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Safeness of Simultaneous Colonic Resection and Hepatic Radiofrequency Ablation

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ABSTRACT

Background and Objectives: Previous reports showed an increased risk of infectious complications when liver radiofrequency ablation (RFA) is performed simultaneously to colorectal resection. The aim of this study was to compare early and long-term outcomes of simultaneous versus staged strategy.

Methods: Data from colorectal cancer liver metastases consecutively treated by surgery of the primary tumor with an associated liver RFA procedure between January 1, 2010 and January 31, 2020. Patients were divided into two groups: RFA performed during colorectal surgery (simultaneous) or in a different moment (staged). Patients were manually matched (1:1) to minimize influence of known covariates.

Results: Seventy-two patients were included. After matching, there was no difference between the two groups in morbidity or mortality. Hospital stay was 2 days shorter in the simultaneous group.

Conclusions: Early or long-term outcomes were identical between the two strategies. The simultaneous strategy was associated with a shorter duration of hospitalization although not significant. Simultaneous colorectal resection and liver RFA is safe and must be included in surgeons' armamentarium.

Key Words: Colorectal cancer, Morbidity, Liver metastasis, Radiofrequency ablation.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers in Europe and North America, with nearly 1.8 million new cases and about 881,000 deaths worldwide in 2018.[1] Liver metastases are observed in 40% to 60% of CRC cases and in 25% of cases they are already present at the time of diagnosis.[2] To date, resection of both the primary tumor and liver metastases remains the only curative option[3] and improves the patient survival. However, liver resection comes with a high rate of postoperative complications,[4] and not all patients are eligible for hepatic resection. Parenchyma-sparing surgery has a comparable safety and efficacy profile compared with anatomic resections and did not compromise oncologic outcomes.[5] Also, it offers a high rate of repeat resection for liver recurrence.[6]

Radio ablative techniques are commonly used in order to spare liver parenchyma.[7,8] Despite the lack of randomized controlled trials, radio ablative techniques, mostly radiofrequency ablation (RFA) and microwave ablation, are frequently used in the setting of a curative strategy with good results.[9,10]

For synchronous colorectal cancer liver metastases (CRCLM) timing for colorectal resection and liver surgery remains controversial.[11,12] Colorectal resection and simultaneous treatment of liver metastases has the advantage of requiring only one procedure. Some studies show that simultaneous colorectal resection and minor liver resection are safe,[13,14] and does not appear to impair long-term disease-free survival.[15] It also has the

advantage of avoiding the possible disappearance of metastases under chemotherapy, which is considered noncurative and inferior to surgical resection and/or ablation.[16,17] The simultaneous resection strategy is cost efficient with a reduction in the overall length of hospital stay (LOS).[18] Although, retrospective studies have compared these two strategies with conflicting results,[19,20] the only randomized controlled trial published to date showed same rates of postoperative complications and a trend towards worst overall survival associated with the interval strategy.[21]

RFA combined with hepatic resection has become commonplace, but literature analyzing the safety of colorectal resection combined with intraoperative RFA in the treatment of CRCLM is scarce. Liver ablation may be associated with organ-specific complications[22,23] and when simultaneously performed with colorectal resection can be associated with a higher rate of infectious complications[24] and tumor recurrence rate.[25]

The presented study aimed to compare early- and long-term results of both strategies (simultaneous versus staged) in a tertiary university hospital.

PATIENTS AND METHODS

We retrospectively collected data from all patients consecutively operated for CRCLM between January 1, 2010 and December 31, 2020. This retrospective observational study complies with the French regulation MR004 for which no ethical approval is required. The database of the study was declared to the "Commission Nationale de l'Informatique et des Libertés (CNIL: 2225942)".

We identified all patients who underwent colorectal resection and liver RFA whether simultaneously or by a staged approach. Exclusion criteria included associated major hepatic resection,[26] defined as resection of three or more Couinaud's segments, colorectal resection in an emergency setting, T4b colorectal cancers with multiorgan resection, and low/mid rectal cancer qualifying for neoadjuvant chemoradiation. **Figure 1** shows the study's flowchart.

Variables included were: age, gender, obesity (defined by a body mass index [BMI] > 30), infectious risk factors (including smoking,[27] diabetes,[28] and use of steroids[29]) previous abdominal surgery, pre-operative malnutrition (defined as weight loss ≥ 10% within six months),[30] number of liver metastases, neoadjuvant chemotherapy,

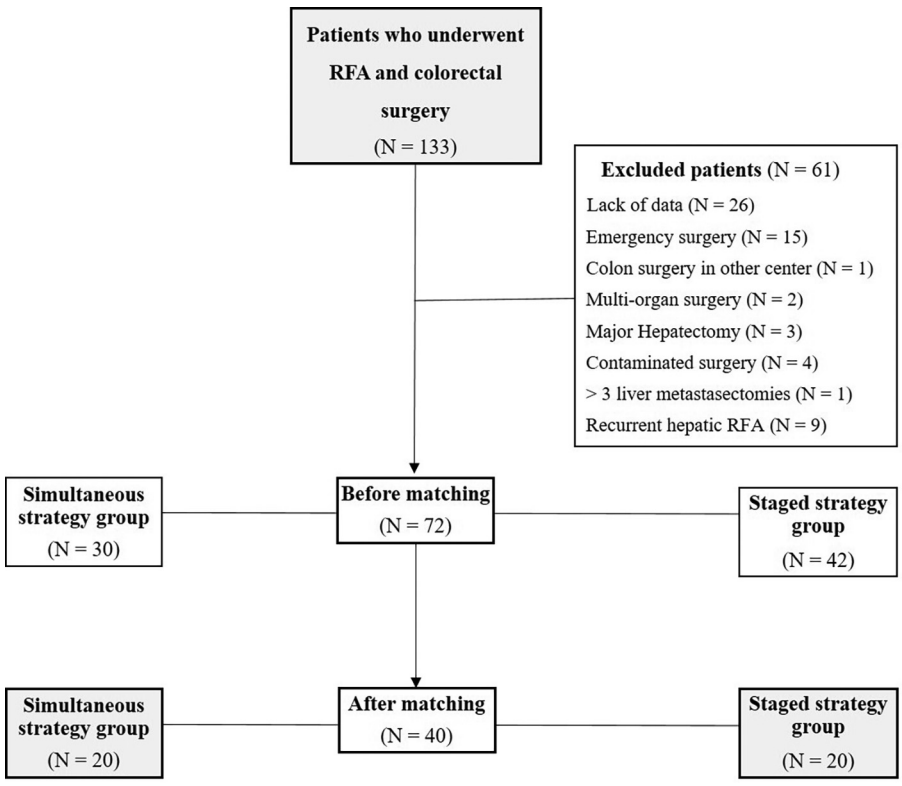

Figure 1. Study flow chart.

targeted therapy, type of colorectal resection (colectomy or rectal resection), surgical approach (laparoscopy or laparotomy), RFA approach (percutaneous or intraoperative), number of lesions treated by RFA at the same procedure, LOS, and 90-day mortality.

Pre-operative evaluations were in accordance with French guidelines.[2] For each patient, the surgical strategy was decided pre-operatively during a multidisciplinary team staff including oncologic surgeons, oncologists, radiologists, and gastroenterologists.[31] Radiologists performed the liver ultrasound in every patient. The interventional radiology team performed all RFA procedures, whether in the operating room for simultaneous cases or at the radiology department for staged strategy patients. Postoperative morbidity was graded according to the Dindo-Clavien classification.[32] We defined Dindo-Clavien grade ≥ 3 as major complication. We took in account all anastomotic fistula whether it was clinically relevant[33] or not.[34] Mortality was defined as any death occurring within 90 days after surgery.

Each patient who underwent the simultaneous procedure was manually matched to a patient who underwent a staged strategy. The matching criteria were age (< 75 or > 75), number of liver lesions (1, 2 – 3, or > 4), and localization of lesions (unilateral or bilateral). The investigators were blinded for the outcomes during matching procedure.

Postoperative complications were the study's primary end-point. Secondary end-points included mortality and survival.

Statistical Analysis

Continuous variables were expressed as median (range) or mean ± standard deviation and were compared using *t* test. Categorical variables were compared using χ^2 test or Fisher's exact test, as appropriate. Values of $p \leq .05$ were considered statistically significant. Survival curves were plotted using the Kaplan-Meier method. Median survival was compared using the Log-Rank test. Patients who did not experience any event and were still alive at the end of follow-up were right censored at this time. All statistical tests were 2-sided and performed using IBM® SPSS® Statistics V22.

RESULTS

During the study period we identified 133 patients with CRCLM treated by liver RFA and surgery of the primary CRC. Seventy-two patients met the inclusion criteria and were included in the analysis, including 30 patients who had the simultaneous strategy and 42 with a staged strategy. Before matching, the simultaneous group had bilateral lesions more often whereas the staged group had older patients, more American Society of Anesthesiology (ASA) level 3 patients, and more patients presenting risk factors for postoperative infections; however, none of these variables were statistically significant. **Table 1** shows the baseline characteristics of the included patients. Before matching, the staged group had a significantly higher rate of patients who received more pre-operative chemotherapy. The pre-operative chemotherapy regimen (FOLFOX or FOLFIRI) and the use of targeted therapy (Bevacizumab or Cetuximab or Panitumumab) did not differ between groups. Liver lesions were more often bilateral in the simultaneous group.

Table 2 summarizes intraoperative characteristics and outcomes. The groups did not differ on the approach of colorectal resection (laparoscopy or laparotomy, P = .903 and P = .744 before and after matching respectively), on the type of colorectal resection (colonic or rectal resection, P = .671 and P = .49 before and after matching respectively), on the number of liver lesions treated, nor the size of the liver lesions. There was a higher rate of associated minor liver resections in the staged group but it was not significant (P = .112 and P = .053 before and after matching respectively). In addition, in the staged group, 36% of RFA were performed percutaneously whereas all patients in the simultaneous group had it performed through laparotomy or laparoscopy.

Before matching, two patients in the staged group had major complications directly associated with the liver ablation. One patient had a radiological drainage of a biloma and one patient had a pleural breach needing the placement of a chest tube. Minor complications included undrained asymptomatic biloma and hematoma. In the simultaneous group, no major complications directly associated with the liver RFA were observed. Also, there were no infectious complications.

After matching, 40 patients were analyzed (20 in each group). There were no differences for baseline characteristics, shown in **Table 1**. Rate of overall complications, major complications or specific liver ablation complications were comparable between both groups (**Table 2**).

The re-operation rate was significantly higher in the staged group. Reasons for re-operation were mainly linked to peritonitis secondary to anastomotic leakage in both groups (two in the simultaneous group; six in the staged group). This difference was no longer significant after matching. One patient, who had the RFA before the colorectal resection, died from postoperative peritonitis.

Table 1.
Baseline Characteristics Before and After Matching

	Before Matching (N = 72)			After Matching (N = 40)		
Variables	Simultaneous Group, N = 30, (n) %	Staged Group, N = 42, (n) %	*P* Value	Simultaneous Group, N = 20, (n) %	Staged Group, N = 20, (n) %	*P* Value
Male sex, N (%)	22 (73.3%)	26 (61.9%)	0.317	15 (75%)	11 (55%)	0.185
Mean age, years	58.9	64.0	0.084	56.0	60.7	0.225
BMI > 30 kg/m^2, N (%)	3 (10%)	6 (14.6%)	0.569	3 (15%)	3 (15%)	1
ASA ≥ 3, N (%)	0 (0%)	5 (12.1%)	0.048	0 (0%)	0 (0%)	1
Infectious risk factor, N (%)	7 (23.3%)	17 (40.4%)	0.132	7 (35%)	8 (40%)	0.744
Previous abdominal surgery, N (%)	13 (43.3%)	16 (38.0%)	0.66	9 (45%)	8 (40%)	0.749
Malnutrition, N (%)	5 (16.6%)	3 (7.31%)	0.224	5 (25%)	3 (15%)	0.429
Neoadjuvant chemotherapy, N (%)	24 (80%)	12 (29.2%)	0.001	17 (85%)	10 (50%)	0.018
> 6 cycles	7/29 (24.1%)	6/41 (14.6%)	0.345	5 (25%)	5 (25%)	
FOLFOX	14 (46.6%)	16 (38.0%)	0.69	7 (35%)	8 (40%)	0.744
FOLFIRI	4 (13.3%)	7 (16.6%)	0.731	3 (15%)	5 (25%)	0.429
anti-vascular endothelial growth factor or anti-epidermal growth factor receptor	5 (16.6%)	8 (19%)	0.72	2 (10%)	3 (15%)	0.633
Targeted therapy, N (%)	13 (43.3%)	17/41 (41.4%)	0.389	9 (45%)	12 (60%)	0.342
Type of colorectal resection, N (%)			0.671			0.49
Colectomy	20 (66.6%)	30 (71.4%)		13 (65%)	15 (75%)	
Rectal Resection	10 (33.3%)	12 (28.5%)		7 (35%)	5 (25%)	
Associated liver resection, N (%)	8 (26.6%)	19 (45.2%)	0.112	5 (25%)	11 (55%)	0.053
Number of liver lesions, N (%)			0.006			1
1	3 (10%)	11/41 (26.8%)		3 (15%)	3 (15%)	
2 or 3	5 (16.6%)	14/41 (31.1%)		3 (15%)	3 (15%)	
> 3	22 (73.3%)	16/41 (39.0%)		14 (70%)	14 (70%)	
Bilateral liver lesions, N (%)	25 (83.3%)	22 (52.3%)	0.006	16 (80%)	13 (65%)	0.288
Staging of the primary CRC, N, (%)						
T3 – 4	28 (93.3%)	35/41 (85.3%)	0.301	19 (95%)	18 (90%)	0.548
N+	23 (76.6%)	27/41 (65.8%)	0.508	17 (85%)	13 (65%)	0.144

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; CRC, colorectal cancer; SLM, synchronous liver metastases.

Table 2.
Operative and Postoperative Outcomes Before and After Matching

	Before Matching (N = 72)			After Matching (N = 40)		
Variables	Simultaneous Group, N = 30, n (%)	Staged Group, N = 42, n (%)	*P* Value	Simultaneous Group, N = 20, n (%)	Staged Group, N = 20, n (%)	*P* Value
Type of surgical approach, N (%)			0.903			0.744
Laparoscopic	19 (63.3%)	26 (61.9%)		13 (65%)	12 (60%)	
Open	11 (36.6%)	16 (38.0%)		7 (35%)	8 (40%)	
Type of RFA approach, N (%)			0.434			0.004
Percutaneous	0	15 (35.7%)		0	7 (35%)	
Surgery	30 (100%)	27 (64.2%)		20 (100%)	13 (65%)	
Number of liver RFA, N (%)			0.75			1
1	17 (56.6%)	25 (59.5%)		13 (65%)	13 (65%)	
2 or 3	9 (30%)	13 (30.9%)		6 (30%)	6 (30%)	
> 3	4 (13.3%)	4 (9.5%)		1 (5%)	1 (5%)	
Size of the largest liver lesion, mm			0.502			0.151
<30	26/28 (92.2%)	36/41 (87.8%)		19 (95%)	16 (80%)	
≥ 30	2/28 (7.1%)	5/41 (12.1%)		1 (5%)	4 (20%)	
Complications, N (%)	7 (23.3%)	13/38 (34.2%)	0.336	6 (30%)	6 (30%)	1
Clavien-Dindo > 3	2 (6.6%)	8/38 (21.0%)	0.099	2 (10%)	3 (15%)	0.633
Anastomotic leak	2 (6.6%)	7/38 (18.4%)	0.16	2 (10%)	2 (10%)	1
Nondigestive infectious complications	5 (16.6%)	11/38 (28.9%)	0.242	3 (15%)	3 (15%)	1
Liver-related complications	2 (6.6%)	5 (11.9%)	0.467	1 (5%)	2 (10%)	0.548
Clavien-Dindo ≤ 3	2 (6.6%)	3 (7.1%)	0.467	1 (5%)	1 (5%)	1
Clavien-Dindo ≥ 3	0	2 (4.7%)	0.232	0	0	1
Completion of the full oncological strategy, N (%)	21/25 (84%)	36/40 (90%)	0.482	15 (75%)	18 (90%)	0.339
Recurrence, N (%)						
Local recurrence	2/26 (7.6%)	6/41 (14.6%)	0.401	2 (10%)	3 (15%)	0.633
Hepatic recurrence	21/29 (72.4%)	28/41 (68.2%)	0.716	13 (65%)	16 (80%)	0.288
Number of nodes harvested during CRC surgery (Mean), N (%)	30.1	26.6	0.375	33.5	30.2	0.853
Number of invaded nodes (Mean), N (%)	3.4	2.8	0.508	3.2	2.5	0.797
Reoperation, N (%)	2 (6.6%)	8/38 (21.0%)	0.033	2 (10%)	3 (15%)	0.633
90 days mortality, N(%)	0	1/39 (2.5%)	0.315	0	0	1

Table 2. Continued

Variables	Before Matching (N = 72)			After Matching (N = 40)		
	Simultaneous Group, N = 30, n (%)	Staged Group, N = 42, n (%)	*P* Value	Simultaneous Group, N = 20, n (%)	Staged Group, N = 20, n (%)	*P* Value
LOS (Mean ± SD)	8.7 (±4)	12.9 (±11)	0.077	10.3 (±6)	12.4 (±10.1)	0.413
Overall survival, months (median 95% CI)	45.2 (20.2 – 70.2)	56.4 (41 – 71.9)	0.235	45.2 (24.2 – 66.2)	65.5 (51.9 – 79.1)	0.238

Abbreviations: RFA, radiofrequency ablation; LOS, length of hospital stay; CRC, colorectal cancer; SD, standard deviation; CI, confidence interval.

The LOS was shorter by two days in the simultaneous group (10.3 ± 6 d vs. 12.4 ± 10.1 d). There were no differences in terms of recurrence (whether local, hepatic, or overall). The full oncology strategy was equally completed in most cases in both groups. **Table 2** summarizes early and long-term outcomes before and after matching.

Before matching the median overall survival was 45.2 months (95% confidence interval [CI]; 20.2 –70.2) and 56.4 months (95% CI; 41 – 71.9) for staged and simultaneous group respectively (P = .235). After matching, the median overall survival was 45.2 months (95% CI; 24.2 – 66.2) for the staged group and 65.5 (95% CI; 51.9 – 79.1) for the simultaneous group. This difference was not significant (P = .238). **Figure 2** shows Kaplan Meier's overall survival curves.

DISCUSSION

The use of RFA has become widely accepted in the realm of metastatic colorectal cancer for extending survival in patients.[5,7,8] Ablation techniques are safe, but there is limited available data on the morbidity of liver ablation when simultaneously performed with potentially contaminated colorectal resection.[24,35] The present study compares simultaneous and staged colorectal resection in association with liver RFA for the treatment of simultaneous CRCLM.

With the development of increasingly effective chemotherapeutic agents, dramatic tumor reduction has been observed following initiation of therapy in many cases of CRLM. The phenomenon in which there is a complete radiologic response in hepatic tumors on cross-sectional imaging is referred to as disappearing liver metastases (DLM). DLM can represent a unique problem in patients treated with neoadjuvant chemotherapy because although the tumor may become undetectable radiologically, this does not necessarily equate complete pathologic response.[17]

The current management of missing liver metastases (MLM) from the liver surgeon's point of view. Regarding clinical management, liver surgery is deemed the fundamental pillar in the therapeutic strategy of these patients.[16] Meta-analysis due to data heterogeneity was inconclusive. Depending on the clinical context, MLM monitoring appears to be a valid therapeutic alternative. Nevertheless, prospective randomized clinical studies are needed.[36]

We found that the use of liver RFA simultaneously with a colorectal resection was as safe as the staged strategy. In the simultaneous group, LOS was shorter by two days, although it did not reach statistical significance. In addition, it has the theoretical advantage of requiring one single hospitalization.

In our study, the rate of complications associated with the liver RFA was comparable to the literature.[35,37] We found a slightly higher rate of complications in the staged group, although this difference was not significant. The lack of increased infectious risk with a combined strategy is consistent with the studies of Cathryn et al.[24] and Fu et al.[25] In our study, RFA was always performed by the same expert interventional radiology team, which results in less interoperative variability.[38]

After matching, the rate of liver recurrence (whether isolated or associated with another site) was relatively high (65% vs 80%).

The rate of local and hepatic recurrence was higher in the staged group although it did not reach statistical significance. Overall survival before and after matching was not statistically different. We chose median survival because it is easier to grasp than hazard ratios.[39] This result is in accordance with the only RCT published[21] to date comparing simultaneous colorectal and liver surgery with an

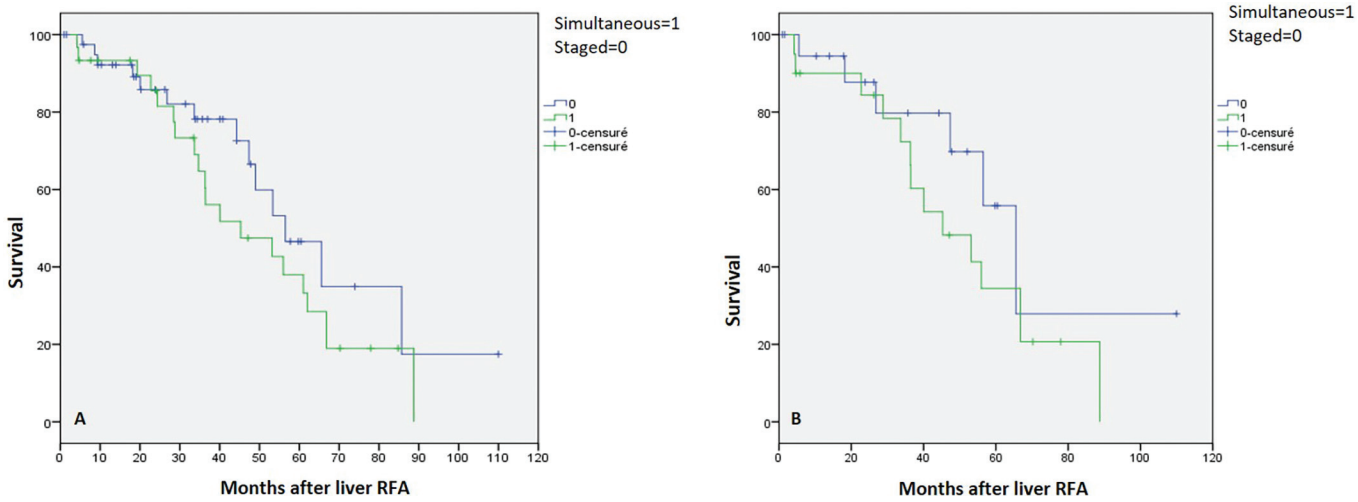

Figure 2. Kaplan-Meier's survival curves before and after matching.

staged surgical approach, but we think our results should be considered cautiously. Noteworthy, a recent meta-analysis found a minimal correlation between recurrence-free survival and overall survival after resection of colorectal liver metastases.[40]

During the long period of accrual, improvements in chemotherapy regimens and oncological strategies,[38,41] may have impacted the outcomes. In the staged group, one-third of patients had RFA performed percutaneously, which may explain the different nonsignificant recurrence rate observed between the two groups, although the literature on that point is scarce and highly controversial.[42,43]

It is important to point out that liver recurrence was higher than expected. It has been shown that the principal factors associated with liver recurrence include rectum as the primary tumor site, primary tumor lymph node metastasis, synchronous presentation, and history of RFA.[44] A meta-analysis from van Amerongen et al. showed that RFA is associated to lower rate of complications, but also a lower survival and a higher rate of recurrence as compared to surgical resection.[45]

It is important to point out that the quality of the colorectal resection, measured by the number of harvested lymph nodes and surgical margins (data not shown) did not differ between the two groups. Hamady et al.[46] showed that the awareness of the presence of liver metastases by the operating surgeon was an independent predictor of intra-abdominal recurrence following potentially curative hepatic resection, which may worsen oncological results of a staged strategy.

Our study has potential biases. First, it does not avoid the usual limitations of any retrospective study. Second, the number of patients studied after matching is relatively small, with a risk of type II error. Treatment choices were made at surgeon's discretion, without validated criteria for patients' assignments to one therapeutic strategy, although we tried to overcome it through a case-matched analysis using clinically pertinent pre-operative data.

In conclusion, this case-matched study suggested that simultaneous liver RFA and colorectal resection can be safely performed without increasing postoperative morbidity rates and has the potential benefit of reducing LOS.

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