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ORIGINAL REPORT

Response, Survival, and Long-Term Toxicity After Therapy With the Radiolabeled Somatostatin Analogue [^{90}Y-DOTA]-TOC in Metastasized Neuroendocrine Cancers

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ABSTRACT

Purpose
To investigate response, survival, and safety profile of the somatostatin-based radiopeptide ^{90}yttrium-labeled tetraazacyclododecane-tetraacetic acid modified Tyr-octreotide ([^{90}Y-DOTA]-TOC) in neuroendocrine cancers.

Patients and Methods
In a clinical phase II single-center open-label trial, patients with neuroendocrine cancers were treated with repeated cycles of [^{90}Y-DOTA]-TOC. Each cycle consisted of a single intravenous injection of 3.7GBq/m^2 body-surface [^{90}Y-DOTA]-TOC. Additional cycles were withheld in case of tumor progression and/or permanent toxicity.

Results
Overall, 1,109 patients received 2,472 cycles of [^{90}Y-DOTA]-TOC (median, two; range, one to 10 cycles per patient). Of the 1,109 patients, 378 (34.1%) experienced morphologic response; 172 (15.5%), biochemical response; and 329 (29.7%), clinical response. During a median follow-up of 23 months, 491 patients (44.3%) died. Longer survival was correlated with each: morphologic (hazard ratio [HR], 0.46; 95% CI, 0.38 to 0.56; median survival, 44.7 *v* 18.3 months; $P < .001$), biochemical (HR, 0.75; 95% CI, 0.59 to 0.96; 35.3 *v* 25.7 months; $P = .023$), and clinical response (HR, 0.68; 95% CI, 0.56 to 0.82; 36.8 *v* 23.5 months; $P < .001$). Overall, 142 patients (12.8%) developed grade 3 to 4 transient hematologic toxicities, and 103 patients (9.2%) experienced grade 4 to 5 permanent renal toxicity. Multivariable regression revealed that tumoral uptake in the initial imaging study was predictive for overall survival (HR, 0.45; 95% CI, 0.29 to 0.69; $P < .001$), whereas the initial kidney uptake was predictive for severe renal toxicity (HR, 1.59; 95% CI, 1.17 to 2.17; $P = .003$).

Conclusion
This study documents the long-term outcome of [^{90}Y-DOTA]-TOC treatment in a large cohort. Response to [^{90}Y-DOTA]-TOC is associated with longer survival. Somatostatin receptor imaging is predictive for both survival after [^{90}Y-DOTA]-TOC treatment and occurrence of renal toxicity.

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INTRODUCTION

Differentiated neuroendocrine cancers frequently express subtypes of the somatostatin receptor family.[1] This feature allows treatment with the somatostatin analog octreotide LAR,[2,3] facilitates receptor imaging with radiolabeled somatostatins,[4] and provides the rationale for somatostatin-based radiopeptide therapy.

Somatostatin-based radiopeptide therapy with ^{90}yttrium-labeled tetraazacyclododecane-tetraacetic acid modified Tyr^3-octreotide ([^{90}Y-DOTA]-TOC) was developed and introduced into clinical practice by our department in 1997.[5] The introduction of tyrosine into the third position of the octreotide sequence increases the hydrophilicity and receptor affinity of the peptide, and conjugation with the β emitter ^{90}Y allows for irradiation of the tumor. [^{90}Y-DOTA]-TOC is administered intravenously, binds to somatostatin receptors on the target cell, and exerts cytotoxic effects via β irradiation.

Initial reports showed that [^{90}Y-DOTA]-TOC was able to induce morphologic responses (10 of 41 patients),[6] biochemical responses (nine of 31 patients),[7] and clinical responses (13 of 21 patients)[8] in progressive metastasized neuroendocrine cancer.

Table 1. Baseline Characteristics and Spectrum of Outcomes in Different Types of Neuroendocrine Cancer (N = 1,109)

Characteristic	Patients		Morphologic Response		Biochemical Response		Clinical Response		Mean Survival	95% CI
	No.	%	No.	%	No.	%	No.	%		
Sex										
Female	477	43.0								
Male	632	57.0								
Age, years										
Median	58.9									
Range	11.2-91.1									
Disease duration, years										
Median	1.9									
Range	0.1-37.8									
Pretreatment										
Surgery	605	54.6								
Chemotherapy	329	29.7								
Radiation	143	12.9								
Extent of disease										
Single metastasis	110	9.9								
Liver metastases	912	82.2								
Bone metastases	212	19.0								
Creatinine, μmol/L										
Median	70.0									
Range	22-434									
Tumor uptake score										
1	68	6.1								
2	68	6.1								
3	973	87.7								
Kidney uptake score										
0	56	5.0								
1	130	11.7								
2	259	23.3								
3	657	59.2								
Histology										
Carcinoids	479	43.2								
Thymus	8		3	37.5	2	25.0	2	25.0	37	19 to 56
Bronchus	84		24	28.6	11	13.1	32	38.1	40	31 to 50
Esophagus	1		0	0	0	0	1	100	4	
Stomach	6		1	16.7	1	16.7	2	33.3	31	5 to 56
Small bowel	265		71	26.8	47	17.7	73	27.5	55	48 to 62
Appendix	4		1	25.0	1	25.0	1	25.0	13	0 to 32
Large bowel	44		21	47.7	4	9.1	10	22.7	33	25 to 42
Unknown primary	67		23	34.3	6	9.0	22	32.8	49	37 to 60
PNET	342	30.8								
Gastrinoma	25		5	20.0	10	40.0	3	12.0	32	21 to 42
Insulinoma	8		3	37.5	1	12.5	3	37.5	17	6 to 29
Glucagonoma	8		4	50.0	1	12.5	1	12.5	39	20 to 57
VIPoma	4		3	75.0	1	25.0	0	0	40	5 to 76
ACTHoma	2		1	50.0	0	0	0	0	5.3	
Nonfunctioning	295		145	49.2	40	13.6	85	28.8	60	50 to 69
Rare NET	103	9.3								
Medullary thyroid cancer	29		2	6.9	7	24.1	7	24.1	36	20 to 52
Neuroblastoma	4		1	25.0	0	0	1	25.0	11	0 to 25
Pheochromocytoma	11		4	36.4	2	18.2	5	45.5	32	15 to 49
Paraganglioma	28		3	10.7	4	14.3	6	21.4	82	56 to 109
Small-cell lung cancer	12		1	8.3	0	0	4	33.3	21	0 to 47
Pituitary gland tumor	3		0	0	0	0	1	33.3	74	0 to 203
Merkel cell cancer	8		2	25.0	1	12.5	1	25.0	6	3 to 10
Cervix uteri	2		0	0	0	0	0	0		
Other locations*	6		2	33.3	0	0	0	0	22	4 to 39
Unknown primary	185	16.7	63	34.1	33	17.8	68	36.8	47	36 to 58

Abbreviations: ACTHoma, adrenocorticotropic hormone–producing tumor; NET, neuroendocrine tumor; PNET, pancreatic neuroendocrine tumor; VIPoma, vasoactive intestinal peptide–producing tumor.

*Tumors of other location included one Klatskin tumor, one neuroendocrine tumor of the ovary, two neuroendocrine tumors of the prostate, and two hepatic neuroendocrine tumors.

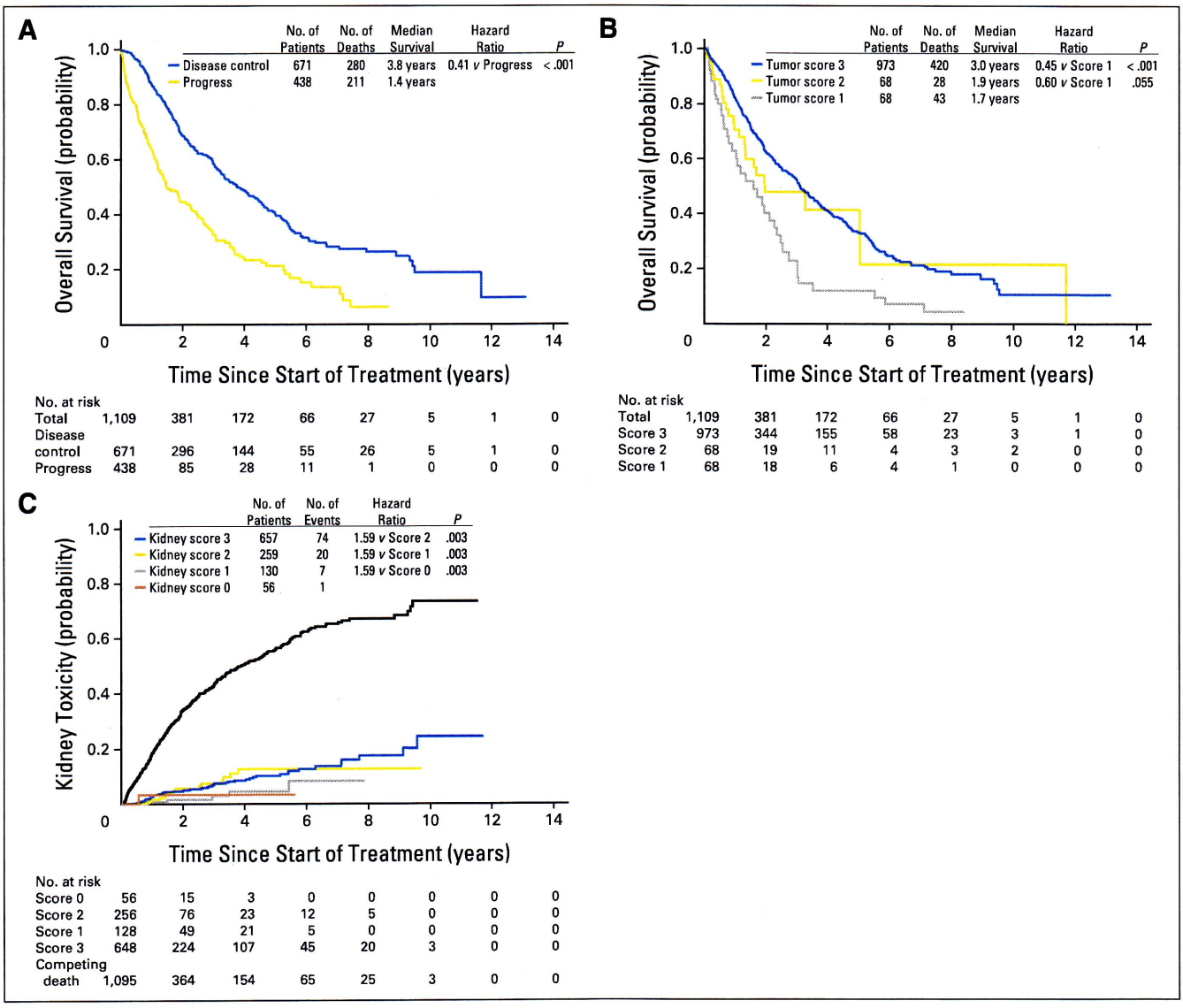

Fig 3. Survival and kidney toxicity after ^{90}yttrium-labeled tetraazacyclododecane-tetraacetic acid modified Tyr-octreotide ([^{90}Y-DOTA]-TOC; n = 1,109). Covariate-adjusted estimates of overall survival are shown for disease control versus progression after [^{90}Y-DOTA]-TOC, whereas disease control was defined as (A) response (n = 631) or stable disease (n = 40) and (B) different scores of tumoral DOTA-TOC uptake. Disease control and high tumoral [^{90}Y-DOTA]-TOC uptake are associated with longer survival from time of first [^{90}Y-DOTA]-TOC treatment. (C) Cumulative incidence functions display the proportion of patients with renal toxicity for different scores of renal [^{90}Y-DOTA]-TOC accumulation and competing event of death.

response was found in 172 patients (15.5%), with a median tumor marker decrease of 56.9% (interquartile range, 39.8% to 72.8%). Clinical response was found in 329 patients (29.7%).

Overall, 671 patients (60.5%) showed clinical response, biochemical response, and/or morphologic disease control after [^{90}Y-DOTA]-TOC and thereby qualified for repeated cycles. Of these, 206 patients (20.2%) showed more than one type of response; the correlation between types of response is displayed in Appendix Figure A1 (online only).

Survival

Overall, 491 patients (44.3%) died, 609 (54.9%) survived, and nine (0.8%) were not available for follow-up. The median survival from diagnosis was 94.6 months. Cox regression analyses revealed that longer survival was found with morphologic (HR, 0.46; 95% CI, 0.38 to 0.56; median survival, 44.7 *v* 18.3 months; $P < .001$), biochemical (HR, 0.75; 95% CI, 0.59 to 0.96, median survival, 35.3 *v* 25.7 months; $P = .023$), and clinical response (HR, 0.68; 95% CI, 0.56 to 0.82; median survival, 36.8 *v* 23.5 months; $P < .001$). Additional analyses revealed that patients qualifying for re-treatment because of clinical response, biochemical response, and/or morphologic disease control had longer survival from both time of initial diagnosis (HR, 0.41; 95% CI, 0.34 to 0.50; median survival, 102.2 *v* 81.6 months; $P < .001$) and time of first [^{90}Y-DOTA]-TOC treatment (HR, 0.68; 95% CI, 0.57 to 0.82, 45.6 *v* 16.8 months; $P < .001$; Fig 3A).

High tumor uptake of the radiopeptide, indicated by a high tumor score, was significantly associated with longer survival after [^{90}Y-DOTA]-TOC treatment (36.0 *v* 22.8 *v* 20.4 months for tumor

