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Radioiodine Dose for Remnant Ablation in Differentiated Thyroid Carcinoma: A Randomized Clinical Trial in 509 Patients

C. S. BAL, AJAY KUMAR, AND G. S. PANT

Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India, 110029

Remnant ablation can be achieved by either administering an empiric fixed dose or using dosimetry-guided techniques. Because of the technical and logistic difficulties, most centers have adapted the fixed-dose or standard-dose technique for remnant ablation using ^{131}I. In the late 1970s, low-dose ^{131}I remnant ablation was introduced, and subsequently many centers confirmed the effectiveness of such therapy. However, the optimal dose (administered activity) of ^{131}I for remnant ablation is not yet settled. In a randomized clinical trial to find out the smallest possible effective dose for remnant ablation in cases of differentiated thyroid carcinoma, between July 1995 and January 2002, 565 patients were randomized into eight groups according to ^{131}I administered activity, starting at 15 mCi and increasing activity in increments of 5 mCi until 50 mCi. In the postrandomization phase, 56 patients were excluded from the study for various reasons, and final analysis was done with 509 patients. The mean age of the patients was 37.5 ± 12.7 yr with a female to male ratio of 2.6. The surgical procedure was total/near-total thyroidectomy in 72% and subtotal or hemithyroidectomy in the rest. Histology was papillary thyroid carcinoma in 80.6% of patients and follicular thyroid carcinoma in the rest. With one dose of ^{131}I, remnant ablation was achieved in 59.6, 63.6, 81.4, 83.6, 79.4, 78.3, 84.4, and 81.8% of patients in the 15- to 50-mCi groups, respectively (overall ablation rate, 77.6%). The successful ablation rate was statistically different in patients receiving less than 25 mCi of ^{131}I compared with those receiving at least 25 mCi [63 of 102 (61.8%) *vs.* 332 of 407 (81.6%); $P = 0.006$]. However, there was no significant intergroup difference in outcome among patients receiving 25–50 mCi of ^{131}I. Patients with small tumor size (≤5 cm), adequate surgery (total/near-total thyroidectomy), and radioiodine neck uptake of less than or equal to 10% had odds ratios of 2.4 [confidence interval (CI), 1.3–3.98], 2.6 (CI, 1.6–4.2), and 2.2 (CI, 1.4–3.5), respectively, for successful remnant ablation. Patients receiving at least 25 mCi of ^{131}I had a three times better chance of getting remnant ablation than patients receiving lesser activity of ^{131}I. Any activity of ^{131}I between 25 and 50 mCi appears to be adequate for remnant ablation. (*J Clin Endocrinol Metab* 89: 1666–1673, 2004)

TOTAL OR NEAR-TOTAL thyroidectomy (TT or NTT) followed by radioiodine (^{131}I) ablation of residual thyroid tissue (remnant ablation) is considered the ideal treatment for differentiated thyroid carcinoma (DTC). There are several compelling reasons for remnant ablation in cases of DTC. First, the presence of remnant thyroid tissue makes detection and treatment of nodal or distant metastases difficult (1, 2). Second, high TSH levels necessary to enhance tumor ^{131}I uptake cannot be ordinarily achieved with a large thyroid remnant (3). Third, serum thyroglobulin (Tg) measurement made under TSH stimulation, which is the most sensitive test for the detection of recurrence, is not reliable in the presence of normal thyroid tissue. Thus, ablation of remnant thyroid tissue is imperative and facilitates subsequent follow-up (4). Some authors also argue that remnant ablation may probably destroy residual follicular cells that might become malignant over time (5) and any occult multifocal cancer that may recur years later (6–12), thereby reducing tumor recurrence, and probably mortality rate, significantly (8, 13–16), although not all thyroidologists agree (17).

Unfortunately, the optimal ^{131}I activity required to achieve remnant ablation with a single administration remains controversial. Some advocate that a large activity of 100–150 mCi of ^{131}I is required for successful ablation (18–20), whereas others believe that an activity as small as 30–50 mCi is sufficient to achieve the same goal (21–30). Most of these studies are retrospective historical descriptions of heterogeneous groups of patients with different criteria used for patient selection, nonuniformity of treatment methodology, and different criteria used to describe remnant ablation. Our institutional policy over the last three decades is to ablate all significant residual thyroid tissue. Our previous pilot work in this field had concluded that administered ^{131}I activity beyond 50 mCi does not give any incremental success rate of ablation but rather increases whole-body radiation absorbed dose (29). However, that study did not give any definitive answer regarding the lower limit of effective administered activity. Hence, there was need of a large randomized trial to settle this issue of small effective activity of ^{131}I for remnant ablation. The argument is not how large an activity of ^{131}I one may/can administer for remnant ablation but rather how small an effective activity of ^{131}I one can administer to get reasonably good ablation (~80%). Equivalence trials are required more than superiority trials when comparing small activity of ^{131}I with higher activities. Therefore, the objective

Abbreviations: CI, Confidence interval; DTC, differentiated thyroid carcinoma; HT, hemithyroidectomy; NTT, near-total thyroidectomy; RAIU, radioiodine neck uptake; rem, roentgen-equivalent-man; STT, subtotal thyroidectomy; Tg, thyroglobulin; TT, total thyroidectomy; WBS, whole-body scan.

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of the present study was to find out how small should a small dose of ^{131}I (administered activity) be to achieve successful remnant ablation in DTC by using a randomized control trial.

Patients and Methods

Study design

All India Institute of Medical Sciences, New Delhi, India, is a tertiary care teaching hospital serving the approximately one half billion population of Northern India. The Department of Nuclear Medicine has run a specialty thyroid cancer clinic for the last 35 yr. We have blanket institutional ethics committee approval of using ^{131}I activity from 15–250 mCi as a single administration for carcinoma thyroid ablation/therapy. Any single administration beyond the upper limit needs fresh approval on a case-to-case basis with proper justification. The individual informed written consent was obtained from all patients who participated in this randomized clinical trial. Currently, we are treating approximately 250–260 new DTC patients annually. Between July 1995 and January 2002, in a prospective randomized clinical trial, 565 patients with DTC, who fulfilled the inclusion criteria, were randomized into eight treatment groups. The groups were decided according to the amount of ^{131}I, starting at 15 mCi and increasing the activity in increments of 5 mCi until 50 mCi.

Inclusion criteria. Included in the study were patients having disease confirmed to be limited to the thyroid bed only by clinical, radiological, peroperative, and postsurgical ^{131}I scintigraphic examination and having no evidence of extrathyroid or distant metastases at the time of presentation.

Exclusion criteria. If at any time, extrathyroid disease in the form of either nodal or distant metastases was detected before the first-dose outcome, such patients were excluded from the study. Patients with Hurthle cell carcinoma, poorly differentiated carcinoma, insular carcinoma, medullary thyroid carcinoma, and aggressive variant of papillary carcinoma were also excluded, as they need a different management approach.

The minimum required sample size was determined by using an appropriate formula (for equivalence study) by taking the level of significance (α) of 0.05, power of the study ($1 - \beta$) to be 80%, and precision (d) at 20%. Approximately 48 patients were required to be recruited in each group to fulfill the aim of the study. A simple randomization method (1000 random numbers were generated through a random number table) with concealment was used for allocating the patients to different activity groups in this prospective study. We needed only 384 patients to achieve our target. However, the problem with simple randomization is that, although it gives equal probability for each patient to receive any one of the eight dose schedules, it does not ensure that an equal number of patients will be in each group before 1000 patients are recruited. We went on recruiting patients till each group had at least 48 patients treated in a particular regime. That explains the unequal numbers in the eight groups. This inequality will be smaller and smaller as we approach 1000.

In the postrandomization phase, 56 patients were excluded for various reasons. In 19 patients, nodal/distant metastases (nine nodal and 10 pulmonary/skeletal metastases) were revealed in posttherapy ^{131}I whole-body scans (WBSs), and another 37 patients were either lost to follow-up or had incomplete follow-up data. Therefore, the final analysis was done with 509 patients. Figure 1 depicts the trial profile in detail.

The median duration of the illness before surgery was 36 months (range, 1–480 months). Mean tumor size was 4.6 ± 2.4 cm. The large tumor size was probably due to late referral to surgery. The initial surgical intervention was not uniform due to different surgical units operating upon them. The surgical procedure followed was near NTT/TT in 72% of patients and subtotal or hemithyroidectomy (STT/HT) in the rest. The group-wise distribution of 142 patients with inadequate surgery (58 STT and 84 HT) is depicted in Table 1. The histopathological diagnosis was established in all patients and classified according to the World Health Organization criteria (31). Four hundred

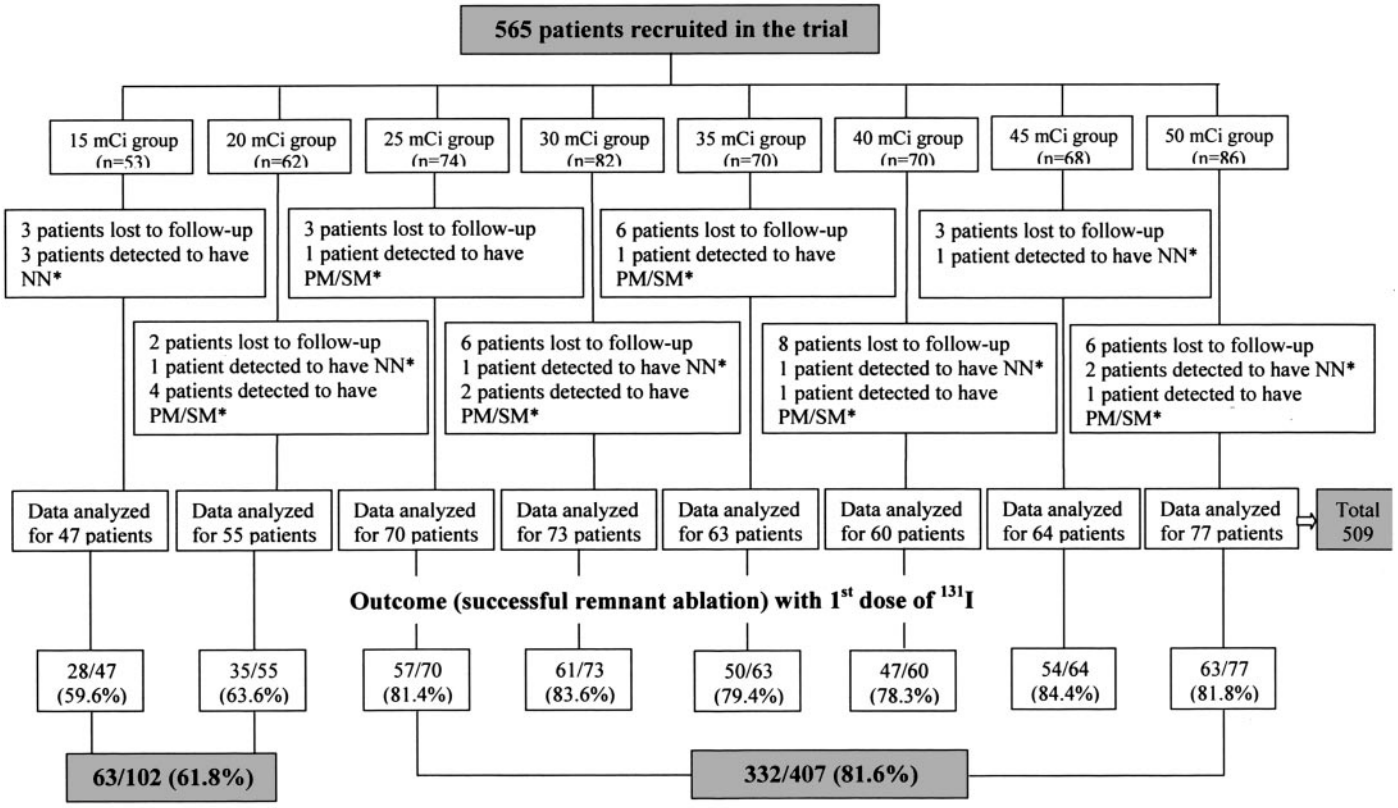

FIG. 1. Trial profile.

TABLE 1. Demographic and clinical profiles of all patients

Parameters	Total	15 mCi	20 mCi	25 mCi	30 mCi	35 mCi	40 mCi	45 mCi	50 mCi	*P* value
Age (yr)	37.5 ± 12.7 (7–75)	36.5 ± 10.7 (14–60)	37.7 ± 11.5 (8–70)	38.9 ± 13.7 (12–73)	37.3 ± 13.2 (13–74)	35.3 ± 10.8 (12–63)	34.3 ± 14.0 (9–68)	38.3 ± 13.6 (7–65)	40.3 ± 12.3 (12–75)	0.167
Sex (female:male)	2.6:1	2.4:1	2.5:1	3.4:1	3.6:1	1.7:1	3:1	2.6:1	2.4:1	0.675
Duration of illness (months)[†]	18 (1–480)	12 (1–180)	19 (1–240)	16 (1–300)	23 (1–480)	14 (1–204)	24 (2–240)	12 (1–300)	18 (1–360)	0.578
Tumor size (cm)	4.6 ± 2.4 (1–16)	4.5 ± 1.6 (2–7)	3.8 ± 1.9 (1.5–10)	5.3 ± 2.8 (2–15)	4.7 ± 2.5 (1–10)	3.6 ± 1.5 (1–7)	4.9 ± 3.3 (2–16)	4.4 ± 2.1 (2–10)	4.6 ± 1.8 (2–10)	0.067
Surgery[a]										
NTT	367	35	42	50	54	44	41	46	55	0.986
STT/HT	142	12	13	20	19	19	19	18	22	
Histopathology[a]										
Papillary	410	37	48	60	57	49	49	52	58	0.675
Follicular	99	10	7	10	16	14	11	12	19	

Age and tumor size are given in terms of mean ± SD; duration of illness is given as median (range).
[a] Number of patients.

and ten (80.6%) patients had papillary thyroid carcinoma, and 99 (19.4%) had follicular thyroid carcinoma.

The interval between surgery and referral to the Department of Nuclear Medicine for remnant ablation ranged from 1–108 months with a median value of 2 months. Postsurgical WBS was performed with 2–3 mCi of ^{131}I along with 48-h radioiodine neck uptake (RAIU) after keeping patients off L-thyroxin for 4–6 wk. Preablation serum TSH values ranged between 25 and 107 μIU/ml (mean, 68 ± 28) in 87% of the patients; the remaining patients had TSH values between 1 and 24 μIU/ml. Although no special low-iodine diet was prescribed to the patients, they were advised not to take known rich iodine-containing foods and drugs. The patients were randomly assigned into one of the eight treatment groups. Informed consents were obtained from all adult patients or from legal guardians of minor patients, before administration of ^{131}I.

The absorbed radiation dose to the thyroid gland was calculated using the formula described by Thomas *et al.* (32):

$$D\ (\text{rad}) = \sum_{m}^{\tilde{A}} {}_i\Delta_i\Phi_i = C_0[1.44 \times T_{1/2\text{eff}} \times 0.4135 + 0.8041 \times \Phi_\gamma],$$

where $\tilde{A}$ (μCi-h) is the cumulative activity, m (g) is the mass of the lesion, C_0 (μCi/g) is the initial radionuclide concentration in the lesion, $T_{½\text{eff}}$ (h) is the effective half-time in the lesion, Δ_i (g-rad/μCi-h) is the equilibrium dose constant, and Φ_i is the absorbed fraction. For the purpose of simplification and convenience for the large number of patients, we had made the assumption of an effective $T_{1/2}$ of 5 d as described by Snyder *et al.* (33). Maxon *et al.* (34) had reported a similar effective half-life in cases of DTC. Moreover, we also observed the mean value of 118 ± 14 h for effective half-life after calculating it in randomly selected patients; the remaining patients in whom we could not perform $T_{1/2}$ estimation, we assumed 120 h (5 d) as a reasonable approximation. Remnant mass was estimated by going through the surgical notes and talking to the operating surgeons, as and when required.

After ^{131}I therapy, WBS (post-therapy scan) was done in all patients to look for any nodal/distant metastases missed on low-dose WBS. The patients were then advised to take levothyroxine (2 μg/kg body weight) daily on an empty stomach as suppressive therapy. This was continued until 4–6 wk before the repeat diagnostic studies 6 months later. The preparation for the 6-month posttherapy evaluation was similar to that for the preablation scan. No recombinant human TSH was used in this study. All patients were prepared by conventional methods with serum TSH more than 30 μIU/ml. The repeat diagnostic studies consisted of 2–3 mCi ^{131}I WBS, 48-h RAIU, Tg, and anti-Tg antibody assay. The criteria for ablation were as follows: major criterion of negative ^{131}I WBS and minor criteria of 48-h RAIU less than or equal to 0.2% and Tg less than or equal to 10 ng/ml (29). Fulfillment of any two criteria was required to declare successful ablation. If, after the first posttherapeutic evaluation, the patients did not meet the criteria for thyroid ablation, then additional ^{131}I treatment (25–50 mCi) was administered. Repeat ^{131}I doses were administered until thyroid ablation was achieved, after which annual check-ups were planned with Tg estimation.

Tg was estimated by sequential competitive RIA with a double-antibody method using DPC kits from Diagnostic Products Corp. (Los Angeles, CA). The assay had a detection limit (sensitivity) and functional limit of 2.6 and 10.0 ng/ml, respectively. Intraassay and interassay coefficients of variation were 5.7 and 8.7%, respectively. Anti-Tg antibody was estimated by immunoradiometric assay based on a sandwich method using kits from Immunotech A.S. (Prague, Czech Republic). The assay had a sensitivity of 10 IU/ml (normal values < 100 IU/ml). Intraassay and interassay coefficients of variation were 5.7 and 9.7%, respectively.

Statistical analysis

The values are expressed as mean ± SD. Under univariate analysis, *t* test and χ^2 had been applied for quantitative and qualitative variables, respectively. The baseline comparison, *i.e.* comparison of different demographic and clinical parameters in different groups, was made and reported accordingly. Furthermore, ANOVA was used to compare the various quantitative parameters in the eight dose groups. Under multivariate analysis, multiple stepwise logistic regressions had been ap-

plied for independent covariates such as age, sex, histopathology, tumor size, type of gland, first dose, *etc.* with first-dose outcome as the dependent variable (ablation/nonablation). A P value < 0.05 was considered significant. The statistical packages SAS (version 8.0) and SPSS (version 10.5) were used for the statistical analyses.

Results

The mean age of the patients was 37.5 ± 12.7 yr with a female to male ratio of 2.6. The mean tumor size and postsurgical RAIU was 4.6 cm and 9.1 ± 7.2%, respectively. There was no statistical difference between various baseline clinical parameters, such as age, sex ratio, duration of illness, type of gland (solitary thyroid nodule/multinodular goiter), type of surgery, histopathology, tumor size, and postsurgical RAIU among the groups. Group-wise demographic and treatment profiles along with statistical P values are given in Tables 1 and 2.

With one dose of ^{131}I, successful remnant ablation was achieved in 395 (77.6%) of 509 patients with mean Tg being 2.8 ± 2.4 ng/ml. The remaining patients showed partial ablation, objectively assessed by reduction in RAIU (it came down to 3.5 ± 5.5%). There was no statistically significant difference in the first-dose outcome (remnant ablation) between patients receiving 15 mCi (59.6%) or 20 mCi of ^{131}I (63.6%). Similarly, remnant ablation rates were almost identical among patients administered 25–50 mCi of ^{131}I (81.4, 83.6, 79.4, 78.3, 84.4, and 81.8% ablation rates, respectively). When ablation in the 15-mCi and 20-mCi groups was compared against the 25-mCi group, the difference in ablation rates was statistically significant. Even when grouped together (15-mCi + 20-mCi group), the ablation rate was statistically different compared with the 25-mCi group. Finally, when grouped into less than 25 mCi *vs.* more than or equal to 25 mCi of administered activity of ^{131}I for remnant ablation, there was a statistically significant difference in first-dose ablation rate (61.8 *vs.* 81.6%; $P = 0.006$) (Fig. 1).

Under univariate analysis, χ^2 test for the association of categorical variables, such as sex, type of gland, type of surgery, and histopathology, with first-dose outcome revealed that only type of surgery had influence over the remnant ablation, with adequate surgery (NTT) having a much higher ablation rate (307/367 = 83.2%) than inadequate surgery (HT/STT) (88/142 = 63.3%). The difference was statistically significant ($P = 0.0001$). Female to male ratio was 2.9 *vs.* 1.9 ($P = 0.052$), type of gland (solitary thyroid nodule/multinodular goiter) was 293/102 *vs.* 75/39 ($P = 0.07$), and histopathology (papillary/follicular) was 320/75 *vs.* 90/24 ($P = 0.624$) in ablated and nonablated groups, respectively. However, unpaired t test applied to assess the relationship between various quantitative variables, such as age, duration of disease, tumor size, interval between surgery and ^{131}I treatment, postsurgical RAIU, and radiation-absorbed dose with first-dose outcome revealed that only tumor size and postsurgical RAIU had any effect on the first-dose outcome. Mean tumor size and mean RAIU was 4.4 ± 1.8 cm and 8.1 ± 6.4%, respectively, in the ablated patients *vs.* 5.4 ± 3.6 cm and 12.1 ± 8.2%, respectively, in nonablated patients ($P = 0.006$ and 0.0001, respectively). There was no statistical difference in the rest of the variables, mean age being 37.9 ± 12.5 *vs.* 35.9 ± 13.2 yr ($P = 0.154$), mean duration of illness (before

TABLE 2. ^{131}I treatment profile

	Total	15 mCi	20 mCi	25 mCi	30 mCi	35 mCi	40 mCi	45 mCi	50 mCi	P value
Interval between surgery and ^{131}I treatment (months)[a]	2 (1–108)	3 (1–42)	3 (1–39)	3 (1–84)	2 (1–108)	2 (1–27)	2 (1–47)	2.4 (1–108)	2 (1–72)	0.148
Post surgical RAIU (%)	9.1 ± 7.2	9.2 ± 7.6	10.2 ± 8.7	8.1 ± 5.6	8.3 ± 7.8	10.5 ± 7.1	10.4 ± 7.9	8.9 ± 7.1	8.1 ± 6.7	0.318
RAD (Gy)	241 ± 234	93 ± 74	135 ± 122	173 ± 120	194 ± 152	269 ± 188	296 ± 233	356 ± 296	374 ± 323	0.00
RAIU in nonablated patients, after 1st dose	3.5 ± 5.5 (0.3–24)	2.9 ± 3.2 (0.6–12.5)	4.5 ± 6.3 (0.8–24)	4.5 ± 6.7 (0.48–21)	1.9 ± 1.3 (0.5–9.6)	5.5 ± 5.8 (0.47–19)	3.4 ± 3.7 (0.35–11.4)	1.7 ± 1.1 (0.3–8.2)	3.1 ± 4.4 (0.34–14)	0.481

Values are given in terms of mean ± SD. RAD, radiation-absorbed dose.
[a] Median (range).

surgery) 43.0 ± 49.7 *vs.* 47.8 ± 49.9 months ($P = 0.086$), interval between surgery and ^{131}I treatment 5.5 ± 11.4 *vs.* 6.5 ± 10.6 months ($P = 0.375$), and radiation-absorbed dose to the thyroid remnant 255 ± 226 *vs.* 238 ± 227 Gy ($P = 0.452$) in ablated and nonablated groups, respectively.

When multivariate stepwise logistic regression analysis was applied to the whole group (n = 509), tumor size, type of surgery, postsurgical RAIU, and administered activity of ^{131}I were found to have a statistically significant effect on the first-dose outcome. Patients with less than or equal to 5-cm tumor size had a 2.4 times better chance of having remnant ablation than patients with more than 5-cm tumor size. Similarly, chances of remnant ablation was 2.6 times more in patients with adequate surgery than in patients with STT/HT and 2.2 times more in patients with less than or equal to 10% RAIU. Although there was no statistically significant difference in first-dose outcome between patients receiving 25–50 mCi of ^{131}I, they had a three times better chance of remnant ablation compared with patients receiving less than or equal to 20 mCi of ^{131}I (Table 3).

To critically assess the influence of surgery in the outcome of ^{131}I therapy in remnant ablation, we separately analyzed the data for the NTT group (n = 367) and the inadequate surgery group (n = 142). The rate of successful ablation in the adequate surgery group was 83.6% and in the inadequate group was 62% ($P = 0.001$). However, there was no statistical significant difference between the ablation rates of 58.6 and 64.3% in the STT (n = 58) and HT (n = 84) groups, respectively ($P = 0.49$). Interestingly, multivariate stepwise logistic regression analysis revealed that among patients having adequate surgery, the first dose of ^{131}I was significantly associated with the outcome. Patients receiving at least 25 mCi of ^{131}I had a 2.8 times better chance (95% CI for odds ratio, 1.5–5.4) of remnant ablation in the adequate surgery group than patients receiving less than 25 mCi administered activity. However, for the groups receiving between 25 and 50 mCi, there was no difference in remnant ablation outcome. In addition to the first dose of ^{131}I, the adequate surgery group had two additional factors, namely tumor size and postsurgery RAIU, found to significantly affect the outcome (i.e. ablation) (Table 4). The multivariate stepwise logistic regression analysis among patients having inadequate surgery revealed that only the first dose of ^{131}I was significantly associated with the outcome (ablation). Patients receiving at least 25 mCi of ^{131}I had a four times better chance (95% CI for odds ratio, 1.6–9.8) of remnant ablation in the inadequate surgery group than patients receiving less than 25 mCi administered activity.

TABLE 3. Multivariate stepwise logistic regression analysis in all patients (n = 509): effect of independent covariates on the first-dose outcome (remnant ablation)

Variable	Odds ratio (OR)	95% CI for OR
Tumor size[a]	2.35	1.31–3.98
Type of surgery[b]	2.59	1.59–4.24
Postsurgical RAIU[c]	2.16	1.35–3.45
First dose[d]	3.05	1.8–5.01

Reference category is 0.
[a] Tumor size: ≤5 cm, 1; >5 cm, 0.
[b] Type of surgery: adequate, 1; inadequate, 0.
[c] Postsurgical RAIU: ≤10%, 1; >10%, 0.
[d] First dose: ≤20 mCi, 0; >20 mCi, 1.

TABLE 4. Multivariate stepwise logistic regression analysis after adequate surgery (n = 367): effect of independent covariates on the first-dose outcome (remnant ablation)

Variable	Odds ratio (OR)	95% CI for OR
Tumor size	3.0	1.5–6.1
Postsurgical RAIU	3.2	1.7–5.8
First dose	2.8	1.5–5.4

Reference category is 0.
[a] Tumor size: ≤5 cm, 1; >5 cm, 0.
[b] Postsurgical RAIU: ≤10%, 1; >10%, 0.
[c] First dose: ≤20 mCi, 0; >20 mCi, 1.

Two doses of ^{131}I were administered to 114 patients and three doses to 21 patients. The cumulative rate of remnant ablation achieved after the second and third doses of ^{131}I was 95.5 and 97.6%, respectively. Two and 10 patients are still to come for additional evaluation after the second and third doses, respectively. So far, no cases of local recurrence or nodal/distant metastasis have been observed in this study cohort. Also, no death has been encountered.

Discussion

Remnant ablation has been well established and accepted in the management protocol of DTC, as it is associated with lower recurrence rates, lower rates of distant metastases, and reduced cancer mortality rates, compared with only surgery or surgery and L-thyroxine therapy alone (6, 10, 15, 35–37). After four decades of follow-up and based on regression modeling of their 1510 patients without distant metastases at the time of initial therapy, Mazzaferri and Kloos (15) found remnant ablation to be an independent variable that reduced locoregional recurrence, distant metastases, and cancer death. A similar observation has also been made by the National Thyroid Cancer Treatment Cooperative Study group, and they had reconfirmed that postoperative RAI treatment was associated with improved cancer-specific mortality rates and reduced disease progression in both papillary and follicular cancer (16).

Remnant ablation can be achieved by either administering an empiric fixed activity of ^{131}I or using dosimetry-guided techniques. The clinical merits of dosimetry-guided ^{131}I therapy have been clearly demonstrated in the literature. Although Benua *et al.* (38) first introduced the dosimetric approach in thyroid cancer treatment in the early 1960s, it has not gained wide acceptance in routine management of DTC patients. Because of the technical and logistic difficulties, most centers have adapted the fixed-activity or standard-activity technique using 30–200 mCi ^{131}I. However, the most appropriate or effective administered activity of ^{131}I to ablate remnant thyroid tissue remains controversial. Some favor low activity around 30 mCi, and others argue for higher activity up to 200 mCi of ^{131}I for remnant ablation (17–30). It was believed for a long time that a higher amount of ^{131}I is more effective in achieving complete ablation with a single administration. The proponents of large-activity ^{131}I remnant ablation argue that large administered activity not only ablates remnants but also ablates possible micrometastatic deposits. They presume that low activity is less effective to

ablate the micrometastases not visualized in a posttherapy WBS and thereby will lead to a higher recurrence rate, local as well distant (39). However, this issue is already addressed by Mazzaferri and Kloos (15), who found no difference in 30-yr recurrence rates (4 and 6%, respectively; $P = 0.1$) between low-activity (29–50 mCi) and high-activity (51–200 mCi) ^{131}I remnant ablation groups.

The interest in administering the smallest effective dose of ^{131}I is the advantage of outpatient treatment (as the radiation exposures to household members of patients given less than 30 mCi is well below the maximum annual limit of 5.0 mSv) with the attended economy and convenience (40). There is also a theoretical advantage of decreasing the risk of leukemogenesis and extrathyroid organ damage from lower whole-body radiation, which has been estimated to be 6.1 roentgen-equivalent-man (rem) for 30 mCi, 8.5 rem for 50 mCi, and 12.2 rem for 60 mCi of ^{131}I, especially in young patients with favorable prognostic factors (23). In 1976, McCowan *et al.* (21) reported that 80–100 mCi of ^{131}I were not more effective than 30 mCi in achieving remnant ablation. Subsequently, other retrospective and prospective studies confirmed similar findings. Review of the literature, coupled with our previous experience, suggests that remnant ablation in up to 80% of cases could be achieved with ^{131}I activity of 30–50 mCi, which doesn't change significantly after increasing the activity, provided the surgeon had left a small remnant and ablation is defined by a diagnostic WBS using 2–5 mCi ^{131}I. In our previous randomized study using a fixed amount of ^{131}I ranging from 25–200 mCi for remnant ablation, we observed that increasing the empirical administered activity beyond 50 mCi resulted in a plateau of the dose-response curve (29). Although, the χ^2 test showed no statistical difference between the 30-mCi group and the 50-mCi group, no final and statistically valid conclusion regarding the lowest possible dose could be drawn because there were only two dose groups with a wide interval and sample size was relatively small. Then we had proposed to have another randomized trial incorporating a larger number of patients and a narrower ^{131}I activity interval to see whether it is possible to reduce the administered activity of ^{131}I without compromising the successful ablation rate less than 50 mCi (41).

Our present study shows that a dose as small as 25 mCi was good enough for remnant ablation after adequate surgery. It was associated with an 81% ablation rate, which did not change even after increasing the dose up to 50 mCi. The strength of the present study, however, is that it is a single institutional trial incorporating a large number of patients with uniform inclusion, exclusion, and ablation criteria. Apart from ^{131}I activity ($<$ or $\geq$25 mCi), tumor size, type of surgery, and postsurgical RAIU were also found to have a statistically significant effect on remnant ablation. Patients with small tumor ($\leq$5 cm), adequate surgery (TT/NTT), and lower RAIU ($\leq$10%) had more successful outcome. However, all three factors are somehow interlinked with each other. It is sometimes difficult to remove all tumor mass in patients with large tumor; hence, they will have significant remnant and therefore high RAIU. Similarly, if inadequate surgery had been performed because of some reason or other, again there will be large remnant and high RAIU. The rate of successful ablation would be low in both cases.

There have been some strong suggestions that patients with functioning thyroid remnant should be individualized by careful dosimetry after appropriate tracer studies. It had been proposed that at least 30,000 rad (300 Gy) cumulative absorbed dose should be delivered to the thyroid remnant for successful ablation (42). However, we have made some interesting observations regarding the radiation-absorbed dose *vs.* the ablation rate in this study. We found that radiation-absorbed doses of 173–374 Gy had similar rates of ablation. The univariate and multivariate stepwise logistic regression analysis did not reveal that radiation-absorbed dose had any influence on remnant ablation. The rationale of using the highest possible administered activity is based on the radiobiological fact that the radiation treatment efficacy is directly related to the radiation dose delivered. However, dosimetric calculations assume a homogeneous ^{131}I distribution throughout a target lesion, which is often not true in reality. The other possible error is the estimation of residual mass and effective half-life of tracer. All these add up to give an error margin in dosimetric calculation of one magnitude or more. The reported cytolethal doses of ^{131}I for normal and neoplastic thyroid tissue show significant variations. Successful ablation was achieved in a patient receiving only 120 Gy of radiation-absorbed dose, whereas a radiation-absorbed dose of 600 Gy could not achieve ablation in another patient. This observation could possibly be explained by varying radiosensitivity of thyroid tissue, measurement of which remains an elusive factor. This biological variable is unknown, undefined, and unpredictable and varies from individual to individual. This could be considered as one of the causes of unpredictable outcome of radioablation in individual patients. Therefore, it appears that although one can aim to deliver roughly 300 Gy to the thyroid remnant to achieve successful remnant ablation, the lesser absorbed dose can do a similar job and needs critical appraisal.

Some authors believe the relationship between extent of surgery and successful remnant ablation may be stronger than that between the radioiodine dose and remnant ablation. To critically assess the influence of surgery in the outcome of ^{131}I therapy in remnant ablation, we separately analyzed the data for the NTT group (n = 367) and the inadequate surgery group (n = 142). The rate of successful ablation in the adequate surgery group was much higher than in the inadequate group, which was statistically significant. However, multivariate stepwise logistic regression analysis revealed that only the first dose of ^{131}I was significantly associated with the outcome in both groups. Patients receiving at least 25 mCi of ^{131}I had 2.8 and 4.0 times better chances of remnant ablation in the adequate and inadequate surgery groups, respectively. In addition to the first dose of ^{131}I, the adequate surgery group had two additional factors, namely tumor size and postsurgery RAIU, also found to significant affect the outcome. However, the inadequate surgery group had no other influencing factor other than ^{131}I administered activity. Because absorbed radiation dose is inversely proportional to residual mass, keeping all other factors constant and assuming equal radiosensitivity, higher activities to be administered to ablate larger masses is logical.

In other words, in a meticulously operated patient, it is likely that the benefits of a lower dose gets progressively closer to that of a higher dose and may even be equal to a higher dose if surgery has left behind a less than 5-g remnant or uptake less than 10% at 48 h.

Some thyroidologists may argue that the ablation rate achieved by administering 25 mCi of ^{131}I may not be reproducible by other centers or may be a regional phenomenon that may not be applicable at a global level. With any amount of administered activity of ^{131}I, no group has ever achieved a successful ablation rate of 100% at first dose. Even after performing painstaking individual dosimetry, Maxon *et al.* (42) and Samuel and her colleagues (43) had achieved an ablation rate of approximately 80%. They had concluded that the vast majority of patients due for remnant ablation require approximately 30 mCi of ^{131}I. Lin *et al.* (44) from Taiwan, Pacini *et al.* (45) and Barbaro *et al.* (46) from Italy, DeGroot *et al.* (23) from Chicago, and Samuel *et al.* (43) from Mumbai (another major thyroid cancer treatment center from India) have all observed similar ablation rates. Therefore, it is more of a global than local observation. The environmental iodine distribution is varied in the above mentioned geographical regions, yet the ablation rate is uniform for the given dose of ^{131}I.

Conclusion

Patients with DTC should undergo TT/NTT followed by radioiodine remnant ablation. Twenty-five mCi of ^{131}I appears to be the smallest effective activity for remnant ablation as all patients can be treated on an ambulatory basis with associated low cost, convenience, and low whole-body radiation-absorbed dose to the patients.

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Address all correspondence and requests for reprints to: Dr. C. S. Bal, M.B.B.S., M.D., D.N.B., Additional Professor, Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India, 110029. E-mail: csbal@hotmail.com.

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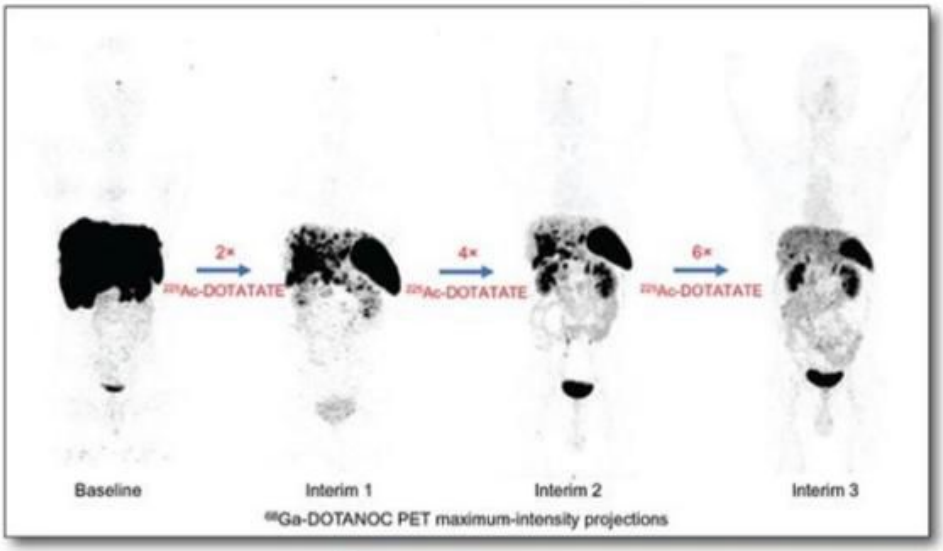
Survival Outcomes in Metastatic Gastroenteropancreatic Neuroendocrine Tumor Patients Receiving Concomitant ^{225}Ac-DOTATATE–Targeted α-Therapy and Capecitabine: A Real-World-Scenario Management-Based Long-Term Outcome Study. Sanjana Ballal et al. See page 211.



Enhanced ^{68}Ga-radiopharmaceutical availability: assessing clinical safety and PET imaging efficacy of integrated cyclotron–produced ^{68}Ga-DOTATATE. Sébastien Tremblay et al. See page 232.

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Survival Outcomes in Metastatic Gastroenteropancreatic Neuroendocrine Tumor Patients Receiving Concomitant ^{225}Ac-DOTATATE–Targeted α-Therapy and Capecitabine: A Real-World-Scenario Management-Based Long-Term Outcome Study

Sanjana Ballal*[1], Madhav P. Yadav*[1], Madhavi Tripathi[1], Ranjit Kumar Sahoo[2], and Chandrasekhar Bal[1]

[1]*Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India; and* [2]*Department of Medical Oncology, BR Ambedkar Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India*

See an invited perspective on this article on page 219.

Although the short-term results of targeted α-therapy (TAT) with ^{225}Ac-DOTATATE in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) have proven the therapy to be effective, to our knowledge no one has assessed the long-term outcome results. In this study, we aimed to evaluate the long-term outcome of ^{225}Ac-DOTATATE TAT in patients with somatostatin receptor–expressing advanced-stage metastatic GEP-NETs. **Methods:** Patients with ^{68}Ga-DOTANOC PET/CT scans showing moderate-to-high somatostatin receptor expression were recruited. Systemic TAT was performed on 91 adults with GEP-NETs (54 men and 37 women; mean age, 54.3 y; range, 25–75 y) using ^{225}Ac-DOTATATE (100–120 kBq/kg of body weight). All patients were given capecitabine therapy as a radiosensitizer (2 g/d) from days 0 to 14 of every ^{225}Ac-DOTATATE treatment cycle. Patients were categorized into 3 groups based on the status of prior ^{177}Lu-peptide receptor radionuclide therapy (PRRT): a prior-^{177}Lu-PRRT–refractory group; a prior-^{177}Lu-PRRT disease-control group; and a ^{177}Lu-PRRT–naïve group. Primary endpoints were overall survival (OS), and secondary endpoints included progression-free survival (PFS), objective tumor response, clinical response, and assessment of treatment-related toxicities. **Results:** Among the 91 patients, 57 underwent prior ^{177}Lu-DOTATATE therapy (24 with controlled disease [partial response/stable disease] and 33 with progressive disease [PD]). In total, 453 ^{225}Ac-DOTATATE TAT cycles were administered (median, 4 cycles per patient; range, 1–10) in a median follow-up of 24 mo (range, 5–41 mo). Median OS was not attained, with a 24-mo OS probability of 70.8%. In multivariate analysis, prognostic factors associated with a poor OS included the presence bone metastases (hazard ratio [HR], 2.501; 95% CI, 1.826–5.791; $P < 0.032$) and ^{225}Ac-DOTATATE therapy–refractory disease (HR, 8.781; 95% CI, 3.843–20.062; $P < 0.0001$). Median PFS was also not reached, with a 24-mo PFS probability of 67.5%. The multivariate analysis revealed only ^{177}Lu-PRRT–refractory disease to be significantly associated with a reduced PFS (HR, 14.338; 95% CI, 1.853–97.698; $P = 0.011$). Two of 79 patients (2.5%) with assessable disease experienced a complete response, 38 (48%) had a partial response, 23 (29%) had stable disease, and 16 (20.2%) had PD. PD was observed in more patients from the prior-^{177}Lu-PRRT–refractory group (11/33, 34%) than in ^{177}Lu-PRRT–naïve patients (4/24, 11%; $P = 0.056$). Patients from the prior-^{177}Lu-PRRT–refractory group had the highest risk of poor PFS (HR, 13.553; 95% CI, 4.343–42.271; $P = 0.0009$). A significant clinical benefit was achieved after ^{225}Ac-DOTATATE therapy with minimal treatment-related toxicities. **Conclusion:** In long-term results, ^{225}Ac-DOTATATE TAT showed promise and improved the OS, even in patients refractory to prior ^{177}Lu-DOTATATE treatment, with transient and acceptable adverse effects.

Key Words: ^{225}Ac-DOTATATE TAT; GEP-NETs; overall survival; progression-free survival; objective response

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Expanded treatment options have recently become available to patients with well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs) (*1*). Surgery offers the best chance of curing patients with localized GEP-NETs; however, surgery is not feasible when extensive metastases are present. In such cases, other options include somatostatin analogs (SSAs; e.g., lanreotide and octreotide) (*2,3*), interferons, tyrosine kinase inhibitors (e.g., sunitinib) (*4*), mammalian-target-of-rapamycin inhibitors (e.g., everolimus) (*5*), peptide receptor radionuclide therapy (PRRT) (*6*), systemic chemotherapy, and liver-targeted therapies, depending on the extent, stage, and location of disease and the tumor grade (*7*). The phase III NETTER-1 trial provided evidence for the efficacy and safety of PRRT using ^{177}Lu in this setting (*8*). However, only 18% of patients achieved a partial or complete response, despite treatment with ^{177}Lu-DOTATATE, a β- and γ-emitting radionuclide, and most patients relapsed within 2−3 y of treatment (*9,10*).

One promising option that has gained interest is using high-linear-energy-transfer α-emitting radioisotopes such as ^{225}Ac and ^{213}Bi instead of low-linear-energy-transfer β-emitting radioisotopes such as ^{90}Y and ^{177}Lu. The theoretic physical advantages of α-radiation over β-radiation are an endearing option to further improve the efficacy of PRRT by labeling the peptides with α-particle emitters (*11*).

Results from preclinical and clinical studies have suggested that an alternative strategy using PRRT delivering an α-emitting radionuclide

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For correspondence or reprints, contact Chandrasekhar Bal (csbal@hotmail.com).
*Contributed equally to this work.
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such as ^{213}Bi and ^{225}Ac-DOTATOC may have promise in patients with advanced GEP-NETs refractory to ^{177}Lu-PRRT (*12–16*).

One clinical study used ^{213}Bi-DOTATOC in 7 patients with neuroendocrine tumor progression on β-PRRT (*17*). Although that study demonstrated the therapeutic potential of this approach, ^{213}Bi-DOTATOC was administered via intraarterial delivery, limiting the more widespread application of α-radionuclide therapy in the real-world setting. ^{213}Bi also has a physical half-life of only 46 min, resulting in logistic challenges for broader adoption.

These studies prompted us to investigate the role of ^{225}Ac-DOTATATE as salvage treatment for patients with GEP-NETs (*18*). Initial results from 32 patients who had previously received ^{177}Lu-PRRT indicated that ^{225}Ac-DOTATATE administered intravenously induced sustained responses. Approximately two thirds of the 24 patients (15/24, 62.5%) who underwent interim morphologic response analysis had a partial response, and the disease control rate was 100% (15 with PR and 9 with stable disease). Furthermore, there was no documented progressive disease (PD), and no deaths occurred during a median follow-up of 8 mo (range, 2−13 mo). We observed minimal and reversible toxicities and no life-threatening adverse events (AEs). These data suggested that multiple cycles of therapy could be safely administered without a significant risk of either acute or delayed radiation toxicity (*18*). Despite the favorable short-term results, as far as we are aware no comprehensive long-term outcome results have been extensively studied to demonstrate the survival benefit of ^{225}Ac-DOTATATE therapy in both prior-^{177}Lu-PRRT and ^{177}Lu-PRRT–naïve groups of GEP-NET patients.

In the current study, we extensively studied the long-term follow-up data in an expanded cohort of patients to assess overall survival (OS), progression-free survival (PFS), factors predicting survival, response to treatment, and the patterns of the delayed AE profile in advanced metastatic GEP-NETs.

MATERIALS AND METHODS

Study Design

The independent institutional review board of All India Institute of Medical Sciences approved the study. All patients provided written informed consent before participating. Ethical clearance was received (reference number IEC-517). The study design and treatment regimen are depicted schematically in Figure 1. The methodology is detailed in the supplemental materials (available at http://jnm.snmjournals.org).

The study was on patients with histologically well-differentiated, inoperable, or metastatic GEP-NETs. Patients were included if they had a history of prior concomitant therapies, such as SSAs and chemotherapy, as well as ^{177}Lu-DOTATATE therapy. Essential prerequisites were significant somatostatin receptor expression and at least 1 measurable lesion on the CT component of the baseline ^{68}Ga-DOTANOC PET/CT scan (uptake ≥ liver or Krenning score ≥ 2 as compared on maximum-intensity-projection, coronal, and transaxial images).

Patients with inadequate laboratory parameters (baseline hemoglobin < 9 g/dL, platelet count < 75,000/μL, serum creatinine > 1.6 mg/dL, or serum bilirubin > 3 mg/dL) or a Karnofsky performance status (KPS) of less than 40 were excluded.

Treatment Planning and Follow-up

Image Acquisition. All patients underwent a baseline diagnostic ^{68}Ga-DOTANOC PET/CT scan as a pretherapeutic work-up. For morphologic assessment, additional ^{68}Ga-DOTANOC PET/CT scans were repeated within 6–8 wk after patients completed every 2–3 cycles of ^{225}Ac-DOTATATE–targeted α-therapy (TAT), when patients presented with clinical disease progression, or at the investigator's discretion.

^{68}Ga-DOTANOC PET/CT Imaging. The ^{68}Ga-DOTANOC PET/CT scans did not require special preparation. A mean activity of 111 MBq (3 mCi) was injected, and PET/CT scans were acquired between 45 and 60 min after injection. For the acquisition, the patient lay supine on the examination table. The protocol constituted of an initial

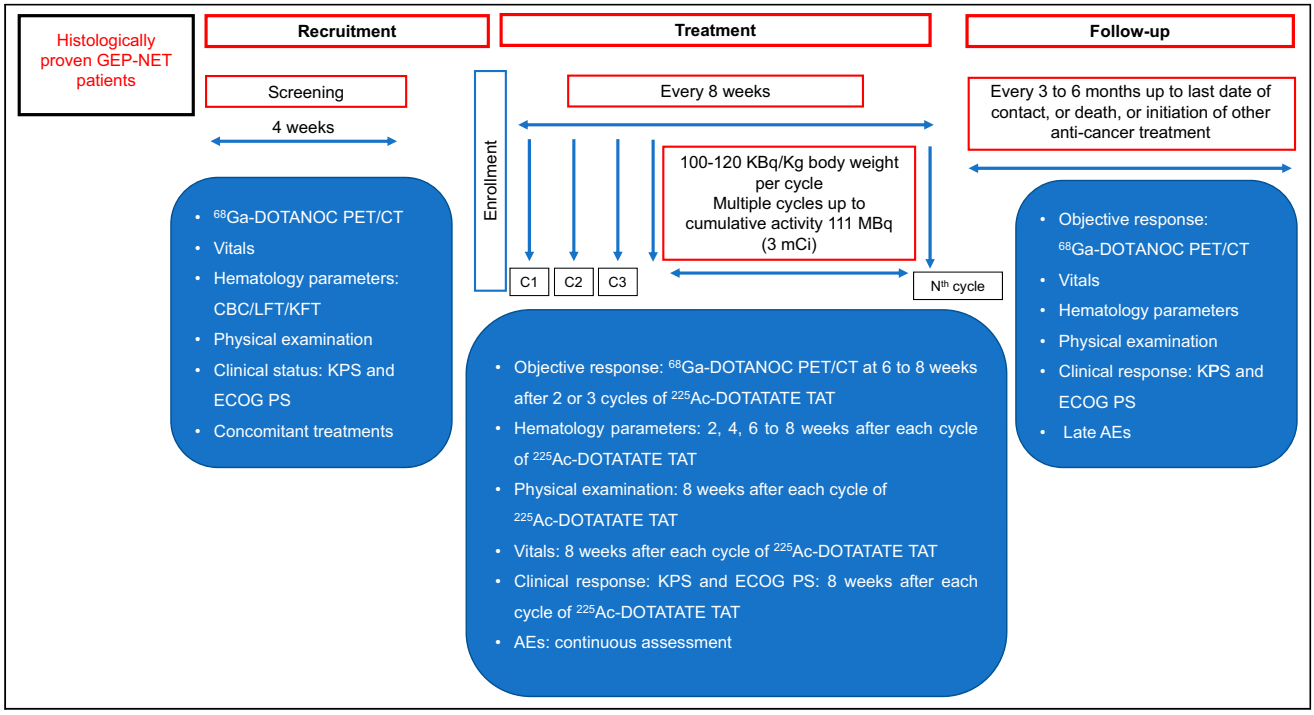

FIGURE 1. ^{225}Ac-DOTATATE TAT treatment regimen and follow-up. CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; KFT = kidney function testing; LFT = liver function testing; PS = performance status.

scout image to define the field of view from vertex to mid thigh, followed by diagnostic CT and PET scans. The diagnostic whole-body CT scan parameters involved a diagnostic-dose CT scan with 300–380 mAs, 120 kVp, a slice thickness of 3.75 mm, and a pitch of 0.6. Additionally, spot views were acquired if required, with a slice thickness of 1.25 mm on CT at 120 kVp, 300–380 mAs, and a pitch of 0.6.

The administration and route of the contrast medium depended on the site of the tumor and scan indication. Generally, CT scans were acquired with a nonionic, isomolar contrast medium (iodixanol injection, U.S. Pharmacopeia; 1 mL/kg of body weight) containing 320 mg I/mL intravenously or orally and a neutral oral contrast medium (water). Fifty-six patients were injected with nonionic, isomolar contrast medium. Positive oral (iodixanol) and neutral (water) contrast media were administered when indicated. All tumors were visualized on the diagnostic CT scan, but only tumors with measurable dimensions according to RECIST, version 1.1, were included for the assessment of morphologic response.

Treatment. Long- and short-acting somatostatin agents were stopped 4–5 wk and 48–72 h, respectively, before ^{225}Ac-DOTATATE therapy. Premedications, including an antiemetic (ondansetron) or corticosteroid (dexamethasone), were administered and repeated if necessary. For kidney protection, a single-day kidney protection protocol was followed, which consisted of an injection solution containing lysine (23.3 g) and arginine (8 g) in 1 L of water. This cocktail was infused over 4 h, starting 30–60 min before the ^{225}Ac-DOTATATE infusion.

As previously described, ^{225}Ac-DOTATATE (100–120 kBq/kg [3–3.2 μCi/kg] of body weight per cycle diluted in 50 mL of saline) was administered over 30 min (flow rate, 1.6 mL/min) every 8 wk up to a maximum cumulative dose of 111 MBq (3 mCi). All patients received capecitabine as a radiosensitizer (2 g/d) from days 0 to 14 of every cycle. Patients were monitored for 24 h after ^{225}Ac-DOTATATE TAT to observe any acute side effects. Patients on supportive care or octreotide continued to receive those treatments at the investigator's discretion.

Patients were withdrawn from the study in the event of any serious AEs; lack of adherence to the treatment protocol due to unavoidable pandemic conditions; demonstration of disease progression; withdrawal of consent to further treatment cycles; or death.

Assessments. Safety was monitored at baseline and at 8-wk intervals thereafter. Assessments included physical examination, vital parameters, laboratory tests (assessed at 2, 4, and 6- to 8-week intervals), and clinical evaluation via KPS and Eastern Cooperative Oncology Group (ECOG) performance status. Patients were given a diary to document any side effects or discomfort. With the exception of blood parameters, all other assessments were conducted at baseline and at 8 wk after each cycle of ^{225}Ac-DOTATATE TAT or on withdrawal from the study or at treatment completion.

Patient Groups. On the basis of ^{177}Lu-PRRT history, patients were categorized into 2 groups: a prior-^{177}Lu-PPRT group and a ^{177}Lu-PRRT–naïve group (Fig. 2). The prior-^{177}Lu-PRRT group was further divided according to cancer status after ^{177}Lu-PRRT, that is, those who were treatment-refractory and those who were stable or responded to ^{177}Lu-PRRT (Fig. 2). Patients in the prior-^{177}Lu-PRRT–refractory group (n = 33) progressed during the ^{177}Lu-DOTATATE treatment course or within 12 mo of completion of the ^{177}Lu-DOTATATE treatment regimen. Patients in the prior-^{177}Lu-PRRT disease-control group (n = 24) completed the ^{177}Lu-DOTATATE treatment regimen and achieved disease control (partial response or stable disease) but were further treated with ^{225}Ac-DOTATATE because of the persistent high tumor burden. Patients in the ^{177}Lu-PRRT–naïve group (n = 34) did not receive ^{177}Lu-DOTATATE therapy at any point in the treatment course.

Outcomes

The primary endpoint was OS (defined as the time from initiation of ^{225}Ac-DOTATATE TAT until death due to any cause or the date of the last contact). Patients who were lost to follow-up were considered alive but were censored (supplemental material). The key secondary endpoint was PFS (defined as the first observation of documented morphologic disease progression on diagnostic CT according to the assessment by RECIST 1.1 (*19*) or the development of pleural/pericardial effusion/malignant ascites or disease-specific death, whichever occurred first. Other cosecondary endpoints included objective tumor response by RECIST 1.1, clinical response assessment with KPS and ECOG performance status (*20*), and evaluation of treatment-related AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) and the Food and Drug Administration document entitled, "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (*21,22*).

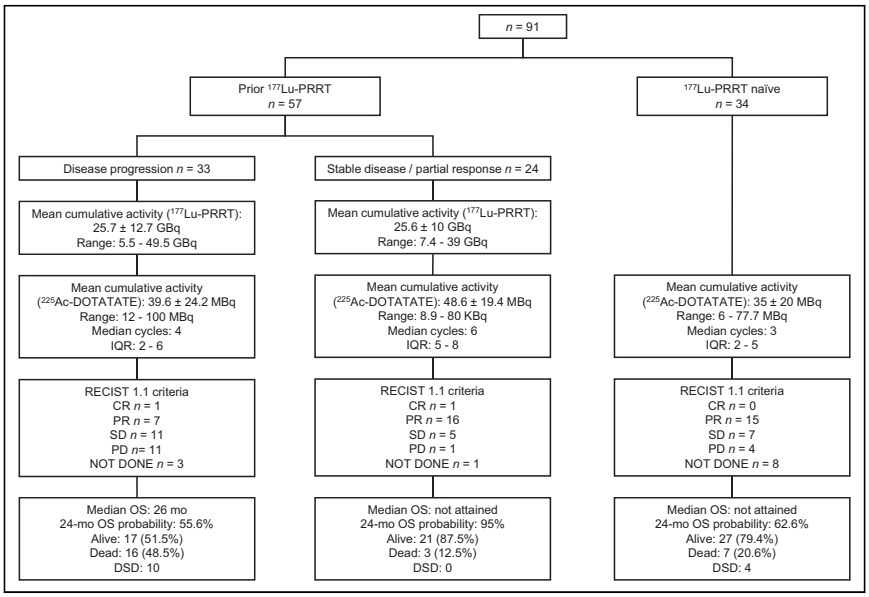

FIGURE 2. Flowchart depicting treatment details and response in various groups of patients. CR = complete response; DSD = disease-specific death; IQR = interquartile range; PR = partial response; SD = stable disease.

Statistical Analysis

Univariate analysis was used to compare characteristics among patient groups. On the basis of the normality of parameters, continuous variables with a normal distribution were represented as mean, SD, range, median, and interquartile range. Parameters of the same population at different time points were compared using a paired t-test (parametric test) or Wilcoxon signed-rank test (nonparametric test). OS and PFS plots were constructed using the Kaplan–Meier methodology; a log-rank test was used to compare survival between groups. The Cox proportional-hazards regression model was performed to determine the predictive and prognostic factors associated with OS and PFS. P values of less than 0.05 were considered to be significant. The analysis was conducted using MedCalc statistical software (version 15.1; MedCalc Software Ltd.).

RESULTS

Baseline Demographic and Clinical Characteristics of Patients

Between April 2018 and February 2022, 91 consecutive GEP-NET patients (54 men and 37 women, mean [±SD] age, 54.3 ± 11.6 y; range, 25–75 y) were enrolled. The first ^{225}Ac-DOTATATE TAT treatment was administered in April 2018, and the last patient was recruited in October 2021. The last date for follow-up cutoff was February 20, 2022. The median follow-up duration was 24 mo (range, 5–41 mo) from the start of ^{225}Ac-DOTATATE TAT.

Baseline characteristics are summarized in Table 1. The pancreas (33%) was the most common site of the primary tumor, followed by the duodenum (14.3%) and ileum (13%). GEP-NETs were World Health Organization grade 1 in 33 patients (36.2%), grade 2 in 48 (52.7%), and grade 3 in 7 (7%) (Table 1; Supplemental Table 1). Primary or residual tumor was noted in 55 patients (60.4%), and all patients demonstrated metastases on somatostatin receptor PET/CT, with the most common metastatic sites being the liver (n = 88, 96.7%), lymph nodes (n = 66, 72.5%), and bone (n = 25, 27.5%) (Supplemental Table 2). Eighteen patients (20%) had received prior chemotherapy (Supplemental Table 3), most of whom had 1 previous line (n = 12, 66.6%); 4 patients (22.2%) had 2 prior lines, and 2 (11%) had at least 3 prior lines. Ten symptomatic patients were on long-acting SSAs, which were stopped 4 wk before commencing ^{225}Ac-DOTATATE TAT.

TABLE 1
Patient Characteristics at Baseline (n = 91)

Characteristic	Value
Age (y)	
Mean ± SD	54.3 ± 11.6
Range	25–75
Sex	
Male	54 (59.4%)
Female	37 (40.6%)
Tumor location	
Pancreas	30 (33%)
Stomach	7 (7.7%)
Appendix	1 (1%)
Ileum	12 (13%)
Duodenum	13 (14.3%)
Jejunum	2 (2.2.%)
Colon	2 (2.2%)
Rectum	8 (8.8%)
Abdominal neuroendocrine tumor with unknown primary	16 (17.6%)
WHO tumor grade (Ki-67 tumor proliferation index)	
Grade I (<2%)	33 (36.2%)
Grade II (3%–20%)	48 (52.7%)
Grade III (>20%)	7 (7%)
Not accessible	3 (3.3%)
Previous surgery	20 (22%)
Prior chemotherapy	20 (22%)
Prior ^{177}Lu-DOTATATE therapy	57 (62.6%)
ECOG status	
1–2	63 (69%)
3–4	28 (31%)

WHO = World Health Organization.
Data are number and percentage, except for age.

Treatment

The mean cumulative radioactivity administered was 35.52 MBq (range, 21.64–59.47 MBq [960 μCi; range, 583.7–1,607.3 μCi]). The median interval between treatment cycles was 8 wk. In total, 453 cycles of ^{225}Ac-DOTATATE TAT were administered: 32 patients received 1–3 cycles, and the remaining 59 patients received 4–10 cycles (Supplemental Table 4). Three patients received a single cycle of ^{225}Ac-DOTATATE TAT: the first patient died after the first cycle, the second was lost to follow-up, and the third withdrew consent.

Efficacy Assessment

OS and PFS. Twenty-six patients (26.5%) died during follow-up. The causes of death are detailed in Supplemental Table 5. In the overall patient population, the median OS was not attained, with a 24-mo survival probability of 70.8% (Fig. 3A). On subcategoric analysis, whereas 16 (16/33, 48.5%) deaths occurred in the prior-^{177}Lu-PRRT–refractory group (median OS, 26 mo), 3 deaths (3/24, 12.5%) and 7 deaths (7/34, 20.6%) occurred in the prior-^{177}Lu-PRRT disease-control group and ^{177}Lu-PRRT naïve group, respectively (P = 0.0003) (Fig. 3B). Interestingly, in patients who demonstrated disease control on ^{177}Lu-PRRT, none of the 3 deaths was disease-specific (Supplemental Table 5). The prior-^{177}Lu-PRRT disease-control group showed significantly better OS than the ^{177}Lu-PRRT–native group (95% vs. 67%) (Fig. 2). We speculated that these differences might be due to inherent differences in the baseline demographic or clinical characteristics of the patient cohorts. However, univariate comparison between the groups did not reveal any differences in the demographic parameters (Supplemental Table 6).

On univariate analysis, the presence of bone metastases (Fig. 3C), a cumulative ^{225}Ac-DOTATATE TAT dose of less than 37,000 kBq (Fig. 3D), and PD to ^{225}Ac-DOTATATE TAT (Fig. 3E) were associated with significantly poorer OS (Supplemental Table 7). However, on multivariate analysis, the presence of bone metastases (hazard ratio [HR], 2.501; 95% CI, 1.826–5.791; P = 0.032) and ^{225}Ac-DOTATATE therapy–refractory disease (PD) persisted as significant prognostic factors associated with poor OS (HR, 8.781; 95% CI, 3.843–20.062; P < 0.0001) (Fig. 3E).

At the time of this analysis, median PFS had not been attained in the overall patient population. The median PFS was 30 mo in the prior-^{177}Lu-PRRT–refractory group and was not reached in the prior-^{177}Lu-PRRT disease-control group (HR, 13.553; 95% CI, 4.343–42.271; P = 0.0009) (Fig. 4A). Similarly, univariate analysis revealed an association between the presence of bone metastases (Fig. 4B) and a cumulative ^{225}Ac-DOTATATE dose of less than 1 mCi and PD (HR, 2.718; 95% CI, 0.999–7.393; P = 0.028) (Fig. 4C; Supplemental Table 8). However, on multivariate analysis, only ^{177}Lu-PRRT–refractory disease was significantly associated with a significantly reduced PFS (HR, 14.3; 95% CI, 1.853–97.6; P = 0.011).

Objective Response. Morphologic response to ^{225}Ac-DOTATATE TAT according to the disease status on prior ^{177}Lu-PRRT therapy is shown in Table 2. Two of the 79 evaluable patients (2.5%), both previously treated with ^{177}Lu-PRRT, had a complete response; no complete responses were observed in the ^{177}Lu-PRRT–naïve group. ^{68}Ga-DOTANOC PET/CT revealed a partial response in 38

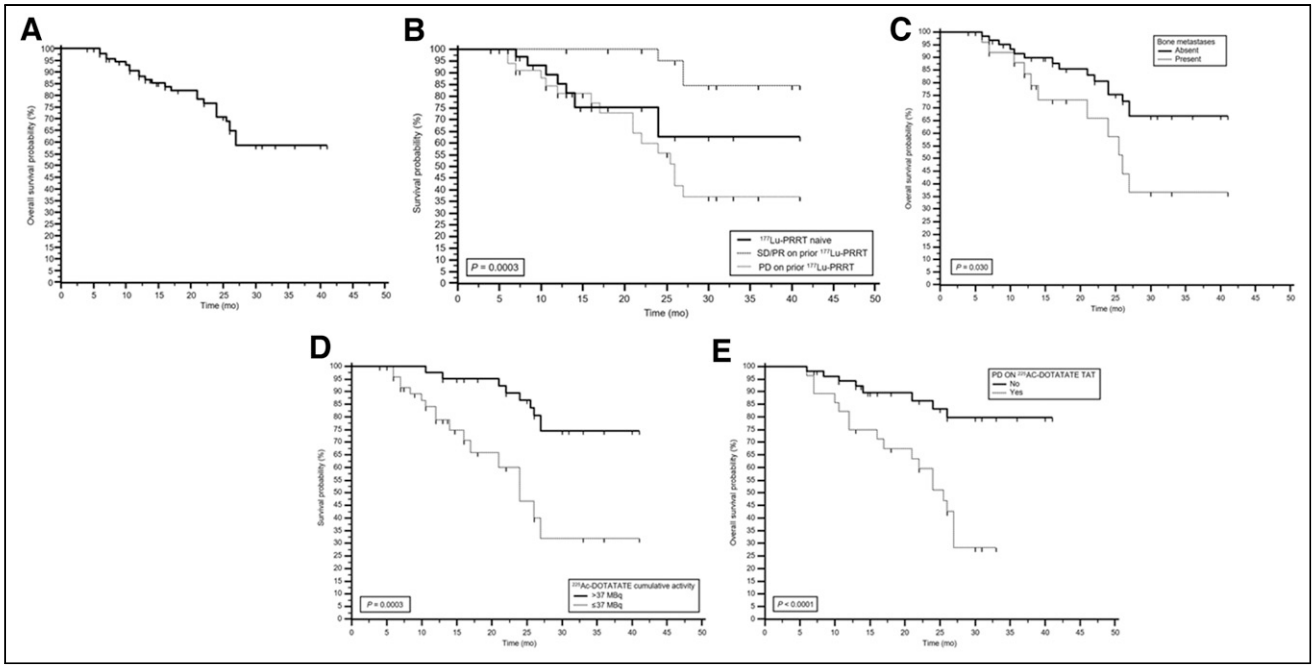

FIGURE 3. OA in entire cohort of 91 patients who had been treated with ^{225}Ac-DOTATATE (A), based on disease status on prior ^{177}Lu-PRRT (B), based on presence of bone metastases (C), based on cumulative dosage of ^{225}Ac-DOTATATE received (D), and based on disease status on ^{225}Ac-DOTATATE therapy (E). PR = partial response; SD = stable disease.

patients (48%) and stable disease in 23 (29%), for a disease control rate of 80%. Twelve and 4 progression events occurred in the prior-^{177}Lu-PRRT and ^{177}Lu-PRRT–naïve groups, respectively, representing a 40% lower estimated risk of progression in the ^{177}Lu-PRRT–naïve group than in the prior-^{177}Lu-PRRT group.

In the prior-^{177}Lu-PRRT group, among 24 patients who experienced disease control with ^{177}Lu-PRRT, 17 (74%) further showed a response to ^{225}Ac-DOTATATE TAT. Promising response rates were also observed in 8 of 30 patients (27%; 1 complete response and 7 PRs) belonging to the prior-^{177}Lu-PRRT–refractory group, with stable disease in a further 11 patients (36.6%; Fig. 1). PRs were observed in 15 of 27 patients (55.5%) in the ^{177}Lu-PRRT–naïve groups.

Of the 17 patients with PD, 14 experienced disease-specific deaths, 2 have been rechallenged with an escalated 150 kBq/kg dose of ^{225}Ac-DOTATATE and have shown disease stability, and the remaining patient refused to undergo any further treatment but is alive.

Clinical Response. Among the patients who were alive till the end of analysis, the median KPS significantly improved from 60 at baseline to 70 after treatment ($P < 0.0001$), and the median ECOG score enhanced from 2 to 1 ($P < 0.0001$). In the overall population, whereas the KPS improved from 60 to 70 ($P = 0.053$), ECOG status remained the same as the median baseline value of 2.

Toxicity and AEs

Treatment-related AEs occurring during ^{225}Ac-DOTATATE TAT are shown in Supplemental Table 9. No renal or liver toxicity and no tumor-lysis syndrome were observed. One patient had grade 3 thrombocytopenia. Clinical disease-related symptoms, such as fatigue, loss of appetite, nausea, gastritis, abdominal pain, abdominal distension, and myalgia, were caused mainly by the nature of the cancer and the site of metastasis and were prevalent before the initiation of ^{225}Ac-DOTATATE treatment. All the above symptoms improved after treatment.

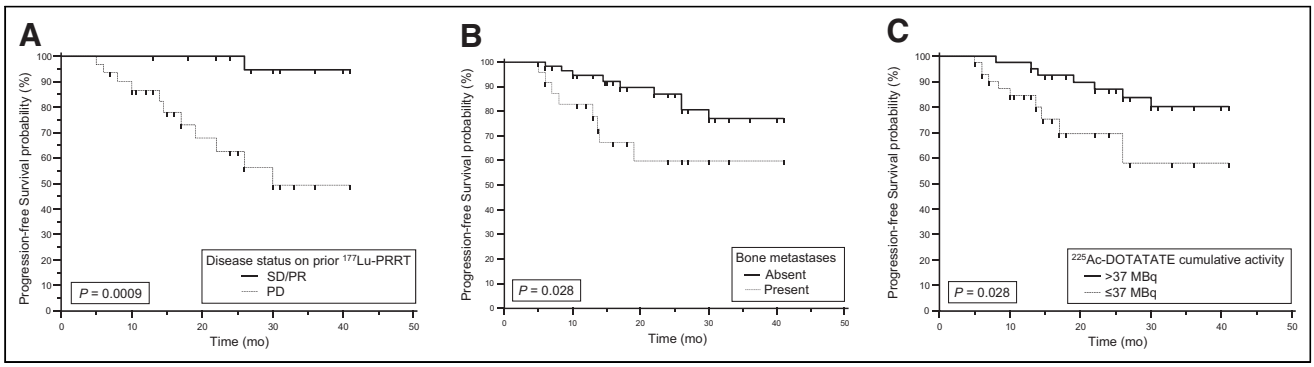

FIGURE 4. Radiologic PFS according to disease status on prior ^{177}Lu-PRRT (A), presence or absence of bone metastases (B), and cumulative activity of ^{225}Ac-DOTATATE received (C).

TABLE 2
Morphologic Tumor Response Based on Primary Tumor Site

Site of primary	Prior ^{177}Lu-PRRT (n = 57)					^{177}Lu-PRRT–naïve (n = 34)					
	CR	PR	SD	PD	Not assessed	Site of primary	CR	PR	SD	PD	Not assessed
Foregut (n = 32)	1 (3%)	13 (40.6%)	10 (31%)	6 (18.7%)	2 (6%)	Foregut (n = 15)	0	7 (46.6%)	2 (13.3%)	3 (20%)	3 (20%)
Midgut (n = 11)	0	6 (54.5%)	3 (27.3%)	1 (9%)	1 (9%)	Midgut (n = 9)	0	5 (55.6%)	2 (22.2%)	0	2 (22.2%)
Hindgut (n = 7)	1 (14.3%)	2 (28.6%)	2 (28.6%)	2 (28.6%)	0	Hindgut (n = 1)	0	0	1 (100%)	0	0
Unknown (n = 7)	0	2 (28.6%)	1 (14.3%)	3 (42.8%)	1 (14.3%)	Unknown (n = 9)	0	3 (33.3%)	2 (22.2%)	1 (%)	3 (33.3%)
Total (n = 57)	2 (3.5%)	23 (40.3%)	16 (28%)	12 (21%)	4	Total (n = 34)	0	15 (44%)	7 (20.6%)	4 (11.8%)	8 (23.6%)

CR = complete response; PR = partial response; SD = stable disease.
Data are number and percentage.

Malignant ascites and pleural effusion, which are signs of PD, were observed in 14 and 2 patients, respectively. Grade 1 of 2 malignant ascites was present in 8 patients at baseline. Eventually, 4 patients experienced grade 2 malignant ascites, and 10 experienced life-threatening malignant ascites and died. One patient with pleural effusion also died.

Before initiation of ^{225}AC-DOTATATE, flushing was documented in 8 patients, 3 of whom had grade 3 flushing. After treatment, flushing improved to grade 1 in all patients.

Transient symptoms, including nausea, vomiting, and abdominal discomfort, were encountered in most patients during the amino acid infusion and ^{225}Ac-DOTATATE administration and settled within 24 h after treatment. Fatigue, myalgia, and loss of appetite were also observed and resolved within 1 wk after treatment.

DISCUSSION

In our short-term analysis on the first clinical experience with the α-emitting conjugate ^{225}Ac-DOTATATE TAT in 32 patients with GEP-NETs who had exhausted or were refractory to β-emitting ^{177}Lu-DOTATATE therapy, we observed favorable responses with low toxicities (*18*). The study included an expanded cohort of 91 patients with an extended median follow-up of 24 mo, ranging from 5 to 41 mo. Our results provide further evidence that ^{225}Ac-DOTATATE is effective in patients with neuroendocrine tumors, a group with few therapeutic options, especially after progression on other therapies. Median OS and PFS were not attained. The objective response rate and disease control rates were 48% and 80%, respectively, and were lower than our previously reported short-term data showing a response rate of 63% and a disease control rate of 100%.

Though the current study had broad and heterogeneous inclusion criteria, it was conducted in a real-world setting based on everyday clinical practice that includes patients of poor performance status (31%) (ECOG status ≥ 3)—a critical and optimistic perspective of this study. We believe that real-world–based clinical study results can be extended and translated to the general population. Moreover, in this study, several demographic and clinical variables were compared among 3 groups of patients whose categorization was based on the status of prior ^{177}Lu-PRRT therapy and who were matched (Supplemental Table 6), which ruled out the potential inherent bias.

Comparisons with the NETTER-1 median long-term OS result (*23*), 48 mo, revealed that ^{225}Ac-DOTATATE provided an additive OS benefit of 26 mo in the worst-outcome patient cohort, who were refractory to prior ^{177}Lu-PRRT. Well in line with the phase III NETTER-1 (*8*) short-term result showing 14 deaths (12%) in the 116 neuroendocrine tumor patients who underwent ^{177}Lu-DOTATATE therapy as a first-line treatment option, our cohort of 34 ^{177}Lu-PRRT–naïve patients reported a similar disease-specific death rate of 11.7% (4/34) in a median follow-up of 24 mo.

Another finding meriting comment is that in this cohort of patients from our group and the NETTER 1 group, the median OS was not attained. An interpretation of this finding is that the upfront use of ^{225}Ac-DOTATATE therapy in advanced neuroendocrine tumors may not be necessary as a mainstay option. Irrespective of the disease burden, patients can first be challenged with ^{177}Lu-PRRT and eventually be rechallenged with α-based ^{225}Ac-DOTATATE therapy when a high disease burden is persistent despite attaining a maximum tolerable dose of ^{177}Lu (~1.2 Ci) or the patient is refractory to ^{177}Lu-PRRT.

Patients who achieved disease control (partial response or stable disease) with prior ^{177}Lu-PRRT (n = 24) followed by retreatment with ^{225}Ac-DOTATATE showed the best outcome, with a 24-mo OS probability of 95%, which was remarkably higher than in the ^{177}Lu-PRRT–refractory (55.6%) and –naïve (62.6%) groups. Moreover, only 3 deaths occurred in this group of patients, and none of the events was disease-specific. There may be 2 possible explanations for these findings. The first possibility is that ^{225}Ac-DOTATATE significantly increased the OS as an adjuvant treatment option after ^{177}Lu-PRRT. The alternative possibility is simply that patients had already achieved disease control on ^{177}Lu-PRRT and could be followed up with a wait-and-watch approach until the disease progressed. However, only a double-arm randomized, controlled trial between the wait-and-watch group and the group receiving further ^{225}Ac-DOTATATE treatment can be the definitive answer.

Rudisile et al. (*24*) studied the outcomes of ^{177}Lu-PRRT retreatment in the salvage setting for all patients who responded to the initial standard 4 cycles of ^{177}Lu-PRRT. They observed an additional response rate of 3%, PFS of 6 mo, and OS of 51 mo. The largest systematic review and metaanalysis, by Strosberg et al. (*25*), examined published evidence of ^{177}Lu-PRRT retreatment efficacy and safety in patients with advanced progressive neuroendocrine tumors. ^{177}Lu-PRRT retreatment provided encouraging results, with a median PFS of 12.5 mo and a median OS of 26.7 mo. In a similar salvage treatment setting, our results go beyond the previous reports, as we observed a remarkably higher response rate of 74% (17 with complete response and 23 with partial response), and promising prolonged survival benefits, as neither PFS nor OS was attained with ^{225}Ac-DOTATATE therapy.

Although several groups reported variations in the site of metastases associated with poor survival, it is apparent that the presence of distant metastases has a significant impact on survival, irrespective of the treatment modality. Regarding the impact of bone metastases on survival, our results with ^{225}Ac-DOTATATE TAT are similar to those reported by Rudisile et al. (*24*) and Swiha et al. (*26*), who demonstrated that the presence of bone metastases was associated with a shorter OS in patients with well-differentiated neuroendocrine tumors who received ^{177}Lu-DOTATATE.

In addition to morphologic responses, improvements in overall patient well-being were observed, with the median KPS increasing from 60 before treatment (patients requiring medical care and much assistance with self-care) to 70 after treatment (patients being able to care for themselves but unable to do their usual activities or active work). This finding highlights the potential for ^{225}Ac-DOTATATE to improve the quality of life in the worst-outcome patient population.

Treatment with ^{225}Ac-DOTATATE TAT was well tolerated. As previously described, low-grade hematologic AEs were the most common side effect of treatment with ^{225}Ac-DOTATATE. Grade 3 and higher AEs were uncommon and transient or unlikely to be treatment-related. The total amount of ^{225}Ac administered (≤111 MBq) did not correlate with AEs. Interestingly, AEs also did not correlate with ^{177}Lu-naïve or prior ^{177}Lu-PPRT therapy, which suggests that dosing with ^{225}Ac-DOTATATE TAT should not be influenced by prior treatment with ^{177}Lu. Moreover, similar to the short-term results (*18*) by our group on ^{225}Ac-DOTATATE, there were minimal hematologic, kidney, and liver function toxicities. However, over time during the long-term follow-up, when making comparisons with our pilot results we observed a significantly high incidence of malignant ascites and pleural effusion; whether they were related to disease per se or were TAT-related, longer follow-up of this cohort will clarify. In agreement with our findings, another study using ^{225}Ac-DOTATOC reported that cumulative doses of 60,000–80,000 kBq were tolerated with minimal acute and chronic grade 3 or 4 hepatotoxicity in patients with advanced-stage malignancies (*27*). Looking at the toxicity profile, it seems that there is scope to further escalate the individual activity per kilogram or use higher cumulative activity of ^{225}Ac in the future. Thus, the only approach is to rigorously follow these patients for long-term side effects of ^{225}Ac-DOTATATE TAT.

High-level evidence for long-term safety and sustained benefits to OS and radiologic PFS in patients with GEP-NETs treated with ^{225}Ac-DOTATATE is crucial and warrants well-controlled, multicenter, randomized trials to determine its role and the best treatment algorithm for this challenging disease.

Our study had some limitations. The results are exploratory and single-center and are based on a heterogeneous patient population. Although not conducted as a clinical trial with strict inclusion criteria, we believe the study had the advantage of enrolling the largest (to our knowledge) GEP-NET population treated with ^{225}Ac-DOTATATE therapy, including poor-outcome patients, and better reflects the results of treatment-related toxicity, confirming the benefit of efficacy, survival, and improvement in quality of life in a real-world clinical setting. Though all the CT scans of the CT component of PET/CT were of diagnostic quality, contrast was not administered to all patients, resulting in suboptimal-quality images.

CONCLUSION

^{225}Ac-DOTATATE–based PRRT was effective in the heavily pretreated GEP-NET cohort of patients, with good survival rates, high response rates, improvements in KPS, and an acceptable toxicity profile. ^{225}Ac-DOTATATE TAT may be a suitable treatment option for patients with stable disease or PD after ^{177}Lu-DOTATATE β-therapy. Patients refractory to ^{225}Ac-DOTATATE treatment have the worst outcome. We strongly advocate a large multicenter, randomized, controlled trial to assess the potential of this strategy as a new therapeutic paradigm for patients with GEP-NET who have exhausted all other options. Further, a balanced approach that exploits our long-term results and clinical trials can best aid the oncology community in delivering the most beneficial, individualized care to patients.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What is the long-term outcome for GEP-NET patients treated with ^{225}Ac-DOTATATE TAT?

PERTINENT FINDINGS: The median OS was not attained, and the 24-mo OS probability was 70.8%. Median PFS was also not reached, with a 24-mo PFS probability of 67.5%. A significant clinical benefit was achieved after ^{225}Ac-DOTATATE therapy, with minimal treatment-related toxicities.

IMPLICATIONS FOR PATIENT CARE: Even in patients resistant to prior ^{177}Lu-DOTATATE, ^{225}Ac-DOTATATE TAT has shown promising long-term results, with transient and acceptable adverse effects.

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