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POINT OF VIEW

Endoscopic ultrasound in the diagnosis and staging of pancreatic cancer

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ABSTRACT

Pancreatic cancer is the 5th leading cause of cancer-related death in Western countries. The 5-year survival rate is approximately 4%, without significant changes over the last 50 years. This poor survival rate and bad prognosis are associated with the diagnosis of advanced-stage disease, which precludes the only potential curative treatment – surgical resection. In this setting, the main objective in the management of pancreatic cancer is to perform an early diagnosis and a correct staging of the disease. Endoscopic ultrasonography (EUS) appears to be an essential tool for the diagnosis and staging of pancreatic cancer. EUS diagnostic accuracy for detecting pancreatic tumors ranges from 85 to 100%, clearly superior to other imaging techniques. EUS accuracy for the local staging of pancreatic cancer ranges from 70 to 90%, superior or equivalent to other imaging modalities. EUS-guided fine-needle aspiration allows a cyto-histological diagnosis in nearly 90% of cases, with a very low complication rate. At present, the formal indications for EUS-guided fine-needle aspiration are the necessity of palliative treatment or whenever the possibility of neoadjuvant treatment is present. It could be also indicated to differentiate pancreatic adenocarcinoma from other pancreatic conditions, like lymphoma, metastasis, autoimmune pancreatitis or chronic pancreatitis. We can conclude that EUS is an essential tool in the management of patients with pancreatic tumors.

Key words: Endoscopic ultrasound. Pancreatic cancer. Diagnosis. Stanging.

INTRODUCTION

Pancreatic cancer is the 5th leading cause of cancer death in Western countries, and the second cause of cancer death among gastrointestinal tumors (1). The 5-year survival rate is approximately 4%, without significant changes over the last 50 years (2). The only group of patients with pancreatic cancer and an acceptable prognosis are those with potentially resectable pancreatic tumors (3).

Bad prognosis in these patients is related to tumor stage, which may preclude the only potentially curable treatment – surgical resection. Traditionally, patients with pancreatic cancer without distant disease underwent a surgical procedure. However, without an adequate preoperative study, the resectabily rate was between 5 and 25%, with high morbidity (3). On the other hand, by performing a correct study prior to surgery, this resectability rate can reach 75% (4). That is the reason why the primary objective in the management of this disease is to perform both an early diagnosis and a correct staging, which will allow to perform the only potentially curative treatment – surgical resection.

Nowadays, there are many procedures to perform the diagnosis and staging of pancreatic cancer. Some of them are abdominal ultrasounds (AU), helical CT, magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), abdominal arteriography, and more recently endoscopic ultrasonography (EUS).

EUS allows a detailed analysis of the pancreatic parenchyma, pancreatic ducts, and all structures adjacent to the pancreas. It has become an essential tool for the study of pancreatic diseases, and is considered the reference method for the diagnosis and staging of inflammatory pancreatic diseases and solid pancreatic tumors, as well as a key point in the diagnostic and staging algorithms for pancreatic tumors (5,6).

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The aim of this article is to perform an exhaustive revision of the literature regarding the usefulness of EUS in the diagnosis and staging of pancreatic cancer. First we will analyze its usefulness in the diagnosis of pancreatic tumors, afterwards we will discuss its accuracy in the evaluation of local infiltration and lymph-node extension. Finally we will focus on the importance of cyto-histological evaluation for pancreatic tumors.

ENDOSCOPIC ULTRASOUNDS IN THE DIAGNOSIS OF PANCREATIC TUMORS

When analyzing the results of the most important and best-designed studies, the sensitivity of EUS for the diagnosis of solid pancreatic tumors was 96% (range 85-100%) (7-27). However, these studies included benign pancreatic diseases and ampullary tumors, and this may bias the analysis in favor of EUS (7-10,16,17,22-24). But if we only evaluate studies regarding malignant pancreatic tumors, the diagnostic sensitivity is still very high, clearly superior to that of other imaging techniques. When EUS was compared to conventional CT (8,9,11-17,21-24,26,27), EUS diagnostic sensitivity was superior (98 *vs*. 77%, $p < 0.0001$), and differences remained when the comparison was performed with helical CT (16,18,22-24). Among all these studies, we should focus in two of them comparing EUS and multidetector-row CT. In a retrospective study published by Agarwal et al. (26), including 81 patients, EUS sensitivity for tumor detection was 94%, while CT only reached 86%. DeWitt et al. (27) published similar data. They performed a comparative, prospective, cohort study, including 120 patients. EUS sensitivity for tumor detection (98%) was superior to that of multidetector-row CT (86%).

But the point in which EUS has demonstrated to be clearly more accurate is in the identification of small pancreatic tumors (Fig. 1), which have been undetected by other imaging techniques (7,8,12,18,22,26,27-29). For tumors between 15 and 35 mm, Legman et al. (18) reported that EUS and helical CT both detected all tumors in 14 patients; however, when analyzing tumors smaller than 15 mm, EUS detected 6 of 6 cases, whereas CT could only detect 4. Muller et al. (12) analyzed the sensitivity of EUS, CT and MRI in the identification of tumors smaller than 3 cm, showing values of 93, 53 and 67%, respectively. In the same article, for tumors smaller than 2 cm, the sensitivity of each was 90, 40 and 33%, respectively. Ardengh et al. (28) performed a retrospective study including 17 patients with tumors smaller than 3 cm. EUS identified the pancreatic tumor in all cases (100%), whereas CT could only identify the tumor in 94% of cases. However, only the study by DeWitt et al. (27) was performed with multidetector-row CT in this group of patients with smaller tumors. In their study, including 19 patients with tumors smaller than 25 mm, they reported a non-significant trend towards improved detection by EUS as compared to multidetector-row CT (89 *vs*. 53%, $p = 0.08$). Recently, two new papers have confirmed these data, showing that EUS allows to detect pancreatic lesions not clearly visualized by CT or MRI, and is able to diagnose pancreatic tumors (from pancreatic adenocarcinomas to pancreatic metastases or endocrine tumors) in nearly 65% of cases (30,31).

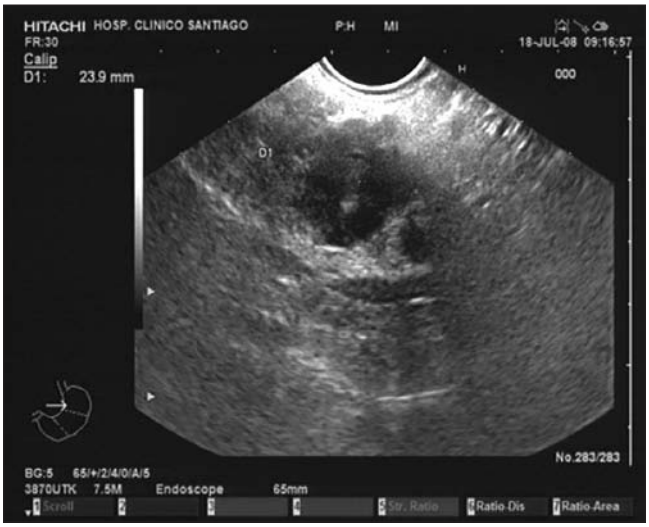

Fig. 1. Pancreatic adenocarcinoma, 23 mm in size, located in the body-tail of the pancreas - irregular margins, hypoechoic, not affecting adjacent structures.

EUS is also considered very accurate in ruling out the presence of a pancreatic tumor. Catanzaro et al. (32) retrospectively identified 80 patients with clinical suspicion of pancreatic cancer and normal EUS. After a mean follow-up of 24 months, one patient with evidence of chronic pancreatitis on EUS was found to have a pancreatic cancer at surgery. No patient with normal pancreatic EUS results developed cancer during the follow-up period. In the study performed by Agarwal et al. (26) in patients with clinical suspicion of pancreatic cancer, and without identifiable lesions on multidetector-row CT, the diagnostic accuracy of EUS was 92%, able to exclude the presence of a pancreatic tumor when EUS was normal.

In this context, the most important paper summarizing all the above data has been the systematic review published by DeWitt et al. (33). They compared CT and EUS for the diagnosis of pancreatic cancer. They analyzed the 11 better-designed studies, including a total of 678 patients. Nine of these studies analyzed the diagnostic accuracy of EUS for the detection of pancreatic tumors. All studies included were consecutive series of patients, with a good standardization of imaging techniques, independently compared to the gold standard, and almost all were prospective studies. In all these studies, the diagnostic sensitivity of EUS was superior to that of helical CT, even more so for pancreatic tumors smaller than 3 cm. They concluded that EUS is superior to CT for the detection of pancreatic cancer.

ENDOSCOPIC ULTRASOUNDS IN THE STAGING OF PANCREATIC CANCER

At this point we will review the existing evidence on local staging (with specific data on vascular and lymph-node infiltration) and the evaluation of resectability. The staging of pancreatic cancer is based on the TNM classification published by AJCC in 2002 for pancreatic adenocarcinoma (Table I).

Table I. TNM staging of pancreatic adenocarcinoma

Tumor
T-x: Primary tumor cannot be assessed
T-0: No evidence of primary tumor
T-is: Carcinoma *in situ*
T-1: Tumor limited to the pancreas, < 2 cm
T-2: Tumor limited to the pancreas, > 2 cm
T-3: Tumor extension beyond the pancreas (duodenum, bile duct, portal o superior mesenteric vein)
T-4: Tumor involving the celiac axis and superior mesenteric arteries
Regional lymph nodes
N-x: Regional lymph nodes cannot be assessed
N-0: No regional lymph node metastasis
N-1: Regional lymph node metastasis
Distant metastasis
M-x: Distant metastasis cannot be assessed
M-0: No distant metastasis
M-1: Distant metastasis
Stage 0 – Tis, N0, M0
Stage IA – T1, N0, M0
Stage IB – T2, N0, M0
Stage IIA – T3, N0, M0
Stage IIB – T1, N1, M0 o T2, N1, M0 o T3, N1, M0
Stage III – T4, any N, M0
Stage IV – any T, any N, M1

(AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag; 2002. p. 209-20).

Local staging

Several studies have been published evaluating the accuracy of EUS in the loco-regional staging of pancreatic cancer, in most cases compared to CT scanning, and in more recent studies with MRI and/or selective abdominal arteriography. Globally, the reported accuracies of local staging by EUS in pancreatic cancer range from 62 to 94%, and those of nodal staging range from 72 to 92% (34-46). The most important study, as previously mentioned, has been the systematic review published by DeWitt et al. (33), comparing CT and EUS for the staging of pancreatic cancer. In this setting, the authors analyzed the 11 best designed studies, including a total of 678 patients, comparing the accuracy of both techniques for the local staging of this tumor. All studies included were consecutive series of patients with a good standardization of imaging techniques, independently compared to the gold standard, and almost all were prospective studies. The authors conclude that EUS appears to be superior to CT for T-staging and regarding the vascular invasion of the splenoportal confluence; however both techniques appear to be equivalent for nodal staging and overall vascular invasion.

Vascular invasion

For the overall evaluation of vascular invasion the accuracy of EUS ranges from 40 to 100% (14,15,21,23, 24,38,41,42). The sensitivity and specificity of EUS for malignant vascular invasion range from 42 to 91% and from 89 to 100%, respectively (21,38,41,42,47). However, when comparing EUS to CT in this setting, some studies have demonstrated that EUS is more accurate (14,21,23,24), and other authors have reported that the accuracy of CT is superior (15,41,42). MRI showed similar results to EUS (41,42). When evaluating the different vessels separately, for venous invasion EUS demonstrated to be equal or superior to CT, with a sensitivity and overall accuracy of 56 and 50%, respectively (11,13). For the evaluation of portal vein and confluence invasion, the sensitivity of EUS increases to 60-100%, in all cases superior to all other imaging techniques (7,9,17,22,48). However, for the evaluation of the superior mesenteric vein, superior mesenteric artery and celiac axis, the sensitivity of EUS decreases to 17-83% (37), 17% (23) and 50% (9), respectively, with better results for helical CT (9,22,23). This is in contrast to the splenic artery and vein, an area easily seen and staged by EUS (7,48,49). A systematic review of the literature and a meta-analysis have been recently published, analyzing the usefulness of EUS in this setting. A total of 29 studies were evaluated (n = 1,308), in which EUS showed a sensitivity for the detection of vascular invasion of 73%, with a specificity of 90.2% (50).

Lymph node infiltration

The main node stations to be evaluated in pancreatic cancer are the perigastric, periduodenal, and celiac nodes, as well as the hepatic hilium. Mediastinal lymph nodes should also be evaluated (up to 5% of patients with pancreatic cancer may present with lymph node metastases at this level). The accuracy of EUS for N staging ranges from 64 to 82% (9,11,12,19,21,22,24, 27,33-39). Although EUS is highly sensitive for detecting regional lymph nodes, it has difficulties in distinguishing between malignant and inflammatory adenopathies, the performance of a EUS-guided fine-needle aspiration (FNA) of lymph nodes being necessary on many occasions (51-53).

Evaluation of respectability

At present, tumors considered irresectable are those with metastatic disease, invasion of the superior mesenteric artery, celiac axis and hepatic artery, and/or significant invasion of the portal vein and superior mesenteric vein (Fig. 2).

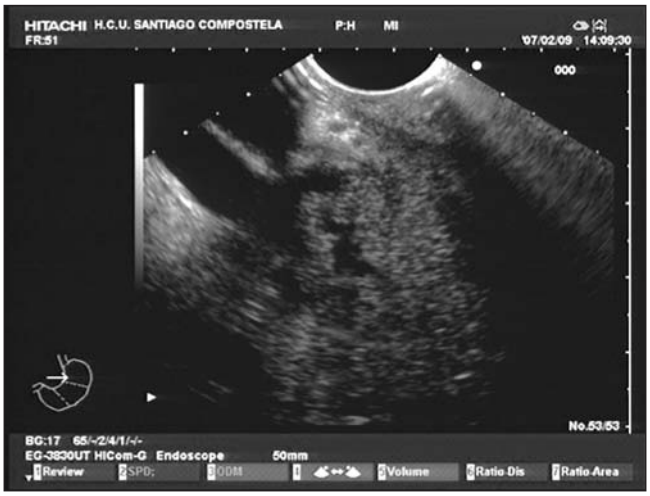

Fig. 2. Pancreatic adenocarcinoma located at the head of the pancreas, infiltrating the common bile duct, and with a complete obstruction of the portal vein.

In the various series published in the literature, the sensitivity and specificity of EUS for the evaluation of resectability in pancreatic cancer was 69 and 82%, respectively (16,18,21,27,36,39,40,45,54). When comparing EUS to other imaging techniques, results are contradictory. Generally, most studies showed a similar accuracy of EUS, helical CT, and MRI in the evaluation of resectability for pancreatic cancer. The study from Soriano et al should be emphasized (41). The authors found the initial use of CT or EUS more accurate, followed by other technique to complete the evaluation. Tierney et al. (47) suggested that helical CT should be performed initially, and that EUS should also be employed in most patients because of its improved detection of vascular invasion. DeWitt et al. (27) showed similar conclusions, supporting the use of various imaging techniques, mainly EUS and helical CT. Again, the most important study in this setting has been the systematic review published by DeWitt et al. (33) comparing CT and EUS for the evaluation of resectability in pancreatic cancer. In this setting, the authors analyzed 4 out of the 11 best-designed studies, which specifically analyzed this item. All studies included were consecutive series of patients with a good standardization of imaging techniques, independently compared to the gold standard, and almost all were prospective studies. The authors conclude that EUS appears to be superior to CT for the evaluation of resectability in pancreatic cancer.

EUS can also help in the evaluation of tumor extension to the liver (allowing the performance of a EUS-guided FNA for cyto-histological confirmation), peritoneum and/or pleura (with the possibility to perform a EUS-guided FNA of ascites or pleural effusion) (55-61).

CYTO-HISTOLOGICAL CONFIRMATION OF PANCREATIC TUMORS

From an oncologist's point of view, it is necessary to obtain a cytological or histological sample in order to confirm the diagnosis of pancreatic adenocarcinoma when the patient requires chemotherapy and/or radiotherapy, or whenever the possibility of neoadjuvant treatment is present (62-64). However, many authors accept other indications to reach a histological confirmation of pancreatic adenocarcinoma in the presence of a pancreatic mass. Among them, the ability to identify lesions other than pancreatic adenocarcinoma, like lymphoma, pancreatic metastasis, autoimmune pancreatitis or an inflammatory mass in chronic pancreatitis, because these lesions require completely different treatments; there is also the possibility of additional information that may assist in preoperative patient and family counseling and therapy selection, as is the case with other tumors (65,66).

In this context, EUS-guided FNA has proven be an essential tool because of its high accuracy and minimum complications (Fig. 3). In the studies published in the liter-

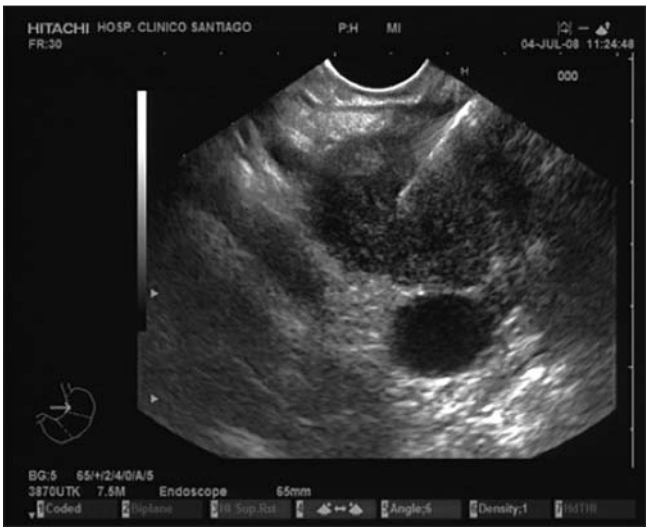

Fig. 3. EUS-guided fine-needle aspiration with a 22-gauge needle of a pancreatic tumor located in the head of the pancreas, corresponding to a pancreatic adenocarcinoma. The tip of the needle may be seen inside the tumor.

ature, the diagnostic accuracy of EUS-guided FNA ranges between 72 and 96% (67-79). Among them, we will focus on the most complete papers. In the study by Harewood et al. (76), prospectively including 185 consecutive patients with the suspicion of pancreatic cancer, all patients underwent a CT scan (61 with CT-guided FNA) and 91 ERPC (41 of them with cytology). In 58 patients with a negative cytology after CT-guided FNA, EUS-guided FNA showed a sensitivity for malignancy of 90%. Similarly, in 36 patients with a negative cytology at ERCP, the diagnostic sensitivity for malignancy with EUS-guided FNA was 94%. Eloubeidi et al. performed a study prospectively including 158 patients with the suspicion of pancreatic cancer. With a median of 3 passes, the diagnostic sensitivity, specificity and overall accuracy of EUS-guided FNA was 84.3, 97, and 84%, respectively (78).

EUS-guided FNA, apart from determining whether a lesion is benign or malignant, also allows a definitive diagnosis to be established. Iglesias-García et al. (80), in a prospective study including 62 consecutive patients with pancreatic solid tumors, were able to diagnose lesions other than pancreatic adenocarcinoma, like lymphoma, oat-cell metastasis from lung cancer, anaplastic carcinoma, and up to 24 inflammatory masses. The overall diagnostic accuracy obtained was 90.2%. However, the most important point in this setting was the differential diagnosis with chronic pancreatitis and autoimmune pancreatitis. In this context, EUS-guided FNA has also shown a high accuracy (81-84). Varadarajulu et al. (82), in a study including 282 patients with pancreatic solid tumors with and without chronic pancreatitis, EUS-guided FNA showed a lower diagnostic sensitivity in the group of patients with chronic pancreatitis (73.9 *vs*. 91.3%; p = 0.02). There were no differences in terms of specificity (100 *vs*. 93.8%) and overall accuracy (91.5 *vs*. 91.4%). In another study published by Ardengh et al. (83), including 69 pancreatic masses in chronic pancreatitis, EUS-guided FNA increased diagnostic sensitivity, specificity and overall accuracy in the differential diagnosis between inflammatory conditions and pancreatic adenocarcinoma (72.7 *vs*. 63.6%; 100 *vs*. 75.9%; 95.7 *vs*. 73.9%; respectively).

However, the best study, in terms of design and final conclusions, is the one published by Eloubeidi et al. (84) – 547 patients who underwent EUS-guided FNA over a 4.5-year period were enrolled. Patients underwent surgical exploration and resection based on their comorbidity status, and on evidence of resectability based on spiral computed tomography (CT) and EUS imaging reviewed in a multidisciplinary approach. The operating characteristics of EUS-guided FNA for solid pancreatic masses were: sensitivity 95% (95% CI: 93.2-95.4), specificity 92% (95% CI: 86.6-95.7), positive predictive value 98% (95% CI: 97-99), negative predictive value 80% (95% CI: 74.9-82.7). The overall accuracy of EUS-guided FNA was 94.1% (95% CI: 92.0-94). Of the 414 true positive patients according to EUS-guided FNA, 138 (33%) were explored; 82% of true positive patients were ultimately found inoperable and received palliative therapy or chemotherapy. They concluded that EUS-guided FNA is a safe and highly accurate method for tissue diagnosis in suspected pancreatic cancer. This approach allows for a preoperative counseling of patients, minimizing surgeon's operative time in cases of unresectable disease, and avoids surgical biopsies in a majority of patients with inoperable disease. However, they recommend a surgical exploration of patients with a clinical scenario suspicious for pancreatic cancer – a mass found on EUS or CT, but inconclusive or negative cytology.

Finally, in the study published by Lambert et al. (85), EUS-guided FNA had important clinical implications for patient management; in fact, it can contraindicate surgical procedures in 41% of patients, avoid the performance of other diagnostic techniques in 57% of cases, and modify the therapeutic attitude in 68% of cases.

But a crucial point of EUS-guided FNA is the low rate of complications associated with the technique. The risk of bacteremia is very low; the risk of acute pancreatitis ranges from 1 to 2%, and the probability of bleeding or peritonitis is rare. The group of cystic lesions is more dangerous, mainly due to the risk of infection; therefore, antibiotics are always recommended following pancreatic cyst aspiration (86). The largest study included 355 patients who underwent EUS-guided FNA for solid pancreatic lesions. Major complications were encountered in 9 patients (2.54%, 95% CI 1.17-4.76). Acute pancreatitis occurred in 3 of 355 (0.85%, 95% CI 0.17-2.45); 2 patients were hospitalized, and 1 patient recovered with outpatient analgesics. Three patients were admitted for severe pain after the procedure; all were treated with analgesics and subsequently discharged with no sequels. Two patients (0.56%, 95% CI 0.07-2.02) developed fever and were admitted for intravenous antibiotics; one patient recovered with intravenous antibiotics and the other required surgical debridement for necrosis. One patient required the use of reversal medication. Overall, 1.97% (95% CI 0.80-4.02) of patients was hospitalized for complications. None of the patients experienced clinically significant hemorrhage, perforation, or death (87). The rate of tumoral seeding with EUS-guided fine-needle aspiration is significantly lower than with percutaneous-guided fine-needle aspiration. In the paper published by Micames et al., in the EUS-guided FNA group only one patient out of 46 developed peritoneal carcinomatosis, compared to 7 out of 43 in the percutaneous-guided FNA group (2.2 *vs*. 16.3%; p < 0.025). The authors recommended EUS-guided FNA as the method of choice for diagnosis in patients with potentially resectable pancreatic cancer (88).

CONCLUSIONS

We can conclude that EUS is superior to other imaging techniques for the detection of pancreatic tumors, mainly in small pancreatic solid lesions. EUS seems to be

superior to other imaging procedures for local staging (T), mainly in the evaluation of vascular invasion of the portal vein and splenic vessels. However, EUS seems to be equivalent to the other imaging techniques (mainly CT scan) in the evaluation of nodal staging and overall vascular invasion, and in the assessment of tumor resectability. However, it is important to point out that EUS is clearly operator-dependent, and in very experienced hands its accuracy is very high; new multidetector-row CT equipments have been developed recently, which may probably be similar in terms of accuracy to EUS.

EUS-guided FNA is also becoming essential in the management of pancreatic cancer, mainly related to its high accuracy and low morbidity and mortality. At present, a diagnosis of pancreatic adenocarcinoma must be confirmed when the patient requires chemotherapy and/or radiotherapy, or whenever the possibility of neoadjuvant treatment is present. It is also very important that conditions other than pancreatic adenocarcinoma, which require specific treatment, be identified.

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