Thallium-201 Scintigraphy in Bone Sarcoma: Comparison with Gallium-67 and Technetium-MDP in the Evaluation of Chemotherapeutic Response

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This study attempts to characterize thallium-201 (^{201}Tl) uptake in patients with bone and soft-tissue sarcoma and to compare these findings with gallium-67 (^{67}Ga) and bone scintigraphy with emphasis on evaluating tumor viability before and after chemotherapy. Thirty-eight patients with surgically-proven sarcomas were evaluated. All patients had gallium and thallium studies. Nineteen patients underwent pre- and post-chemotherapy thallium and evaluation. Seven patients also had technetium-99m-MDP (^{99m}Tc-MDP) bone scintigraphy comparisons. Pathologic changes pre- and postchemotherapy were graded on the basis of %tumor necrosis as defined histologically. Scintigraphic comparisons demonstrated a high degree of correlation with ^{201}Tl and poor correlation with ^{99m}Tc-MDP. Thallium-201 was superior to ^{99m}Tc-MDP and ^{67}Ga in predicting tumor response to chemotherapy as determined by %tumor necrosis determined histologically. Gallium was superior to Tc-MDP in predicting response to chemotherapy. However, both ^{67}Ga and ^{99m}Tc-MDP appear to be affected by factors other than tumor activity.

J Nucl Med 1990; 31:567–572

The imaging evaluation of bone sarcomas have included bone and gallium scintigraphy as well as radiographic studies, including plain x-rays, computerized tomography (CT), magnetic resonance imaging (MRI) studies, and angiography. Bone scintigraphy is exquisitely sensitive for detection of primary bone tumors as well as osseous involvement by contiguous spread of soft-tissue sarcoma or metastasis (*1*). However, bone imaging, in general, is not helpful in accurately defining the extent of the tumor and in assessing response to treatment because osseous uptake is reflected by both blood flow as well as healing response (*2–4*). Although the gallium scan has some potential (*5–7*), it is not consistently accurate in defining the extent of bone lesion and in assessing treatment response. Because of its bone-seeking property, gallium imaging may reflect healing and, therefore, is not ideal in assessing response to therapy. CT and MRI have not been shown to be superior in defining the anatomic extent of lesions and are often not sensitive indicators of response to therapy.

Thallium-201 (^{201}Tl) has been shown to have affinity for a variety of neoplastic processes (*8–22*), including bone and soft-tissue sarcomas. Recently, ^{201}Tl has been demonstrated to have the potential of more accurately reflecting viable tumor burden (*23–25*). The purpose of the current study is to evaluate ^{201}Tl in characterizing tumors of the osseous structures and to determine whether it accurately reflects tumor burden and response to therapy.

MATERIALS AND METHODS

Patient Population

The study encompasses 38 patients with a variety of sarcomas of the bone (Table 1). Nineteen patients from this group underwent pre- and postchemotherapy ^{201}Tl and gallium-67 (^{67}Ga) studies. Seven patients also had pre- and post-therapy bone scans.

The time sequence of initial biopsy, baseline ^{201}Tl and ^{67}Ga scans, initiation of chemotherapy, follow-up scans, and final tumor resection is outlined in Figure 1.

Response to Therapy

Clinical response to chemotherapy was assessed by an oncologist (GR), which included a subjective evaluation of pain and swelling of the affected area. The results were classified as improvement, no change, or worsening. Biochemical response was measured by serum alkaline phosphatase levels taken before and after chemotherapy. Percent change was calculated for each pair of determinations. Histological tumor response was determined by comparing the pre-treatment

Received Nov. 23, 1988; revision accepted Dec. 8, 1989.

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TABLE 1
Histologic Types of Bone and Soft-Tissue Sarcomas

Osteogenic sarcoma	18
Ewing's sarcoma	6
Chondroblastic osteosarcoma	1
Differentiated chondrosarcoma	1
Malignant fibrous histiocytoma (MFH)	5
Malignant schwannoma	2
Myosarcoma	1
Myosarcoma, spindle cell sarcoma	1
Leiomyosarcoma	2
Recurrent Angiosarcoma	1
Total cases	38

biopsy specimen to a postchemotherapy surgical specimen. The percent tumor necrosis was determined by a pathologist (JM) examining the slides of the resected specimens. Tumor necrosis of 95% or greater was considered as significant improvement. Values <95% were considered as nonsignificant partial responses. The percent of tumor necrosis was determined for each patient.

Imaging Techniques

Radioisotope imaging sequences included a total-body scan beginning 5 min following an intravenous (i.v.) administration of 3 mCi of ^{201}Tl with a scanning Anger camera at a speed of 10 cm/min. A large field rectangular camera with a ⅜-in. sodium iodide crystal was used in all cases. The ^{201}Tl imaging study was immediately followed by a total-body bone imaging study using 20 mCi of technetium-99m-MDP (^{99m}Tc-MDP). The patient was then injected with 8 mCi of ^{67}Ga-citrate and a total-body gallium study was performed 48–72 hr postinjection.

Low-energy high-resolution collimators were used for thallium and technetium studies with medium-energy collimation used for gallium examination. High resolution spot views were obtained in all studies to include regions of interest.

Image Analysis

The thallium, gallium, and bone images were visually evaluated by two blinded independent observers (LR, AW). Thallium activity in the tumor was graded on a scale of 0–4, with 0 = background activity, 1+ = equivocal increase, 2+ = definite activity, but less than heart, 3+ = definite activity equal to heart, 4+ activity in tumor greater than heart. Gallium activity was graded on a scale of 0–4, with 0 = background activity, 1+ = equivocal activity, 2+ = activity in tumor, but less than sternum, 3+ equal to sternum and 4+ greater than sternum. The ^{99m}Tc-MDP bone scan was rated relative to the contralateral site within the skeletal system. Zero equals no increase, 1+ = equivocal, 2+ = mild increase, 3+ = moderate increase, and 4+ = major increase.

In patients undergoing pre- and post-therapy comparative studies, all images were visually rated as improved, unchanged or worse. Image response was then correlated with clinical and tissue response to therapy.

RESULTS

All 38 patients with sarcoma had positive ^{201}Tl and ^{67}Ga studies. Bone scans also were positive in all patients with primary bone tumors.

Comparison of pre- and postchemotherapeutic thallium, gallium, bone scans, clinical observation, biochemical studies, and pathology including tumor type and percent necrosis is summarized in Table 2.

Figure 2 compares the percent tumor necrosis histologically with changes in the scintigraphic studies. Of the eight patients demonstrating a >95% tumor necrosis histologically, seven patients demonstrated improvement on the thallium study, while only four patients demonstrated improvement on gallium. Conversely, in the >95% necrosis group, one patient demonstrated worsening on thallium, two patients demonstrated worsening on gallium, and two patients demonstrated no change with gallium. Of interest were two patients with >95% tumor necrosis who demonstrated no change on the bone scan. There were no cases studied with either thallium, gallium, or Tc-MDP that demonstrated improvement with <95% tumor necrosis.

Biochemical Markers

Figure 3 is a correlation of percent tumor necrosis with change in alkaline phosphatase following chemotherapy. There is no statistically significant correlation noted, indicating the alkaline phosphatase to be a poor indicator of tumor response to chemotherapy.

Clinical Correlation

Clinical evaluation including subjective improvements in pain and swelling correlated poorly with percent tumor necrosis, with many patients demonstrating reductions in pain and swelling with tumor necrosis well below the 95% tumor necrosis level.

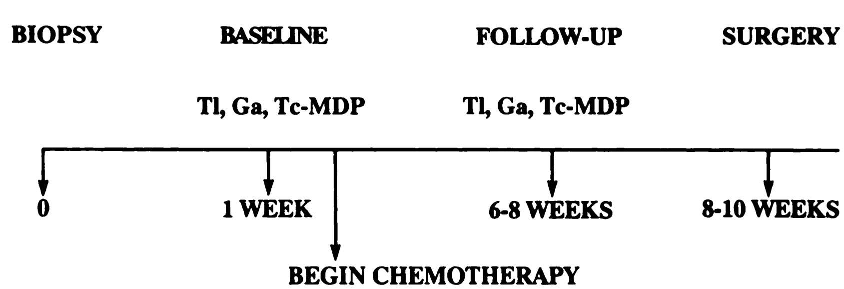

FIGURE 1
Time-sequence diagram of patients undergoing chemotherapy for sarcoma of bone. The initial biopsy precedes the base-line thallium and gallium study by 7–10 days. Chemotherapy is then started and follow-up scans are obtained 6–8 wk later. Surgery is generally done within 1 wk of the final follow-up scans with the patients still on chemotherapy.

TABLE 2
Comparison of Scintigraphic, Clinical, and Biochemical Studies with Tumor Necrosis Following Chemotherapy

No.	Patient	Age/Sex	Diagnosis	Tumor site	Change in scans: ^{201}Tl	Change in scans: ^{67}Ga	Change in scans: ^{99m}TC-MDP	Clinical evaluation: Pain	Clinical evaluation: Swelling	Chemical ALK PO units/litre (% change)	% Tumor necrosis
1	A.T.	16/M	OS	Right distal femur	Improved	Improved	—	Decreased	Decreased	598–225 (62)	100
2	B.K.	16/F	OS	Left prox. tibia	No change	No change	—	Decreased	No change	—	90
3	B.R.	44/M	OS	Left knee	Improved	No change	No change	Decreased	Decreased	114–89 (28)	98
4	C.B.	15/M	OS	Left distal femur	Worse	Worse	—	Decreased	Decreased	239–139 (42)	95
5	G.D.	16/M	OS	Left distal femur	Worse	Worse	No change	Decreased	No change	—	80
6	P.M.	16/M	OS	Right distal femur	No change	No change	No change	Decreased	Decreased	161–152 (6)	35
7	S.J.	15/M	OS	Left distal femur	No change	No change	—	Decreased	No change	—	80
8	S.D.	17/M	OS	Left distal femur	Worse	Worse	—	Decreased	No change	—	70
9	W.J.	13/F	OS	Right distal femur	Worse	Worse	—	Decreased	No change	2255–421 (81)	60
10	B.G.	18/M	OS	Right distal femur	Improved	Improved	—	Decreased	Decreased	—	95
11	A.A.	11/F	OS	Left distal femur	Improved	Improved	Improved	Decreased	Decreased	208–169 (19)	100
12	D.K.	16/F	OS	Left humerus	Improved	Worse	No change	Decreased	No change	372–269 (28)	>98
13	B.R.	13/M	OS	Left prox. femur	No change	Worse	—	Increased	No change	424–121 (71)	60–80
14	A.L.	23/F	ES	Left hip	Improved	No change	—	Decreased	No change	—	>95
15	H.M.	22/M	ES	Right scapula	No change	—	Sl. worse	Decreased	No change	—	60
16	S.S.	34/M	ES	Left S.I. joint	No change	No change	—	No change	No change	—	70
17	S.B.	19/M	ES	Left hemipelvis	Worse	Worse	No change	No change	Size	79–91 (15)	70
18	K.L.	44/M	MFH	Right distal femur	Improved	Improved	—	Decreased	Decreased	—	100
19	R.H.	53/M	MFH	Left prox. femur	No change	Worse	—	Decreased	Decreased	—	70

OS = osteogenic sarcoma; ES = Ewing's sarcoma; MFH = malignant fibrous histiocytoma; and ALK PO_4 normal range = <108 units/litre.

Illustrative Cases

Figure 4 is a comparison of the thallium, gallium, and bone scan in a 16-yr-old male with an osteogenic sarcoma of the right distal femur. The thallium study shows a peripheral area of marked increase surrounding an area of reduced activity. Most bone sarcomas demonstrate maximum cell activity peripherally with reduction of activity centrally (*26*). The gallium study performed 48 hr following the thallium study demonstrates a significant accumulation in the distal portion of the right femur with no obvious area of reduced activity centrally. The bone scan performed 48 hr prior to the thallium examination shows an intense focus of increased activity involving the entire distal femur with increased activity also demonstrated in the proximal tibia. The findings on the bone scan in general were more extensive than abnormalities seen with thallium or gallium.

Figure 5 is an example of a 16-yr-old male with osteogenic sarcoma of the left distal femur. Figure 5A demonstrates intense activity on the thallium, gallium, and bone examinations. Figure 5B demonstrates complete resolution with thallium, mild abnormality with ^{67}Ga, and moderate abnormality on bone scintigraphy. The bone scan again overestimates the extent of tumor, with increased activity noted in the left proximal tibia. At surgery, the patient was demonstrated to have a localized tumor within the femur and no extension to the tibia.

Figure 6 shows a 12-yr-old female patient with an osteoblastic osteogenic sarcoma of the left upper humerus. Significant reduction in thallium activity following chemotherapy is noted. The thallium scans were concordant with a markedly improved clinical picture and a tumor necrosis of >98%. The gallium scan demonstrates worsening of the humeral abnormality possibly related to bone healing. Increased humeral activity may also be related to the redistribution of gallium following the chemotherapy, with a significant decrease of gallium noted in the liver when compared to the prechemotherapy study. The bone scan remained unchanged.

DISCUSSION

Advances in chemotherapy for bone and soft-tissue sarcomas have greatly improved patient survival in recent years (*27,28*). Improved results have been reported in patients in whom postoperative chemotherapy is selected based upon the histologic response of tumor to preoperative chemotherapy. Patient evaluation during preoperative chemotherapy traditionally includes clinical assessment, biochemical markers such as serum alkaline phosphatase levels, diagnostic radiology including CT, MRI and angiography as well as

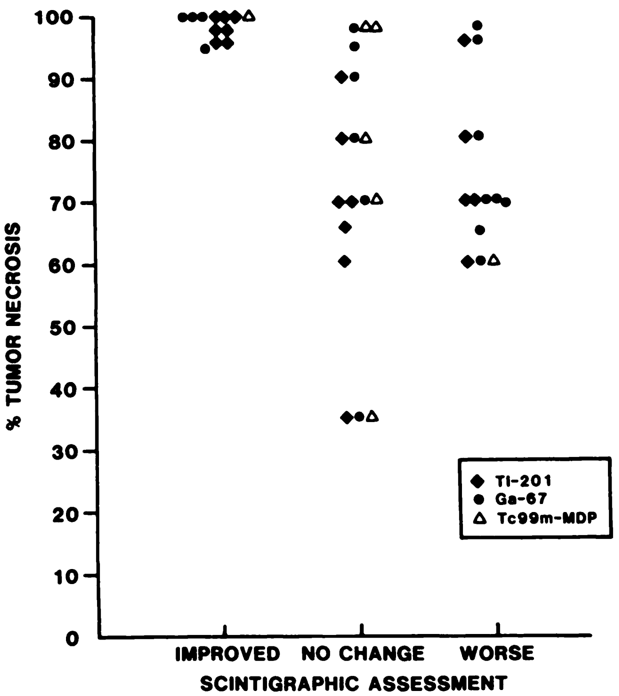

FIGURE 2
Comparison of %tumor necrosis determined histologically with scintigraphic studies performed pre- and postchemotherapy. Thallium-201 correlated best with the presence or absence of significant tumor necrosis as defined by >95% tumor necrosis. The poorest correlation was with the ^{99m}Tc-MDP bone studies while ^{67}Ga was intermediate.

radionuclide imaging. Many investigators have reported the clinical utility of bone scintigraphy in following patients postchemotherapy (*29–32*). Our study does not support the use of bone scintigraphy as an accurate measure of therapeutic response. Bone scintigraphy gave an accurate correlation with clinical and pathologic response in only one of seven cases in our series. It is postulated that the bone scan reflects a healing response in these patients similar to the reported "flare phenomenon" following chemotherapy in a variety of

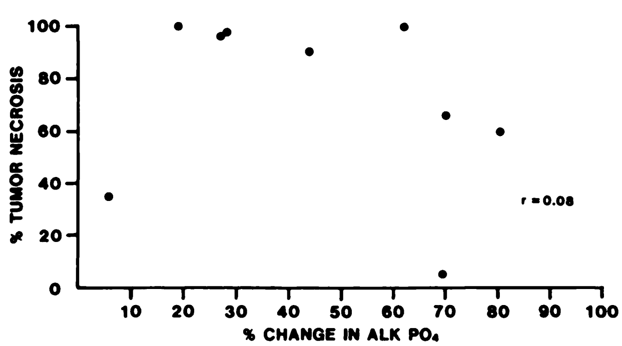

FIGURE 3
Correlation of %tumor necrosis with percent change in alkaline phosphatase following chemotherapy. No statistically significant correlation between the %tumor necrosis and alkaline phosphatase change was noted.

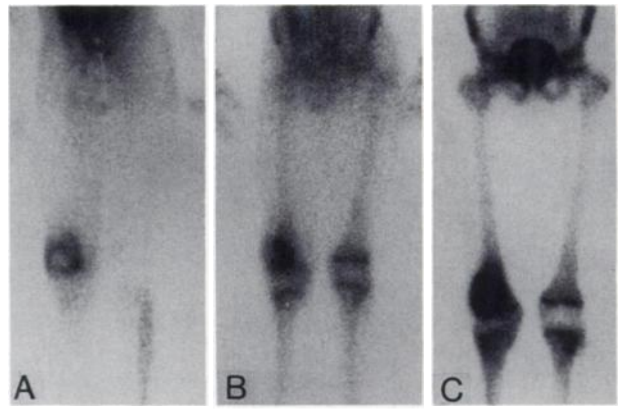

FIGURE 4
Comparison of ^{201}Tl (A), ^{67}Ga (B), and bone scintigraphy (C) in a 16-yr-old male with osteogenic sarcoma of the right distal femur. Findings on the bone scan done with ^{99m}Tc-MDP generally were more extensive than abnormalities noted on the thallium or gallium study. In several cases of bone sarcoma, a rim of increased activity surrounding a central area of reduced uptake was noted on the thallium study while gallium and ^{99m}Tc-MDP bone studies demonstrated the entire area to be active.

metastatic tumors to the osseous system (*4,33–35*). In many patients, the bone scan appeared to overestimate the extent of disease probably on the basis of increased blood flow to the affected extremity.

Gallium imaging had a better correlation than bone scintigraphy, but was not ideal possibly because of its bone seeking properties, also most likely reflecting healing response in many cases and showing extended uptake similar to the bone imaging studies.

Thallium-201 is a readily available potassium analog and can be used with standard Anger camera instrumentation. Since it does not accumulate in the underlying osseous structures, the scintigraphic findings do not appear to reflect bone healing and, therefore, represents viable tumor mass. The tumor detection is probably dependent upon a combination of blood flow, tumor mass, and cellular viability. Thallium scintigraphy is logistically superior to bone and gallium scintigraphy in that it requires a single patient visit in which imaging is started immediately after injection. The overall examination requires less than one hour for a routine study. The radiation levels to total body and critical organs are acceptably low (*36*).

The discordant patterns between thallium, gallium, and bone scintigraphy also may be partially explained on the basis of the natural growth pattern of bone sarcomas. The bone sarcomas appear to grow radially with an active tumor front present peripherally as the tumor grows and a central area of reduced cellular activity accompanied often by a poor blood supply and some tumor necrosis (*26*). This most likely explains the "doughnut" appearance of thallium scintigraphy in many of the patients with rapidly growing bone sarco-

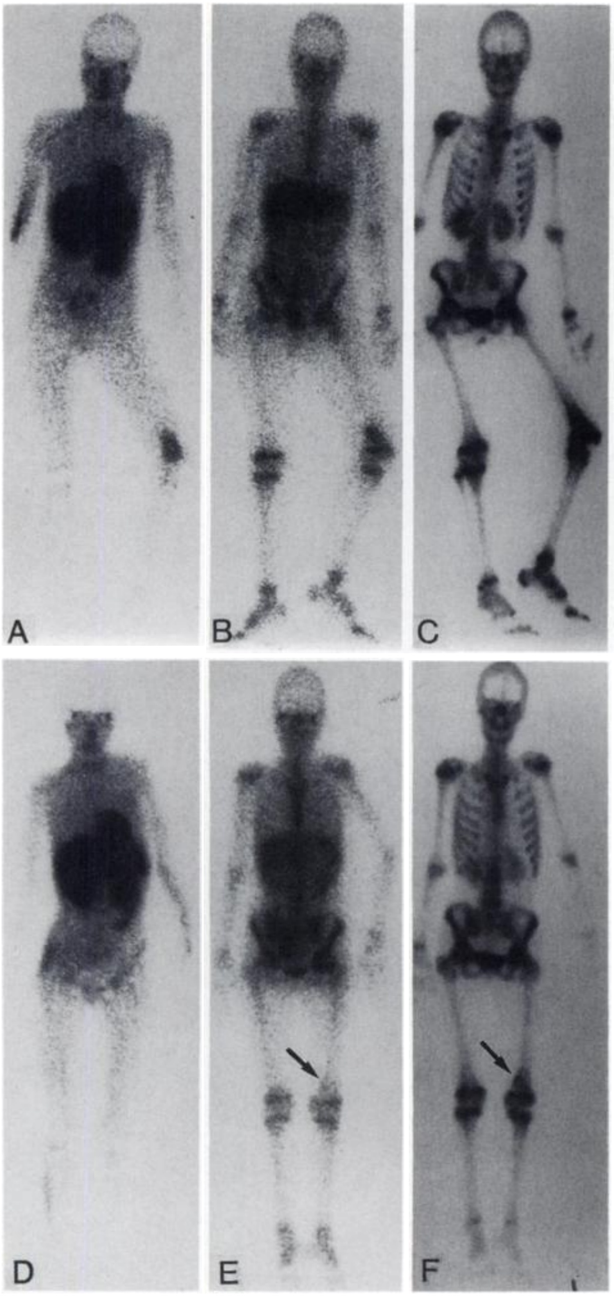

FIGURE 5
A 16-yr-old male with osteogenic sarcoma of the left distal femur. (A) A pre-chemotherapy study demonstrating intense uptake on the ^{201}Tl-201 (A), ^{67}Ga (B), and ^{99m}Tc-MDP (C) studies. (B) Post-chemotherapy studies demonstrating significant improvement. The patient had a 98% tumor necrosis rating. The ^{201}Tl-201 (D) shows complete resolution of the prior findings. Gallium-67 (E) demonstrates slight residual while the ^{99m}Tc-MDP (F) demonstrates the distal femur to still be considerably active. These findings were felt to reflect significant healing of bone in this region.

mas. The bone scan does not appear to directly assess cellular activity of tumor, but rather looks at a combination of bone blood flow and available receptors within the bony matrix. Gallium is an intermediate material which is taken up by tumor cells as well as healing bone.

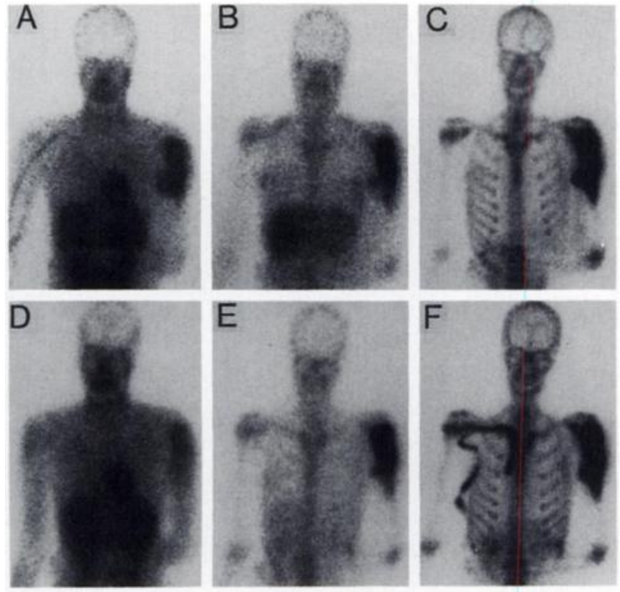

FIGURE 6
A 12-yr-old patient with osteoblastic osteogenic sarcoma of the left upper humerus. The patient demonstrated a tumor necrosis rating of >98% and had significant reduction in pain and swelling following chemotherapy. Pre- and post-thallium demonstrated a significant reduction (A and D), while the gallium scan became somewhat worse (B and E). The bone scan (C and F) remained unchanged.

Thallium-201 is a sensitive radiopharmaceutical for detection of bone sarcoma and appears to be an accurate test for evaluating the response to specific therapeutic regimens. Correlation with significant (>95%) tumor necrosis was extremely high with ^{201}Tl as compared to Tc-MDP. Gallium-67 correlation with tumor necrosis was also superior to Tc-MDP, but less reliable than ^{201}Tl.

ACKNOWLEDGMENTS

This study was supported in part by E.I. Du Pont De Nemours & Co., (Grant-CG-87010).

The authors wish to thank Joyce Jemison and Kathy Wenzel for invaluable secretarial help in the preparation of this manuscript.

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