Improved Tumor Dosimetry by Combining ^{131}I-MIBG and ^{90}Y-DOTATOC in Patients with Carcinoid Tumors

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Background

^{131}I meta-iodobenzylguanidine (MIBG), and ^{90}Y DOTA Phe1-Tyr3-Octreotide (DOTATOC), have each shown effectiveness for treatment of metastatic neuroendocrine tumors.

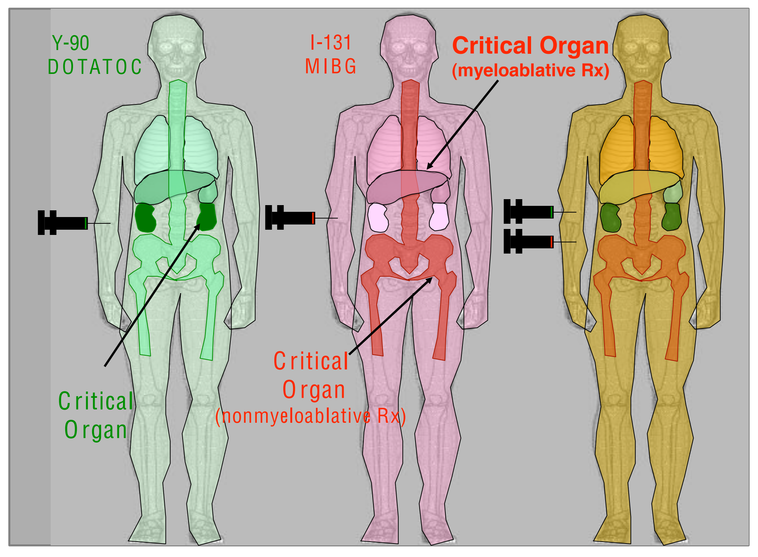
However, delivering sufficient radiation dose to the tumor to result in a high percentage of objective tumor responses or cure is challenging because of the radiation dose limits imposed by damage to normal tissues.c

Concept I

Organ biodistribution and kinetics of ^{90}Y DOTATOC are substantially different compared to ^{131}I MIBG leading to different "dosage" limiting organs for these radioactive drugs when they are used for therapy

Kidneys are dosage limiting organ for ^{90}Y-DOTATAC while bone marrow is limiting for ^{131}I MIBG.

Having different dose limiting normal organs makes it possible to combine ^{131}I MIBG with ^{90}Y-DOTATAC to deliver a higher radiation dose to the tumor than would be achievable with the maximum safe amount of either drug alone.



Concept II

For Therapy with
Y-90 DOTATOC and I-131 MIBG:

We have demonstrated mathematically that when the following dosimetric conditions are satisfied for a given patient

$(T/K)^{MIBG} > (T/K)^{DOTATOC}$ and $(T/M)^{DOTATOC} > (T/M)^{MIBG}$

where
T= Tumor dose/mBq
K= Kidney dose/mBq
M= Marrow dose/mBq

then a combination of each drug can be precisely determined which delivers a maximum tumor dose greater than that for either Y-90 DOTATOC or I-131 MIBG given individually, without exceeding the limiting dose to either critical organ

(Madsen, Bushnell et al. J Nucl Med 2006; 660-667.)

Study Objectives

1. **Determine the percentage of adult patients with midgut carcinoid tumors, or children with neuroblastoma, who would receive an increase in tumor radiation dose, above that for either Y-90 DOTATOC or I-131 MIBG given individually, by using patient specific dosimetry to deliver an optimized combination of these drugs**
2. **Determine the magnitude of increase in tumor radiation dose, above that for either Y-90 DOTATOC or I-131 MIBG given individually, by using an optimized combination of these drugs**

DESIGN

I. **PROOF OF CONCEPT**

Median* dose/MBq *values were taken from the literature for I-131 MIBG and Y-90 DOTATOC for Kidneys, Bone Marrow, and Tumor, and were used to simulate a "representative" patient. We input this data into our previously published mathematical method to determine expected tumor dose increase from combination therapy above that achievable with individual drug therapy.

II. **CLINICAL STUDY**

- ***SPECT images of the chest/abdomen along with blood samples were obtained at 1, 4, 24, and 48 hours following simultaneous injection of both I-131 MIBG and In-111 pentetreotide (as surrogate for Y-90 DOTATOC) on a series of subjects with known, CT defined (within one month), metastatic soft tissue midgut carcinoid tumors.***
- ***From this data we calculated* dose/MBq *for Kidneys, Bone Marrow, and Tumor sites for both Y-90 DOTATOC and I-131 MIBG for each subject. Y-90 DOTATOC Kidney dose/MBq was then decreased by 20% for each subject to simulate the effect of amino acid infusion during an actual therapy.***
- ***These patient specific* dose/mBq *values were then used to calculate maximum achievable tumor radiation doses from either Y-90 DOTATOC or I-131 MIBG separately compared to an optimized* combination of both.**

Results (proof of concept)

For a "representative" patient with the following I-131 MIBG and Y-90 DOTATOC dosimetry values (dosimetry data obtained from literature):

BM_{MIBG} = 0.19 mGy/MBq
BM_{DOTA} = 0.13 mGy/MBq
K_{MIBG} = 0.08 mGy/MBq
K_{DOTA} = 2.16 mGy/MBq
T_{MIBG} = 8.0 mGy/MBq

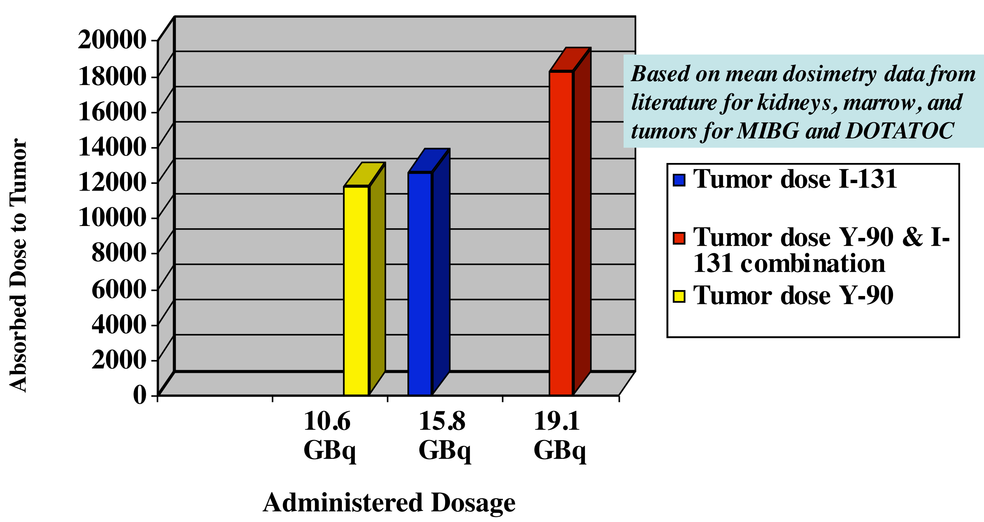
BM = Bone Marrow
K = Kidney
T = tumor

And applying KIDNEY DOSE LIMIT of 2300 cGy & BM LIMIT 300 cGy we get:

Maximum tumor dose from Y-90 DOTATOC = 11,712 cGy
Maximum tumor dose from I-131 MIBG = 12,631 cGy
Maximum tumor dose from COMBINATION = 18,337 cGy

And thus a 45% increase in tumor dose would be expected from combination Rx in this simulated patient

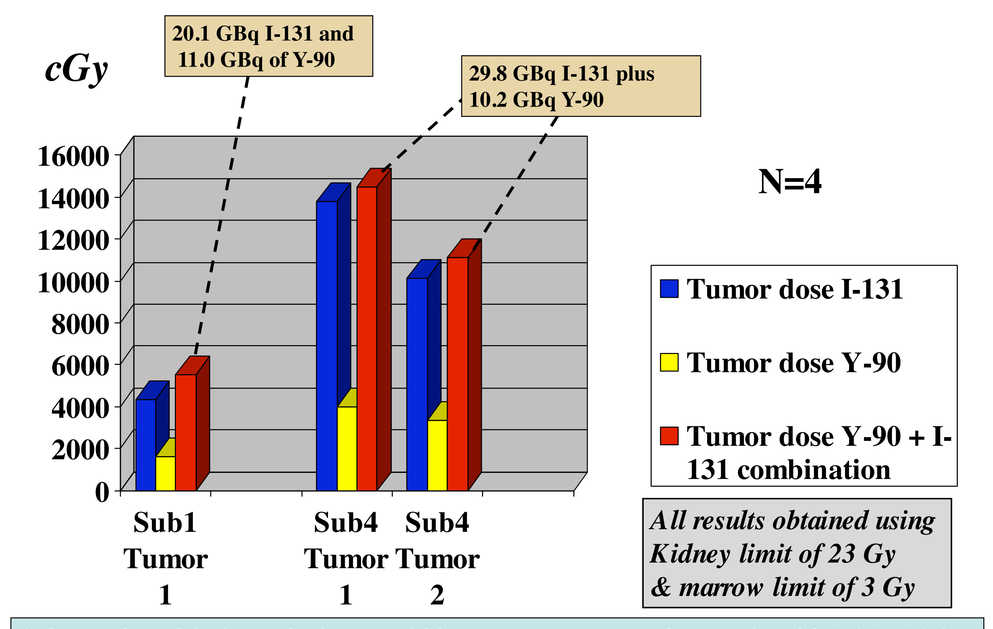
Maximum Achievable Safe Tumor Dose Level for



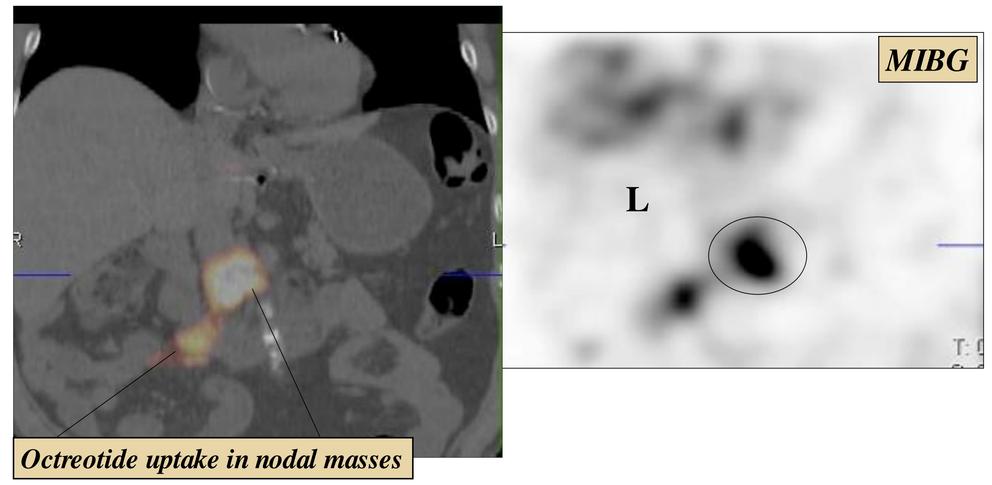
Results from Clinic Study

To date we have completed study and analysis on 4 subjects with metastatic carcinoid tumors. We have enrolled 4 additional subjects. Each of the 4 subjects had at least one measurable soft tissue tumor site on contrast enhanced CT. There were a total of 9 CT defined metastatic lesions involving either the liver or abdominal lymph nodes in the 4 subjects. In 2 of the 4 subjects, tumor sites were seen only on In-111 pentetreotide images. Whereas in the other 2 individuals (subjects 1 and 4), all 4 tumor sites were visualized with both In-111 pentetreotide and I-131 MIBG. Technical problems limited our ability to complete measurements in 1 of these 4 tumors. Dosimetry results for the other 3 tumors from 2 subjects are presented in figure 2. In all three of the tumors from the 2 subjects the radiation dose was calculated to have been greater for a combination of Y-90 DOTATOC and I-131 MIBG than for either agent given alone. In subject #1 the single tumor tumor site radiation dose was higher by 24%. In subject #4 the increase in tumor radiation dose levels was around 10%.

Maximum Achievable Tumor Dose Levels for Subjects with tumors visible on both I-131 and Y-90 Images



Subjects 2 and 3 showed what would be maximum tumor dose with Y-90 DOTATOC alone



Left: Co-registered In-111 pentetreotide coronal SPECT and CT for subject #4.
Right: Coronal SPECT of I-131 MIBG at approximately the same level.
Note discordant location of MIBG vs octreotide in larger (superior) nodal mass.

Discussion

One of the limits of this study relates to our use of In-111 pentetreotide as a surrogate for Y-90 DOTATOC, particularly since Y-90 DOTATOC has a higher binding affinity for type II somatostatin receptors. Optimal dosimetry measurements might eventually best be made with I-124 MIBG and Y-86 DOTATOC PET/CT. In addition, the 48 hour time interval we used for measuring biodistribution and kinetics for these drugs is somewhat short. And of course, further study is need on additional subjects to confirm our findings.

There may be other potential advantages to combining I-131 MIBG with Y-90 DOTATOC for treatment of carcinoid tumors besides the enhanced macroscopic tumor dosimetry advantage that we have demonstrated here.

Possible additional Value of Combined therapy with ^{131}I MIBG plus ^{90}Y DOTATOC

Due to differences in mechanism of tumor targeting
- VMAT1 and SSTR 2 density may vary within a metastatic NET site
- VMAT1 and SSTR 2 density may vary from one metastatic lesion to another
- Therefore some metastatic sites only MIBG + while others only Octreo +

Due to differences in beta particle energy from ^{131}I and ^{90}Y
- Ebmax 2.3 MeV for 90Y
- Ebmax 0.6 Mev for 131I
- 90Y more effective with larger tumors (> 1 cm)
- 131I more effective with smaller tumors (< 1 cm)

Conclusion

These initial results support the concept that larger tumor radiation doses can be delivered to at least some carcinoid tumors without exceeding acceptable dose limits for kidneys and bone marrow by combining treatment with Y-90 DOTATOC and I-131 MIBG