

Feasibility of Hybrid ^{67}Ga -Citrate SPECT/CT Fusion Imaging for Identifying Patients with Osteomyelitis Awaiting Ostectomy

Sonoko Kirinoki-Ichikawa

Nippon Medical School

Gen Takagi (✉ gen52@nms.ac.jp)

<https://orcid.org/0000-0002-9527-5220>

Masaaki Miyamoto

Nippon Medical School

Yoshimitsu Fukushima

Nippon Medical School

Shuhei Tara

Nippon Medical School

Shinichiro Kumita

Nippon Medical School

Wataru Shimizu

Nippon Medical School

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Abstract

Purpose

Co-existence of ischemia and osteomyelitis strongly increase the risk of limb amputation, however, there is no established non-invasive assessment. This single-center cohort study used propensity score-matched analysis. We evaluated the clinical feasibility of hybrid ^{67}Ga -citrate single photon emission computed tomography and X-ray computed tomography (SPECT/CT) for early diagnosis, severity assessment, and prognosis determination in these patients.

Method

We enrolled consecutive patients with suspected osteomyelitis with mean follow-up of 5.5 years. All patients underwent ^{67}Ga SPECT/CT before and 4 weeks after treatment. Osteomyelitis diagnosis was based on histopathology and bacteriology of surgical sample, bone probing, or imaging follow-up. The diagnostic accuracy of bone resection rates and long-term prognoses were determined based on the target-to-background ratio (TBR).

Results

Among 90 patients who underwent ^{67}Ga SPECT/CT imaging, the initial average TBR of ^{67}Ga -citrate accumulation was 9.1 ± 12.3 . TBR significantly improved following treatment (4.3 ± 3.8 , $p < 0.01$, Wilcoxon test), and the rate of limb salvage was 80%. After propensity score matching, the pre-treatment TBR cutoff for bone resection was 10.1 (sensitivity: 85%, specificity: 82%, area under the curve: 0.87). Significant differences in long-term prognosis following bone resection were also observed often when above this cutoff point (TBR ≥ 10.1 , 85.2% vs TBR < 10.1 , 17.2%, $p < 0.001$, log-rank test).

Conclusions

Coupling of hybrid ^{67}Ga -citrate SPECT/CT fusion imaging by TBR analysis revealed severity thresholds for bone resection, and could be used to assess long-term limb prognosis. ^{67}Ga SPECT/CT fusion imaging may aid in making decisions regarding cases of suspected osteomyelitis.

Trial registration:

UMIN000022208, date of registration. Registered 1 January 2012, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000009900

Background

Antibiotics or bone resection are the recommended approaches for foot osteomyelitis; however, major limb amputation is often necessary in cases complicated by peripheral artery disease (PAD). The co-existence of ischemia and infection strongly increases the risk of limb amputation, especially in patients with diabetes. Indeed, these factors often interact to decrease the rate of limb salvage. In such patients, the faster rate of progression observed due to wound healing is prohibited by reduced blood flow, and underlining complications such as diabetes show poor prognosis even after limb amputation[1, 2]. The European Society of Cardiology guidelines indicate these combined conditions as chronic limb-threatening ischemia (CLTI)[3]. To reduce major limb amputation in CLTI, immediate and accurate decision-making for bone resection is important. Furthermore, the severity of infection influences both prognosis and the duration of bone resection procedures. However, previous studies offer limited information regarding diagnostic technique, as they have excluded patients with ischemic osteomyelitis[4, 5] or have utilized relatively short observation periods[6]. In addition, although soft tissue cultures can be an inaccurate and invasive method, bone biopsies are rarely performed. While non-invasive imaging modalities are suitable, the specificity of magnetic resonance imaging (MRI) is relatively low under ischemic conditions[7, 8]. The appropriate delivery of antibiotics is also difficult in CLTI, and precise tools for determining the need for early surgical intervention have yet to be developed[9, 10].

Previous research has indicated that bone scanning with ^{67}Ga -citrate can be used to evaluate the extent of inflammation; however, this method is associated with poor resolution when a recommendation is rated as Grade 2B[11]. In the present study, we aimed to determine the usefulness and feasibility of hybrid ^{67}Ga -citrate single photon emission computed tomography and X-ray computed tomography (SPECT/CT) fusion imaging and target-to-background ratio (TBR) scores for improving diagnostic quality in patients with suspected osteomyelitis including type 2 diabetes and CLTI.

Materials And Methods

Study population and protocol

From January 2012 and July 2017, we enrolled consecutive patients with suspected osteomyelitis with foot gangrene or ulcers. The physicians suspected osteomyelitis based on the following conditions and then performed a comprehensive diagnostic evaluation: (a) histopathology, bacteriology of surgical samples, (b) imaging follow-up through bone erosion and/or osteolysis on X-rays, and (c) morphological bone destruction detected by probing. Surgical bone resection was performed following bone probe analysis when patients experienced severe, intractable pain at rest or rapid serological worsening of inflammatory changes despite treatment. Those patients were followed up at outpatient in same hospital. Exclusion criteria were as follows: (a) active systemic infection requiring immediate amputation or soft-tissue infection exist above foot joint, (b) inability to participate in initial radionuclide imaging studies, (c) any type of blood circulation re-constructive therapy within the preceding month.

Radionuclide detection of osteomyelitis

All patients underwent ^{67}Ga SPECT/CT using a SPECT/CT hybrid system, which combined a dual-head gamma camera with a two-row multi-section computed tomography (CT) scanner: Symbia T2 (Siemens Healthineers Japan, Tokyo, Japan). SPECT images were acquired at rest, 24 hours after intravenous injection of ^{67}Ga -citrate 148 MBq (the half-life of ^{67}Ga is 3.26 days). The ^{67}Ga SPECT images were acquired over 10 min per bed position (30 projections over an orbit of 180° , 6° per step, and 20 steps per projection). The acquisition range included the entire femur, lower leg, and foot. A middle-energy general purpose collimator was used for image acquisition (matrix: 128×128 pixels). The Flash 3D iterative image reconstruction algorithm was used to reconstruct ^{67}Ga SPECT images. The reconstruction parameters for the numbers of subsets and iterations were 6 and 8, respectively. Non-contrast-enhanced CT images (tube voltage: 110 kVp; tube current time product: 10–40 mA; detector configuration: 2×4 mm; matrix: 256×256 pixels; reconstruction thickness: 5 mm from femur to feet and 3 mm from ankle joint to toe) were also acquired to enable CT attenuation correction and create ^{67}Ga SPECT/CT images. When accumulation of ^{67}Ga -Citrate was found adjacent to chronic ulcers/gangrene, we performed assessments to determine whether such changes reflected osteomyelitis or connective tissue inflammation, depending on the anatomical information acquired via CT during the same exam sequence. When the area of ^{67}Ga -Citrate accumulation and bone sites matched, the patient was diagnosed with osteomyelitis. To analyze the data acquired from hybrid ^{67}Ga SPECT/CT images, regions of interest (ROI) were drawn around the bone(s) with suspected osteomyelitis. The radionuclide count within the ROI was determined, along with the intact femoral uptake radionuclide count (background). The TBR was defined as the count of ^{67}Ga -citrate accumulation per pixel in the ROI divided by the count per pixel in the femur[12]. Reconstruction and fusion imaging were managed by using the Symbia T2 workstation (Siemens Healthineers Japan). The count of ^{67}Ga -citrate accumulation per pixel was analyzed by using a medical image viewer (Natural Viewer, Hitachi Co., Ltd., Tokyo, Japan). Examinations were performed at the initial stage of treatment and approximately 4 weeks after the first examination as a follow up.

Ischemia evaluation

Tissue ischemia was defined by transcutaneous oxygen tension (TcPO_2 , less than 50 mmHg).

Patient outcomes

To determine the clinical turning point using an appropriate scoring system, we adopted the incidence of bone resection (minor amputation) as the primary end point. Secondary endpoints included limb survival, which was defined as retention of the bilateral calcaneus bones, and the occurrence of major adverse events including cardiovascular events, cerebrovascular events, and all causes of mortality.

Statistics

Within-treatment analyses of changes were performed using Wilcoxon rank-sum tests. Cumulate survival was determined via Cox hazard analysis with Kaplan–Meier analysis. We also evaluated the diagnostic accuracy of ^{67}Ga SPECT/CT based on the results of sensitivity, specificity, and receiver-operating characteristic (ROC) curve analyses. The area under the ROC curve and standard deviation were obtained by assuming a nonparametric distribution. ROC curves were constructed for the occurrence of bone resection due to osteomyelitis. Propensity score-matched multivariate regression analysis was carried out using the incidence of bone resection as the dependent variables, such as sex, age, hemodialysis, type 2 diabetes, history of cardiovascular disease, and TcPO_2 , in Cox regression analysis. The hazard ratio (HR) is expressed as a 95% confidence interval (CI). The level of statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS statistics software (version 25, IBM Corporation, Armonk, NY, USA).

Results

We enrolled 90 patients with suspected osteomyelitis. The baseline characteristics of the included participants are shown in Table 1. A representative ^{67}Ga SPECT/CT fusion image is shown in Fig. 1. The fusion image demonstrated the location of osteomyelitis with better resolution than the ^{67}Ga SPECT image alone. The mean duration of follow up was 5.5 ± 0.3 years. The overall rate of limb salvage was 80%, and the rate of survival was 80% (Fig. <link rid="fig2">2</link>-A and 2-B). Among patients who had undergone hybrid ^{67}Ga SPECT/CT in the initial stage, 27 (30%) underwent bone resection (Table 1). TBR values were significantly higher in the bone resection group (average TBR: 20.5 ± 12.5)

than in the non-bone resection group (average TBR: 4.3 ± 3.7) ($p < 0.05$). The relationship between $TcPO_2$ and TBR is shown in Fig. 2-C. Major limb amputation was necessary in six (22%) and nine patients (14%) in the bone resection group and the non-bone resection group, respectively ($p = 0.26$). Death occurred in four (15%) and 10 cases (16%) in the bone resection group and the non-bone resection group, respectively ($p = 0.59$). The average pre-treatment TBR of the entire group was 9.1 ± 12.3 , while the average follow-up TBR was 4.3 ± 3.8 ($p < 0.01$, Wilcoxon test, Fig. 3-A), which indicates that medical interventions significantly reduced ^{67}Ga -citrate accumulation. In the treatment base analysis, the pre-treatment TBR cutoff for the incidence of bone resection due to osteomyelitis was 10.1 (sensitivity: 0.85, specificity: 0.82, area under the curve: 0.87, predictive accuracy: 0.86). Bone resection was performed in 25 of the 36 patients in the $TBR \geq 10.1$ group (69.4%), and in two of the 52 patients in the $TBR < 10.1$ group (3.8%) ($p < 0.001$, chi-square test; Fig. 3-B). The incidence of bone resection was expressed via Kaplan–Meier analysis ($p < 0.01$, log-rank test, Fig. 3-C). Regarding the radiographic reliability of the TBR assessment, the linear weighted κ values indicated a moderate interobserver agreement of 0.71 and an intraobserver agreement of 0.67, based on previous findings[13]. A multivariate regression analysis was performed using the incidence of bone resection as a dependent variable. After the propensity score matching, TBR of more than 10.1 was a strong risk factor for bone resection ($p < 0.001$, HR 9.17, 95% CI 3.14-27.0). However, hemodialysis, type 2 diabetes and lower $TcPO_2$ did not show statistical significance (Fig. 3-D). Additionally, the Cox hazard analysis indicated that this cutoff shows significant difference in the detection limit both in CLTI ($p < 0.001$, odds ratio 4.88, 95% CI 1.35–17.7) and non-CLTI ($p < 0.001$, odds ratio 5.15, 95% CI 1.81–14.6).

Table 1
Patient characteristics

	Original				Propensity Score-Matched				Std diff
	All patients (n = 90)	Control (n = 62)	Bone resection (n = 28)	p value	Control (n = 28)	Bone resection (n = 28)	p value		
Age – yr	63.9 ± 13.6	64.2 ± 13.9	63.2 ± 13.1	0.75	62.3 ± 14.7	63.2 ± 13.1	0.85	0.02	
Female sex – no. (%)	27 (30)	22 (35)	5 (19)	0.12	3 (11)	5 (19)	0.28	0.64	
Type 2 Diabetes mellitus (%)	65 (72)	42 (67)	23 (85)	0.06	23 (85)	23 (85)	1.00	0.04	
Hemodialysis (%)	25 (28)	16 (25)	9 (33)	0.44	6 (22)	9 (33)	0.54	0.15	
CVD	55 (61)	39 (62)	16 (59)	0.60	16 (59)	16 (59)	1.00	0.11	
Limb ischemia	50 (56)	38 (60)	12 (44)	0.07	18 (67)	20 (74)	0.64	0.24	

CVD, history of cardiovascular disease. Std diff, standard difference score.

Representative Case

Figure 4 is a successful representative case without bone resection, which shows the changes in TBR and the location of osteomyelitis before and after treatment. The patient was a 68-year-old man with type 2 diabetes (HbA1c 7.4%, National Glycohemoglobin Standardization Program). He was referred to our hospital with a foot ulcer that was suspected osteomyelitis, induced by a low-temperature burn, which had been present for 4 months. He originally lost four left toes during childhood, although this was not related to diabetes. There was no evidence of limb ischemia (ABI = 1.23). Pre-treatment ^{67}Ga SPECT/CT fusion imaging revealed osteomyelitis at the distal end of the left fourth metatarsal bone. We opted for non-invasive treatment involving hyperbaric oxygen therapy (HBO). After 20 sessions of HBO without antibiotics or bone resection, his TBR had decreased from 8.16 to 6.74, and his foot ulcer had healed. We speculated that osteomyelitis had prevented ulcer epithelialization, and that the effect of HBO on the enhancement of leukocyte activity and osteogenesis and augmentation of antibiotic action may have alleviated osteomyelitis, thereby enabling complete epithelialization. This case indicated that the non-invasive procedure could be an alternative for the osteomyelitis with lower TBR cutoff.

Discussion

The incidence of limb amputation has increased along with the number of patients with diabetes or PAD[14]. However, only a few studies have investigated the role of early changes in diagnosing and determining the severity of osteomyelitis[15]. Imaging modalities such as X-ray and CT only show osteolysis in the delayed phase. Further, MRI is limited by its low specificity[7, 8] and contraindications in certain patients, as well as its inability to precisely reflect severity under ischemic conditions[16]. Although fluorodeoxyglucose positron emission tomography (FDG-PET)/CT could also allow for a precise diagnosis while reducing radiation exposure[17, 18], it is not yet a common diagnostic method for

osteomyelitis in Japan because it is not yet covered by health insurance. In contrast, ^{67}Ga -citrate scintigraphy allows for radiotracer uptake into the site of local inflammation via diffusion (i.e., phagocytosis into leukocytes) as a chelating agent[19]. Moreover, ^{67}Ga -citrate is known to enter cells in its ionic form[20]. While such planar images are associated with high specificity, their resolution is low. However, CT can provide detailed images of toe/tarsal anatomy with acceptable resolution, a hybrid ^{67}Ga SPECT/CT machine allows for simultaneous examination using a single scanner, avoiding artifacts due to changes in the patient's position, and precise detection of osteomyelitis locations. In addition, ischemia (low TcPO_2) and infection (high TBR) can vary in foot ulcer patients; thus, TBR scores determined via ^{67}Ga SPECT are useful for early diagnosis, decision-making regarding bone resection, severity scoring, and prognostic determination in patients with refractory ischemic osteomyelitis awaiting bone resection. In the present study, diagnostic accuracy was comparable to that reported for other radionuclide examinations and MRI studies[21]. Furthermore, multi-regression analysis indicated that TBR cutoff is an independent risk factor for bone resection (Fig. 3-D). When TBR is less than cutoff, imaging follow-up and non-invasive treatment such as hyperbaric oxygen therapy may be one of the options[22, 23].

As a limitation, first, ^{67}Ga SPECT/CT is associated with exposure to radiation[24]. We minimized radiation exposure: the radiation dose for whole-body gallium scintigraphy is 14.8 mSv and the computed tomography dose index (CTDI) in our imaging study was 1.3 mGy. We believe ^{67}Ga SPECT/CT is not hazardous since it is performed commonly in daily medical care for decades. Second, we did not perform any comparisons using other tracers in this study. Some previous studies diagnosed osteomyelitis by bone scintigraphy and white blood cell scintigraphy[8, 25]. However, we think those two tracers are not the optimal choice for quantitative evaluation of osteomyelitis. Bone scintigraphy cannot be used for the quantitative evaluation of inflammation because it merely visualizes the process of bone matrix synthesis followed by osteomyelitis and bone necrosis. White blood cell scintigraphy is seldom performed because of its complicated labeling procedure and the Japanese health insurance coverage regulation. Third, we did not speculate about the correspondence between imaging and histopathological findings. We performed pathological assessment in 11 of 27 bone-resected patients, and 8 patients were diagnosed with osteomyelitis histopathologically. However, as shown by our representative case, it is difficult to perform histopathological assessment in some cases whose osteomyelitis healed without bone resection. Finally, the sample size of this study was small.

Conclusions

This study demonstrates the usefulness and feasibility of hybrid ^{67}Ga -citrate SPECT/CT fusion imaging and TBR scores for improving diagnostic quality among patients with osteomyelitis awaiting bone resection even in ischemic conditions. Coupling of ^{67}Ga -citrate hybrid SPECT/CT fusion imaging by TBR analysis revealed severity thresholds (TBR 10.1) for bone resection and aided in anatomical localization; therefore, this may prevent unnecessary amputation and could be used to assess long-term limb prognosis.

List Of Abbreviations

ABI ankle-brachial index

CI confidence interval

CLTI chronic limb-threatening ischemia

CTDI computed tomography dose index

ESC the European Society of Cardiology

FDG-PET fluorodeoxyglucose positron emission tomography

^{67}Ga ^{67}Ga gallium

HBO hyperbaric oxygen therapy

HR hazard ratio

MRI magnetic resonance image

PAD peripheral arterial disease

ROC receiver-operating characteristic

ROI regions of interest

SPECT/CT single photon emission computed tomography/X-ray computed tomography

TBR target-to-background ratio

TcPO₂ transcutaneous oxygen tension

UMIN University Hospital Medical Information Network

Declarations

Ethics approval

The present observational diagnostic study was performed at Nippon Medical School Hospital and approved by the appropriate Institutional Review Board (ethical committee of Nippon Medical School). The protocol was registered with the University Hospital Medical Information Network (UMIN)-Clinical Trial Registry, which is accepted by the International Committee of Medical Journal Editors (No. UMIN000022208). The study was conducted in accordance with the Declaration of Helsinki as revised in 2000.

Consent for publication

All patients included in this study provided written informed consent before surgical treatment. Also, all patients included gave written informed consent that their data could be used for scientific purposes.

Availability of data and material

Please contact the author for data request.

Competing interest

The authors declare that they have no competing interests.

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Author's contributions

S. K-I. wrote the manuscript and researched data. G. T. researched data, reviewed/edited the manuscript. M.M. researched data and contributed to discussion. Y.F. researched data. S.T. researched data. S.K. contributed to the discussion and reviewed/edited the manuscript. W.S. contributed to discussion.

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Figures

⁶⁷Ga-SPECT

CT

Fusion Image

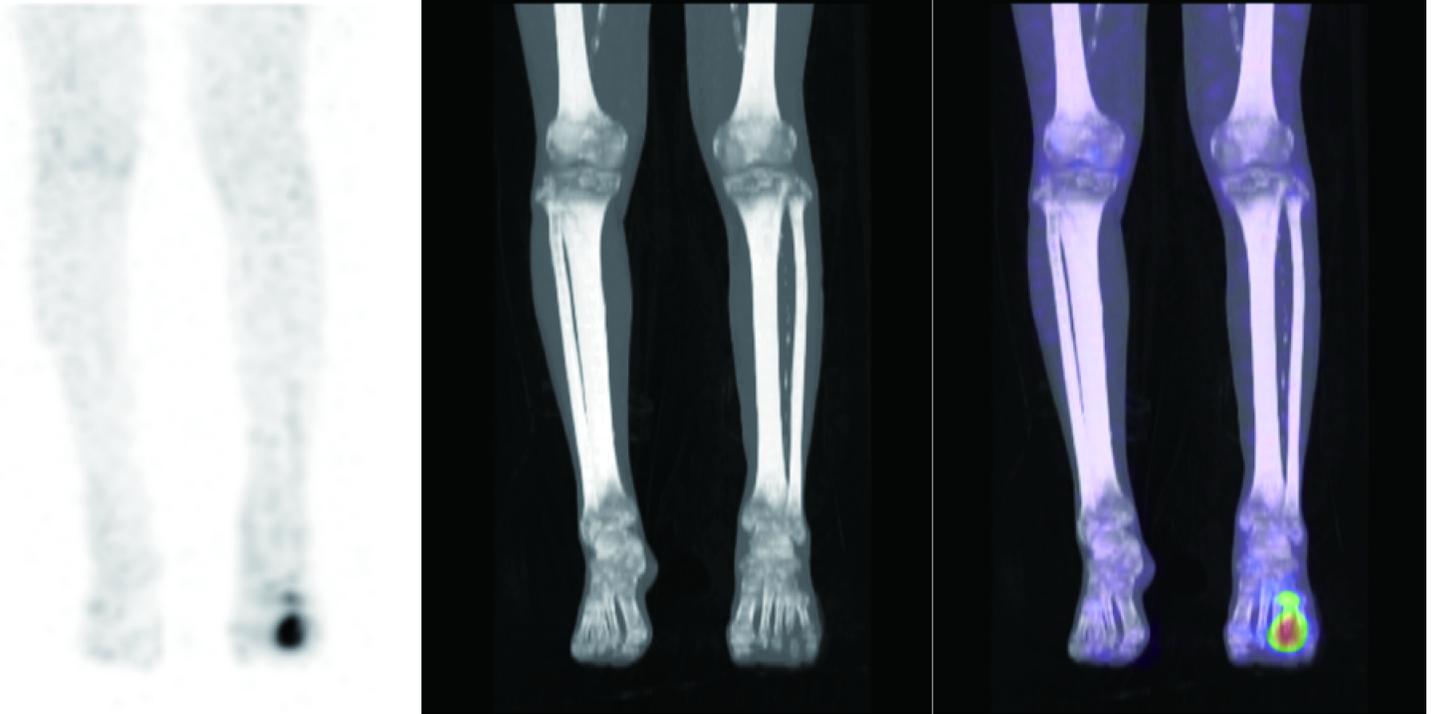


Figure 1

Representative picture and hybrid ⁶⁷gallium single photo emission computed tomography/X-ray computed tomography (⁶⁷Ga SPECT/CT) images. Left-side ⁶⁷Ga-SPECT, CT and ⁶⁷Ga SPECT/CT fusion images from the same patient. The fusion image reveals hot uptake in the left fourth digit, indicative of osteomyelitis.

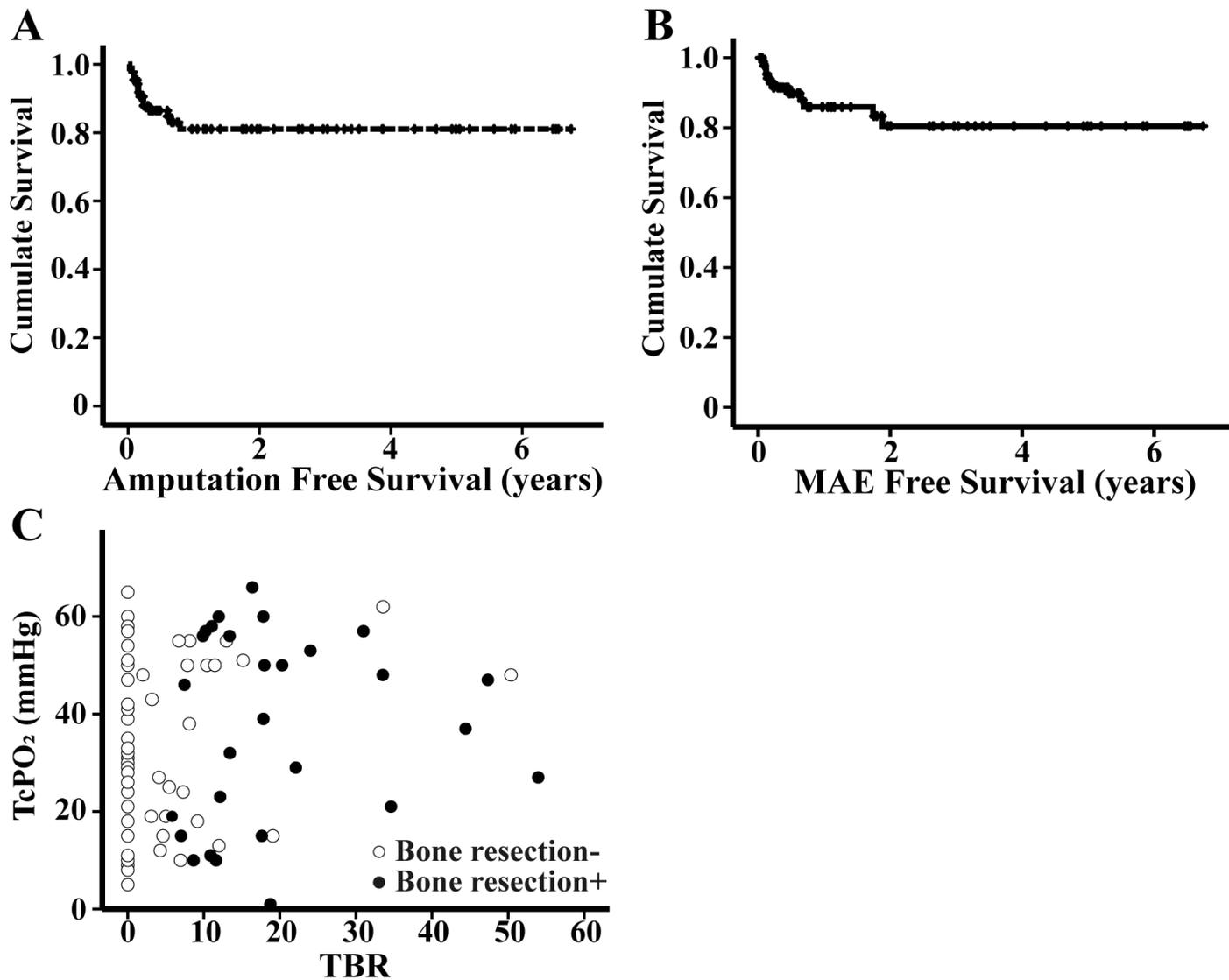


Figure 2

A. Kaplan–Meier analysis of limb amputation-free survival. B. Kaplan–Meier analysis of major adverse events (MAE)-free survival. C. Correlation plot between transcutaneous oxygen tension (TcPO₂) and target-to-background ratio (TBR).

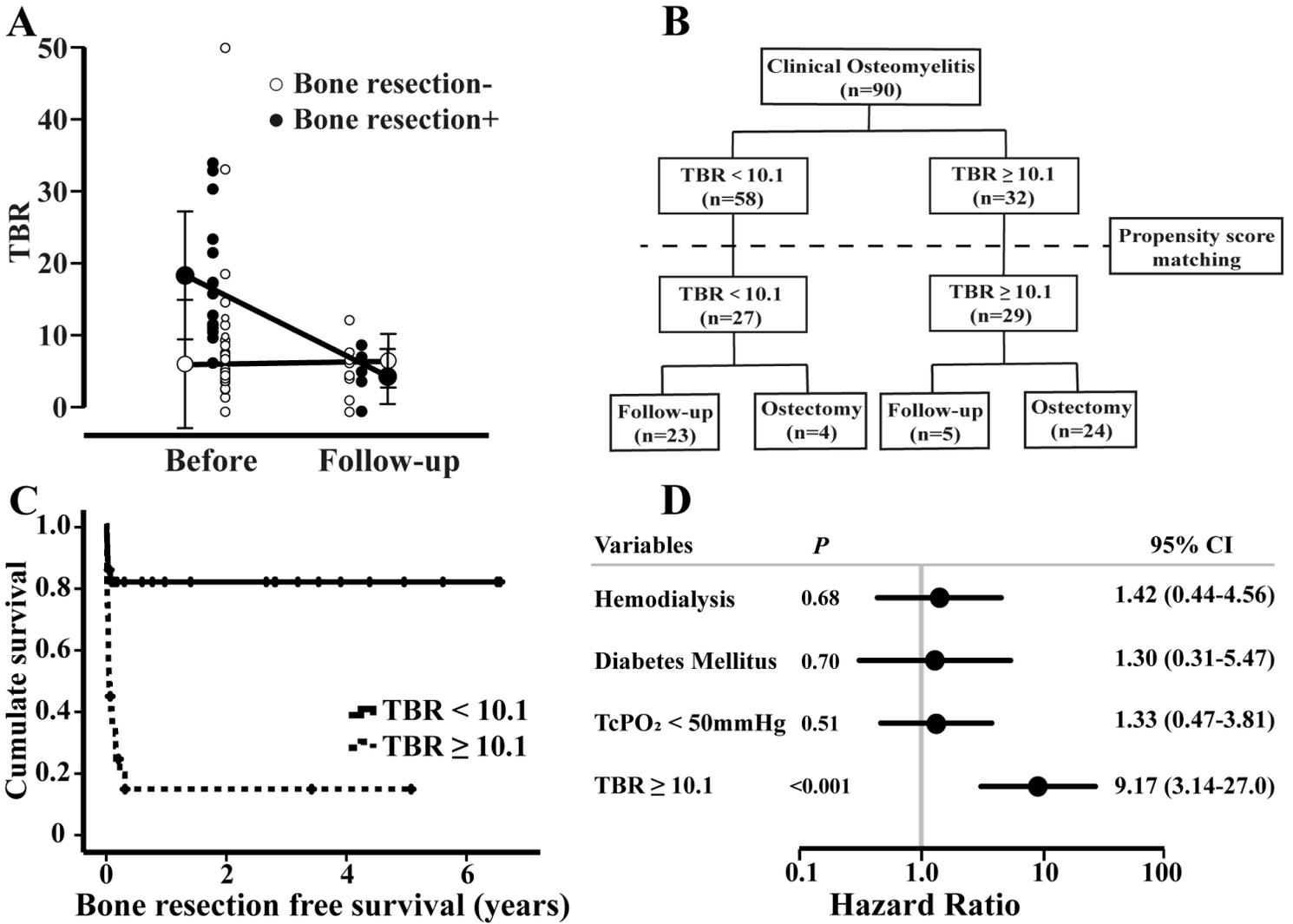


Figure 3

Target-to-background ratio (TBR) changes, receiver-operating characteristic (ROC) curve, and results of Kaplan–Meier analysis. A. Changes in TBR before and after treatment. Open circles indicate the non-bone resection group, while closed circles indicate the bone resection group. TBR improved in the bone resection group ($p < 0.01$). However, no significant differences are observed between the groups ($p =$ not significant, repeated-measures analysis of variance). B. participants flow diagram and number from eligibility criteria, and methods of selection. C. Kaplan–Meier analysis for bone resection incidence using a TBR cutoff of 10.1. D. The independent predictors of bone resection. The results of hemodialysis, type 2 diabetes mellitus, transcutaneous oxygen tension (TcPO₂) value < 50 mmHg. TBR ≥ 10.1 is matched by propensity score-matched analysis before regression analysis. The circle indicates hazard ratio. Lines represent 95% confidence intervals (CIs).

Pre treatment

1 month after HBO



TBR 8.16

TBR 6.74

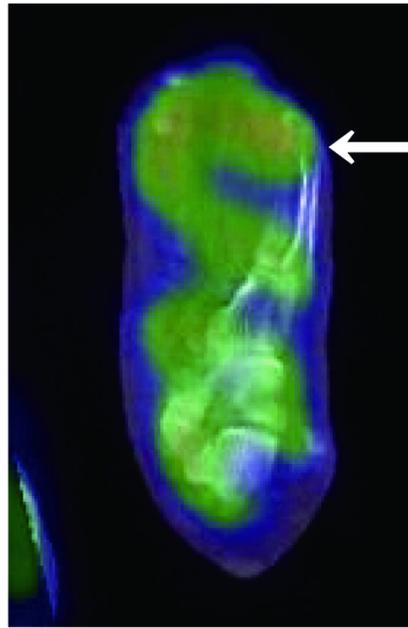
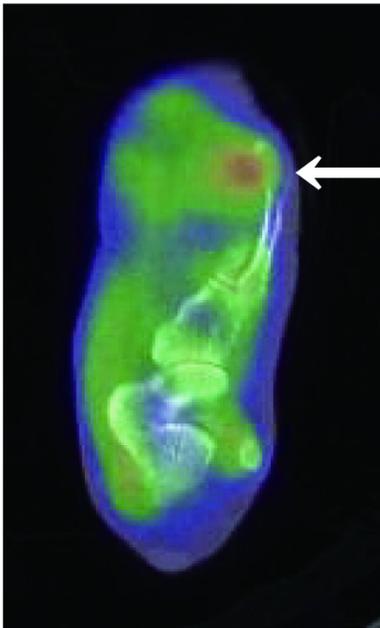


Figure 4

Picture and hybrid 67gallium (^{67}Ga) single photon emission computed tomography/X-ray computed tomography images of a representative case. Pre-treatment images are shown on the left side, while post-treatment images are shown on the right side. The arrows in the lower panels indicate ^{67}Ga accumulation in the end of the metatarsal bone. HBO, hyperbaric oxygen therapy; TBR, target-to-background ratio.