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Predictors of survival in 211 patients with stage IV pulmonary and gastroenteropancreatic mIBG positive neuroendocrine tumors treated with I-131 mIBG

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Running Title: Survival following I-131 mIBG therapy

ABSTRACT

Purpose: This retrospective analysis identifies predictors of survival in a cohort of patients with mIBG positive stage IV pulmonary and gastroenteropancreatic neuroendocrine tumor (P/GEP-NET) treated with I-131 mIBG therapy, in order to inform treatment selection and post-treatment monitoring.

Methods: Survival, symptoms, imaging, and biochemical response were extracted via chart review from n=211 P/GEP-NET patients treated with mIBG between 1991-2014. For patients with computed tomography (CT) follow up (n=125), imaging response was assessed by Response Evaluation Criteria on Solid Tumors (RECIST) 1.1 where images were available (n=76) or by chart review of the radiology report where images could not be reviewed (n=49). Kaplan Meier analysis and Cox multivariate regression estimated survival and progression free survival benefits predicted by initial imaging, biochemical and symptomatic response.

Results: All patients had stage IV disease at time of treatment. Median survival was 29 months from time of treatment. 71% of patients demonstrated symptomatic response with median duration of symptomatic relief of 12 months. Symptomatic response at first follow-up predicted a survival benefit of 30 months ($p<0.001$). Biochemical response at first clinical follow up was seen in 34% of patients with stability of labs in 48%; response/stability vs. progression extended survival 40 months ($p<0.03$). Imaging response (20% of patients) or stability (60%) at initial 3 month follow up imaging extended survival 32 months

($p<0.001$). Additionally, multiple mIBG treatments was associated with 24 months additional survival ($p<0.05$).

Conclusion: Therapeutic I-131-mIBG for metastatic pulmonary or gastroenteropancreatic neuroendocrine tumors appears to be an effective means of symptom palliation. Imaging, biochemical, and symptomatic follow-up each help prognosticate expected survival following mIBG therapy. Multiple rounds of mIBG are associated with prolonged survival.

INTRODUCTION

The incidence and prevalence of pulmonary and gastroenteropancreatic neuroendocrine tumor (P/GEP-NET, formerly referred to as carcinoid tumor) has been steadily increasing over the last several decades (*1*). Neuroendocrine tumors present with metastatic disease in up to 40% of cases (*2*). Options for treatment of metastatic disease include somatostatin analogues, targeted therapies, systemic chemotherapy, and locoregional therapies (*1*). Radiopharmaceuticals have been widely used for imaging and increasingly as therapeutics, most commonly in the form of peptide receptor radiotherapy consisting of a somatostatin receptor binding peptide linked to a chelator bearing the radionuclide of interest. However, 10-20% of neuroendocrine tumors lack sufficient somatostatin receptor expression for peptide receptor radionuclide therapy (*3-5*). Further, over the course of the disease, patients frequently exhaust multiple treatment modalities. An alternative is Iodine-131-meta-iodobenzylguanidine (I-131-mIBG), an injectable radiolabeled norepinephrine analog that is taken up by chromaffin cells within neuroendocrine tumors (*6*). The cells concentrate the radioactive molecule within the neurosecretory granules where I-131 emits beta radiation while sequestered in the tumor cells. This offers a molecular targeted method of *in vivo* radiation treatment for neuroendocrine tumors.

Prior reports including one from our group have provided outcome data following I-131-mIBG therapy from small cohorts, short follow-up intervals, or time periods with more limited therapies for neuroendocrine tumors (*7-15*). The majority of prior reports also grouped multiple subtypes of neuroendocrine tumors into a single patient group. This current report analyzes our long-term experience with the survival and progression free survival of I-131-mIBG in 211 patients with metastatic neuroendocrine tumors. Specifically, the goal was to identify predictors of improved overall survival following therapeutic mIBG and how these findings may inform appropriate post-treatment monitoring.

MATERIALS AND METHODS

This study was performed as a retrospective review of records for consecutive patients referred to Duke Health for I-131-mIBG therapy for metastatic neuroendocrine tumors at Duke University Hospital from 1991-2014. The Duke University institutional review board (Institutional Review Board) approved this retrospective study and the requirement to obtain informed consent was waived. 211 patients with stage IV gastroenteropancreatic or pulmonary NET were identified for further analysis. Chart review extracted relevant clinical and demographic data. Survival was determined by chart notation or the Social Security Death Index (*16,17*). For survival, patients alive at the end of the study period were censored at that time. For progression free survival, patients were

censored at end of study period or last available follow-up for imaging or symptom assessment.

All patients underwent I-131-mIBG or I123-mIBG scan at our institution prior to treatment, demonstrating abnormal radiotracer uptake in at least one site of disease. I-131-mIBG was obtained from the University of Michigan radiopharmaceutical production facility (Ann Arbor, Michigan) before 2006, and Nuclear Diagnostic Products (Cherry Hill, NJ) after 2006. Total radioactivity in each vial was determined using a radionuclide dose calibrator. Prior to I-131-mIBG administration and for one week post-treatment, patients were given either Lugol solution or a saturated solution of potassium iodide to block thyroid accumulation of radioiodine. I-131-mIBG was administered intravenously by slow infusion over 30 – 40 minutes. Per our institutional protocol, 18500 MBq was administered, with adjustment downward where GFR, blood counts or liver function tests suggested the patient may be more susceptible to adverse effects. 18500 MBq was selected by our empirical practice and assessment of risk/benefit using estimated critical organ dose with a margin of safety.

I-131-mIBG therapy was performed on an inpatient basis after discussion of risks and benefits, and after providing written, informed consent to therapy. The patients were monitored while in radiation isolation until they met the federal regulatory criteria for discharge in effect at the time they were treated, based either upon dose rate measured at one meter < 5 mrem / hour (preceding 1997)

or expected radiation dose to the general public < 500 mrem (after 1997). For the subset of patients referred for repeat I-131-mIBG therapy by their oncologists, a repeat diagnostic mIBG scan was performed, and patients with activity in at least one site of metastatic disease received repeat treatment.

CT and diagnostic mIBG imaging was reviewed by a radiologist on Centricity PACS (General Electric, 2013) and response to treatment was assessed using Response Evaluation Criteria on Solid Tumors (RECIST) 1.1. When images were not available for primary review, the dictated reports were used to assess response by noting appearance of new lesions, disappearance of lesions, change in size of reference lesions, or no change; RECIST 1.1 criteria were applied to given measurements where possible. Patients were grouped into complete response, partial response, stable, and progressive disease. Initial imaging response was assessed at first follow-up imaging that ranged from 3-9 months (median 3 months) post-treatment. Symptomatic response was assessed by an oncologist and patient subjective response in clinical follow-up visits. Patients who reported no change in symptoms or worsening symptoms were grouped into non-responders. Laboratory response was assessed where possible with non-responders identified by a rise in Chromogranin A or urine 5-hydroxyindoleacetic acid (5-HIAA) with persistence of greater than 20% increase from the pre-treatment value over two serial measurements.

Statistical analysis was performed using SPSS Statistics version 22.0.0.2 (IBM 2013). Kaplan-Meier survival analysis was performed using the log-rank test for significance with a threshold set to $p<0.05$. Survival reporting statistics use the median survival. Cox Regression was used for a subset multivariate analysis of survival.

RESULTS

Demographic data are shown in Table 1. All patients had stage IV disease at the time of I-131 mIBG treatment and 64% had received prior surgical, radiation or chemo therapies (Table 2); the clinical charts provided inadequate detail regarding the number of prior treatments in each category. The median administered activity of I-131 mIBG at first treatment was 18500 (interquartile range 11359-18870) MBq with 19% of patients receiving two and 4% receiving 3 and one patient receiving 4 administrations of mIBG (Table 1). Among those receiving multiple treatments, the median follow-up dose was 12950 (11100-18907) MBq and the median total cumulative dose was 33670 (22200-37999) MBq. Median time between first and second dose was 14 (6-25) months, and between second and third dose, 37 (14-62) months. The location of the primary and metastatic lesions as well as ancillary treatments prior and following I-131 mIBG is described in Table 2.

Median overall survival from the first I-131 mIBG treatment was 2.4y ± 0.2 (Figure 1A). Actual overall 5-year survival from diagnosis was 60%, from

metastatic disease 50%, and from eventual treatment with I-131 mIBG 27%. Among patients lost to follow up, those without follow up imaging data had median survival 14 months vs. 41 months in those with follow up imaging available; patients lost to follow-up for biochemical data had a median survival of 23 months, vs. 53 months in those with follow up labs available; patients lost to symptomatic follow-up had median survival 17 months vs. 39 months in those with symptomatic follow-up ($p<0.01$ for each median survial). Multiple I-131 mIBG treatments predicted improved survival compared to those only receiving one treatment, 4.0y ± 0.5 vs. 2.0y ± 0.3, $p<0.05$ (Figure 2A). Cox regression analysis demonstrated no significant interaction between multiple mIBG treatments, initial treatment response, or octreotide LAR (Sandostatin) usage.

125 patients had computed tomography (CT) imaging data at initial follow-up (median 3 months post treatment) of which 76 had images available for primary review and application of RECIST 1.1 criteria. 49 patients had radiographic reports for CT follow up available for review. Where images were not available, but measurements were provided in reports, RECIST criteria were applied to these measurements (n=26). 32 patients had follow-up mIBG imaging available for review, including 18 patients with mIBG but not CT follow up. mIBG scans were classified as complete response (n=1, no residual abnormal activity), partial response (n=6, decreased activity), stable (n=16) or progression (n=9, increased abnormal activity). Of the 14 cases with both CT and mIBG follow-up, CT and mIBG were concordant in all but 6 cases. Among these 6, 3 showed

progression on CT but stability on MIBG, 1 showed stability on CT and response on mIBG and 1 showed stability on CT and progression on mIBG. Patients were considered to have progressed by imaging if they progressed on either modality, and to have responded if they responded on either modality. (In no case did one modality show response and the other progression).

Initial post-treatment imaging follow-up demonstrated 80% of patients were stable or responded (n=125, 2% CR, 18% PR, 60% Stable, 20% PD) with median progression free survival based on imaging of 1.7y ± 0.1 (n=143, Figure 1C). Median duration of imaging response was 13 months (n=143). Stability or response at first imaging follow-up predicted improved survival as compared to radiographic progression 4.0y ± 0.4 vs. 1.3y ± 0.3, $p<0.001$ (Figure 2B).

158 patients had documentation of symptomatic change in the medical chart at initial post-treatment follow-up. The level of detail across oncology notes was highly variable, allowing only binary assessment of symptomatic response. 71% of patients reported improvement in pre-treatment symptoms; improvement rates were 44% for pain, 63% for gastrointestinal complaints (bloating, nausea, vomiting), 43% for fatigue, 34% for flushing and 14% for unintentional weight loss. Median progression free survival based on symptoms was 1.4y ± 0.3 (Figure 1B) and median duration of symptomatic response was 12 months. Symptomatic response to therapy predicted improved survival, 4.2y ± 0.4 vs. 1.7y ± 0.6, $p<0.001$ (Figure 2C).

62 patients had quantitative biochemical data available for review at initial clinical follow-up; 31 with 5-HIAA, 35 with chromogranin A and 4 with both. 34% of patients demonstrated response, 48% were stable, and 18% progressed (defined by 20% increase in 2 consecutive values in either lab from baseline. Outcomes did not significantly differ for 5-HIAA compared to chromogranin A. 43% of patients remained without biochemical progression after treatment throughout follow-up time, with median time to biochemical progression of 2.5y ± 0.5. Response or stability of Chromogranin A or urine 5-HIAA at initial follow-up predicted improved survival, 6.2y ± 1.5 vs. 2.9y ± 1.6, $p<0.03$ (Figure 2D).

DISCUSSION

Here we provide outcomes for the largest available analysis in the literature of patients with stage IV mIBG positive pulmonary and gastroenteropancreatic neuroendocrine tumor (formerly known as carcinoid) treated with I-131-mIBG. Prior research in this area has been primarily comprised of small patient case series (*7-14*). Overall median survival in our patient group was 29 months from time of mIBG treatment. Prior studies have demonstrated median survival following treatment of 17-29 months (*7,8,14,15*).

Receiving multiple I-131-mIBG treatments was associated with 24 months additional survival compared to single treatment. It is unclear whether this represents an additional survival benefit of subsequent therapy, or a form of

reverse causation where patients who survive longer are more likely to have time to receive additional therapy. A test of the interaction of receiving multiple treatments with initial imaging response on follow up was not significant, suggesting initial response did not alter the efficacy of subsequent treatment. The possibility of a benefit of multiple treatments has potential management implications if it can be confirmed in prospective investigation. In particular, future studies would benefit from more consistent documentation of performance status in the clinical record, as well as the use of some objective index of general wellness in order to separate the influence of multiple therapies independent of the propensity to survive.

Symptomatic palliation was observed in over 70% of patients post I-131-mIBG therapy; symptomatic improvement lasted median 12 months with median 16 months to subsequent progression. Prior literature reports range from 50-90% symptomatic response rate and median time to progression 15-17 months (*7-15,18*). Similar to prior studies, symptomatic response predicted improved survival (*11,15*); in our population this benefit was 30 months.

Radiographic response (20%) or stability (60%) observed post I-131-mIBG treatment are in line with prior studies reporting radiographic response rates at 25-35% and stability at 40-50% (*7,8,11*). Most prior studies found no prognostic value in radiographic response (*7,11,15,18*). In contrast, radiographic response or stability in the current study predicted a 32 month survival benefit compared to

radiographic progression. (Radiographic stability and response were clustered as their survival benefits did not differ.)

I-131-mIBG treatment yielded a 34% biochemical response rate and 48% stability rate. Prior investigations demonstrated biochemical response of 14-55% (*7,11,14,15*). No prior studies have found a survival benefit from biochemical response which has been perplexing, particularly given the expected correlation between biochemical abnormalities and symptoms/quality of life and systemic effects such as cardiac disease. This is perhaps in part due to measurement error introduced by heterogeneity in the range of assays used in clinical practice. In our chart review, with many cases pre-dating our electronic record and others relying on clinical notes of outside providers, insufficient information on the specific assays were available. In spite of this additional source of variability, our sample was large enough to demonstrate improved survival with biochemical response / stability compared to biochemical progression, with a 40 month survival benefit.

Peptide receptor radiotherapy has also demonstrated important survival benefits and symptom palliation. Radiolabeled somatostatin analogues are a more recently developed radioactive labeled peptide group. Prior studies, and the recently reported Neuroendocrine Tumors Therapy (NETTER-1) trial, have demonstrated impressive progression free survival and symptomatic benefits in midgut neuroendocrine tumors. Radiographic response rates with peptide

receptor radiotherapy of 18-27% and stability of 60% are similar to our findings of 20% response and 60% stability (*19-21*). Of note, Kwekeboom et al reported a decreased responsiveness in gastroenteropancreatic neuroendocrine tumor (carcinoid) compared to other neuroendocrine tumors (*20*). These studies found median progression free survival for all patients with neuroendocrine tumors between 30-32 months compared to the current study in carcinoid-only patients with 21 months median progression free survival (*19-21*). Only Forrer et al analyzed symptom response and demonstrated good response rates with Y90-DOTATOC to gastrointestinal symptoms and flushing, similar to our study population. They also reported good results in pain reduction although they did not provide specific numeric outcomes (*19*). None of the peptide receptor radiotherapy trials reported comprehensively on biochemical response for comparison to our current study.

Prior studies of chemotherapy demonstrated poor effectiveness for neuroendocrine tumors with a 3%-10% biochemical or imaging response rate and very little symptom palliation (*22,23*). Median duration of response for chemotherapy was 5 months (*22,24*). Octreotide has become a standby for symptomatic neuroendocrine tumor treatment with high symptom response rates ranging from 30-88% (*25-29*). However, octreotide has limited survival benefit with initial reports from Rinke et al demonstrating a median time to radiographic progression of 14 months vs 6 months in placebo group, and the more recent interval release of data from the randomized controlled Neuroendocrine Tumors

Therapy (NETTER-1) trial demonstrating a median time to progression of 8 months in patients in the octreotide arm (*21,29*). Patients with hepatic metastatic disease have the option for endovascular embolic treatments that have demonstrated high efficacy including response rates of over 70%, median duration of response 17 months, median progression free survival 19 months, and 60% symptomatic response (*30,31*).

As a retrospective trial dependent on clinical chart review, many outcomes suffered from missing data. Performance status was not reliably ascertainable from chart review, and we are uncertain whether it may interact with the other variables tested herein. This problem was compounded by the very large catchment area producing referrals to our center for I-131 mIBG therapy, as many of these patients returned to follow up with their local oncologists rather than following up at our center. Because death dates were available for all participants regardless of clinical follow up, overall survival curves are unaffected by missing data. In contrast, loss to follow up or incomplete medical records precluding assignment was significant for imaging (41% missing follow-up data), biochemical (n= 28% missing follow up data) and symptomatic (n= 71% missing follow-up data) progression. Patients with missing data had shortened survival compared to those with complete information, and their loss to follow up at our center may be explained in part by an overall worsening clinical course. We employed customary listwise deletion in managing missing data, finding the

remaining sample adequately powered to detect the influence of imaging, symptom and biochemical response on survival.

CONCLUSION

In summary, we found therapeutic I-131-mIBG for metastatic pulmonary and gastroenteropancreatic neuroendocrine tumors to be an effective means of symptom palliation with improved prognosis for those patients with symptomatic improvement, radiographic response or stability, and biochemical response or stability. This suggests that despite previous recommendations (*11*), regular imaging, biochemical assay, and clinical follow-up should be performed in patients with metastatic neuroendocrine tumors, particularly those undergoing I-131-mIBG treatment (*1*). Our results lend tangible data that oncologists may utilize to provide patients with pre-treatment prognostic information, as well as that based upon the patient's individual response to treatment. Multiple mIBG treatments were also shown to result in improved survival, suggesting that patients might benefit from multiple rounds of treatment rather than a single treatment session; however, additional research is required to ensure that this association is not confounded by general patient wellness.

Over the course of the disease, many patients with neuroendocrine tumors exhaust the standard options of somatostatin analogues, targeted therapies, and endovascular embolic techniques. Given our findings, I-131-mIBG

may be of benefit in patients who fail these treatments or for patients whose tumors do not demonstrate the necessary scintigraphic uptake with radiolabeled somatostatin analogues.

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TABLE 1. Demographic data of patient cohort (n=211).

Variable	% of Patients
Gender	
Male	50
Female	50
Mean Age (SD)	59 (12)
Race	
Caucasian	86
African American	14
Treatment	
Single	81
Multiple	19
Two	15
Three	3
Four	1
Median Activity of mIBG (IQR)	18500 (11359-18870) MBq

TABLE 2. Summary of location of primary sites of disease, metastases, prior and post mIBG therapies.

Location Primary	N (211)	Location Metastasis	N (211)
Unknown	83	Liver	183
Small bowel	67	Bone	41
Lung	22	Lungs	40
Colon	6	Carcinomatosis	29
Cecum	5	Mediastinum	17
Gastric	5	Mesentery	8
Rectal	5	Adnexa	6
Appendix	4	Pancreas	6
Pancreas	4	Adrenal	4
Mesentery	4	Kidney	3
Thymic	3	Skin	2
Cardiac	1	Bladder	1
Ovary	1	Gastric	1
Retroperitoneal	1	Gallbladder	1
		Muscle	1
		Orbit	1
		Spleen	1

Prior Therapy	% of Patients	Post mIBG Therapy	% of Patients
Surgery	63	Chemotherapy	19
Radiation	10	Embolization	5
Embolization	6	mIBG	19
Chemotherapy	27	Surgery	3
Sandostatin	72	Radiation	4

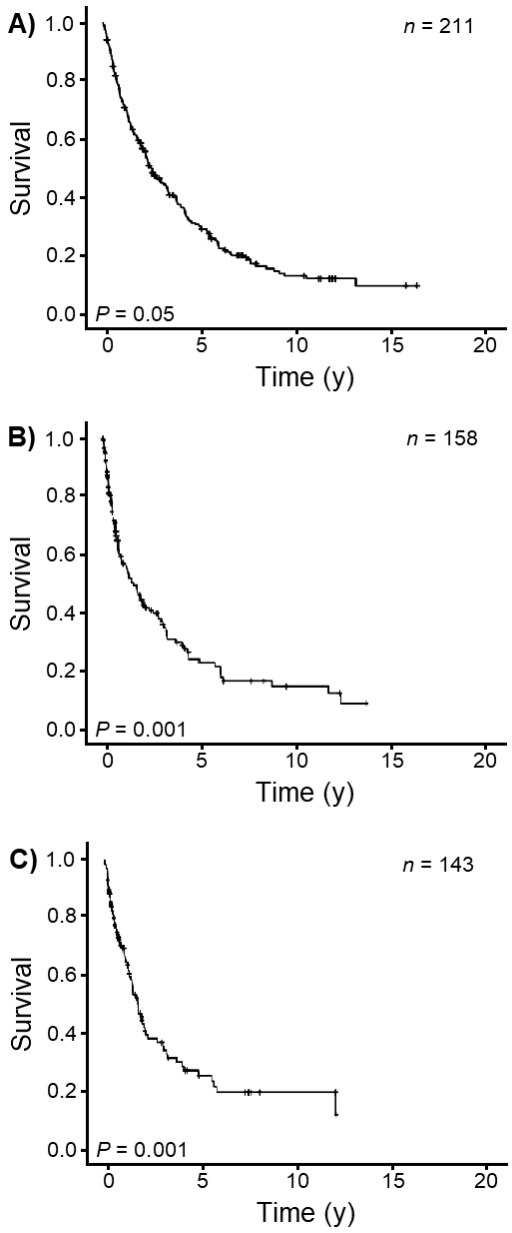

FIGURE 1. Post I-131 mIBG treatment Kaplan Meier curves: A) overall survival, B) symptomatic progression free survival, C) radiographic progression free survival by CT (n=125) or mIBG (n=18) follow-up.

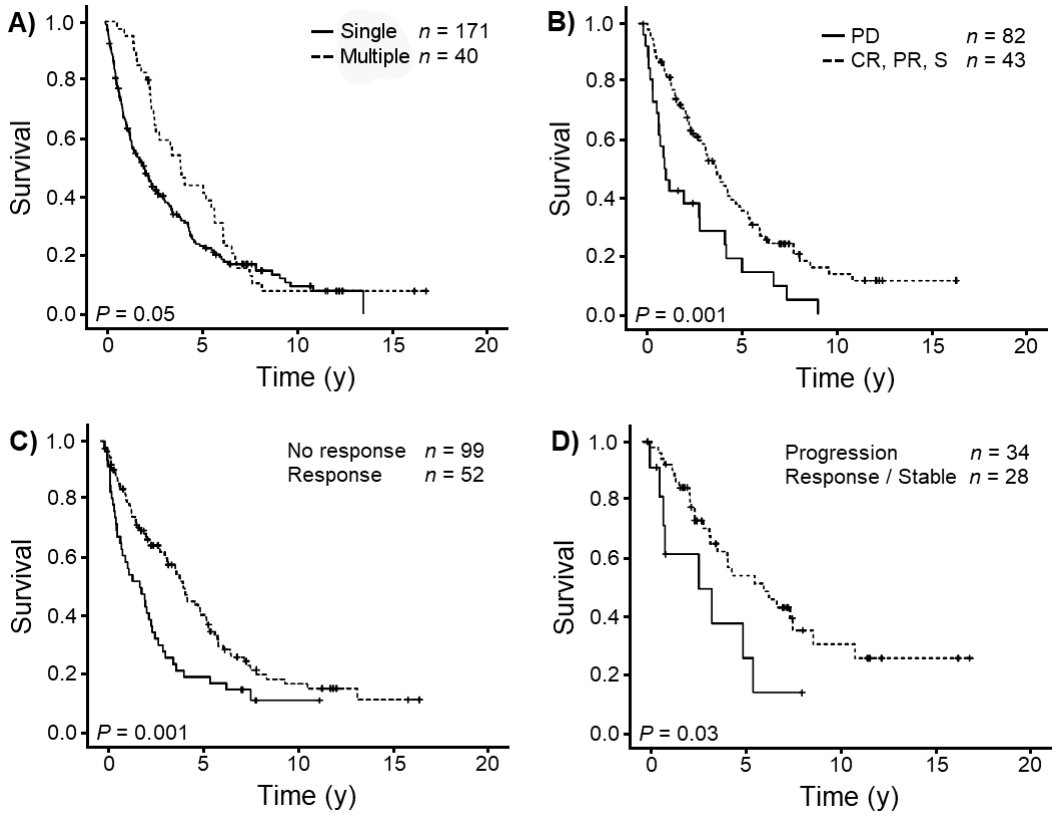

FIGURE 2. Kaplan-Meier survival curves at first follow-up after I-131 mIBG treatment: A) single vs multiple mIBG treatment sessions, B) imaging demonstrating complete response (CR)/partial response (PR)/ stable (S) vs progressive disease (PD), C) symptomatic response vs no response (or worsening), and D) biochemical/laboratory response or stability at follow-up vs progression. P-values for log-rank test at bottom left corner of plots.