicity

Grade of toxicity was scored according to the Common Terminology Criteria for Adverse Events v. 4.03. Among 23 patients receiving adjuvant RT, acute complications of Grade ≥3 were observed in 2 (9%) patients; 1 patient (not receiving concomitant chemotherapy) experienced severe nausea and vomiting, and the other patient (receiving concomitant weekly gemcitabine) had decreased platelet and white blood cell count.

DISCUSSION

In this study, adjuvant RT showed an increase in LRFS as well as a non-significant improvement in OS of patients with EHBD

Figure 2. Local recurrence-free survival curves according to the receipt of radiotherapy.

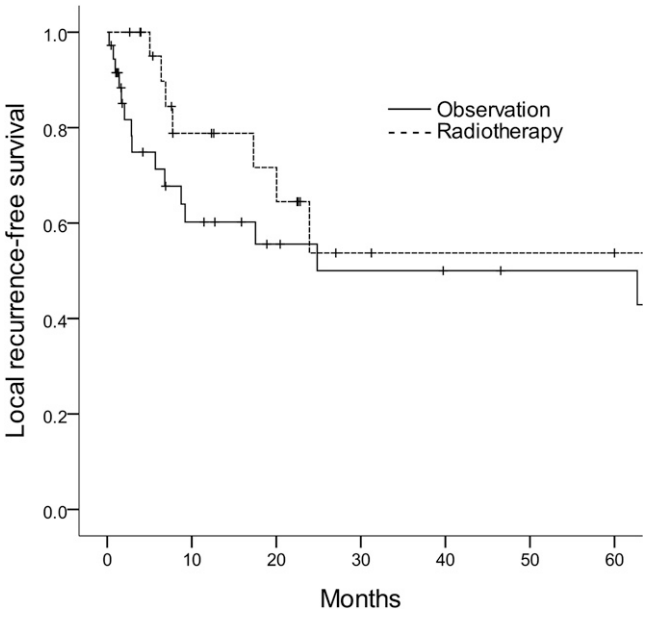
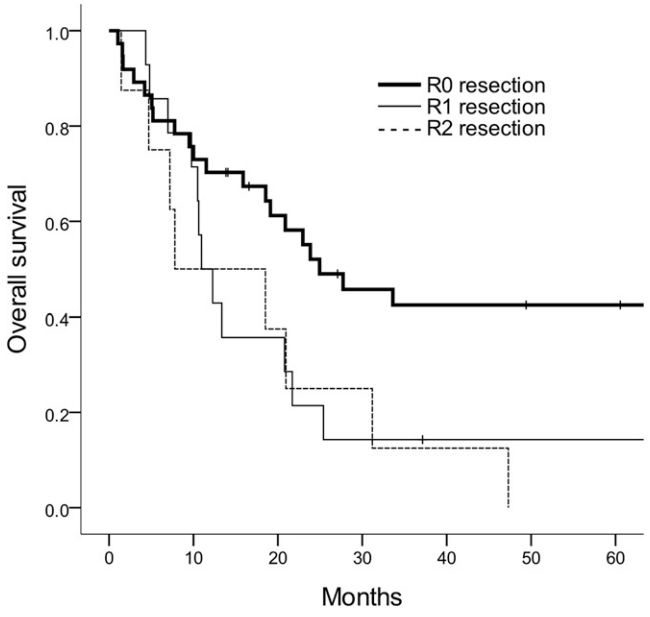


Table 3. Univariable and multivariable analyses for overall survival

Variables	Number of patients	5-year rate (%)	Univariable	Multivariable		
			p-value	*p*-value	HR	95% CI
Age (years)						
<65	28	27.6	0.851	0.962	1	
≥65	31	30.8			0.982	0.466–2.072
Sex						
Male	32	29.7	0.786			
Female	27	29.6				
Performance status (ECOG)						
0–1	50	30.3	0.481			
2–3	9	22.2				
Surgery						
Bile duct resection with hepatectomy	13	30.8	0.981			
Bile duct resection	11	15.9				
Pancreaticoduodenectomy	35	31.4				
RM						
R0	37	42.4	0.071	0.054	1	
R1	14	14.3			1.816	0.853–3.867
R2	8	0.0			3.564	1.175–10.809
Tumour location						
Non-hilar	42	33.4	0.348	0.580	1	
Hilar	17	18.3			1.246	0.571–2.722
Differentiation[a]						
Well	6	100.0	0.131			
Moderate	38	23.5				
Poor	14	25.7				
T stage						
T1–2	33	41.9	0.013	0.101	1	
T3–4	26	15.4			1.768	0.895–3.492
N stage						
N0	36	32.4	0.204	0.056	1	
N1	23	24.2			1.956	0.983–3.892
Perineural invasion[b]						
No	11	36.4	0.887			
Yes	35	23.2				
RT						
No	36	29.3	0.602	0.085	1	
Yes	23	26.3			0.491	0.219–1.102

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; RM, resection margin; RT, radiotherapy.
[a]In one patient, information on differentiation was unavailable.
[b]In 13 patients, information on perineural invasion was unavailable.

Figure 3. Overall survival curves according to the resection margin status.



cancer. Positive RM was associated with poor local control rate and adverse OS. LR was the predominant pattern of failure in the observation group, while distant metastasis was the dominant pattern in the RT group.

Poor prognosis of EHBD cancer was repeatedly observed in our study with a 5-year OS rate of 29%. It is noticeable that a treatment factor (*i.e.* RM status) had a greater impact on prognosis than any other patient or tumour characteristic. Many studies demonstrated that positive RM decreased median OS from 24–74 months (R0) to 12–13 months (R1 or R2).[9,15,24] In our study, the 5-year OS rates according to RM status were 42% in R0 resection, 14% in R1 resection and 0% in R2 resection, suggesting that positive RM would drastically decrease the chance of cure by surgical treatment. Moreover, LR was the major pattern of failure without receiving adjuvant RT in the first site of failure pattern analysis. Also, the 5-year LRFS rate of R0 resection was 75% compared with 21% and 0% of R1 and R2 resections, respectively ($p < 0.001$). These findings suggest that more effective strategies for local control are mandatory to improve OS rate.

Figure 4. Overall survival curves according to the receipt of radiotherapy.

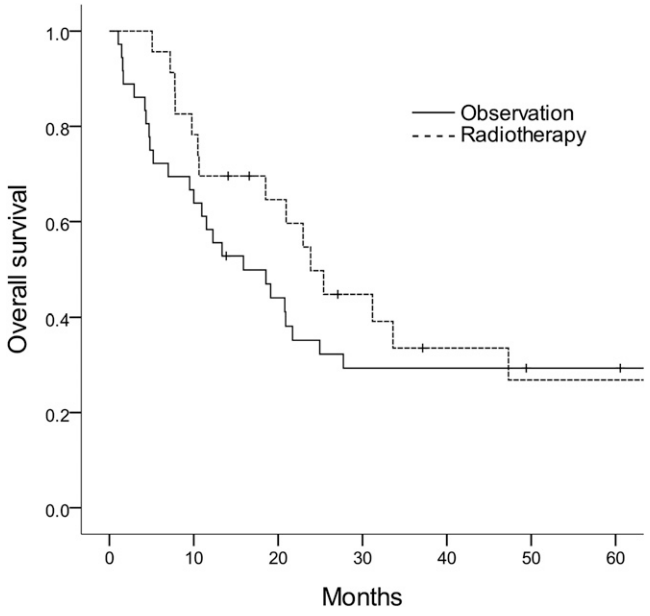


Table 4. Patterns of the first treatment failure

Site of failure	Number of patients/total failures		*p*-value
	Observation ($n = 36$)	RT ($n = 23$)	
LR with or without DM			
No	4/20	8/12	0.021
Yes	16/20	4/12	
DM with or without LR			
No	10/20	2/12	0.075
Yes	10/20	10/12	

DM, distant metastasis; LR, local recurrence; RT, radiotherapy.

Additional resection of positive RM could be a reasonable option.[25] Ribero et al[26] demonstrated that reresection of positive proximal bile duct margin to gain secondary R0 resection in patients with hilar cholangiocarcinoma improved median OS to a level similar to that of patients who underwent primary R0 resection. However, the success rate of obtaining secondary R0 resection is limited because of procedural difficulties.[9–15] Moreover, another author noted that additional resection of positive proximal bile duct RM in hilar cholangiocarcinoma did not improve OS, suggesting that further studies are indispensable to evaluate the role of additional resection of positive RM.[7]

Several studies investigated the benefit of adjuvant RT to countervail the adverse effect of positive RM.[14,17–19,27–30] Small retrospective studies demonstrated that there was no significant OS difference between negative RM group without adjuvant RT and positive RM group with adjuvant RT.[14,18] Gwak et al[17] reported that patients with R1 resection who received adjuvant RT had significantly higher median disease-free survival than those who received R1 resection alone.

In our study, adjuvant RT group was compared with non-RT group, retrospectively. The RT group had more adverse features than its counterpart; among eight patients who had R2 resection, six patients were included in the RT group (26% of the RT group), whereas the remaining two patients were in the observation group (6% of the observation group). After incorporating RM status in multivariable analysis, adjuvant RT significantly improved LRFS (HR 0.310) and showed a trend towards increased OS (HR 0.491). Reduced LR rate by using adjuvant RT might result in OS improvement.

In spite of the high LR rate of EHBD cancer, RT has not yet been a well-established adjuvant treatment.[31] An analysis of data from the Surveillance, Epidemiology, and End Results program demonstrated that only 32% of patients with EHBD cancer underwent adjuvant RT.[2] Because of the rarity of this disease, only small retrospective studies were available in many institutions, resulting in limited statistical powers. One meta-analysis, however, revealed that adjuvant RT derived survival benefit in R1 resection (odds ratio 0.33), although this improvement was not observed in R0 resection.[19]

In the present study, median age for the observation group and RT group was 71 years and 61 years, respectively. In the elderly patient, adjuvant RT was less likely to be administered because of concerns regarding RT-related morbidity. On univariate and multivariable analyses, however, age was not a significantly poor prognostic factor for survival. Toxicity of adjuvant RT was minor; only 2 (9%) patients in RT group presented Grade ≥3 side effects. Therefore, more assertive utility of adjuvant RT might improve treatment outcomes in elderly patients with good performance status.

This study is a retrospective study with a small sample size in a single institution. While no patients received chemotherapy in the observation group, a major portion of patients in the RT group received chemotherapy with various regimens. Chemotherapy regimens and treatment durations were too heterogeneous to analyze. Benefits of adjuvant RT and chemotherapy could not be evaluated separately in this small study.

In conclusion, adjuvant RT improved LRFS for patients with localized EHBD cancer. RM status was a significant prognostic factor.

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