
Potential Increased Tumor-Dose Delivery with Combined ^{131}I -MIBG and ^{90}Y -DOTATOC Treatment in Neuroendocrine Tumors: A Theoretic Model

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^{131}I -Metaiodobenzylguanidine (MIBG) and ^{90}Y -DOTA-D-Phe1-Tyr3-octreotide (DOTATOC) have been used as radiotherapeutic agents for treating neuroendocrine tumors. The tumor dose delivered by these agents is often insufficient to control or cure the disease. However, these 2 agents used together could potentially increase tumor dose without exceeding the critical organ dose because the dose-limiting tissues are different. In this paper, we investigate the conditions in which combined-agent therapy is advantageous and we quantify the expected tumor-dose gain. **Methods:** A series of equations was derived that predicted the optimal combination of agents and the fractional increase in tumor dose available from combined-agent therapy with respect to either ^{131}I -MIBG or ^{90}Y -DOTATOC. The results obtained from these derivations were compared with direct dose calculations using published dosimetric organ values for ^{131}I -MIBG and ^{90}Y -DOTATOC along with critical organ-dose limits. Tumor dose was calculated as a function of the tumor-dose ratio, defined as the ^{90}Y -DOTATOC tumor dose per megabecquerel divided by the ^{131}I -MIBG tumor dose per megabecquerel. Comparisons were made between the dose delivered to tumor with single-agent therapy and the dose delivered to tumor with combined-agent therapy as a function of the tumor-dose ratio and the fraction of activity contributed by each agent. **Results:** The dose model accurately predicted the optimal combination of agents, the range at which combined-agent therapy was advantageous, and the magnitude of the increase. For the published organ dosimetry and critical organ-dose limits, combined-agent therapy increased tumor dose when the tumor-dose ratio was greater than 0.67 and less than 5.93. The maximum combined-agent tumor-dose increase of 68% occurred for a tumor-dose ratio of 2.57, using 92% of the maximum tolerated ^{90}Y -DOTATOC activity supplemented with 76% of the maximum tolerated activity of ^{131}I -MIBG. Variations in organ dose per megabecquerel and dose-limiting values altered both the magnitude of the increase and the range at which

combined-agent therapy was advantageous. **Conclusion:** Combining ^{131}I -MIBG and ^{90}Y -DOTATOC for radiotherapy of neuroendocrine tumors can significantly increase the delivered tumor dose over the dose obtained from using either agent alone. Prior knowledge of the normal-organ and tumor dosimetry of both agents is required to determine the magnitude of the increase.

Key Words: radionuclide therapy; neuroendocrine cancer; combined-agent therapy; ^{131}I -MIBG; ^{90}Y -DOTATOC

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Tumors originating from the neuroendocrine system include neuroblastoma, carcinoids, and pancreatic endocrine tumors. Although relatively rare, these tumors may be life threatening. When the disease has metastasized, 5-y survival is less than 20% (1,2). ^{131}I -Metaiodobenzylguanidine (MIBG) and ^{90}Y -DOTA-D-Phe1-Tyr3-octreotide (DOTATOC) have shown potential as therapeutic agents in patients with neuroendocrine tumors (3–6). However, delivering to the tumor a radiation dose sufficient to result in a high percentage of objective antitumor responses or cure is challenging because of the radiation-dose limits imposed by damage to normal tissues. In this paper, we investigate a possible way to increase the radiation dose delivered to tumors without exceeding radiation-dose limits to critical organs by combining both ^{90}Y -DOTATOC and ^{131}I -MIBG. As shown in Table 1 (7,8), these 2 agents have different normal whole-body biodistributions, leading to different critical organs: the kidney for ^{90}Y -DOTATOC and the red marrow for ^{131}I -MIBG (9,10). Our novel approach is based on the premise that this difference will enable the combining of large fractions of the maximum tolerated activity of each agent into a single treatment regimen to deliver a higher tumor dose without exceeding the dose limits to normal organs.

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TABLE 1
⁹⁰Y-DOTATOC (7) and ¹³¹I-MIBG (8) Dosimetry

Site	⁹⁰ Y-DOTATOC		¹³¹ I-MIBG	
	mGy/MBq	rad/mCi	mGy/MBq	rad/mCi
Intestine	0.05	0.18	0.08	0.29
Red marrow	0.05	0.18	0.07	0.27
Liver	0.66	2.43	0.78	2.90
Urinary bladder	1.03	3.81	0.76	2.80
Spleen	2.32	8.58	0.05	0.18
Kidneys	2.73	10.09	0.09	0.33
Kidneys with amino acids	2.16	8.0		

In this paper, a theoretic model of the combined-agent approach is derived and the results of the model are compared with direct dose calculations that were based on published dosimetric data for normal organs and for tumors. The conditions that are best suited for combined-agent therapy with ⁹⁰Y-DOTATOC and ¹³¹I-MIBG are explored, and estimates of potential improvements in the therapeutic ratios of combined-agent therapy with respect to either agent used alone under various conditions are presented.

MATERIALS AND METHODS

Theory

This section presents a set of equations that describe the combined-agent approach and the expected benefits from its application. Although the equations were developed with ¹³¹I-MIBG and ⁹⁰Y-DOTATOC in mind, the method is completely general and can easily be adapted to any similar pair or to a larger number of radiotherapeutic agents. The terms used in the equations are summarized in Table 2. The maximum activity that can be administered for a therapeutic agent is limited by the critical

TABLE 2

Definition of Terms Used in the Combined-Agent Model

Term	Definition
MLD	Marrow limiting dose (Gy)
KLD	Kidney limiting dose (Gy)
CTD	Combined-agent tumor dose (Gy)
CMD	Combined-agent marrow dose (Gy)
CKD	Combined-agent kidney dose (Gy)
A _{MIBG}	Maximum single-agent ¹³¹ I-MIBG activity
A _{DOTA}	Maximum single-agent ⁹⁰ Y-DOTATOC activity
m _{MIBG}	¹³¹ I-MIBG red marrow dose per megabecquerel
m _{DOTA}	⁹⁰ Y-DOTATOC red marrow dose per megabecquerel
k _{MIBG}	¹³¹ I-MIBG kidney dose per megabecquerel
k _{DOTA}	⁹⁰ Y-DOTATOC kidney dose per megabecquerel
t _{MIBG}	¹³¹ I-MIBG tumor dose per megabecquerel
t _{DOTA}	⁹⁰ Y-DOTATOC tumor dose per megabecquerel
t _{DOTA} /t _{MIBG}	Tumor-dose ratio
α _{opt}	Optimal fraction of A _{MIBG} for combined-agent therapy
β _{opt}	Optimal fraction of A _{DOTA} for combined-agent therapy

organ dose. Thus, the maximum activity of ¹³¹I-MIBG administered as a single agent, A_{MIBG}, is given by

$$A_{MIBG} = MLD/m_{MIBG}, \quad \text{Eq. 1}$$

where MLD is the maximum dose tolerated by the red marrow and m_{MIBG} is the dose per megabecquerel delivered by ¹³¹I-MIBG to the red marrow.

Similarly, the maximum activity of ⁹⁰Y-DOTATOC administered as a single agent, A_{DOTA}, is given by

$$A_{DOTA} = KLD/k_{DOTA}, \quad \text{Eq. 2}$$

where KLD is the maximum dose tolerated by the kidneys and k_{DOTA} is the dose per megabecquerel delivered by ⁹⁰Y-DOTATOC to the kidneys.

The dose delivered to tumor by each of the agents administered singly is given by

$$T_{MIBG} = A_{MIBG} \times t_{MIBG} \quad \text{and} \quad T_{DOTA} = A_{DOTA} \times t_{DOTA},$$

where T_{MIBG} and T_{DOTA} are the tumor doses delivered by the agents and t_{MIBG} and t_{DOTA} are the respective tumor dose per megabecquerel.

The following equations describe the situation in which both agents are combined to treat a subject:

$$\begin{aligned} \text{Combined tumor dose (CTD)} = & \alpha A_{MIBG} t_{MIBG} \\ & + \beta A_{DOTA} t_{DOTA} \end{aligned} \quad \text{Eq. 3}$$

$$\begin{aligned} \text{Combined marrow dose (CMD)} = & \alpha A_{MIBG} m_{MIBG} \\ & + \beta A_{DOTA} m_{DOTA} \end{aligned} \quad \text{Eq. 4}$$

$$\begin{aligned} \text{Combined kidney dose (CKD)} = & \alpha A_{MIBG} k_{MIBG} \\ & + \beta A_{DOTA} k_{DOTA}. \end{aligned} \quad \text{Eq. 5}$$

α and β are fractions with a range of 0–1.

When combined-agent therapy is more advantageous (i.e., delivers more tumor dose) than therapy with either single agent, the optimal combination of tracers occurs when the combined marrow dose is equal to the marrow limiting dose and the combined kidney dose is equal to the kidney limiting dose. When that occurs, Equations 4 and 5 are simultaneous equations and α and β can be uniquely solved using the method of determinants:

$$\begin{aligned} \alpha_{opt} = & (MLD \times A_{DOTA} k_{DOTA} - KLD \\ & \times A_{DOTA} m_{DOTA}) / \text{DENOM}, \end{aligned} \quad \text{Eq. 6}$$

$$\begin{aligned} \text{where DENOM} = & (A_{MIBG} m_{MIBG} \times A_{DOTA} k_{DOTA} \\ & - A_{MIBG} k_{MIBG} \times A_{DOTA} m_{DOTA}), \end{aligned}$$

and

$$\begin{aligned} \beta_{opt} = & (A_{MIBG} m_{MIBG} \times KLD - A_{MIBG} k_{MIBG} \\ & \times MLD) / \text{DENOM}. \end{aligned} \quad \text{Eq. 7}$$

To judge whether combined-agent therapy is advantageous, we consider the fractional increase in tumor dose, defined as

$$\begin{aligned} & (\text{CTD} - \text{single-agent tumor dose}) / \text{single-agent tumor-dose}, \\ & \quad \text{Eq. 8} \end{aligned}$$

where the highest dose resulting from either ^{90}Y -DOTATOC or ^{131}I -MIBI is used in the calculation. By combining Equations 3 and 4, we can eliminate α from the equation, yielding

$$\text{CTD} = ((\text{CMD} - \beta A_{\text{DOTA}} m_{\text{DOTA}})/m_{\text{MIBG}}) t_{\text{MIBG}} + \beta A_{\text{DOTA}} t_{\text{DOTA}},$$

which can be rewritten as

$$\text{CTD} = \text{CMD} t_{\text{MIBG}}/m_{\text{MIBG}} + \beta A_{\text{DOTA}} (t_{\text{DOTA}} - t_{\text{MIBG}} m_{\text{DOTA}}/m_{\text{MIBG}}). \quad \text{Eq. 9}$$

Equation 9 is a linear function of β with the slope equal to $A_{\text{DOTA}}(t_{\text{DOTA}} - t_{\text{MIBG}} m_{\text{DOTA}}/m_{\text{MIBG}})$. In order for CTD to increase, we require a positive slope, and this implies that

$$t_{\text{DOTA}}/t_{\text{MIBG}} > m_{\text{DOTA}}/m_{\text{MIBG}}. \quad \text{Eq. 10}$$

The ratio of the ^{90}Y -DOTATOC tumor dose per megabecquerel to the ^{131}I -MIBG tumor dose per megabecquerel, $t_{\text{DOTA}}/t_{\text{MIBG}}$, which we refer to as the tumor-dose ratio, is the independent variable for the function defined by Equation 8. When the tumor-dose ratio is less than $m_{\text{DOTA}}/m_{\text{MIBG}}$, ^{131}I -MIBG is the best single agent and delivers more dose to the tumor than does the combination therapy. In a similar fashion, Equations 3 and 5 can be combined to yield the upper limit of the tumor-dose ratio at which combined-agent therapy is effective, with the following result:

$$t_{\text{DOTA}}/t_{\text{MIBG}} < k_{\text{DOTA}}/k_{\text{MIBG}}. \quad \text{Eq. 11}$$

When the tumor-dose ratio is greater than $k_{\text{DOTA}}/k_{\text{MIBG}}$, ^{90}Y -DOTATOC is the best single agent and delivers more dose to the tumor than does the combination therapy. Over the tumor-dose ratio range from $m_{\text{DOTA}}/m_{\text{MIBG}}$ to $k_{\text{DOTA}}/k_{\text{MIBG}}$, the combination of ^{131}I -MIBG and ^{90}Y -DOTATOC will deliver more dose to the tumor than will the use of either single agent without exceeding the critical organ doses.

The tumor-dose ratio that results in the maximum fractional dose increase can be found from the realization that Equation 8 is maximized when the denominator is as small as possible. This occurs when the total single-agent tumor dose from each tracer is the same:

$$A_{\text{MIBG}} \times t_{\text{MIBG}} = A_{\text{DOTA}} \times t_{\text{DOTA}}. \quad \text{Eq. 12}$$

Thus, the combined-agent therapy will be most advantageous when

$$t_{\text{DOTA}}/t_{\text{MIBG}} = A_{\text{MIBG}}/A_{\text{DOTA}}. \quad \text{Eq. 13}$$

It is also possible to calculate the magnitude of the fractional increase of the combined-agent approach, compared with the better of the 2 single agents, from the equations presented above. When ^{131}I -MIBG is the best single agent,

Fraction tumor-dose increase

$$\begin{aligned} &= (\text{CTD} - A_{\text{MIBG}} t_{\text{MIBG}})/A_{\text{MIBG}} t_{\text{MIBG}} \\ &= (\alpha_{\text{opt}} A_{\text{MIBG}} t_{\text{MIBG}} + \beta_{\text{opt}} A_{\text{DOTA}} t_{\text{DOTA}} \\ &\quad - A_{\text{MIBG}} t_{\text{MIBG}})/A_{\text{MIBG}} t_{\text{MIBG}} \\ &= \alpha_{\text{opt}} + \beta_{\text{opt}} (A_{\text{DOTA}}/A_{\text{MIBG}}) \times (t_{\text{DOTA}}/t_{\text{MIBG}}) - 1. \end{aligned} \quad \text{Eq. 14}$$

When ^{90}Y -DOTATOC is the best single agent,

Fraction tumor-dose increase

$$\begin{aligned} &= (\text{CTD} - A_{\text{DOTA}} t_{\text{DOTA}})/A_{\text{DOTA}} t_{\text{DOTA}} \\ &= \alpha_{\text{opt}} (A_{\text{MIBG}}/A_{\text{DOTA}}) \times (t_{\text{MIBG}}/t_{\text{DOTA}}) + \beta_{\text{opt}} - 1. \end{aligned} \quad \text{Eq. 15}$$

Using either of these equations, we can estimate the maximum possible fractional increase in tumor dose from using the combined-agent approach. Recalling from Equation 13 that at the maximum fractional increase $A_{\text{MIBG}}/A_{\text{DOTA}} = t_{\text{DOTA}}/t_{\text{MIBG}}$, Equations 14 and 15 both reduce to

$$\begin{aligned} &(\text{CTD} - A_{\text{MIBG}} t_{\text{MIBG}})/A_{\text{MIBG}} t_{\text{MIBG}} \\ &= (\text{CTD} - A_{\text{DOTA}} t_{\text{DOTA}})/A_{\text{DOTA}} t_{\text{DOTA}} \\ &= \alpha_{\text{opt}} + \beta_{\text{opt}} - 1. \end{aligned} \quad \text{Eq. 16}$$

The equations can also be used to define the range of tumor-dose ratios at which the fractional increase will be greater than a desired amount. For example, to calculate the tumor-dose rate when the fractional increase is greater than or equal to 0.25, we proceed as follows. The lower limit of the tumor-dose ratio is calculated from

$$\begin{aligned} &(\text{CTD} - A_{\text{MIBG}} t_{\text{MIBG}})/A_{\text{MIBG}} t_{\text{MIBG}} = 0.25 \\ &= \alpha_{\text{opt}} + \beta_{\text{opt}} (A_{\text{DOTA}}/A_{\text{MIBG}}) \times (t_{\text{DOTA}}/t_{\text{MIBG}}) - 1 \\ &t_{\text{DOTA}}/t_{\text{MIBG}} = (0.25 + 1 - \alpha_{\text{opt}})/\beta_{\text{opt}} (A_{\text{DOTA}}/A_{\text{MIBG}}). \end{aligned} \quad \text{Eq. 17}$$

The upper limit of the tumor-dose ratio is calculated from

$$\begin{aligned} &(\text{CTD} - A_{\text{DOTA}} t_{\text{DOTA}})/A_{\text{DOTA}} t_{\text{DOTA}} = 0.25 \\ &= \alpha_{\text{opt}} (A_{\text{MIBG}}/A_{\text{DOTA}}) \times (t_{\text{MIBG}}/t_{\text{DOTA}}) + \beta_{\text{opt}} - 1 \\ &t_{\text{DOTA}}/t_{\text{MIBG}} = \alpha_{\text{opt}} (A_{\text{MIBG}}/A_{\text{DOTA}})/(0.25 + 1 - \beta_{\text{opt}}). \end{aligned} \quad \text{Eq. 18}$$

Spreadsheet Calculations

To verify the model of combined radionuclide therapy with ^{131}I -MIBG and ^{90}Y -DOTATOC, we calculated doses using the published dosimetric values for the 2 agents shown in Table 3. An Excel (Microsoft) spreadsheet was configured to perform the following operations. First, the optimum administered activity for ^{90}Y -DOTATOC was calculated to achieve the assumed kidney critical organ dose (23 Gy) using Equation 2. Next, the amount of ^{90}Y -DOTATOC activity was reduced in 1% increments and the associated amount of ^{131}I -MIBG activity that could be additionally given without exceeding either the kidney or the red marrow limiting dose was calculated. The resultant ^{90}Y -DOTATOC and

TABLE 3
Dosimetric Values used in the Spreadsheet Calculations

Parameter	Kidneys	Red marrow
Optimum dose (Gy)	23	2
^{131}I -MIBG dose (mGy/MBq)	0.09	0.07
^{90}Y -DOTATOC dose (mGy/MBq)	2.16	0.05

^{131}I -MIBG activities from these operations were used to calculate the dose delivered to a tumor as a function of the tumor-dose ratio. The tumor-dose ratio was varied from 0.1 to 30. In the dose calculations, the tumor dose per megabecquerel for ^{131}I -MIBG was assumed to be 2.9 mGy/MBq, which corresponds to the mean tumor dose reported by Matthay et al. (11) for 27 patients with neuroblastoma treated with ^{131}I -MIBG. The tumor dose per megabecquerel for ^{90}Y -DOTATOC was determined from the tumor-dose ratio. This approach allows the calculation of tumor dose from each of the agents separately as well as in combination, and from those results the fractional increase in tumor dose from the combined-agent approach was determined.

Using the spreadsheet, we investigated different aspects of the combined-agent therapy and compared them directly with the model results. Because tumor and normal-tissue uptake and residence times are expected to vary widely among individuals, we changed the assumed values for the limiting critical organ dose and the critical organ dose per megabecquerel and calculated examples using these values. Specifically, changes were made to the kidney dose limit, and the red marrow dose per megabecquerel value.

RESULTS

The values in Table 3 were used to determine the optimal fractions of each of the agents resulting in an α_{opt} of 0.76 and a β_{opt} of 0.92. These results match the fractions found by inspecting the spreadsheet calculations that yield the maximum dose delivery for the combined-agent approach. The optimal values of α and β found from the spreadsheet calculations are independent of the tumor-dose ratio within the range at which the combined-agent approach provides an increased dose. This result is consistent with the model prediction. Figure 1 shows a plot of the percentage increase in dose for combined-agent therapy as a function of the tumor-dose ratio using the dosimetric values in Table 3, and the results from the model calculations are given in Table 4. The numeric results from the model calculations exactly match the plotted results. When the tumor-dose ratio is less than $m_{\text{DOTA}}/m_{\text{MIBG}}$, there is no advantage to combined-agent therapy and ^{131}I -MIBG is the best agent. Above that limit, the combined-agent method provides an increased dose, reaching a maximum fractional increase of 0.68 at a tumor-dose ratio of 2.57. Beyond the maximum, the dose advantage decreases with increasing tumor-dose ratio, reaching 0 at a tumor-dose ratio of 24.24. Beyond that point, treating with only ^{90}Y -DOTATOC yields the highest tumor dose. Within the tumor-dose ratio range from 1.37 to 5.93, the dose advantage for the combined-agent approach exceeds 25%.

Figure 2 shows how the percentage increase in tumor dose from the combined-agent approach depends on the relative amount of each agent. The graph was plotted for the optimal tumor-dose ratio of 2.57, again using the normal-tissue dose values and limits from Table 3. The lower x -axis is expressed in terms of the percentage of the optimum activity that could be administered for ^{90}Y -DOTATOC alone (A_{DOTA}), whereas the upper x -axis

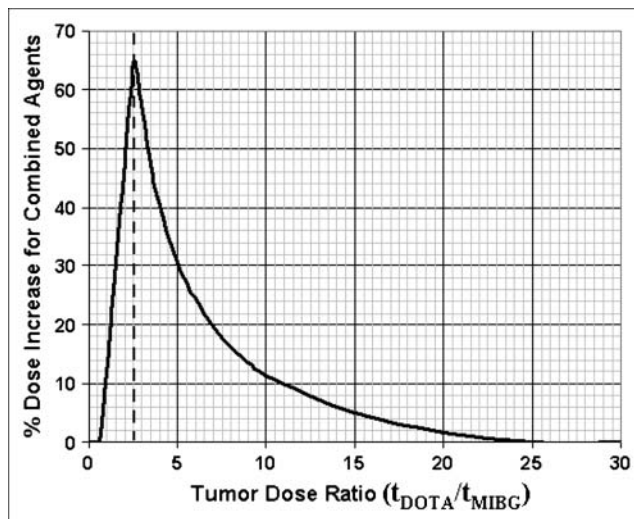


FIGURE 1. Percentage increase in delivered tumor dose from combined-agent therapy with respect to single-agent therapy as function of ^{90}Y -DOTATOC-to- ^{131}I -MIBG tumor-dose ratio. Benefit from combined-agent therapy is optimal when tumor-dose ratio is 2.57, at which the combined-agent approach delivers 68% more dose to tumor than does either agent used alone. ^{131}I -MIBG is the better of the 2 agents used alone when tumor-dose ratio is less than 2.57 (left of dotted line), and ^{90}Y -DOTATOC is the better single agent when tumor-dose ratio is greater than 2.57 (right of dotted line).

is expressed in terms of the percentage of the administered ^{131}I -MIBG activity as the only agent (A_{MIBG}). The optimal combination occurs for 92% of the maximum tolerated ^{90}Y -DOTATOC administered activity and 76% of the maximum tolerated ^{131}I -MIBG administered activity, again matching the results of the model. As noted on the graph, points to the left of maximum represent marrow-dose-limited administered activity whereas points to the right of maximum represent kidney-dose-limited administered activity.

The next figures illustrate how changes in the dosimetric parameters affect the performance of the combined-agent approach. Figure 3 shows a series of plots from the spreadsheet results as the ^{90}Y -DOTATOC kidney dose per megabecquerel varies from 0.7 to 2.8 mGy/MBq, keeping

TABLE 4

Model Results for the Dosimetric Values in Table 3

Parameter	Value
α_{opt}	0.76
β_{opt}	0.92
$t_{\text{DOTA}}/t_{\text{MIBG}}$ maximum	2.58
Maximum fractional increase	0.68
$t_{\text{DOTA}}/t_{\text{MIBG}}^*$	0.67
$t_{\text{DOTA}}/t_{\text{MIBG}}^\dagger$	24.24
$t_{\text{DOTA}}/t_{\text{MIBG}} 0.25^*$	1.37
$t_{\text{DOTA}}/t_{\text{MIBG}} 0.25^\dagger$	5.93

*Lower level for tumor-dose ratio.

†Upper level for tumor-dose ratio.

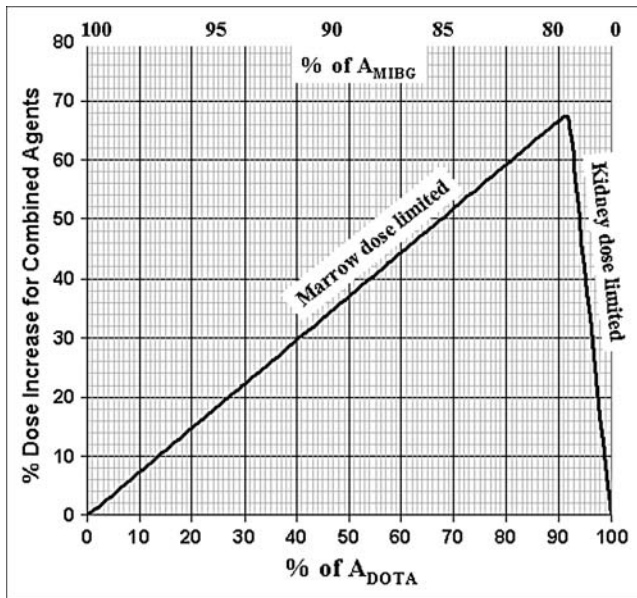


FIGURE 2. Percentage tumor-dose increase from combined-agent therapy with respect to single-agent therapy plotted as function of fraction of optimal administered activities of ^{90}Y -DOTATOC and ^{131}I -MIBG. Plot uses results obtained at optimal tumor-dose ratio (2.57). Maximum fraction increase occurs when $\alpha = 0.76$ and $\beta = 0.92$ as predicted by model.

the other parameters in Table 3 constant. The results from the model calculations are given in Table 5, and they accurately represent the plotted curves. When the doses per megabecquerel for the critical organs are similar, such as when k_{DOTA} is 0.7 mGy/MBq, there is little gain in the combined-agent approach regardless of the tumor-dose ratio. As k_{DOTA} increases with respect to the MIBG red marrow dose per megabecquerel, the percentage increase in tumor dose from the combined agents increases substantially, along with the range of tumor-dose ratios, when the combined-agent approach is advantageous.

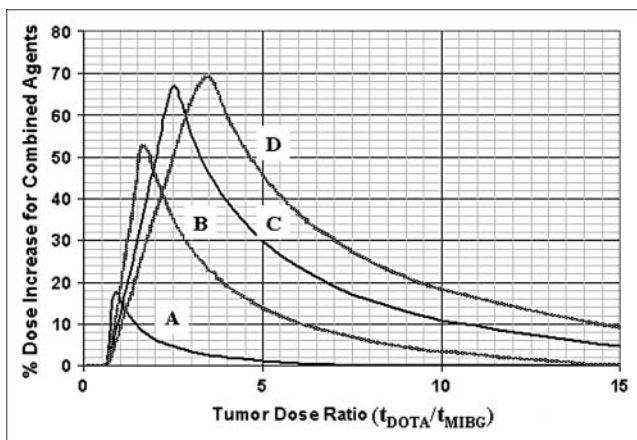


FIGURE 3. Tumor-dose increase from combined-agent therapy with respect to single-agent therapy as function of ^{90}Y -DOTATOC kidney dose in mGy/MBq. Kidney dose was varied from 0.7 to 2.8 mGy/MBq while keeping all other parameters in Table 3 constant. Curves represent k_{DOTA} values of 0.7 (A), 1.4 (B), 2.1, (C), and 2.8 (D) mGy/MBq.

TABLE 5

Model Results for Various ^{90}Y -DOTATOC Kidney Doses per Megabecquerel

Parameter	k_{DOTA} (mGy/MBq)			
	0.7	1.4	2.1	2.8
α_{opt}	0.22	0.63	0.76	0.82
β_{opt}	0.98	0.93	0.92	0.91
$t_{\text{DOTA}}/t_{\text{MIBG}}$ maximum	0.83	1.67	2.58	3.34
Maximum fractional increase	0.20	0.56	0.68	0.73
$t_{\text{DOTA}}/t_{\text{MIBG}}^*$	0.67	0.67	0.67	0.67
$t_{\text{DOTA}}/t_{\text{MIBG}}^\dagger$	7.85	15.70	24.24	31.39
$t_{\text{DOTA}}/t_{\text{MIBG}} 0.25^*$	0.67	1.11	1.37	1.58
$t_{\text{DOTA}}/t_{\text{MIBG}} 0.25^\dagger$	0.88	3.30	5.93	8.10

*Lower level for tumor-dose ratio.

†Upper level for tumor-dose ratio.

Figure 4 shows a series of plots as the red marrow dose limit is varied from 1.5 to 3.0 Gy, keeping the other parameters in Table 3 constant. As this limit is increased, the plot broadens and a shift to higher values occurs for the ^{90}Y -DOTATOC-to- ^{131}I -MIBG tumor-dose ratio at which the fractional increase of tumor dose with combined therapy maximizes. However, the percentage increase in the tumor dose from the combined approach, compared with single-agent therapy, does not increase significantly. The reason for this interesting finding is that as the red marrow dose limit increases, treatment with ^{131}I -MIBG becomes more favorable and the activity that can be administered increases. While more tumor dose is delivered by the combined-agent method, the single-agent treatment dose with ^{131}I -MIBG is also increased. As a result, the magnitude of the fractional increase in tumor dose from combined-agent therapy changes little as the marrow limiting dose is increased. The

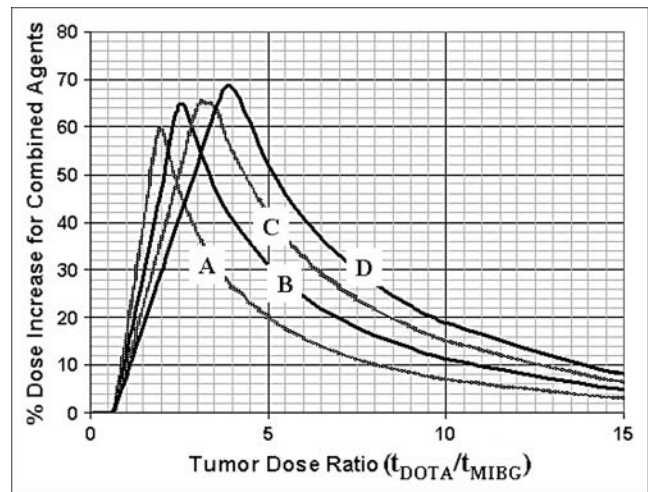


FIGURE 4. Tumor-dose increase from combined-agent therapy with respect to single-agent therapy as function of red marrow dose limit, which was varied from 1.5 to 3.0 Gy while keeping all other parameters in Table 3 constant. Curves represent MLD values of 1.5 (A), 2.0 (B), 2.5 (C), and 3.0 (D) Gy.

model results corresponding to Figure 4 are presented in Table 6 and show excellent agreement with the plotted curves.

Figure 5 shows a series of plots as the ^{131}I -MIBG red marrow dose is varied from 0.024 to 0.120 mGy/MBq, keeping the other parameters in Table 3 constant. As the red marrow dose per megabecquerel increases, the plots shift to the left, changing the threshold of the optimal tumor-dose ratio from 7.0 at a red marrow dose of 0.024 mGy/MBq to 0.6 at a red marrow dose of 0.12 mGy/MBq. This change occurs because as the ^{131}I -MIBG red marrow dose per megabecquerel increases, the amount of ^{131}I -MIBG that can be administered in single-agent therapy decreases, thereby improving the dose that can be delivered with the combined-agent approach. At a lower ^{131}I -MIBG red marrow dose per megabecquerel, more ^{131}I -MIBG can be administered as a single agent. Thus, the advantage from combined-agent therapy is realized only at higher ^{90}Y -DOTATOC-to- ^{131}I -MIBG tumor-dose ratios. The model results corresponding to Figure 5 are presented in Table 7 and show excellent agreement with the plotted curve.

DISCUSSION

The results of this investigation show that combined radionuclide therapy with ^{90}Y -DOTATOC and ^{131}I -MIBG has the potential to substantially increase the dose delivered to the tumor while staying within the dose limits of the critical organs. As the model shows and the calculations support, increases in both the range and the magnitude of the dose depend on the respective kidney, red marrow, and tumor dose per megabecquerel for each agent. Thus, patient-specific dosimetry for the tumor and critical organs must be evaluated to allow prediction of the expected dose improvement from combined-agent therapy.

Using the 2.9 mGy/MBq average tumor dose reported for ^{131}I -MIBG in patients with neuroblastoma, we showed that a tumor-dose ratio of 2.57 resulted in the maximum fractional increase in tumor dose from combined therapy using the parameters in Table 3. Interestingly, this ratio is

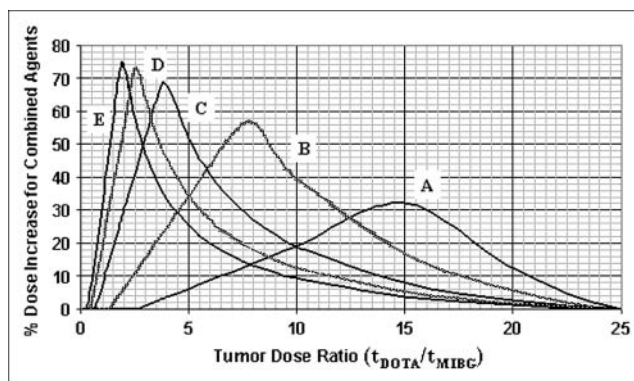


FIGURE 5. Tumor-dose increase from combined-agent therapy with respect to single-agent therapy as function of ^{131}I -MIBG red marrow dose in mGy/MBq. Red marrow dose was varied from 0.024 to 0.12 mGy/MBq while keeping all other parameters in Table 3 constant. Curves represent m_{MIBG} values of 0.024 (A), 0.048 (B), 0.072 (C), 0.096 (D), and 0.12 (E) mGy/MBq.

quite realistic and, on the basis of reported dosimetric estimates with ^{90}Y -DOTATOC, may be expected for the “average” patient population. For example, Pauwels et al. (12) showed that the mean tumor dose for patients with neuroendocrine tumors treated with ^{90}Y -DOTATOC was about 4.4 mGy/MBq, yielding a ^{90}Y -DOTATOC-to- ^{131}I -MIBG ratio of about 1.53. This result is not much lower than the predicted optimal ratio of 2.57 and would, on the basis of our model, result in a 32% increase in tumor dose from combined, compared with single-agent, therapy. We cannot overemphasize, however, that these are only “averaged” estimates and that the tumor radiation doses from ^{90}Y -DOTATOC and ^{131}I -MIBG may vary substantially even in the same patient and for the same tumor. In fact, the study of Matthay et al. (11) showed that the tumor dose from ^{131}I -MIBG ranged from 0.95 to 9.53 mGy/MBq for the various tumors studied. Similar variability was reported

TABLE 6
Model Results for Various Marrow Limiting Doses

Parameter	Marrow limiting dose (Gy)			
	1.5	2.0	2.5	3.0
α_{opt}	0.67	0.76	0.82	0.85
β_{opt}	0.95	0.92	0.89	0.86
$t_{\text{DOTA}}/t_{\text{MIBG}}$ maximum	1.93	2.58	3.22	3.86
Maximum fractional increase	0.62	0.68	0.71	0.72
$t_{\text{DOTA}}/t_{\text{MIBG}}^*$	0.67	0.67	0.67	0.67
$t_{\text{DOTA}}/t_{\text{MIBG}}^\dagger$	24.24	24.24	24.24	24.24
$t_{\text{DOTA}}/t_{\text{MIBG}} 0.25^*$	1.18	1.37	1.57	1.78
$t_{\text{DOTA}}/t_{\text{MIBG}} 0.25^\dagger$	4.29	5.93	7.33	8.53

*Lower level for tumor-dose ratio.

†Upper level for tumor-dose ratio.

TABLE 7
Model Results for Various ^{131}I -MIBG Marrow Doses per Megabecquerel

Parameter	m_{MIBG} (mGy/MBq)				
	0.024	0.048	0.072	0.096	0.12
α_{opt}	0.81	0.77	0.76	0.76	0.75
β_{opt}	0.74	0.88	0.92	0.94	0.95
$t_{\text{DOTA}}/t_{\text{MIBG}}$ maximum	7.91	3.92	2.61	1.96	1.57
Maximum fractional increase	0.55	0.65	0.68	0.70	0.71
$t_{\text{DOTA}}/t_{\text{MIBG}}^*$	2.05	1.01	0.68	0.51	0.41
$t_{\text{DOTA}}/t_{\text{MIBG}}^\dagger$	24.24	24.24	24.24	24.24	24.24
$t_{\text{DOTA}}/t_{\text{MIBG}} 0.25^*$	4.73	2.13	1.39	1.03	0.82
$t_{\text{DOTA}}/t_{\text{MIBG}} 0.25^\dagger$	12.45	8.08	5.99	4.77	3.95

*Lower level for tumor-dose ratio.

†Upper level for tumor-dose ratio.

by Pauwels et al. (12), who showed that the tumor dose from ^{90}Y -DOTATOC ranged from 0.88 to 48.8 mGy/MBq in their patients. It is likely that many of these patients would have much better tumor targeting with the one agent than with the other and that, therefore, the ^{90}Y -DOTATOC-to- ^{131}I -MIBG tumor-dose ratio might vary considerably among patients and even for multiple tumors in the same patient. This possibility has been indirectly shown by several investigators (13,14), who observed considerable variability in tumor imaging with ^{123}I - or ^{131}I -MIBG and ^{111}In -pentetreotide in the same patients and even for the same tumors in some patients. The implication is that there exists a combination of tumor sites with good somatostatin analog uptake together with poor MIBG uptake, and vice versa. In a recent study, each of 92 patients with an existing diagnosis of carcinoid tumor underwent both ^{123}I -MIBG imaging and ^{111}In -pentetreotide imaging. Although 30% of the combination studies showed effectively the same tumor-targeting pattern for each agent, 15% of subjects had completely negative ^{123}I -MIBG findings for ^{111}In -pentetreotide-positive lesions, and 6% had completely negative ^{111}In -pentetreotide findings for ^{123}I -MIBG-positive metastases (15). Most important, fully 48% of the 92 subjects showed positive ^{111}In -pentetreotide findings and negative ^{123}I -MIBG findings in combination with positive ^{123}I -MIBG findings and negative ^{111}In -pentetreotide findings in the same patient. These data clearly emphasize the importance of performing patient-specific dosimetry for both the tumor and the critical organs before administering combined-agent therapy.

To demonstrate how combined-agent therapy would be used in the situation of multiple tumors with different affinities for ^{131}I -MIBG and ^{90}Y -DOTATOC, we offer the following example. We assume that there is a patient with 5 known neuroendocrine tumors. First, imaging studies would have to be performed to determine the absorbed dose per megabecquerel for the critical organs (red marrow and kidneys) and the absorbed dose per megabecquerel for each of the tumors. The dosimetry for ^{131}I -MIBG can be measured directly using a diagnostic administration, whereas the dosimetry for ^{90}Y -DOTATOC will have to be inferred from using either ^{111}In -pentetreotide as a surrogate or, if available, ^{86}Y -DOTATOC. The optimal fractions of ^{131}I -MIBG and ^{90}Y -DOTATOC used in combination de-

pend only on the critical organ dose per megabecquerel and are independent of the tumor dose per megabecquerel. Thus, the values of α_{opt} and β_{opt} determined by Equations 6 and 7 are also appropriate for delivering the highest combined-agent dose when applied to multiple tumors. In this example, it will be assumed that the measured doses per megabecquerel for the red marrow and kidney, as well as the limiting doses, are the same as those given in Table 3. Table 8 gives hypothetical but realistic values for the tumor dose per megabecquerel that span the range of tumor-dose ratios to include 1 lesion to which ^{131}I -MIBG delivers the largest dose and 1 lesion to which ^{90}Y -DOTATOC delivers the largest dose, with the remaining lesions obtaining the largest dose from combined-agent therapy. This information is used to calculate the tumor dose for each lesion for 3 different treatments: ^{131}I -MIBG given as a single agent, ^{90}Y -DOTATOC given as a single agent, and ^{131}I -MIBG and ^{90}Y -DOTATOC used in combination with the optimal fractions obtained from Equations 6 and 7.

The calculated doses resulting from the model given in Table 8 show that the mean dose delivered to all the tumors is 50% greater with combined-agent therapy than with only ^{131}I -MIBG and 90% greater with combined-agent therapy than with only ^{90}Y -DOTATOC. More important, the dose delivered to each of the 5 tumors with combined therapy is either greater than (lesions 2, 3, and 4), similar to (lesion 5), or only slightly lower than (lesion 1) the dose that would be delivered using either of the 2 agents as a single therapy. However, if single-agent therapy is used, at least 1 of the 5 tumors would receive an extremely low tumor dose (lesion 1 with ^{90}Y -DOTATOC and lesion 5 with ^{131}I -MIBG), essentially precluding any significant antitumor effect for that particular lesion. From this example, it is clear that the single-agent approach is the best choice only when the tumor-dose ratios for all the lesions are very low, when ^{131}I -MIBG will work best, or very high, when ^{90}Y -DOTATOC will work best. For multiple tumors with variation across the tumor-dose range, as the example illustrates, the combined-agent approach is clearly superior because every tumor at worst will receive a substantial fraction of the best single-agent dose.

Even when combined therapy does not offer any significant dose advantage, there might still be a therapeutic advantage. Evidence suggests that the distribution within

TABLE 8
Example Results for Multiple Tumors with Variable Tumor-Dose Ratios

Lesion no.	Tumor dose (mGy) per megabecquerel			Tumor dose (Gy)		
	t_{MIBG}	t_{DOTA}	$t_{\text{DOTA}}/t_{\text{MIBG}}$	^{131}I -MIBG	^{90}Y -DOTATOC	Combined
1	2.9	0.3	0.10	82.9	3.2	64.9
2	2.9	2.9	1.00	82.9	30.9	91.3
3	1.5	4.4	2.93	42.9	46.9	76.7
4	0.5	4.4	8.80	14.3	46.9	55.3
5	0.1	4.4	44.00	2.9	46.9	46.8
Mean				45.1	34.9	67.0

neuroendocrine tumor sites for DOTATOC and MIBG is not the same and that combining them could therefore ensure that all parts of the tumor receive a radiation dose (16). Another consideration is the energy of the β -particles emitted by ^{90}Y and ^{131}I . ^{90}Y emits a β -particle with a maximum energy of 2.27 MeV, which is better suited for tumors larger than 2 cm in diameter, whereas the β -particle of ^{131}I , with a maximum energy of 0.6 MeV, is better suited for tumors smaller than 1 cm. Because it is possible and even likely that a patient will have multiple lesions of varying size, using combined-agent therapy will potentially be more efficacious than using either radiotracer alone.

One potential concern with the proposed combined therapy with ^{90}Y -DOTATOC and ^{131}I -MIBG is that combining these 2 agents may cause some other organ or tissue, such as the lungs or liver, to reach the critical dose. Fortunately, this situation does not seem to occur with these 2 agents. The liver dose will not exceed its limit of 30 Gy even if the optimum amounts of ^{90}Y -DOTATOC and ^{131}I -MIBG are administered to the same patient. The lung uptake for both these agents is low, and the dose to the lungs from optimal administrations will be nearly a factor of 10 less than the 20-Gy limiting dose for this organ.

CONCLUSION

Use of ^{90}Y -DOTATOC and ^{131}I -MIBG together as therapy for neuroendocrine tumors has the potential to increase tumor-dose delivery without exceeding critical organ limits. Calculations predict tumor-dose increases exceeding 65% of the maximum tumor dose that could be delivered by use of either agent alone. Combined-agent therapy may also have additional targeting and dose delivery benefits. The magnitude of the fractional dose increase associated with combined-agent therapy depends on the tumor and critical organ dose per megabecquerel values and on the maximum dose that can be delivered to each critical organ. Individual dosimetry studies are required to determine which patients will benefit from combined-agent therapy.

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