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COMPARISON of EMPIRIC versus WHOLE BODY/BLOOD CLEARANCE DOSIMETRY-BASED RADIOACTIVE IODINE TREATMENT IN PATIENTS WITH METASTASES FROM DIFFERENTIATED THYROID CANCER.

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ABSTRACT

RATIONALE: The optimal management of radioactive iodine (RAI) treatment in patients with metastatic thyroid cancer (TC) is still a matter of debate. **METHODS:** We retrospectively analyzed 352 patients with RAI avid metastatic well differentiated TC treated with ¹³¹I by empiric fixed activity of 3.7 GBq at Gustave Roussy (GR, n=231) or by personalized activity (2.7 to 18.6 GBq) based on whole body/blood clearance dosimetry (WB/BC) at Memorial Sloan Kettering Cancer Center (MSKCC, n=121). The primary endpoint was to compare Overall Survival (OS) in the two groups of patients by log-rank test. **RESULTS:** Patients received a median cumulative activity of 14.8 GBq at GR and 24.2 GBq at MSKCC, respectively (p< 0.0001). Median follow-up after the diagnosis of metastases was 7.2 years (0.4 -31). Five year OS was 86.8 % and 78.8 % for patients treated at GR and at MSKCC, respectively (p<0.01). However, there was no statistical difference in OS after correction for gender, age at the diagnosis of distant metastases, metastases site and metastases extension between the two centers (p=0.16). Five year OS was 96 % and 96% for patients < 40 yrs with micrometastases, 70% and 65% for patients > 40 yrs with macro or multiple metastases, 92% and 87% for younger patients with macrometastases or older patients with micrometastases treated at GR and MSKCC, respectively (p=NS). **CONCLUSION:** Routine use of WB/BC dosimetry without lesional dosimetry provided no OS advantage when compared to empiric fixed RAI dosing in the management of thyroid cancer patients with RAI-avid distant metastases.

INTRODUCTION

Radioactive iodine (^{131}I) has been used since the late 1940s for the treatment of patients with distant metastases from differentiated thyroid cancer (1). The optimal management in terms of administered ^{131}I activity, number of treatment courses and their frequency remains unclear.

In order for radioactive iodine to have a therapeutic effect, it is necessary to deliver a tumoricidal radiation dose to the metastatic foci (2-5). Based on the assumption that higher administered activities (> 9.25 GBq) of radioactive iodine would be more likely to deliver therapeutic lesional radiation doses, many centers use WB/BC dosimetry to define the maximum tolerated activity (MTA) that can be safely administered (3,6). Others use empiric fixed activities (3.7-9.25 GBq) to treat metastatic disease based on the assumption that any increase in lesional radiation dose achieved with larger administered activities is unlikely to confer therapeutic benefit (7-8). Finally studies on "lesional dosimetry" support the concept that tumoral lesions absorbed dose can predict the response to radioactive iodine treatment (9).

While acknowledging the "theoretical advantages" of dosimetry, the American Thyroid Association guideline taskforce found insufficient evidence in the literature to recommend a preferred approach (10). The effectiveness of radioactive iodine therapy is associated with many clinico-pathological features. In a previous study of 444 differentiated thyroid cancer patients with RAI avid distant metastases, three distinct groups with markedly different overall survivals have been defined. Young patients (< 40 years of age) with disease that was not visible on radiological imaging demonstrated a 10 year survival rate of 95%, while older patients with macroscopic pulmonary metastases (> 1cm) or multiple bone metastases showed a 10 year survival of only 14%. An intermediate 10 year survival of 64% was seen in young patients with macroscopic disease and older patients with subcentimeter pulmonary nodules (8).

Therefore, the aim of this study is to compare overall survival within the three previously described outcome groups in patients with RAI avid distant metastases from a differentiated thyroid cancer treated by radioactive iodine according either to an empiric approach at Gustave Roussy or to a WB/BC dosimetric approach at MSKCC.

MATERIALS AND METHODS

We retrospectively evaluated medical records of patients with distant metastases from differentiated thyroid cancer who were treated either at Gustave Roussy (empiric approach) or at MSKCC (WB/BC dosimetric approach) from 1980 to 2010. The institutional review board of both centers approved this retrospective study and the requirement to obtain informed consent was waived. A common electronic medical database was created and the key clinical variables entered. All patients with the following criteria were included: - histologically confirmed well differentiated thyroid cancer; -RAI-avid metastatic lesions on the 131I WB scan after a therapeutic activity of 131I; -at least one administration of 131I for treatment of metastases. Patients with no demonstrated 131I avid metastases or with metastases from a poorly differentiated thyroid cancer were excluded from the analysis. The extent of metastasis was classified as previously described: Category 1= metastases detectable on 131I WB scan but normal radiological imaging (x-rays and/or CT scan); Category 2= micronodular (< 1 cm) lung metastases or single bone metastasis; Category 3= macronodular lung metastases or multiple bone metastases or both bone and lung metastases (1,7,8).

The primary endpoint was Overall Survival in the two Centers.

OS was analyzed within 3 predetermined patient groups based on the two major known prognostic indicators for survival: age at the time of metastases diagnosis and metastases category (8). Group 1 included patients < 40 years of age with no visible disease on radiological imaging (Category 1), micronodular lung metastases or single bone lesion (Category 2). Group 2 included patients < 40 years of age with either macrometastases (Category 3) or patients with an age > 40 years with micrometastases (Categories 1 and 2). Finally, Group 3 included patients with > 40 years of age with lung macrometastases and/or multiple bone metastases (Category 3) (8).

Primary tumor treatment

As initial treatment of primary tumor, all included patients underwent a total thyroidectomy with or without lymph node dissection, based on local practice patterns.

Radioactive iodine treatment

Empiric approach: Each 131I treatment course in adult patients consisted in the administration of a standard activity of 3.7 GBq of 131I after thyroid hormone withdrawal (THW) for 4-6 weeks (Thyroid-Stimulating Hormone, TSH > 30 mUI/L). Low iodine diet was not recommended but contrast

product injection was avoided within the 2 months before RAI treatment. In children an activity of 37 MBq /Kg body weight and in patients with renal failure a fixed activity ranging between 1.1-2.2 GBq was administered at each treatment. Post-therapeutic WB scan was performed 3-5 days after each ¹³¹I treatment course. Anterior and posterior images were obtained with a double head gamma-camera equipped with high energy collimators and thick crystals (AXIS, General Electric Medical System, Milwaukee, WI, USA). In case of ¹³¹I avid distant metastases on the post-therapy scan, another ¹³¹I treatment was administered 3-9 months later for 2 years and then once a year, until the disappearance of any significant uptake on the post-therapy WB scan. No diagnostic ¹³¹I WB scan was performed before any ¹³¹I treatment course. There was no fixed limit to the cumulative activity of ¹³¹I administered.

Dosimetric approach : The MTA calculation at each ¹³¹I treatment course was based on sequential ¹³¹I body retention measurements on diagnostic ¹³¹I WB scan and blood ¹³¹I clearance studies as previously described (6,11). Prior to 1999, all ¹³¹I treatments were administered after THW for 6 weeks and in case of TSH > 30 mUI/L. After 1999, ¹³¹I was usually administered following recombinant human TSH (rhTSH) (Thyrogen, Genzyme Corp.) administration (12). In all patients RAI was administered after 7-10 days of a low iodine diet. Whole body images and counts and blood samples were obtained at 0, 2, 4, 24, 72 and 96 hours after administration of a tracer activity of ¹³¹I (150 MBq) for the THW patients and at 0, 2, 4, 24, 48, 72, and 120 h for the rhTSH patients. At each time interval, blood was drawn, and the fractional blood clearance was determined. Total body clearance curves were generated, and the activity was calculated with the constraint of 200 cGy to the blood or 2.96 GBq of whole body retention at 48 hours in case of diffuse lung uptake, as previously described (6,11,12). For rhTSH protocol, 0.9 mg IM rhTSH was administered on two consecutive days during week 1 for dosimetry and then 2 additional rhTSH doses were given in week 2 in preparation for the therapeutic administration of RAI. Calculated activity according to MTA was administered the day after the 2nd rhTSH injection. For the diagnostic WB scan, anterior and posterior projection was obtained using a dual headed Genesys EPIC imaging system (ADAC Corporation, Malpitas, CA). Whole body images in anterior and posterior views associated with anterior, posterior and lateral spot of the neck and the thorax were acquired 4-7 days after ¹³¹I treatment administration in all treated patients.

The timing between additional treatment courses ranged from 6 months to 2 years (or longer) and was based on individual clinical characteristics such as the volume of metastatic lesions, their RAI avidity, the effectiveness of previous therapies, the trend in serum thyroglobulin levels and the side effect profile of previous treatments.

Other treatments for metastatic disease

During RAI treatment patients received surgery in 27.3 and 24 % of cases, radiation therapy in 28.1 % and 34.7% of cases and cytotoxic chemotherapy for progression after RAI treatment in 4.3 and 10.8% of cases at GR and MSKCC respectively (Supplemental Table 1) .

Statistical analysis

A descriptive analysis was performed for the two groups of patients. Chi-square and Mann-Whitney-Wilcoxon tests were performed to identify differences in the two groups for qualitative and quantitative variables, respectively.

OS was estimated from the time of the diagnosis of the metastases until patient last follow-up or death by the Kaplan–Meier method. OS in the two groups were first compared using the log-rank test. A Cox model was then used for the evaluation of the risk of death. Key factors possibly contributing to OS were explored, including age at diagnosis of distant metastases, gender, tumor histology, extent of metastases and location. These were first tested individually (univariate analysis). Multivariate analysis was then performed to compare the OS between the two groups, taking into account the aforementioned variables that were significant in the univariate analysis (significance level: $P < 0.05$) and the year of diagnosis of the metastases. For all analyses, two-sided t tests were employed, and the 0.05 level of significance was used. Ninety-five percent confidence intervals (CIs) were calculated for the relative risks (RRs) in the Cox proportional hazard regression analysis. Statistical analysis was performed using SAS version 9.4 System (Cary, NC, USA).

RESULTS

Patient population

A total of 701 and 155 medical records of patients with distant metastases of DTC were evaluated at Gustave Roussy and MSKCC, respectively. At GR 231/701 met inclusion criteria for the study. Four hundred and seventy patients were excluded because of poorly differentiated cancer (n=205), because treated before 1980 (n=104), because they were not treated by RAI (n=67), had no RAI avid metastases (n=82) and did not received any RAI treatment at GR (n=12). At MSKCC 121/155 patients met inclusion criteria for the study. Thirty four patients were excluded because of poorly differentiated cancer (n=28), because they had no RAI avid metastases (n=2) and did not received any RAI treatment at MSKCC (n=4). Finally a total of 352 patients were analyzed. Clinical characteristics of the patients are reported in Table 1.

Patients received a median of 4 (range: 1-14) ¹³¹I treatment courses at GR and of 3 (range: 1-9) at MSKCC for a median cumulative activity of 14.8 GBq (range: 1.8-52.5 GBq) at GR and 24.2 GBq (range: 2.7-112 GBq) at MSKCC, respectively ($p < 0.0001$). The median activity for each treatment was 3.7 GBq (range: 1.1-11.1) at GR and 9.3 GBq (range: 2.7-18.6) at MSKCC ($p < 0.0001$) (Supplemental Table 1). At GR, 19 patients received a ¹³¹I activity lower than 3.7 GBq due to younger age ($n=14$), renal failure ($n=1$), older age ($n=1$) or brain metastases ($n=1$). Three patients received more than 3.7 GBq (5.2, 8, 7 and 11.1 GBq, respectively) at their first treatment course in other centers and then were referred to GR for further treatments. At MSKCC, only 17% of patients received all treatments exclusively after THW. Of the remaining 83%, more than 3/4th of treatments were administered after rhTSH stimulation.

The median number of treatments, the median administered activity and the median cumulative activity according to patient group (Group 1, 2, 3) are summarized in Table 2. This table is better here or at the end of Overall survival paragraph?

Overall survival for the entire cohort

After a median follow-up of 7.2 years (0.4 -31 yr), [8 years (0.4 -31 yr) for patients treated at GR and 6.4 years (1-25.6 yr) for patients treated at MSKCC ($p < 0.001$)], 68.2% of the patients were still alive (70.6% vs 63.6 % at GR and MSKCC, respectively). Thyroid cancer was the cause of death in 69.7% of the patients. Death related to a second cancer was reported in 7.4% (5/231) and 9.1 % (4/121) of cases at GR and MSKCC, respectively. OS at 5 years was 86.8 % and 78.8 %, at 10 years was 73.2% and 53.1% at GR and MSKCC, respectively ($p < 0.01$) (Fig.1).

In univariate analysis, male gender, age over 40 years at the diagnosis of distant metastases, follicular histology, macro or multiple metastases, the presence of both lung and bone metastases had a negative impact on OS (Table 3). In multivariate analysis, male gender, age over 40 years at the diagnosis of distant metastases and metastases extension were prognostic factors. Despite differences between the patient cohorts at the two centers, when statistically corrected for these factors, OS did not differ in the two centers (RR.1.41 for MSKCC patient, $p=0.16$) (Table 3).

Overall survival within the predefined patient groups

To further control for the differences between the patient characteristics between GR and MSKCC, OS was evaluated in the patients groups matched by age, size and site of distant metastases (Fig.2). The best OS was seen in Group 1 with no difference between the two

centers. Five year and 10 year OS was 96% (CI 95% 0.73-0.99) and 96% (CI 95% 0.73-0.99) for MSKCC and 96% (CI 95% 0.88-0.99) and 96% (CI 95% 0.88-0.99) for GR, respectively (p=NS). The poorest OS was seen in Group 3 both for MSKCC and GR patients. Five and 10 y OS was 65% (CI 95% 0.50-0.77) and 23% (CI 95%0.09-0.41) for MSKCC and 70% (CI 95% 0.58-0.81) and 49% (CI 95%0.35-0.62) for GR, respectively (p=NS). Group 2 demonstrated intermediate outcomes. Five and 10 year OS was 87% (CI 95% 0.71-0.94) and 67% (CI 95%0.46-0.81) for MSKCC and 92% (CI 95% 0.83-0.97) and 72% (CI 95%0.58-0.82) for GR, respectively (p=NS).

Is it sufficient p=NS or we have to add p value

DISCUSSION

This is the largest study comparing patients with RAI avid distant metastases from well differentiated thyroid cancer treated with radioactive iodine either with fixed activities at GR or with WB/BC-determined activities at MSKCC. The MSKCC cohort received higher median RAI administered activities per treatment course (9.3 vs 3.7 GBq), higher cumulative RAI activities (24.2 vs 14.8 GBq), were older (median 53 vs 42 yrs, $P < 0.01$), were more likely to have macroscopic lung metastases (36% vs 22%, $p = 0.02$), were less likely to have small volume RAI avid pulmonary metastases (12% vs 30%, $p < 0.001$) and more likely to receive RAI therapy following rhTSH (83% vs 0%, $p < 10^{-10}$). However, when adjusted in a multivariate analysis for the prognostically important differences between the centers (age at the discovery of distant metastases, metastases extension, gender and histology), overall survival did not significantly differ between the two institutions. In addition, 5 and 10 year overall survival did not differ between the two institutions when considering predefined matched patients cohorts (Groups 1, 2, and 3).

Therefore, it does not appear that routine use of the MSKCC whole body/blood clearance dosimetry management approach without lesional dosimetry provides a significant survival advantage over the GR empiric dosing approach. While not demonstrating differences in progression free survival, one previous retrospective study of 87 patients did demonstrate a clinical benefit from a dosimetry based approach (compared with empiric dosing) with respect both to increasing the likelihood of complete response and decreasing the odds of progression by a factor of 0.29, particularly in patients with locally advanced differentiated thyroid cancer (13). In these patients, higher activities may be more efficient to control the disease comparing to lower fractionated activities.

In previous GR series, most patients younger than 40 years with small metastases were cured with a cumulative administered activity of less than 22 GBq and their life expectancy was close to that of the normal population with 5 years OS of 98% (7-8). Small bone metastases without abnormalities on morphological imaging are most likely to be cured with few radioactive iodine treatments especially in young patients (14-15). On the other hand, in these previous studies only few patients with large and multiple metastases were cured with ¹³¹I, and the 5 years OS in these patients was 60%, in accordance with the present study (8). In these selected patients higher activities might be more beneficial and lesional dosimetry could be critical for decision making and to define the optimal administered activity that would be predicted to achieve a therapeutic tumoricidal dose. Some authors showed that ¹²⁴I PET guided lesional 3D dosimetry associated to blood clearance study can predict absorbed lesion doses and can help to calculate the safest and the most effective ¹³¹I activity to be administered (4,9, 16-18). The possibility of modern quantification procedure by SPECT/CT could also allow to calculate absorbed dose in normal organs and tumoral lesions (19).

Concerning patient stimulation, the efficacy of ¹³¹I administered either after thyroid hormone withdrawal or rhTSH is another matter of debate. Even if absorbed dose in tumoral lesions may be higher after THW than after rhTSH administration, in a previous study no difference in OS was found in metastatic patients treated after either THW or rhTSH stimulation, with a 5 years OS at 75-80% in both groups of patients and with a median OS of 12.5 years for patients with micrometastases and of 4.4 years in patients with macrometastases (12,20,21).

Concerning toxicity, empiric high activity can be above the MTA. Tuttle et al reported that an empiric activity of 7.4 GBq exceeded the MTA in 8%-15% of patients younger than 70 years and in 22%-38% of patients older than 70 years and an empiric activity of 9.25 GBq exceeded the MTA in 22% of patients younger than 70 years and in 50% of patients older than 70 years (22). However, no serious acute adverse event has been reported for empiric activity of 3.7 GBq (23).

This study presents the following limits. First of all, safety data are not available due to the retrospective nature of the study and several missing data in medical reports. Only data on death from second cancers has been reported and this does not differ between the two centers. We cannot conclude on long term safety profile of the two different approaches. The study of Gwiedzinska et al showed a similar safety profile on dosimetric approach compared to empiric approach (13). Second, we cannot compare the remission rate with each of the two

approaches, because the follow up was not standardized. Third, even if OS does not differ in patients treated with an empiric or a dosimetric approach, the populations in the two centers are not perfectly matched and the effect of rhTSH vs THW preparation on I131 efficacy still remains unknown.

In conclusion, this is the first study comparing OS in a large number of patients with RAI avid distant metastases of thyroid cancer treated either with the empiric or the WB/BC dosimetric approach. These data indicate that using a whole body/blood dosimetric approach without lesional dosimetry to safely administer higher RAI activities was not associated with an improvement in OS. Standard activity of 3.7 GBq can be considered efficient and certainly safe in treating patients with distant metastases. However, future studies that use accurate measurements of lesional dosimetry are likely to define a subset of patients in whom whole body and blood dosimetry studies may be required to ensure that the administered activity necessary for therapeutic efficacy does not exceed safety limits, for example in patients in whom empiric dosing may be associated with an increased risk of toxicity (renal failure, diffuse miliary lung metastases). Finally, approaches to reprogram the biology of metastatic thyroid cancer cells by restoring expression of genes required for iodide uptake and accumulation may be coupled to WB/BC as well as lesional dosimetry to optimize both safety and efficacy (24).

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Table 1: Clinical characteristics of patient population

	GR (N= 231)	MSKCC (N=121)	GR+MSKCC (N=352)	p-value
Gender (%)				
Woman	153 (66)	68 (56)*	221 (63)	0.09
Primary thyroid tumor				
Median Age at diagnosis (Min-Max)	40 (5-90)	49 (7-77)	42 (5-90)	0.03
Histology (%)				
FTC	74 (32.0)	32 (26.5)	106 (30.1)	NS
PTC	156 (67.5)	89 (73.5)	245 (69.6)	
Other	1(0.3)	0	1 (0.3)	
Distant Metastases				
Median Age at diagnosis (Min-Max)	42 (6-90)	53 (10-80)	46 (6-90)	<0.01
Median year of diagnosis (Min-Max)	1999(1983-2007)	2000(1982-2008)	1997(1981-2008)	<0.00010.0001
Synchronous metastases (%)**	143 (61.9)	67 (55.4)	210 (59.7)	NS
Site (%)				
Lung	139 (60.2)	66 (54.6)	205 (58.2)	NS
Bone	55 (23.8)	29 (24.0)	84 (23.9)	
Lung and bone(+/- others)	37 (16,0)	26 (21.5)	63 (17.9)	
Metastases size (%)				
Macronodular lung metastases	37 (21.5)	31 (35.6)	68 (26.3)	0.02
Multiple Bone lesions	62 (68.9)	41 (77.4)	103 (72.0)	NS
Extent of metastases***				
Category 1	69 (29.9)	14 (11.6)	83 (23.6)	<0.001
Category 2	66 (28.6)	43 (35.5)	109 (31.0)	
Category 3	96 (41.6)	64 (52.9)	160 (45.4)	

* not known 2 patients**6 months before or after primary tumor diagnosis*** according to Durante classification (Durate et al, JCEM-2006).

Category 1= patients with metastases on 131I WB scan but with normal cross sectional imaging (x-rays and/or CT scan) Category 2= patients with micronodular lung metastases defined radiologically < 1 cm or with a single bone metastasis identified by cross sectional imaging Category 3= macronodular lung metastases or multiple bone metastases or both bone and lung metastases.

Table 2. Median number of I131 treatments, Median administered activity and Median Cumulative activity (GBq) according to predefined patient groups.

	Group 1		Group 2		Group 3	
	(N=106)		(N=114)		(N=132)	
	GR	MSKCC	GR	MSKCC	GR	MSKCC
	(N=79)	(N=27)	(N=74)	(N=40)	(N=78)	(N=54)
5 yr OS	0.96	0.96	0.92	0.87	0.70	0.65
(95%CI)	(0.88-0.99)	(0.73-0.99)	(0.83-0.97)	(0.71-0.94)	(0.58-0.80)	(0.50-0.77)
Total 131I treatment						
Median Number	4	2	4	3	4	3
(min-max)	(1-14)	(1-7)	(1-14)	(1-9)	(1-13)	(1-8)
Median administered activity GBq (min-max)	3.7 (1.4-5.2)	7.5 (2.7-14.0)	3.7 (1.1-8.7)	8.9 (4.6-18.6)	3.7 (1.8-11.1)	10.5 (3.7-16.7)
Median Cumulative activity GBq(min-max)	14.8 (3.7-39.2)	17.2 (2.7-56.4)	14.8 (2.2-52.5)	23.1 (5.5-112)	14.8 (1.8-52.5)	29.8 (3.7-83.9)

Group 1: patients < 40 years of age with no visible disease on cross sectional imaging micronodular lung metastases or single bone lesion Group 2 : patients < 40 years of age with either macrometastases or patients with an age > 40 years with micrometastases Group 3 : patients with > 40 years of age with lung macrometastases and/or multiple bone metastases (8).

Table 3. Univariate and multivariate analyses of factors predicting Overall Survival

	Nb Subjects/death	Crude RR (CI95%)	p	Adjusted RR* (CI95%)	p
Gender					
Men	129/57	1 (ref)	<0.001	1 (ref)	<0.001
Women	221/55	0.42 (0.29-0.62)		0.49 (0.33-0.74)	
Age at the diagnosis of distant metastasis					
0-29	80/3	1 (ref)		1 (ref)	
30-39	54/11	6.43 (1.79-23.10)		4.54 (1.24-16.61)	
40-49	56/18	9.87 (2.91-33.52)	<0.0001	7.65 (2.22-26.32)	<0.0001
50-59	70/31	21.57 (6.55-71.10)		11.49 (3.33-39.59)	
60-69	57/31	23.60 (7.15-77.95)		13.18 (3.83-45.31)	
70-90	35/18	42.88 (12.39-148.37)		23.03 (6.24-85.08)	
Extent of metastases*					
Cat 1	83/8	1 (ref)		1 (ref)	
Cat 2	109/31	3.65 (1.68-7.94)	<0.001	2.71 (1.22-6.03)	<0.01
Cat 3	160/73	8.43 (4.04-17.58)		3.49 (1.56-7.81)	
Site of metastases					
lung	205/51	1 (ref)		1 (ref)	
Bone	84/32	2.17 (1.38-3.39)	<0.001	1.33 (0.77-2.31)	0.24
Lung and bone +/- other	63/29	3.58 (2.24-5.72)		1.63 (0.92-2.91)	
Histology					
PTC	245/72	1 (ref)		1 (ref)	
FTC	107/40	1.61 (1.09-2.39)	0.02	0.67 (0.42-1.07)	0.09
Center					
GR	231/68	1 (ref)		1 (ref)	
MSKCC	121/44	1.77 (1.20-2.62)	0.01	1.41 (0.87-2.29)	0.16

*Category1= patients with metastases on 131I WB scan but with radiological imaging ; Category 2= patients with micronodular lung metastases defined radiologically < 1 cm or with a single bone metastasis identified radiologically Category 3= macronodular lung metastases or multiple bone metastases or both bone and lung metastases.

Figure 1. Overall Survival for GR and MSKCC patients estimated from the time of the diagnosis of distantmetastases until patient last follow-up or death.

Figure 2. Overall survival according to age and extent of metastases estimated from the time of the diagnosis of distantmetastases until patient last follow-up or death.