SUPPLEMENTAL DATA:

Statistics.

The significance of group differences (between survivors and deceased patients, and between early-treatment and delayed-treatment groups) was assessed with the Chi-square test or Wilcoxon/Kruskal-Wallis test. Patients were stratified and analyzed by univariate analysis using the log-rank test. The crude and age-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using the Cox proportional hazards regression model. The significance of group differences for survival was assessed with the log-rank test in the Kaplan-Meier life-tables. The 'person-years' of follow-up were calculated from the date of initial RIT to the primary endpoint, or the date of censoring. Cumulative disease-specific survival (DSS) rates were obtained using the Kaplan-Meier method. According to the univariate analysis, significant factors were selected for the multivariate analysis using the stratified Cox proportional hazards model in total patients and also in the patients with age 45 y.o. or more at the time of initial RIT.

RESULTS

Univariate Analysis of Each Prognostic Factor.

Supplemental Table 1 showed the prognostic factors evaluated by Cox regression analysis, in which univariate analysis using two or three way segmentation was performed. Age-adjusted hazard ratio was also examined (Supplemental Table 1 right column).

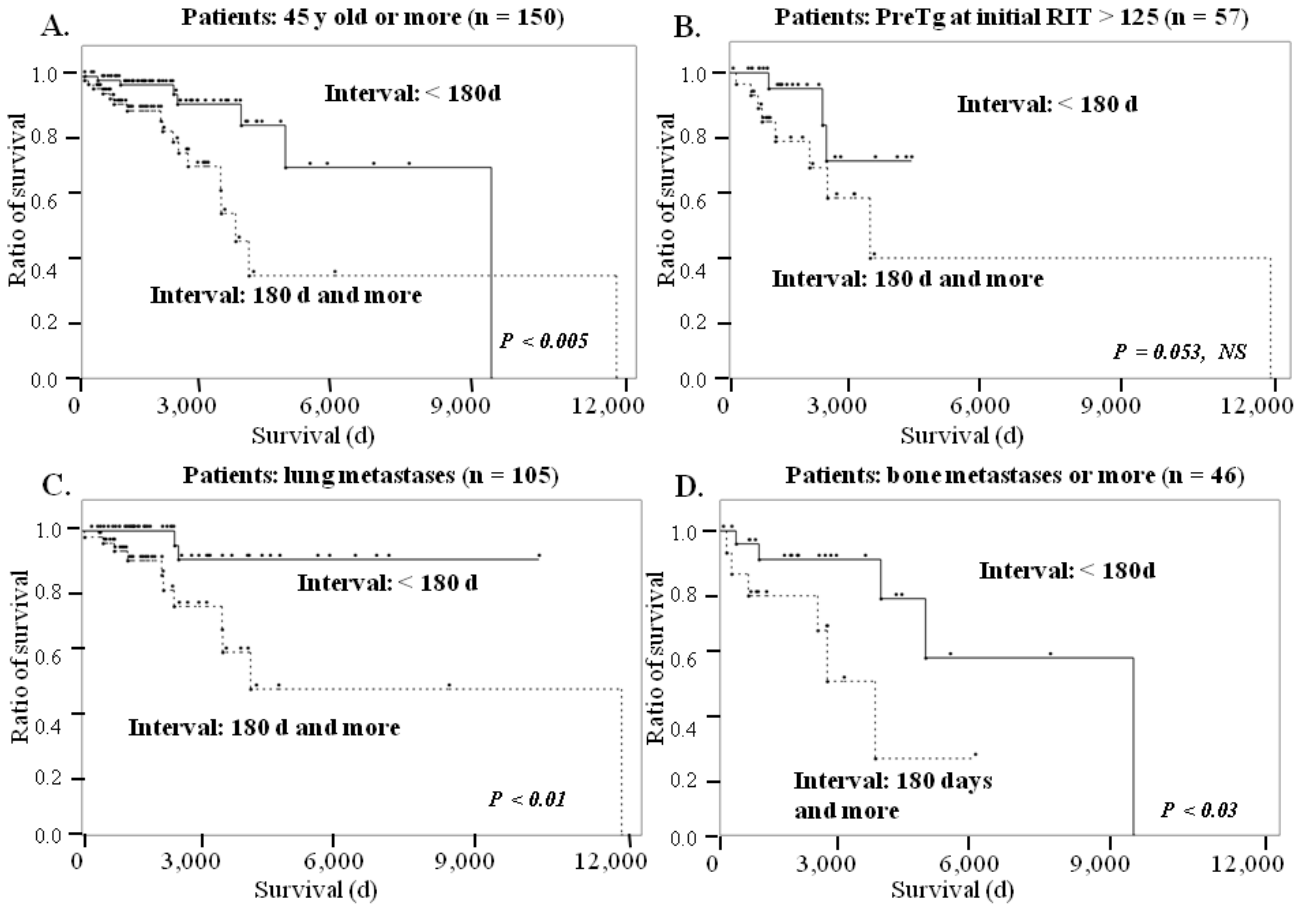
To confirm the results of Supplemental Table 1, these prognostic factors were also evaluated by Cox regression analysis using quartile segmentation (Supplemental Table 2). The factor, interval between total thyroidectomy and the initial RIT also had significant prognostic values both in total examination and in age-adjusted examination. There was no significant difference in prognostic value between two subgroups, interval (-75 days) and interval (-157 days).

Comparison between Early-Treatment Group and Delayed-Treatment Group

Supplemental Table 3 showed comparative results between early-treatment group (RIT was performed within 180 days after total thyroidectomy) and delayed-treatment group (180 days or more after total

thyroidectomy). There was no significant difference between these two groups in the following factors, average number of RIT, gender, prescribed dose of radioiodine at initial RIT, pathology, extent of metastasis, past history of thyroid surgery, and Tg levels. The other factors, number of RIT (separated in 4-grade-scale), follow-up periods, age at initial RIT, showed significant differences. Delayed-treatment group consisted of relatively higher percentage of papillary adenocarcinoma cases, as compared to early-treatment group (n.s.). Grade of WBS was worse in delayed-treatment group than in early-treatment group (n=0.010). Other therapeutic procedures in the interval between initial thyroidectomy (hemi, subtotal or total) and initial RIT were performed more frequently in the delayed-treatment group (n=0.002). The longest blank period of therapy (observation period without therapy) in the interval between initial thyroidectomy (hemi, subtotal or total) and initial RIT was significantly shorter in the early-treatment group (n=0.001).

To confirm the prognostic role of early-treatment, the following four subgroups of patients were also analyzed using Kaplan-Meier analysis; 1) patients with age 45 y.o. or more (n=150), 2) patients with preTg at initial RIT more than 125 ng/ml (n=57), 3) patients with lung metastases with/without LN metastases, but without bone metastases or others (n=105), and 4) patients with bone metastases or more (n=46) (Supplemental Fig 1). The log-rank test in the Kaplan-Meier life-tables showed that the factor, interval between total thyroidectomy and initial RIT (180days or more), showed significant prognostic values in all the subgroups, except for the subgroup with preTg > 125.



Supplemental Fig. 1. Survival curves of various subgroups of DTC patients analyzed by Kaplan-Meier life-tables separated by the interval=180days.

A. Patients who are 45 y.o. or more.

B. Patients with pre-treatment thyroglobulin (preTg) > 125 ng/ml.

C. Patients with lung metastasis (including LN metastasis) without bone or other metastasis (extent of metastasis: 2).

D. Patients with bone metastasis (including LN and lung metastasis) without other metastasis (extent of metastasis: 3).

Supplemental Table 1. Cox regression Analysis of Prognostic Factors at the time of Initial RIT
Univariate Analysis using Two or Three Way Segmentation

	Primary Endpoint: Disease-specific Death					
	Person-years	Cases	HR (95% CI)	*P* value	Age adjusted HR (95% CI)	*P* value
All treatment (n=198)	1073.4	24				
Age at initial RIT						
< 45 y.o. (n=48)	302.8	0	1.00		-	
45 y.o. or more (n=150)	770.6	24	-	**0.002**	-	-
Gender						
Male (n=77)	367.0	11	1.00		1.00	
Female (n=121)	706.5	13	0.66 (0.29-1.51)	0.324	0.68 (0.29-1.57)	0.360
Prescribed dose of I-131 at initial RIT						
< 100mCi (n=82)	474.4	7	1.00		1.00	
100mCi or more (n=116)	599.0	14	1.99 (0.82-4.85)	0.121	1.23 (0.50-3.02)	0.650
Number of RITs						
Single treatment (n=71)	240.1	6	1.00		1.00	
Multiple treatment (n=127)	833.3	18	0.98 (0.36-2.69)	0.963	0.74 (0.27-2.05)	0.560
Pathology						
PAC (n=164)	868.8	20	1.00		1.00	
FAC and others (n=34)	204.6	4	0.78 (0.26-2.28)	0.645	0.77 (0.26-2.28)	0.630
Grade of uptake in WBS at initial RIT						
Excellent: 0 or Good: 1 (n=145)	853.8	14	1.00		1.00	
Fair: 2 or Poor: 3 (n=53)	219.6	10	2.05 (1.14-3.70)	**0.015**	1.36 (0.74-2.48)	0.330
Extent of metastasis at initial RIT						
Local disease or LN mets only:1 (n=47)	226.7	0	1.00		1.00	
Lung mets with or without LN mets: 2 (n=105)	578.4	13	-	**0.003**	-	**0.003**
Bone mets or more: 3 or 4 (n=46)	268.2	11	-	**0.003**	-	**0.003**
up to lung metastasis (n=152)	805.2	13	1.00		1.00	
bone metastasis or more (n=46)	268.2	11	2.78 (1.25-6.22)	**0.009**	2.03 (0.91-4.53)	0.086
Interval between total thyroidectomy and initial RIT						
< 180 days (n=106)	649.9	7	1.00		1.00	
180 days or more (n=92)	423.5	17	4.07 (1.67-9.89)	< **0.001**	3.18 (1.29-7.82)	**0.012**
PreTg at initial RIT						
< 125 ng/ml (n=51)	231.3	0	1.00		1.00	
125 ng/ml or more (n=57)	243.8	12	-	< **0.001**	-	**0.003**
PeakTg at initial RIT						
< 1000 ng/ml (n=91)	415.9	2	1.00		1.00	
1000 ng/ml or more (n=73)	347.1	14	8.35 (1.90-36.8)	< **0.001**	6.20 (1.39-27.6)	**0.017**
PostTg at initial RIT						
< 50 ng/ml (n=70)	305.9	2	1.00		1.00	
50 ng/ml or more (n=73)	303.3	12	6.11 (1.37-27.3)	**0.007**	4.86 (1.09-21.7)	**0.039**

HR (95% CI) = Hazard ratio (95% Confidence interval)
RIT: radioactive iodine therapy
PAC: papillary adenocarcinoma, FAC: follicular adnocarcinoma
WBS: I-131 whole body scintigraphy, LN: lymph node, mets: metastases
PreTg: thyroglobulin before RIT; PeakTg: thyroglobulin at the time of RIT; PostTg: thyroglobulin after RIT

Supplemental Table 2. Cox Regression Analysis of Prognostic Factors at the Time of Initial RIT Univariate Analysis Using Quartile Segmentation

Variables	Person-years	Cases	HR (95% CI)	*P* value	Age adjusted HR (95% CI)	*P* value
All treatment (n=198)	1073.4	24				
Age at initial RIT						
1st quartile (7 - 45 y.o.)	334.8	0	-	< **0.001**	-	-
2nd quartile (46 - 57 y.o.)	248.4	5	1.00		-	-
3rd quartile (58 - 65 y.o.)	254.6	12	2.13 (0.16-1.34)	0.151	-	-
4th quartile (66 - 84 y.o.)	235.5	7	1.71 (0.17-2.03)	0.393	-	-
Prescribed dose of I-131 at initial RIT						
1st quartile (18 - 80 mCi)	189.4	2	1.00		1.00	
2nd quartile (81 - 116 mCi)	391.8	7	1.20 (0.23-6.27)	0.831	1.38 (0.23-8.36)	0.727
3rd quartile (117 - 125 mCi)	254.9	9	2.50 (0.53-11.8)	0.231	2.01 (0.42-9.61)	0.38
4th quartile (126 - 162 mCi)	237.3	6	2.98 (0.61-14.5)	0.158	2.62 (0.51-13.45)	0.249
Interval between total thyroidectomy and initial RIT						
1st quartile (25 - 75 days)	322.5	2	1.00		1.00	
2nd quartile (76 - 157 days)	286.8	6	2.37 (0.43-13.0)	0.305	7.79 (0.92-65.85)	0.059
3rd quartile (158 - 1059 days)	200.7	6	5.05 (1.04-24.5)	**0.026**	5.99 (1.20-30.03)	**0.029**
4th quartile (1060 - 11300 days)	263.4	10	6.81 (1.48-31.3)	**0.004**	5.56 (1.20-25.74)	**0.028**
PreTg at initial RIT						
1st quartile (3 - 30 ng/ml)	106.7	0	-	**0.001**	-	**0.001**
2nd quartile (31 - 123 ng/ml)	139.2	0	-	**0.001**	-	**0.001**
3rd quartile (124 - 825 ng/ml)	90.5	4	1.00		1.00	
4th quartile (826 - 46400 ng/ml)	138.9	8	1.07 (0.33-3.44)	0.110	1.17 (0.37-3.74)	0.260
PeakTg at initial RIT						
1st quartile (0.1 - 185 ng/ml)	167.4	0	-	**0.002**	-	**0.002**
2nd quartile (186 - 715 ng/ml)	190.0	1	0.21 (0.02-1.73)	0.150	0.28 (0.03-2.52)	0.260
3rd quartile (716 - 4369 ng/ml)	198.4	6	1.00		1.00	
4th quartile (4370 - 232000 ng/ml)	207.2	9	1.64 (0.22-1.72)	0.35	1.74 (0.20-1.64)	0.30
PostTg at initial RIT						
1st quartile (0.1 - 9 ng/ml)	159.2	0	-	**0.001**	-	**0.001**
2nd quartile (10 - 54 ng/ml)	116.2	2	0.62 (0.12-3.24)	0.569	0.63 (0.12-3.29)	0.580
3rd quartile (55 - 555 ng/ml)	151.3	5	1.00		1.00	
4th quartile (556 - 34500 ng/ml)	182.4	7	1.22 (0.26-2.61)	0.736	1.17 (0.36-3.82)	0.789

HR (95% CI) = Hazard ratio (95% Confidence interval)
RIT: radioactive iodine therapy
PreTg: thyroglobulin before RIT; PeakTg: thyroglobulin at the time of RIT; PostTg: thyroglobulin after RIT (detailed definition: see Materials an

Supplemental Table 3. Comparison Between Early-Treatment Group and Delayed-Treatment Group

	Early-treatment group (within 180 days)	Delayed-treatment group (180days or more)	*P* value
Patient number	n= 109	n= 89	
Number of RIT			
n=1	38 (35%)	33 (37%)	
n=2-5	49 (45%)	50 (56%)	
n=6-9	17 (16%)	5 (6%)	
n=10 or more	5 (5%)	1 (1%)	**0.043**
Average number of RIT (Min - Max)	3.4 (1 - 26)	2.4 (1 - 10)	0.154
Follow-up periods			
Mean time (Min - Max) (year)	5.98 (1.13 - 26.84)	4.62 (0.14 - 31.74)	**0.009**
Age at initial RIT			
Mean age (Min - Max) (y.o.)	50.4 (7 - 84)	58.4 (10 - 83)	**0.001**
< 45 y.o. : 45 y.o. or more (number)	31 : 78 (28% : 72%)	15 : 74 (17% : 83%)	0.072
Gender			
Male : Female (number)	42 : 67 (38% : 62%)	35 : 54 (39% : 61%)	0.909
Prescribed dose of I-131 at initial RIT			
Mean dose (Min - Max) (MBq)	3,781.4 (1,665 - 5,328)	3,755.5 (296 - 5,994)	
(mCi)	102.2 (45 - 144)	101.5 (18 - 162)	0.973
Pathology			
PAC : FAC : others	85 : 19 : 5 (78% : 17% : 5%)	79 : 9 : 1 (88% : 10% : 1%)	0.093
Grade of uptake in WBS at initial RIT			
excellent: 0	74 (68%)	43 (48%)	
good: 1	10 (9%)	18 (20%)	
fair: 2	25 (23%)	26 (29%)	
poor: 3	0 (0%)	2 (2%)	**0.010**
Extent of metastasis at initial RIT			
Local disease or LN mets only: 1	24 (22%)	23 (26%)	
Lung mets with or without LN mets: 2	56 (51%)	49 (55%)	
Bone mets or more: 3 or 4	29 (27%)	17 (19%)	0.596
Interval between total thyroidectomy and initial			
Mean time (Min - Max) (year)	0.25 (0.07 - 0.48)	5.40 (0.53 - 30.98)	
(day)	90.3 (25 - 177)	1,970.1 (193 - 11,308)	
Past thyroid surgery before total thyroidectomy			
Hemi or subtotal thyroidectomy: none	65 (60%)	59 (66%)	
Hemi or subtotal thyroidectomy: performed	38 (35%)	21 (24%)	
Unknown	6 (6%)	9 (10%)	0.147
Average interval between hemi/subtotal and total (year.	*6.6 (n=38)*	*5.7 (n=21)*	*0.223*
Past other therapeutic history in the interval between initial thyroidectomy (hemi, subtotal or total) and initial RIT			
None	89 (82%)	53 (60%)	
Performed (local resection, LN resection, radiation, etc)	14 (13%)	28 (31%)	
Unknown	6 (6%)	8 (9%)	**0.002**
The longest blank period of therapy in the interval between initial thyroidectomy (hemi, subtotal or total) and initial RIT			
treated within 180 days	67 (61%)	0 (0%)	
treated with interval of 180-364 days	2 (2%)	18 (20%)	
1 - 2 years	1 (1%)	10 (11%)	
2 - 3 years	7 (6%)	6 (7%)	
3 years or more	26 (24%)	47 (53%)	
unknown	6 (6%)	8 (9%)	**0.001**
PreTg at initial RIT			
Mean (Min - Max) (ng/ml)	2,141 (3.0 - 464,386)	1,083 (4.3 - 7,557)	0.296
PeakTg at initial RIT			
Mean (Min - Max) (ng/ml)	8,203 (0.1 - 232,453)	7,047 (16.6 - 78,921)	0.764
PostTg at initial RIT			
Mean (Min - Max) (ng/ml)	1,208 (0.1 - 34,461)	1,143 (0.1 - 19,880)	0.922

RIT: radioactive iodine therapy
PAC: papillary adenocarcinoma, FAC: follicular adnocarcinoma
WBS: I-131 whole body scintigraphy, LN: lymph node, mets: metastases
PreTg: thyroglobulin before RIT; PeakTg: thyroglobulin at the time of RIT; PostTg: thyroglobulin after RIT