Effect of glandular metastases on overall survival of patients with metastatic clear cell renal cell carcinoma in the antiangiogenic therapy era

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Abstract

Background Glandular metastases (GM) (pancreas, breast, parotid, thyroid or contralateral adrenal) are rare in metastatic clear cell renal cell carcinoma (mccRCC).

In a multicenter study we have assessed outcome from mccRCC with or without GM.

Patients and methods mccRCC patients with GM or non-GM (NGN) at first presentation of mccRCC, treated at 9 European centers (5 French, 3 UK and 1 Belgian centers) between January 2004 and October 2013 were retrospectively analysed. Association between OS and site of metastases was assessed using the log-rank test for univariate analysis and the chi-square test for multivariable Cox regression.

Results 138 GM and 420 non-GM mccRCC patients were included. 37.2% GM patients were MSKCC favorable risk vs 18% non-GM patients, 10.7% GM patients were MSKCC poor risk vs 27% non-GM ($p<0.0001$). Median interval from metastases to treatment was 4.2 months (range 0-221.3 months). Median OS was 61.5 months (51.4-81.6 months) for GM and 37.4 months (31.3-42 months) for non-GM (HR=1.7;95%CI=1.3-2.2,$p<0.001$). At univariate OS analysis, age, delay between initial diagnosis and metastases, MSKCC, bone/lung metastases and GM or non-GM group were significant parameters ($p<0.001$). At multivariate analysis, adjusted according to MSKCC risk group, non-GM vs GM was a strong prognostic factor (HR=1.4;95%CI=1.0-1.8,p=0.026); bone or liver metastases were also significant (HR=1.3;95%CI=1.1-1.7,$p<0.02$; HR=1.4;95%CI=1.1-1.7, $p<0.02$ respectively). Even in patients without bone or liver metastases, GM status was significant (HR=1.8;95%CI=1.2-2.7,$p<0.004$).

Conclusions

This large retrospective study shows that the presence of at least one GM site at development of mccRCC was associated with a significantly longer OS. The presence of GM vs NGM disease was an independent prognostic factor for survival whether or not the poor prognostic

factors of bone or liver metastases were present. This finding could impact on daily practice in which mccRCC patients with GM should receive more aggressive treatment with a potential for long-term survival.

The causal mechanisms for this improved prognosis in GM mccRCC will be evaluated in translational studies.

1. Introduction

Renal cell carcinoma (RCC) accounts for 3% of adult malignancies and is the most common malignancy in the kidney. More than two third of patients are diagnosed with localized disease. About 20–30% of all patients undergoing nephrectomy for clinically localized disease will develop metastatic disease. Approximately 20–30% of the patients diagnosed with RCC already have metastatic disease at presentation (1;2). In metastatic clear cell RCC (mccRCC), despite new targeted therapies, prognosis remains poor and 5-year life expectancy is less than 20% (3). The most common sites of metastatic disease include lung (45%), bone (30%), lymph node (22%), liver (20%) and brain (8%) (4). Adrenal metastasis occurred in 9%, but few data are available concerning other glandular metastatic sites such as pancreas, breast, thyroid and parotid. These various metastatic sites that we considered as glandular metastases (GM) are infrequent site of metastasis. However kidney cancer is the most frequent tumor that metastasise to these sites and the evolution frequently indolent (5).

Recent advances in understanding the molecular biology of RCC have led to the development of new targeted agents, which have been proven active in terms of progression-free and survival improvement. Some prognostic factors have been identified and combined to develop prognostic models. The most widely used is the Memorial Sloan–Kettering Cancer Center (MSKCC) score. More recently, the International Metastatic Kidney Cancer Database Consortium (IMDC) developed a new score (6;7). All of these scores were based on biological parameters, time from nephrectomy and Karnofsky performance status. In addition to these scores, it appears that the metastatic site may also have an impact on survival. Recently the International Kidney Cancer Working Group identified that bone or liver metastases confer a significantly poorer overall survival (OS) than other metastatic sites (8).

Glandular metastases, particularly pancreatic and adrenal metastases are often associated with good survival in the literature, although the studies are based on heterogeneous patient

populations (9;10). The aim of this study was to evaluate the impact of glandular metastases in mccRCC on OS in patients treated with targeted therapies, the current standard of care.

2. Materiel and methods

2.1. Population

A retrospective study was performed in five centers in France, one in Belgium and three in the UK. Only patients who had been treated with at least one targeted therapy (anti-VEGF, TKI-VEGFR or mTOR inhibitor) for mccRCC in each institution between January 2004 and October 2013 were considered for analysis. Patients treated by surgery alone, immunotherapy alone or without treatment for mcc-RCC were excluded from this analysis. Three of the centers identified mccRCC patients with or without glandular metastasis, whereas six of the centers only contributed to glandular metastatic RCC patients. Glandular metastatic sites were defined as pancreas, breast, parotid, thyroid and adrenal gland (contralateral to the primary tumor). Patients excluded from the study were: those with ipsilateral adrenal metastases and those whose metastatic disease was treated by metastasectomy alone.

The following patient characteristics at the time of metastatic disease were collected: prognostic factors by MSKCC classification, sites of metastases (based on radiological and pathological data), local and systemic treatments for metastatic disease, survival data. Based on recent published data we evaluated the prognostic impact of bone and liver metastases in patients with glandular metastasis at diagnosis (GM) and patients without glandular metastases at diagnosis (NGM) (8).

2.2. Statistical analysis

Baseline patient and disease characteristics were summarized using descriptive analysis. Differences between patients with GM and NGM, were assessed using the chi-squared test for categorical variables and the Wilcoxon rank sum test for continuous variables. OS was defined as the time between the date of first diagnosis of metastases and the date of death from any cause. We were able to set the date of point since the diagnosis of the first metastases thanks to the consistency of cohort: all patients treated with anti-VEGF/mTOR inhibitor. Patients alive at the end of study were censored at the date of last contact. Survival curves for each group were estimated using the Kaplan-Meier method, and median times to

survival for each sub-cohort were estimated with 95% confidence interval (CI). Univariate association between baseline characteristics and OS were evaluated with the log-rank test. The primary analysis model is a multivariable Cox proportional hazards regression used to evaluate separately the prognostic significance of specific metastatic sites (liver, bone and lung) and the status of the presence of glandular metastases at diagnosis while adjusting for differences independent predictors of poor OS (age at initial disease diagnosis <60 yrs vs >= 60 yrs and MSKCC risk grouping). To include patients who developed glandular metastases later in course, a secondary landmark analysis was conducted (11). Patients still on study at the landmark time, 12 months after the first diagnosis of metastases, were separated into two group categories according to whether they have developed glandular metastases before that time. Patients who died or were censored before the time of landmark evaluation were excluded from the analysis. The prognostic significance of the presence of glandular metastases at the time of landmark was evaluated using a Cox regression model controlling for age at initial disease diagnosis and MSKCC risk grouping

Statistical analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA) with a nominal level of statistical significance (two-tailed) set to 0.05.

3. Results

3.1. Patient characteristics

A total of 558 patients were enrolled into the study (table 1). At the time of initial diagnosis of metastatic disease, 138 patients had glandular metastases (GM) and 420 patients did not have glandular metastases (NGM). Median age was 58.0 years old [15.0-102.0], with 398 (71.3%) men and 160 (28.7%) women. In the GM group, the predominant glandular sites were contralateral adrenal gland (55.1%) and pancreatic metastases (53.6%) (Table2). The frequency of lung, bone and liver metastases with GM at metastatic presentation were 52.2%, 27.5%, 14.5% compared to 74.8%, 43.1% and 25.7% for the NGM group. In the NGM group 19.3% of patients developed one or more glandular metastases later in the course of their metastatic disease. Median time between initial diagnosis of kidney cancer and first diagnosis of metastases was significantly longer for GM compared with NGM: 22.0 months versus 4.4 months ($p<0.001$).

The majority of patients (86.2%) had a nephrectomy, only 14,5% and 13,6% didn't undergo nephrectomy in GM and NGM group respectively. Of the patients who did not undergo a nephrectomy, 70% had primary metastatic disease and were in the poor or intermediate MSKCC risk group. Fuhrman grade was available for 78% of nephrectomised patients. Predominant Fuhrman grade of I/II was35.79% for GM vs 20.63% for NGM and grade III/IV 79.38% for NGM vs 64.21% for GM (p=0.0024). The Fuhrman grade was not an independent prognostic factor for survival from MSKCC risk group (Independent test p<0.0001). Patients with grade Fuhrman I/II had more frequently delay between diagnosis and metastasis > 12 months (35.5% for NGM vs 15.6% for GM) and patients with grade III-IV had more frequently delay $\leq$ 12 months (84.4% for GM vs 64.5% for NGM p< 0.0001). Significantly more patients were in the MSKCC good prognostic group in GM patients than in NGM group (38.3% vs 21.5%, p< 0.0001) and more patients were poor prognostic group in NGM group 16.5% vs 6.8% in GM group. Median time from diagnosis of metastases and first anti-angiogenic therapy was 4.14 months [0.00-160.9] for GM group and 4.11 months [0.00-221.3] for NGM (p=0.81). There were no differences between groups on the therapeutic class of first anti-angiogenic treatment (Table 2). The most common treatment was Sunitinib (74%).

3.2. Survival outcome

The median follow-up for the entire cohort was 82.6 months [range 68.8-90.7] and was not significantly different between the two groups (p=0.54). The median OS for the entire cohort was 42.0 months [37.6-49.7]. The median survival for patients with GM was 61.5 months [51.4-81.6] and 37.4 months [31.3, 42.0] for NGM patients (Hazard Ratio (HR) [CI 95%]: 1.7 [1.3, 2.2] p<0.001 (Figure 1).

For patients without bone or liver metastases the median OS, in GM group (N=83) was 67.7 months [55.4-115.6 months] and 38.7 months [30.7-50.0 months] in the NGM group (N=176); HR [CI 95%] 2.07 [1.42,3.02], p <0.001 (figure 2).

3.3. Univariate and multivariate analysis of risk factors for overall survival

For the entire cohort, factors that were significant in univariate analysis for longer survival were: younger age (< 60 years), a longer delay between diagnosis of kidney cancer and the first metastases, good and intermediate MSKCC score, I-II Fuhrman grade and glandular metastases at diagnosis (Table 3). Worse outcome was observed for patients with bone and lung metastases.

On multivariate analysis adjusted for MSKCC risk group the presence of bone or liver metastases was significant associated with worse OS: HR [CI 95%] 1.3 [1.1-1.7] p=0.0109, and 1.4 (1.1-1.7) p=0.0170, respectively (Table 4). However the lung metastases were not associated with poorer survival on multivariate analysis (HR [CI 95%] 1.2 [0.9-1.5], p=0.2072). Multivariate analysis for glandular metastases at diagnosis adjusted for MSKCC risk group (Table 5), identified the absence of glandular metastasis irrespective of the metastatic location at first diagnosis, as a poor prognostic factor with an HR [CI 95%] 1.4 [1.0-1.8] p=0.0256 for GM versus NGM. For patients without bone or liver metastases glandular metastases at diagnosis had a positive impact on OS HR [CI 95%] 1.8 [1.2-2.7] (table 6). Multivariate analysis for glandular metastases at landmark time confirmed the independent prognostic value of the presence of glandular status at 12-month. (HR=1.33 [1.00-1.75], p=0.048).

4. Discussion

The objective of this study was to determine whether the presence of glandular metastases at diagnosis of metastatic disease impacted on the survival of patients who received one or more anti-angiogenic therapies for mccRCC. RCC is known as having uncommon patterns of spread. Glandular metastases represent a rare site of metastases although RCC is the most

frequent tumor to metastasize to these locations, frequently with an indolent rate of growth (5;12;13). In our study improvement in survival was observed for patients with GM at diagnosis of metastatic disease compared to NGM patients.

The characteristics of the GM group clearly differed from NGM group, with less aggressive characteristics, for example: more frequent grade I/II, longer delay between kidney tumour and first metastases and a higher proportion of MSKCC good risk at metastatic presentation.

The interval between nephrectomy and the occurrence of metastases correlated with survival and this characteristic was one of the five factors included the MSKCC risk stratification (3). Longer delay both between kidney cancer diagnosis and metastases as well as a good risk group for MSKCC were significantly more frequent in GM group.

MSKCC risk score was used in this study because more complete information was available that for this population recruited since 1994, than for the now more commonly used IMDC risk score(6;7). Poor risk group were more frequently observed in NGM group in our study.

Many prognostic factors have been investigated in RCC, and multiple prognostic models have been developed. The presence of bone or liver metastases has been evaluated and shown to be an independent risk factor for worse OS. The understanding of biological mechanisms underlying these clinical findings need to be explored (8;14) . In our study bone and liver metastases were more frequently observed in NGM than GM and their presence were significant in multivariate analysis for shorter survival. Presence of GM was associated with longer survival in multivariate analysis. However, median survival with or without bone or liver metastases was better for GM patients. The impact on the OS of glandular status at diagnostic of significant in multivariate analyse in patients without bone or liver metastases. This analysis suggests that the presence of glandular metastases at diagnosis has a positive impact on OS irrespective of the presence or absence of liver or bone metastases.

Our study suffers from possible bias in patient selection and retrospective data collection. Although the included patients are consecutive patients, there is the probability of a selection bias. A limitation of this study was that the metastatic status was from chart and radiology review without central review.

Moreover these results are in accordance with previous findings suggesting that glandular metastases, particularly to pancreas and adrenal gland, are often associated with good survival. (9;15). However, most reported cases come from metastasectomy series and little data is available for patients treated by systemic treatment (16). It is well established that patients with limited metastatic RCC disease can achieve an excellent survival with surgery alone (5).

Metastasis to pancreas is a rare distant location for RCC accounting for less than 10%(14;17). This metastatic location is often described as indolent with a frequent long delay between kidney tumor and pancreas metastasis. In a review article including 15 papers with patients undergoing pancreatic metastasectomy had a survival median of 8.8 years, with a 5-year survival of 66 %, was reported (18).

Adrenal metastases have been associated with a favorable outcome among patients with isolated metastases treated by surgery with an estimated 5-year survival of 60% (19). In our analysis we consider only contralateral adrenal metastasis as glandular metastasis. Indeed, some patients may have had an extended nephrectomy with adrenalectomy at the diagnosis of their disease. This rarely undertaken in many surgical teams now, but we wanted to avoid this confounding factor.

Reoccurrence of RCC in thyroid has been described but is rare and indolent with a mean time from kidney cancer to metastasis around 120 months with 51% of 5-year survival after thyroid metastasectomy (13) .

The association between GM localization has been highlighted in three retrospectives studies about thyroid metastasectomy from RCC. Thyroid metastases were associated with pancreatic

metastases from 23 to 30% of cases (20-22). In our report, 17 patients presented a thyroid GM and strikingly 12 (70%) were associated with a pancreatic GM. This observation confirms a potential association between these two rare metastatic localizations. Iesalnieks et al. reported adrenal and thyroid GM association in 13% of patients and we found this association in 29% of patients with thyroid GM (22). These results could encourage more carefully examination of CT-scanner or ultrasonography to detect early thyroid metastases when pancreatic GM is detected during mccRCC evolution.

The study presented here evaluated outcome of patients with glandular metastasis who were not surgical candidates and its strength was to compare patients all receiving anti-angiogenic therapy, which was not the case in most surgical reports for pancreas, thyroid or adrenal metastases from RCC cohorts in published papers.

A few studies have suggested better outcomes in patients with mccRCC with GM particularly for patients treated by anti-angiogenic therapy. The reason for better clinical outcomes associated with GM has yet to be elucidated. Spread to pancreas, breast, thyroid and parotid gland are not routinely explored by standard staging CT scans. A prospective systematic study would elucidate whether this is important, especially regarding the frequent association between pancreas and thyroid localizations.

The biology behind these clinical observations needs to be explored in order to compare the molecular characteristics of the tumor and the metastatic site of GM and NGM patients. However, given the significant intratumoral heterogeneity in patients with mccRCC, the unique organ microenvironment of the GM may be selective for a less aggressive clinical phenotype. Molecular characterization of both GM and NGM in patients with mccRCC derived from host, tumor tissue, or plasma, may help inform the development of improved prognostic and predictive biomarkers.

5. Conclusion

To our knowledge this is the largest study suggesting that the presence of at least one GM at metastatic presentation of mccRCC, treated with a least one anti-angiogenic therapy, is associated with a significantly longer overall survival compared to non-GM patients. The site of metastatic disease can provide prognostic information and may possibly be used in guiding clinical decision making. The understanding of biological mechanisms to explain these clinical findings need to be explored.

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Table 1: Patients characteristics at diagnosis of first metastases.

	Glandular metastases	**Non glandular metastases**	***p* value**
N (%)	138	420	
Median age, years (range)	58.0 (32-102)	58.5 (15-82)	0.61
Gender Male (%)	98 (71)	300 (71.4)	0.93
Nephrectomy (%)	118 (85.5)	363 (86.4)	0.79
Furhman grade (%) **I/II** **III/IV**	 34 (35.8) 61 (64.2)	 66 (20.6) 254 (79.4)	 0.0024
Delay: diagnosis-metastases, months (range)	21.9 (0.03-272.8)	4.4 (0.03-334)	<0.001
MSKCC risk groups (%) - **Good** - **Intermediate** - **Poor**	 51 (38.4) 73 (54.9) 9 (6.8)	 82 (21.5) 236 (61.9) 63 (16.5)	 <0.0001

Table 2: Metastatic sites at initial diagnosis of metastases.

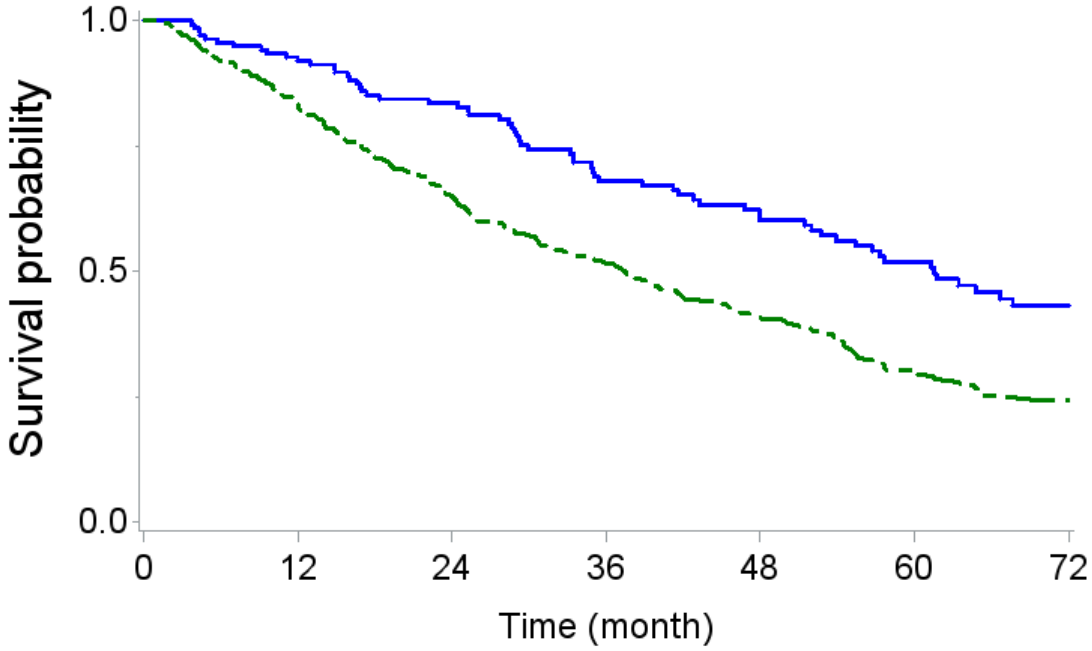
	Glandular metastases	Non glandular metastases
N	138	420
Number of metastatic sites (%)		
1	4 (2.9)	23 (5.5)
>=2	134 (97.1)	397 (94.5)
Glandular metastatic sites (%)		
Contralateral adrenal metastases	76 (55.1)	
Pancreas	74 (53.6)	
Thyroid	17 (12.3)	
Breast	2 (1.5)	
Parotid	2 (1.5)	
Non glandular metastatic sites (%)		
Lung	72 (52.2)	314 (74.8)
Nodes	56 (40.6)	214 (50.9)
Bone	38 (27.5)	181 (43.1)
Ipsilateral adrenal	25 (18.1)	35 (8.3)
Liver	20 (14.5)	108 (25.7)
Contralateral kidney	13 (9.4)	55 (13.1)
Brain	11 (8.0)	48 (11.4)
Soft tissue	7 (5.1)	44 (10.5)
Others	18 (13.0)	47 (11.2)
≥1 non glandular metastatic site (%)	129 (93.5)	420 (100)
Median between metastasis diagnosis and treatment (months) (range)	4.14 [0-160.9]	4.11 [0-221.3]
Anti-angiogenic treatment (%)		
VEGFR-TKI: Sunitinib	92 (67)	323 (77)
Sorafenib	24 (17)	45 (11)
Pazopanib	5 (4)	20 (5)
Other	1(0.7)	1(0.002)
Bevacizumab + Interferon	3 (2)	11 (0,2)
mTOR inhibitor	13 (9.3)	20 (5)

Table 3: Univariate analyses of survival.

Characteristics	N	median [CI 95%]	Hazard Ratio [CI 95%]	*P* value
Sex				
Female	160	40.31 [30.7,49.7]	1	
Male	398	45.4 [37.8,52.0]	1.0 [0.8,1.3]	0.88
Age				
< 60 yrs	301	52.0.98 [41.9,59.8]	1	
>= 60 yrs	257	35.6 [29.0,41.6]	1.6 [1.3,1.9]	<.001
Furhman				
I-II	100	54.9 [48.0,68.0]	1	
III-IV	315	36.9 [30.1,42.8]	0.51 [0.4,0.6]	0.003
Delay				
> 12 mo.	225	61.7 [55.4,68.0]	1	
<= 12 mo.	323	30.6 [25.6,36.8]	2.0 [1.6,2.5]	<.001
MSKCC score				
Good	133	67.6 [57.7,97.4]	1	
Intermediate	309	39.6 [33.4,47.1]	1.9 [1.4,2.5]	<.001
Poor	72	14.01 [11.8,17.0]	5.1 [3.7,7.2]	<.001
At diagnosis				
GM	138	61.5 [51.4,81.6]	1	
Non-GM	420	37.4 [31.3,42.0]	1.7 [1.3,2.2]	<.001
Lung metastases				
No	172	54.6 [43.3,64.7]	1.38 [1.1,1.7]	0.006
Yes	386	38.3 [33.2,44.7]		
Bone metastases				
No	339	50.0 [41.9,57.3]	1	
Yes	219	34.9 [27.1,41.5]	1.6 [1.3,1.9]	<.001
Liver metastases				
No	430	45.4 [37.6,52.0.]	1	
Yes	128	37.8 [24.7,47.8]	1.10 [0.9,1.4]	0.43

Figure 1: Kaplan-Meier for overall survival: glandular versus non glandular at the time of metastatic diagnosis.

Median overall survival
Glandular at metastatic diagnosis (N=138): 61.5 months [51.4,81.6]
Non glandular at metastatic diagnosis (N=420): 37.4 months[31.3,42.0]
HR *[CI 95%]* 1.7 [1.3-2.2] p<0.001



Glandular	138	124	104	73	59	47	30
Non glandular	420	334	235	174	127	86	57

Table 4: Multivariate analysis for survival for bone or liver metastases. Wald chi-square test from multivariable Cox regression adjusted for the MSKCC risk group.

Parameters	Comparison	Hazard Ratio [CI 95%]	p-value
Age	>=60yrs vs. <60yrs	1.3 [1.1,1.7]	0.0117
Liver metastases	Yes vs. No	1.4 [1.1,1.7]	0.0170
MSKCC	Intermediate vs. Good	1.8 [1.3,2.3]	<.0001
MSKCC	Poor vs. Good	4.3 [3.0,6.1]	<.0001
Bone metastases	Yes vs. No	1.3 [1.1,1.7]	0.0109
Lung metastases	Yes vs. No	1.2 [0.9,1.5]	0.2072

Table 5: Multivariate analysis for glandular metastases at diagnosis. Wald chi-square test from multivariable Cox regression adjusted for the MSKCC risk group.

Parameter	Comparison	Hazard Ratio [CI 95%]	p-value
Age	>=60yrs vs. <60yrs	1.4 [1.1,1.7]	0.0059
MSKCC	Intermediate vs. Good	1.7 [1.3,2.3]	<.0001
MSKCC	Poor vs. Good	4.2 [3.0,6.0]	<.0001
Glandular status at diagnosis	Non-GM vs. GM	1.4 [1.0,1.8]	0.0256

Figure 2: Kaplan-Meier for overall survival: glandular metastasis versus non-glandular metastases at the time of metastatic diagnosis for patients without bone or liver metastases.

Median overall survival for patient without bone or liver metastases
Glandular at metastatic diagnosis (N=83): 67.7 [55.4,115.6]
Non glandular at metastatic diagnosis (N=176): 38.7 [30.7,50.0]
HR *[CI 95%]* 2.1 [1.4,3.0] p <0.001

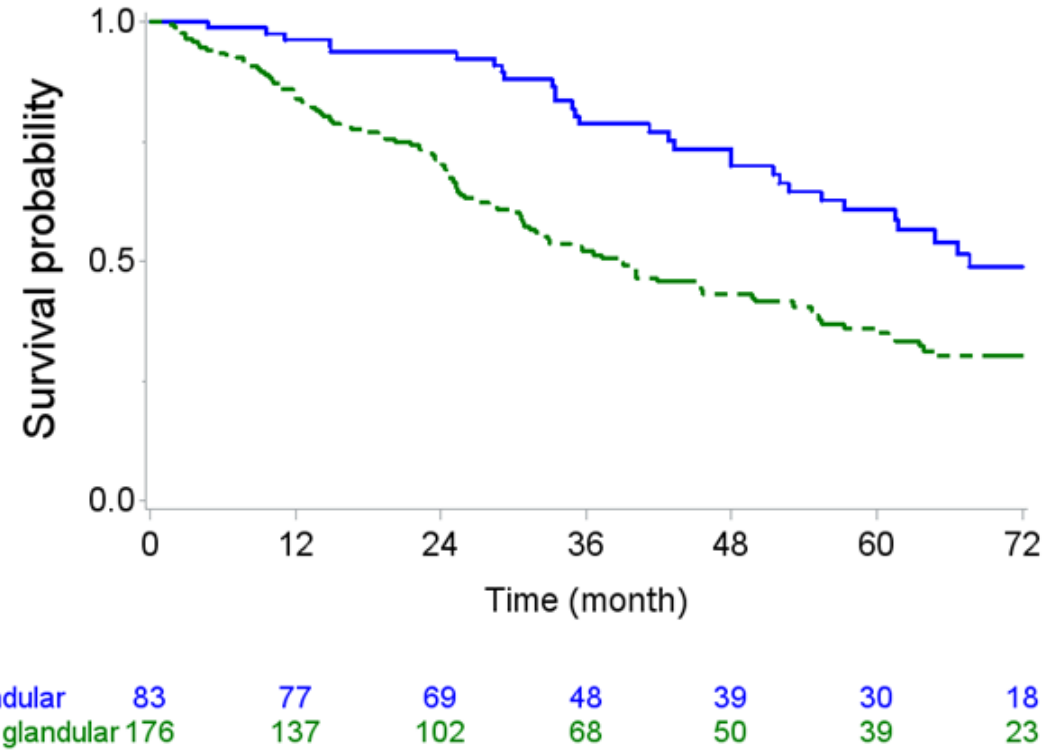


Table 6: Multivariate analysis for glandular metastases at diagnosis for patients without bone or liver metastases. Wald chi-square test from multivariable Cox regression adjusted for the MSKCC risk group.

Parameters	Comparison	Hazard Ratio [CI 95%]	p-value
Age	>=60yrs vs. <60yrs	1.7 [1.2,2.5]	0.0021
MSKCC	Intermediate vs. Good	1.4 [0.9,2.0]	0.1113
MSKCC	Poor vs. Good	2.7 [1.4,4.9]	0.0016
Glandular status at diagnosis	Non-GM vs. GM	1.8 [1.2,2.7]	0.0040