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Rapid on-site evaluation (ROSE) versus macroscopic on-site evaluation (MOSE) for endoscopic ultrasound-guided sampling of solid pancreatic lesions: a paired comparative analysis using newer-generation fine needle biopsy needles

Sridhar Sundaram[a]*, Utkarsh Chhanchure[a]*, Prachi Patil[a], Vishal Seth[a], Akhil Mahajan[a], Munita Bal[b], Rajiv Kumar Kaushal[b], Mukta Ramadwar[b], Neelam Prabhudesai[c], Manish Bhandare[d], Shailesh V. Shrikhande[d], Shaesta Mehta[a]

Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India

Abstract

Background Rapid on-site examination (ROSE) during endoscopic ultrasound-guided fine needle biopsy (EUS-FNB) has been a subject of debate. We compared the yield of EUS-FNB with adequacy assessed using macroscopic on-site evaluation (MOSE), and smear cytology with adequacy confirmed by ROSE, acquired using the same needle.

Methods Consecutive patients with solid pancreatic lesions (SPLs) who underwent EUS-FNB of pancreatic solid lesions between January 2021 and July 2022 were included. Demographic details, site and size of lesion, number of passes, and the diagnosis by cytology and histopathology of core tissue were noted. The first pass was used for ROSE adequacy assessment and was subsequently sent for cytological assessment. Additional passes were taken subsequently to acquire core tissue. Adequacy was confirmed by MOSE (whitish core of more than 4 mm). Final cytology and histopathology (HPE) were compared for diagnostic accuracy.

Results One hundred fifty-five patients were included in the analysis during the study period (mean age 55.1+12.9 years; 60% male; 77% in pancreatic head; median size 3.7 cm). The final diagnosis was malignancy in 129, while 26 were negative for malignancy. Sensitivity and specificity for ROSE with cytology in detecting malignant SPLs were 96.9% and 100%, respectively. HPE with MOSE had sensitivity and specificity of 96.1% and 100%, respectively. A comparison of diagnostic accuracy showed no significant difference (P>0.99) between HPE with MOSE and ROSE with cytology, using an FNB needle.

Conclusion MOSE is as good as ROSE in terms of diagnostic yield for solid pancreatic lesions sampled using newer-generation EUS biopsy needles.

Keywords Endoscopic ultrasound tissue acquisition, rapid on-site evaluation, macroscopic on-site evaluation, pancreatic cancer, diagnostic accuracy

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Conflict of Interest: None

Correspondence to: Sridhar Sundaram, MD, DM (Gastroenterology), Associate Professor, Department of Digestive Diseases and Clinical Nutrition, Tata Memorial Hospital, Homi Bhabha National Institute, Dr. E Borges Road, Parel, Mumbai 400012 India, e-mail: drsridharsundaram@gmail.com/drsridharsundaram@kem.edu

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Introduction

Linear endoscopic ultrasonography (EUS) creates real-time images of the digestive tract and adjacent lesions, allowing the identification of suspected malignancies [1]. EUS-guided fine needle aspiration (FNA) offers an opportunity for sampling mediastinal, intraabdominal, and pancreatic lesions under direct visualization [2]. EUS-FNA is a safe, well-established, and first-line diagnostic tool for the evaluation of solid pancreatic lesions [3]. Its sensitivity and specificity have been reported to be 86.8% and 95.8%, respectively [4]. Solid pancreatic lesions are most commonly pancreatic adenocarcinomas (PAC), followed by neuroendocrine tumors (NET), and solid pseudopapillary tumors (SPT) [5]. PAC remains one of the

most lethal malignancies, with a dismal prognosis and a 5-year survival rate of 5-20% [6,7]. Solid pancreatic lesions may often be secondary to benign pathology. In a previous series, 6.5% of 446 patients who underwent surgery for pancreatic solid lesions had an underlying benign etiology [8]. Hence, tissue diagnosis remains critical in situations with a diagnostic dilemma, while in patients where neoadjuvant therapy is planned, sampling of pancreatic solid lesions to confirm diagnosis is recommended [9].

Despite controversial results in various meta-analyses [10-13], rapid on-site evaluation (ROSE) has the persuasive advantages of providing timely feedback on sample adequacy and optimizing the number of needle passes required to make a diagnosis using EUS-guided sampling. Cytopathologists aid the procedure by indicating when an adequate specimen has been obtained, thereby ensuring maximal yield with the minimum number of passes, as well as assisting with sample triage for ancillary studies, such as microbiology and flow cytometry, as needed. However, the availability of ROSE in tertiary care centres and, even more importantly, in community hospitals is limited because of the complexity of expertise development and related costs [14].

Efforts have been made to succeed in acquiring samples for histologic evaluation to overcome the limitations of ROSE [15]. The newest generation of histology needles has recently become available, divided into those with a modified tip with cutting edges and those with a forward-facing bevel on a side fenestration. All these needles have demonstrated a better histologic and diagnostic yield compared with standard FNA needles [16-18]. EUS-guided fine needle biopsy (EUS-FNB) has a diagnostic yield equal to that of EUS-FNA+ROSE [19-21]. Macroscopic on-site evaluation was first described by Iwashita *et al* in 2015 to assess the adequacy of core tissue using 19-G FNA needles [22]. Now, MOSE has been increasingly used to assess adequacy after EUS-guided sampling using FNB needles. We aimed to do a comparative assessment of the diagnostic yield of EUS-FNB with adequacy assessed by MOSE, and ROSE with cytology, performed using the same newer-generation EUS biopsy needle.

Materials and methods

Study design

This was a retrospective study of prospectively maintained endoscopy database at a tertiary care oncology centre in Western India. Data was retrieved from the endoscopy database and details were extracted from the electronic medical records with the help of the information technology department at our institute. Approval was obtained from the institutional ethics committee prior to commencing the project.

Department of [a]Digestive Diseases and Clinical Nutrition (Sridhar Sundaram, Utkarsh Chhanchure, Prachi Patil, Vishal Seth, Akhil Mahajan, Shaesta Mehta); [b]Pathology (Munita Bal, Rajiv Kumar Kaushal, Mukta Ramadwar); [c]Cytopathology (Neelam Prabhudesai); [d]Surgical Oncology (Manish Bhandare, Shailesh V. Shrikhande), Tata Memorial Hospital, Mumbai, India

*Co-first authors

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Patient population

Consecutive patients with solid pancreatic lesions (SPLs) who underwent EUS-guided sampling of lesions between January 2021 and July 2022 were included. Patients who had a lesion likely to be visualized and sampled by EUS, and were able to provide informed consent, were included. Demographic details, details of site of lesion, size of lesion, number of passes, adequacy by ROSE, diagnosis as achieved by cytology and histopathologic assessment of core tissue were noted. Patients whose lesions had a cystic component were excluded.

EUS procedure and specimen processing

EUS was performed by 2 experts who had experience of more than 100 EUS procedures performed independently. Sampling was done using a 22-G AcquireTM (Boston Scientific, USA) needle in all cases, using the slow stylet pull-through method with fanning technique, with the patient under either conscious sedation or general anesthesia. A minimum of 2 passes, one for ROSE and other for core tissue sampling, were performed. The first pass was given for ROSE to assess for adequacy of smear cytology. Touch imprint cytology was taken for making smears for ROSE by a trained cytopathologist. The tissue was placed on a slide, and by gently pressing down and rubbing with another slide smears were made using the superficial imprints. Smears were stained with toluidine blue and were evaluated for adequacy under the microscope. This sample was subsequently sent to cytology for diagnosis if adequate. Those patients where ROSE was not performed or where core tissue was not taken for histopathology were excluded from the analysis. Additional passes were subsequently made to acquire core tissue from the solid masses. The adequacy of core tissue was confirmed by macroscopic on-site evaluation (MOSE) of a whitish core with length >4 mm. The specimen was expelled over a glass slide to assess adequacy. These samples were submitted for histopathologic examination (HPE) in formalin jars (Fig. 1).

Outcome measures

The primary outcome measure was diagnostic accuracy, defined by the percentage of collected specimens matching the final diagnosis (Fig. 2 A-J). The final diagnosis was based on surgical specimen histopathology, or repeat computed tomography-guided sampling, and in the case of negative samples a clinical follow-up of up to 6 months to determine the nature of the disease. Accuracy was compared between the "ROSE with cytology" group and the "HPE with MOSE" group. Secondary outcome measures were the number of passes

needed for ROSE adequacy, the total number of passes taken, and adverse events related to the procedure. Cytology and ROSE evaluations followed the Papanicolaou classification [23]. Adverse events were reported using the American Society for Gastrointestinal Endoscopy's standard lexicon for endoscopic adverse events [24]. In patients with a negative sample, a repeat biopsy was performed if there was a high pretest probability of cancer. All patients with negative samples were followed-up with serial interval imaging at 3 and 6 months, as well as tumor markers.

Sample size

Considering an accuracy of 95% both ROSE and MOSE, with a non-inferiority margin of 7%, the sample size would have to be 120 patients in each arm in order to achieve a statistical power of 80% within an error of 0.05. Since the study used paired sampling, a total of 120 patients needed to be enrolled.

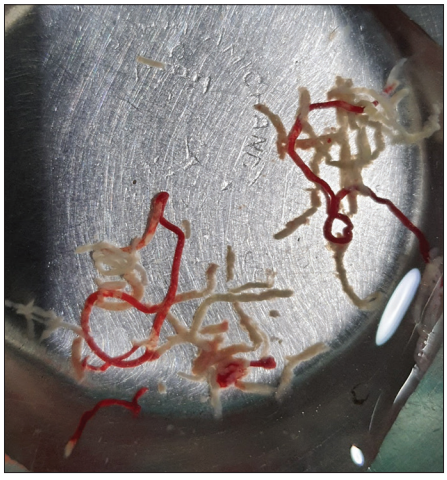

Figure 1 Core tissue sent for histopathology

Statistical analysis

The statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA). Continuous variables were represented as mean and median, with standard deviation and interquartile range, respectively. Categorical variables were represented as percentages. Comparison of diagnostic accuracy between both groups was done using McNemar's test for paired nominal data.

Results

One hundred sixty-eight patients underwent EUS-guided sampling for SPLs during the study period. Of these, 13 patients either underwent only a single pass for ROSE or core tissue acquisition without ROSE, leaving 155 to be included in the final analysis. The mean age of the cohort was 55.1+12.87 years and 60% (93/155) were male. The majority of lesions were located in the head of the pancreas (77%). The mean largest dimension of lesions was 3.7 cm. The reason for sampling the lesion was its borderline resectable nature prior to neoadjuvant therapy in 75 (48.4%) patients, locally advanced unresectable disease in 48 (30.9%) patients, and to confirm the nature of the disease process (benign vs. malignant) in 32 (20.6%) patients.

ROSE with cytology was able to diagnose malignancy in 125 patients, and HPE with MOSE was able to diagnose malignancy in 124 patients. In 3 patients, diagnosis was achieved only by ROSE with cytology, while in 2 other patients it was achieved only by HPE with MOSE. In 2 patients, neither ROSE with cytology nor HPE with MOSE was able to diagnose malignancy. Sensitivity and specificity for malignant SPLs were 96.9% and 100%, respectively, for ROSE with cytology. Final histopathology of core tissue could diagnose malignant SPLs with sensitivity and specificity of 96.1% and 100% respectively. The overall accuracy of ROSE with cytology was 97.42% (95% confidence interval [CI] 93.53-99.29) while the

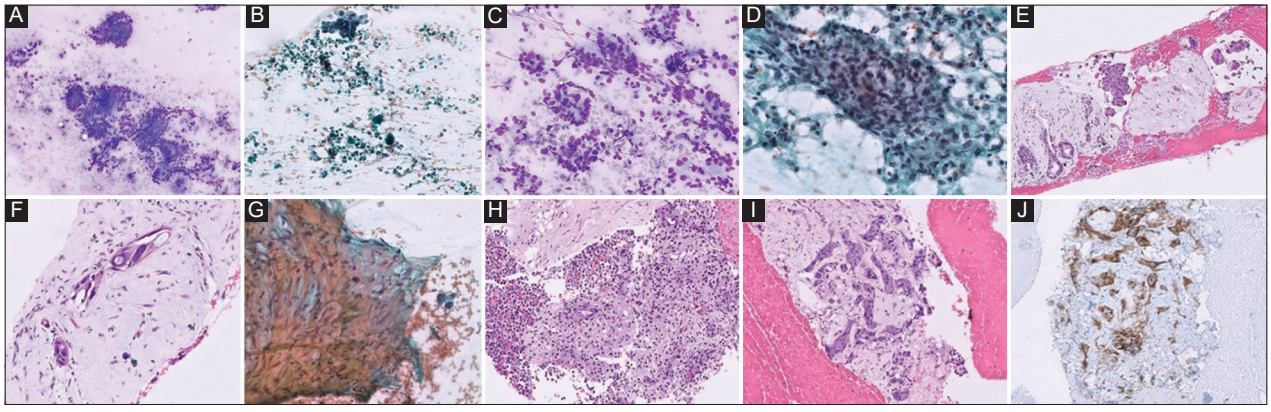

Figure 2 (A-D) A spectrum of adenocarcinoma cases seen on cytology smears. (E-F) Invasive adenocarcinoma seen within a desmoplastic stroma. (G-H) Epithelioid granuloma along with inflammatory cells. (I) Well-differentiated neuroendocrine tumor seen in a hyalinized stroma. (J) Well-differentiated neuroendocrine tumor cells show immunoreactivity for synaptophysin

accuracy for HPE with MOSE was 96.78% (95%CI 92.63-98.95). Comparison using the McNemar chi-square test for paired nominal data showed no significant difference (P>0.99) in accuracy between final HPE with MOSE and ROSE with cytology, when an FNB needle was used.

The median number of passes required overall was 3 (range 2-6): 2 passes were needed in 61 (39.4%) patients and 3 passes in 50 (32.3%). In 13 (8.3%) patients, more than one pass was required for confirming adequacy on ROSE. There was no correlation between the total number of passes and the size (Pearson correlation 0.160, P=0.235) or location (P=0.120) of the lesion (Fig. 1). No significant difference was seen in lesion size or location between those who required additional passes for ROSE and those who required only one pass (P=0.261). The final diagnosis was malignancy in 129 patients (adenocarcinoma 110, NET 14, solid pseudopapillary epithelial neoplasms 2, and lymphoma 3), whereas 26 were negative for malignancy (autoimmune pancreatitis 5, tuberculosis 5). Adverse events related to the procedure included perforation in one patient (Stapfer type 1), requiring surgical closure. A summary of these results is provided in Tables 1 and 2 and Fig. 3.

Table 1 Study characteristics

Attribute	Result
Mean age	55.1 ± 12.87 years
Sex distribution	Male: 93 (60%) Female: 62 (40%)
Site of pancreatic mass	Head of pancreas: 120 (77.4%) Uncinate process: 14 (9.0%) Neck of pancreas: 5 (3.2%) Body-tail of pancreas: 16 (10.3%)
Median largest dimension of lesion (range)	3.7 cm (1.5-8.0 cm)
Reason for sampling	Borderline resectable cancer prior to neoadjuvant therapy: 75 (48.4%) Locally advanced cancer: 48 (30.9%) To establish a diagnosis: 32 (20.6%)
Number of passes	Median 3 (Range 2-6) 2 passes - 61 (39.4%) 3 passes - 50 (32.3%) 4 passes - 34 (21.9%) 5 passes - 7 (4.5%) 6 passes - 3 (1.9%)
Final diagnosis	Malignant - 129 (83.2%): Adenocarcinoma: 110 Neuroendocrine tumor: 14 Solid pseudopapillary epithelial neoplasm: 2 Lymphoma: 3 Benign - 26 (16.8%): Tuberculosis: 5 Autoimmune pancreatitis: 5
Moderate-to-severe adverse events	1 (0.6%): Lateral wall duodenum perforation managed surgically

Discussion

We found that when new-generation biopsy needles were used for the evaluation of SPLs, EUS-FNB alone, with adequacy assessed by MOSE, was not inferior to ROSE with cytology with respect to diagnostic accuracy. Until now, EUS-FNA+ROSE has been the preferred technique for EUS-guided tissue acquisition, with ROSE being an important factor affecting the diagnostic yield, as confirmed in a large randomized controlled trial with 351 patients [25]. Newly introduced needles specifically designed for EUS-FNB have recently achieved significantly better diagnostic accuracy than standard FNA needles. A large retrospective study of 2127 SPLs also confirmed the better accuracy [26]. A systematic review and meta-analysis by van Riet *et al* showed that for SPL sampling EUS-FNB had a higher diagnostic yield than EUS-FNA and required fewer passes [16]. A recent network meta-analysis comparing different needle types showed that end-cutting needles are best for EUS-guided sampling of pancreatic lesions, compared to FNA and side cutting needles [27]. We used only Franseen type end-cutting needles for EUS-FNB in our cohort to ensure homogeneity.

A multicenter retrospective study of EUS-guided sampling of SPLs with ROSE by De Moura *et al* revealed that EUS-FNB, either with ROSE or alone, was more accurate than EUS-FNA. EUS-FNB with ROSE had a higher diagnostic yield compared to FNB alone (93% vs. 88%) [28]. However, the authors did not mention how sample adequacy for EUS-FNB alone was measured. Moreover, there was a wide variation in needle size and type, with a large proportion of patients being sampled using a 25-G needle. Only one previous multicenter randomised controlled trial (RCT) by Crino *et al* showed that EUS-FNB was non-inferior to EUS-FNB with ROSE, having an accuracy >95% [29]. However, that RCT had some issues with respect to inhomogeneity in the type of needle and the technique used for sampling (wet-suction, dry-suction or slow stylet pull-through). Furthermore, the adequacy of the FNB was not assessed and a minimum of 3 passes were performed. Studies suggest that MOSE has a high overall diagnostic accuracy of >90% and can be considered as a tool to increase the diagnostic yield of PSL specimens [30,31]. In our study, unlike previous comparative studies, we assessed the adequacy of EUS-FNB alone using MOSE. In addition, we used the slow stylet pull-through technique with Franseen needles in all patients, ensuring uniformity. Our accuracy was more than 95%, in line with previous studies.

Previous studies suggest that fewer passes are needed per patient when ROSE is used [32,33]. In our study, the median number of passes including ROSE were 3, with most patients needing only one pass for ROSE and 2 passes for FNB. Tumor characteristics (size or site) did not affect the overall number of passes needed for diagnosis. The European Society of Gastrointestinal Endoscopy's guidelines, published in 2017, refer to a minimum of 2-3 passes with an FNB needle for solid lesions, with or without on-site cytopathology [34]. A previous study from Greece suggested that the overall diagnostic yield

Table 2 Primary outcome measures

Outcome measures	FNB with MOSE	ROSE with cytology
True positive	124	125
False negative	5	4
True negative	26	26
False positive	0	0
Sensitivity	96.12% (95%CI 91.19-98.73)	96.90% (95%CI 92.25-99.15)
Specificity	100% (95%CI 86.77-100)	100% (95%CI 86.77-100)
Positive predictive value	100%	100%
Negative predictive value	83.90% (95%CI 68.81-92.48)	86.69% (95%CI 71.28-94.47)
Accuracy	96.78% (95%CI 92.63-98.95)	97.42% (95%CI 93.53-99.29)
McNemar's Chi-square test for paired nominal data	P>0.99	

FNB, fine-needle biopsy; MOSE, macroscopic on-site evaluation; ROSE, rapid on-site evaluation; CI, confidence interval

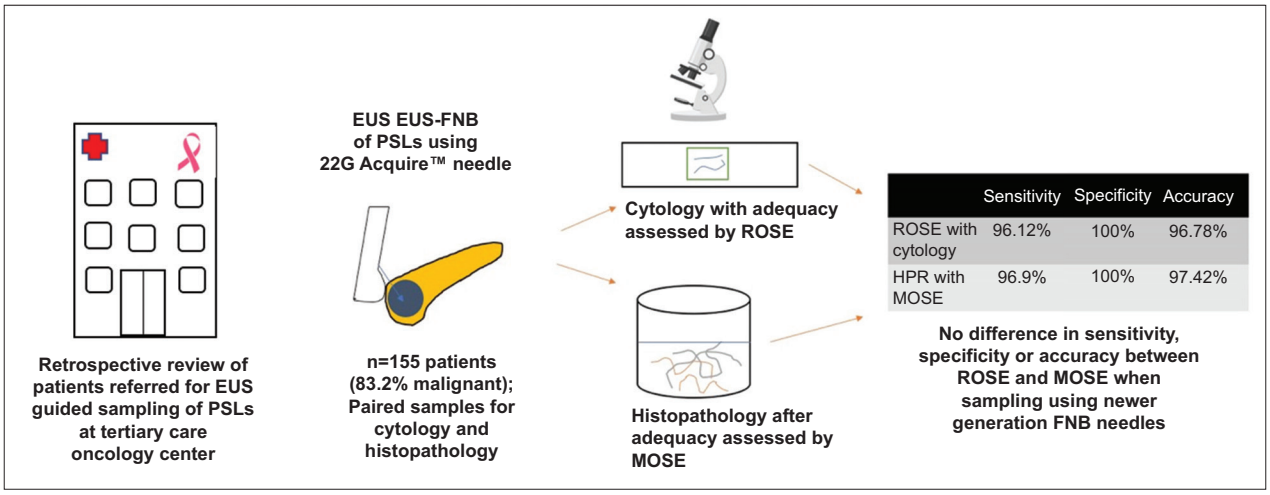

Figure 3 Graphical abstract for results
ROSE, rapid on-site evaluation; MOSE, macroscopic on-site evaluation; EUS, endoscopic ultrasound; FNB, fine-needle biopsy; PSLs, pancreatic sold lesions; HPR, histopathological examination report

is similar in those who undergo 2 or 3 passes in the absence of ROSE [35]. The recommendations and findings of that study are similar to our own, where the majority needed 2 or 3 passes overall. Our rate of adverse events was low, in accordance with the literature and the standard guidelines [36].

The logistic constraints imposed by ROSE may have limited the use of EUS-guided sampling. Centers should give careful consideration to the need for ROSE and to whether adequate accuracy is achieved with MOSE alone [37]. Core tissue acquisition in patients with pancreatic ductal adenocarcinoma may help in molecular stratification and molecular profiling, which may impact therapeutic stratification [38]. Assessment of the Ki-67 index on core tissue specimens is critical for stratification in NET, and is more reliable than cytology specimens [39]. The sampling procedure is significantly shorter in the absence of ROSE, with a mean difference of about 6 min in favor of EUS-FNB alone [29]. This is particularly beneficial for high-volume units to optimise patient flow. In their RCT, Oppong *et al* also demonstrated a shorter pathology viewing time for histologic compared with cytologic samples, suggesting that EUS-FNB with off-site histologic evaluation can be time-saving and cost-effective, especially in high-volume centers [18].

Our study has several strengths, notably the uniformity in the choice of needle in terms of size and type, and the suction technique. We evaluated the adequacy of FNB alone using MOSE, thus eliminating the need for a fixed number of passes as in previous studies. To our knowledge, no previous trials have compared ROSE and MOSE. We used paired testing, which reduces selection bias. Apart from its strengths, our study also had a few limitations, which include its retrospective nature and the fact that only 2 experienced endoscopists performed all the procedures, making it difficult to generalize our findings.

To conclude, EUS FNB alone with MOSE has a high diagnostic accuracy for SPLs. ROSE does not increase the diagnostic yield for SPLs sampled using newer-generation EUS biopsy needles. The utility of ROSE should be reviewed, considering its extra costs and logistics.

Summary Box

What is already known:

- Endoscopic ultrasound (EUS)-guided sampling of solid pancreatic lesions (SPLs) is highly accurate using fine needle aspiration (FNA) needles and rapid on-site evaluation (ROSE)
- Core biopsy needles increase tissue yield, with adequacy of the core assessed using macroscopic on-site evaluation (MOSE)
- Tissue obtained using core biopsy needles with a fixed number of passes (n=3) gives similar accuracy as FNA with ROSE

What the new findings are:

- No previous studies have compared the diagnostic accuracy of EUS sampling of SPLs with adequacy of core tissue assessed by MOSE, vs. cytological assessment with ROSE, performed using core biopsy needles
- MOSE and ROSE can both assess the adequacy of sampling, without any difference in overall diagnostic accuracy for SPLs
- There is need to reevaluate ROSE while using core biopsy needles with respect to cost and logistics

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