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# Exposure to Multiple Lines of Treatment and Survival of Patients With Metastatic Renal Cell Carcinoma: A Real-world Analysis

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1	Exposure to multiple lines of treatment and survival of patients with metastatic renal cell carcinoma: a
2	real-world analysis.
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#### 40 <u>CONFLICT OF INTEREST STATEMENT</u>

- 41 Dr. Giuseppe Procopio reports receiving fees for serving on advisory boards from Bayer, Bristol-Myers
- 42 Squibb (BMS), Ipsen, Novartis and Pfizer.
- 43 Dr. Elena Verzoni reports receiving fees for serving on advisory boards from Pfizer and Novartis.
- 44 Prof. Massimo Di Maio acted as a consultant for Merck Sharp & Dohme, Bristol Myers Squibb, Janssen,
- 45 Amgen, AstraZeneca.
- 46 The other authors declare to have no conflicts of interest.

#### 79 <u>MICROABSTRACT</u>

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The aim of this retrospective analysis was to describe trends in exposure to multiple lines of treatment and survival among 500 metastatic renal cell carcinoma patients who started first-line therapy in two different periods of time (2004-2010 and 2011-2017), in daily practice. Patients who started treatment over the last 5 years received a higher number of treatment lines with an improvement in overall survival.

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# 87 <u>ABSTRACT</u>

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*Background:* The purpose of this retrospective analysis was to describe trends in exposure to multiple lines
of treatment and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC) who started
therapy in two different periods of time (period 1: 2004-2010 and period 2: 2011-2017).

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93 Patients and methods: The proportion of patients who received subsequent lines of treatment after disease 94 progression (PD) was compared between the two groups. OS was measured from the time of start of first-95 line treatment for metastatic disease to the death or last follow-up. Both univariate and multivariate analysis 96 were performed.

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*Results*: 500 patients were included into the study: 274 started a treatment in period 1 and 226 in period 2.
Out of those patients who stopped first-line treatment due to PD, patients in period 2 had a higher conditional
probability to receive second- and third-line treatment as compared to patients of period 1 (77.2% vs 63.7%,
odds ratio [OR] 1.93, 95% Confidence Interval [CI] 1.20-3.11, p=0.0065 and 69.6% vs 48.1%, OR 2.48,
95% CI 1.40-4.40, p=0.002, respectively). Median OS improved from 22.8 months for patients of period 1 to
38.2 months for patients of period 2 (univariate analysis Hazard Ratio [HR] 0.65, 95% CI 0.50-0.83,
p=0.001).

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106 Conclusion: Patients who started a treatment over the last 5 years were exposed to a higher number of 107 treatment lines as compared to those treated before 2011. Our data suggest that the increase of treatment 108 options available as well as the clinicians' expertise could be associated with a better outcome.

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- 110
- 111 Keywords: metastatic renal cell carcinoma, overall survival, targeted therapy, VEGF, mTOR
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#### 118 **INTRODUCTION**

Renal cell carcinoma (RCC) accounts for approximately 330.000 cases diagnosed each year and is responsible for almost 140.000 deaths worldwide (1). Most cases are localized and often accidentally diagnosed; however, one-third of patients present with an advanced disease at diagnosis and 30% of subjects eventually develop metastases after nephrectomy (2).

- In the last decade, the introduction of new therapeutic agents has improved survival of patients with metastatic RCC (mRCC). Specifically, the 5-year survival for RCC has improved from 52% in 1975 to 74% in 2014 (3).
- 126 Until 2005, interferon alfa (IFN- $\alpha$ ) and high-dose interleukin-2 (HD IL-2) were the standard of care for the
- treatment of mRCC (4, 5); however they showed a limited impact on immune-escape mechanisms, resulting
  in few durable responses and bad tolerability (6).
- 129 Recently, a better understanding of the biological and molecular basis of kidney cancer has led to the
- 130 development and approval of new targeted agents: many of them are directed against the vascular endothelial
- 131 growth factor receptors (VEGFRs) (bevacizumab, sorafenib, sunitinib, pazopanib, axitinib and cabozantinib)
- 132 (7-11), the mammalian target of rapamycin (mTOR) pathway (everolimus and temsirolimus) (12, 13) and the
- 133 PD1/PD-L1 pathway (nivolumab) (14). With the advent of targeted agents, there was an improvement of
- clinical outcome, with response rates (RR) exceeding 30% and median overall survival (mOS) of almost 2
- 135 years, depending on patient risk profile, agent used and other clinical variables (15).
- Considering the evolution of the standard of care in the treatment of mRCC, do these changes directly
  translate into survival benefit in clinical practice? We tried to clarify whether improvements in mRCC
  survival also exist in a "real world" cohort of patients.
- The aim of this study was to examine the difference in trends exposure to multiple lines of treatment and OS between patients who started therapy for mRCC in two different time periods (time period 1: 2004-2010 and time period 2: 2011-2017) in a real-world setting.
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#### 157 PATIENTS AND METHODS

#### **158 Patient population and data sources**

Data were retrospectively drawn from the Genitourinary Cancer Unit Database of the Istituto Nazionale dei 159 Tumori of Milan (Italy). Patients were consecutively registered in the database. The data collected included 160 161 patient demographic characteristics (sex, race, age), type of cancer, tumor characteristics, nephrectomy status, disease stage (regional/metastatic) at time of diagnosis, type of treatment received and adverse events 162 related to each treatment. Follow-up on each patient is conducted every six months to assess current vital 163 status. We restricted our study to the advanced RCC cases only, and excluded localized disease cases, 164 because systemic therapy is currently approved only in the locally advanced, unresectable, or metastatic 165 166 stages of RCC.

- Patients were divided into two groups, on the basis of the time period when they started treatment for metastatic disease. Patients of the time period 1 started a treatment for mRCC between 2004 and 2010 (n= 274) while patients of the time period 2 started a treatment between 2011 and 2017 (n=226).
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#### 171 Statistical analysis

172 For each line of therapy (considering second line [2L], third line [3L], fourth line [4L] fifth-line [5L]), the probability of receiving a specific treatment line was calculated dividing the total number of patients who 173 174 received a specific treatment line by the number of patients who had progressed to the previous line. The conditional probability (P) of 2L is the measure of the probability of receiving 2L at disease progression, 175 given that the patient has received first line (1L):  $P(2L \mid 1L)$ . The conditional probability of 3L is the 176 measure of the probability of receiving 3L at disease progression, given that the patient has received 2L: 177 P(3L 2L). The *conditional probability* of 4L is the measure of the probability of receiving 4L at disease 178 progression, given that the patient has received 3L:  $P(4L \mid 3L)$ . The conditional probability of 5L is the 179 180 measure of the probability of receiving 5L at disease progression, given that the patient has received 4L: P(5L | 4L). 181

182 Consequently, the joint probability for a patient to receive each line was calculated as follows: joint 183 probability (2L,3L) = P(2L) \* P(3L | 2L); joint probability (2L,3L,4L) = P(2L) \* P(3L | 2L) \* P(4L | 3L);

184 joint probability (2L, 3L, 4L, 5L) = P(2L) \* P(3L | 2L) \* P(4L | 3L) \* P(5L | 4L).

- OS curves were plotted using the Kaplan-Meier method and compared using the log-rank test. In order to 185 assess the impact of treatment period along with the most relevant clinical characteristics (Heng score, 186 ECOG performance status, synchronous or metachronous metastases, age, gender, liver metastases, lung 187 188 metastases, lymphnodes metastases, bone metastases, brain metastases), multivariable analysis was 189 performed, using the Cox regression model. In order to assess the potential interaction between treatment 190 period and each clinical characteristic, a Cox model including that characteristic, treatment period and their 191 interaction was performed. The chi square test or the Fisher exact test, as appropriate, were used to compare 192 categorical variables among the groups. Wilcoxon test was used to compare continuous variables among the
- 193 groups.
- All statistical tests were two-tailed and p-values less than 0.05 were considered statistically significant.
- All statistical computations were performed using SPSS for Windows Version 24.0.

#### 196 <u>RESULTS</u>

#### **197** Patients characteristics

Five hundred patients with mRCC were included in the study: 274 started a treatment during the period 1 and226 during the period 2.

In the whole study population, the median age was 60 years. Approximately two-thirds of the patients were men (72.8% vs 27.2%) and the predominant histology was clear-cell type (88.3% in period 1 and 87.2% in

period 2). Among patients of period 1, 248 (90.5%) of them underwent a radical nephrectomy versus 170

203 (75.2%) in period 2.

204 Patient demographic and disease characteristics for the mRCC population are listed in Table 1.

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#### 206 Clinical outcomes

We evaluated the conditional probability of patients for period 1 and period 2 to receive a subsequent treatment line after failure of the previous treatment due to PD, defined as per Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1 (Table 2).

210 Out of those patients who stopped first-line treatment due to PD in period 1, 93 patients (36%) received only

one therapeutic line vs. 31 patients (22%) in period 2. In fact, patients in period 2 had a higher conditional

probability to receive second-line treatment as compared to patients of period 1 (77.2% vs 63.7%, odds ratio

[OR] 1.93, 95% Confidence Interval [CI] 1.20-3.11, p=0.0065). Similarly, out of those patients who stopped

second-line treatment due to PD, patients in period 2 had a higher conditional probability to receive a third-

215 line compared to patients treated in the period 1 (69.6% vs 48.1%, OR 2.48, 95% CI 1.40-4.40, p=0.002).

Out of those patients who stopped third-line treatment due to PD, patients in period 2 had a higher conditional probability to receive a fourth-line in comparison to patients treated in the period 1, although difference was not statistically significant (42.9% vs 36.1%, OR 1.33, 95% CI 0.57-3.11, p=0.51). Finally, out of those patients who stopped fourth-line treatment due to PD, patients in the period 2 had a higher conditional probability of receiving a fifth-line in comparison to patients of the period 1, although the difference was not statistically significant (45.5% vs 16.7%, OR 4.17, 95% CI 0.75 – 23.18, p=0.10.

For all the lines of treatment beyond first-line, the joint probability of receiving a treatment was higher in

- period 2 compared to period 1 (77.2% vs 63.7% for second-line, 53.7% vs 31.0% for third-line, 23.0% vs
- 224 11.2% for fourth-line and 10.5% vs 1.9% for fifth-line).

Median follow-up (mFUP) in the overall population was 59.9 months (95% CI, 48.52-71.33) with a mFUP of 112.6 months (95% CI, 99.2-126.0), and 26.5 months (95% CI, 21.0-31.9) for patients in the period 1 and

227 period 2 respectively.

228 Median overall survival (mOS) was 27.3 months for the whole study period population.

Median OS improved from 22.8 months for patients treated between 2004 and 2010 to 38.2 months for patients treated between 2011 and 2017 (Hazard Ratio [HR] 0.65, 95% CI 0.50-0.83, p=0.001) (Figure 1).

Patients with ECOG performance status (PS) 0 at the time of diagnosis of metastatic disease had a mOS of

232 36.7 months, patients with ECOG PS 1 had a mOS of 17.7 months (HR for ECOG PS1 vs PS0 1.78, 95% CI

233 1.42-2.23, p<0.0001) and patients with ECOG PS 2 had a mOS of 6.6 months (HR for ECOG PS2 vs PS0

234 9.47, 95% CI 5.38-16.69, p<0.0001) (Figure 2). There was a statistically significant interaction between

- ECOG PS and treatment period (interaction p value = 0.017), mainly driven by a better outcome of PS0 patients in the more recent period. In detail, median OS was 29.1 months in ECOG PS0, 17.7 months in ECOG PS1 and 6.6 months in ECOG PS2 patients treated between 2004 and 2010, versus 70.1 months in ECOG PS0, 21.5 months in ECOG PS1 and 1.8 months in ECOG PS2 patients treated in the second period.
- Patients with a good Heng prognostic score had a mOS of 43.5 months, patients with an intermediate prognostic score had a mOS of 33.9 months (HR vs good score 1.12, 95% CI 0.80 - 1.59, p=0.51) and those with a poor score had a mOS of 9.2 months (HR vs good score 5.11, 95% CI 3.39-7.72, p<0.0001) (Figure 3), without significant interaction with treatment period (interaction p value = 0.49). Patients who presented with synchronous metastases at diagnosis had a mOS of 20.7 months, while patients who did not present metastases at diagnosis had a mOS of 39.8 months (HR 1.69, 95% CI 1.36-2.11, p<0.0001) (Figure 4), without significant interaction with treatment period (interaction p value = 0.30).
- Patients with liver metastases at diagnosis had a mOS of 15.7 months, while patients without liver metastases had a mOS of 30.3 months (HR at univariate analysis 1.84, 95% CI 1.39-2.42, p<0.0001), without significant interaction with treatment period (interaction p value = 0.19). Patients with lung metastases had a mOS of 24.7 months, while patients without lung metastases had a mOS of 29.0 months, and the difference was not statistically significant at univariate analysis (HR 1.19, 95% CI 0.95 – 1.19, p=0.14), without significant interaction with treatment period (interaction p value = 0.38).
- Patients who presented with lymphnodes involvement at diagnosis of metastatic disease had a shorter mOS in comparison with patients without nodal metastases (mOS was 21.1 and 34.0 months respectively). At univariate analysis, the presence of metastases at lymphnodes was significantly associated with a worst survival (HR 1.33, 95% CI 1.07-1.65, p=0.01). There was no significant interaction between lymphnode metastases and treatment period (interaction p value = 0.32).
- Brain metastases were associated with a shorter survival (median OS was 12.3 vs 27.7 months; HR at univariate analysis 1.96, 95% CI 1.17-3.29, p=0.01), without significant interaction with treatment period (interaction p value = 0.06), while the presence of bone metastases was not significantly associated with mOS (mOS was 23.3 for patients with bone metastases vs. 28.3 months for patients without, HR 1.25, 95% CI 0.98 – 1.60, p=0.07), without significant interaction with treatment period (interaction p value = 0.59).
- At multivariate analysis (Table 3): Heng prognostic score, ECOG PS, presence of metastases at diagnosis were significantly associated with survival while the difference between the 2 time periods did not reach statistical significance (HR for period 2 vs period 1 0.77, 95% CI 0.59 - 1.01, p=0.06).
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#### 266 **DISCUSSION**

267 Until the advent of targeted therapy, mRCC represented a malignancy with poor prognosis, with median 268 survival of 12 months (17). In the last decade, the introduction of several therapeutic agents has 269 revolutionized the treatment of mRCC patients. These agents including TKIs, mTORi and immune-270 checkpoint inhibitors have dramatically changed the treatment landscape of mRCC, which was previously 271 mainly cytokine-based (interleukin 2 and IFN- $\alpha$ ) and has greatly improved patient outcomes including 272 overall survival (18).

- With the approval of new targeted agents for mRCC, several questions raised about placement and thesequential use into the algorithm in the real-world setting .
- The restrictive inclusion criteria of randomized clinical trials limit the generalizability of the results to the broader population of mRCC patients in the real world setting (19). Expanded access trials have provided insights into real-world outcomes before the approval of the new drugs, but detailed data on practice patterns and outcome across sequential lines of therapy are still limited (20).
- We retrospectively collected data from 500 mRCC patients treated at Istituto Nazionale dei Tumori of Milan (Italy). Patients were divided into two time periods on the basis of the beginning of treatment for metastatic disease: patients of period 1 started a treatment between 2004 and 2010, while patients of period 2 started a treatment between 2011 and 2017. We aimed to make an overview of real-world clinical practice for mRCC and investigate difference in OS and trends in exposure to multiple lines of treatment between patients who started first-line therapy in the two periods.
- In our analysis, a significant improvement in OS occurred during the recent years in the mRCC population: from a mOS of 22.8 months (2004-2010) to 38.2 months (2011-2017), although the difference did not reach statistical significance at the multivariate analysis. We also described an increase, in the period 2, of the number of patients who received more therapeutic lines at PD in comparison to patients treated in period 1.
- This improvement over the years may be explained by the intensified medical and surgical strategies in a multidisciplinary approach, aiming to provide the optimal treatment to patients during the course of the disease (21). The increase of locoregional treatments in addition to surgery (in particular radiotherapy and innovative ablation techniques, including radiofrequency ablation, microwave ablation or cryoablation) has been highlighted in our report and the difference in the use of different therapeutic approaches in the period 2 in comparison to the period 1 was statistically significant (p<0.0001). The role of cytoreductive nephrectomy remains debated and should be carefully considered according to patients' and disease characteristics (22).
- Second, for patients who started a treatment between 2011 and 2017, 4 new therapeutic agents for the treatment of mRCC were available in Italy (axitinib, pazopanib, nivolumab and cabozantinib): the availability of new drugs has increased the lines of treatment received by patients. As a consequence, survival of patients receiving more therapeutic agents has increased. A significant association between increased survival and treatment beyond first-line therapy has been highlighted (23). In our analysis we showed that patients treated in period 2 were more likely to receive different therapeutic lines compared to those treated in the period 1 at PD.
- Third, in view of an increased number of drugs available, therapy and adverse events (AEs) management has
  also improved: new schedules have allowed to tailor treatment on patient characteristics (24), allowing to
  treat patients as long as possible.
- 306 Our analysis has some limitations: first of all the retrospective nature of the study, which sometimes led to 307 incomplete or late entries of clinical data, or data input errors. Another limitation is the lack of some 308 information regarding key laboratory values, as well as the lack of a standardization in imaging 309 interpretations to define treatment outcomes. A small number of patients included in our database were 310 enrolled into expanded access programs, but the impact on this analysis is negligible. Finally, the follow-up 311 of patients is different between the two periods of time, so that a significantly lower absolute number of

- 312 patients in period 2 received subsequent lines of therapy at <u>PD in comparison to period 1</u> and a relevant
- percentage of patients who started a therapy in period 2 are still on treatment: this represents a potential bias
- **314** factor of the analysis.
- 315 The goal of our study was to assess population trends in survival over the last years, with the attempt of
- understanding of possible factors able to influence the outcome (ie, improved number of therapies, changesin therapy and adverse events management).
- 318 Despite these limitations, we identified a positive trend in survival in mRCC, that seems to reflect the 319 improvement in therapeutic strategies for this disease.
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# 321 <u>CONCLUSION</u>

- These real-life data support and confirm the positive impact of novel therapies and multimodal approach for mRCC. Prognosis of mRCC patients will likely to improve with either the optimization of current targeted therapy and the approval of novel agents with different mechanisms of action.
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## 326 <u>CLINICAL PRACTICE POINTS</u>

- In the last decade, the introduction of novel targeted agents has revolutionized the treatment of
   mRCC improving overall survival.
- We retrospectively collected data from 500 patients with mRCC treated at Istituto Nazionale dei Tumori of Milan, which were divided in two time periods on the basis of the start of the first-line therapy (period 1 2004-2010 and period 2 2011-2017 respectively). The aim of our analysis was to describe trends in exposure to multiple lines of treatment and analyze differences in survival between period 1 and period 2.
- Our real-world study described a relevant improvement in OS during the recent years in the mRCC
   population. We also described an increase, in the last 5 years, of the number of patients who received
   more therapeutic lines at PD in comparison to patients treated between 2004 and 2010.
- These results may help physicians in daily practice to manage patients with mRCC in order to
   optimize clinical outcomes.
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427 Table 1. Main characteristics of patients who started a treatment in period 1 (2004-2010) and period 2

428 (**2011-2017**).

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	Period 1		Period 2		P value*
Characteristics	N° of patients (total: 274)	%	N° of patients (total: 226)	%	
Nephrectomy					< 0.00001
Yes	248	90.5	170	75.2	
No	26	9.5	56	24.8	
Metastatic at diagnosis					0.68
Yes	153	55.8	122	54	
No	121	44.2	104	46	
Cytoreductive nephrectomy**					0.61
Yes	78	51	66	54.1	
No	75	49	56	45.9	
Risk group (Heng score)					< 0.00001
Good	36	13.1	12	5.3	
Intermediate	181	66.1	198	87.6	
Poor	57	20.8	16	7.1	
Histology					0.56
Clear cell	242	88.3	197	87.2	
Papillary type II	20	7.3	17	7.5	
Chromophobe	6	2.2	3	1.3	
Collecting ducts	6	2.2	5	2.2	
Other	0	0	4	1.8	
Number of metastatic sites					0.22
1	117	42.7	109	48.2	
> 2	157	57.3	117	51.8	
Site of metastasis (at diagnosis)					
Liver	47	17.2	26	11.5	0.07
Lung	187	68.2	131	58	0.02
Lymphnodes	106	38.7	96	42.5	0.39
Brain	11	4	6	2.7	0.40
Bone	72	26.3	57	25.2	0.79
Other	81	29.6	66	29.2	0.93
Therapy prescribed (any line)	01			_>	0170
TKIs	268	97.8	218	95.5	0.36
Anti-VEGF	27	9.9	0	0.0	< 0.0001
mTor inhibitors	82	29.9	53	23.5	0.10
Immunotherapy	7	2.6	26	11.5	< 0.0001
Cytokines		0.4 16 1	6	2.7	0.03
Cytokines	<del>44</del>	10.1	U	0.0	<0.0001

<sup>430</sup> 431

Abbreviations: TKIs: tyrosine kinase inhibitors; VEGF: Vascular Endothelial Growth Factor; mTOR: mammalian target of rapamycin

432mammalian433\*Chi square

434 \*\*out of patients metastatic at diagnosis

435

Table 2. Conditional probability of receiving a subsequent therapeutic line at failure of the previous line because of disease progression (PD).

	Period 1	Period 2	Odds ratio	p value
	(2004-2010)	(2011-2017)	(95% CI)	(Chi square)
	n=274	n=226		
1st line	274	226	n.a.	n.a.
	(100%)	(100%)		
2 <sup>nd</sup> line / Failure of 1 <sup>st</sup> line	163 / 256	105 / 136	1.93	0.0065
	(63.7%)	(77.2%)	(1.20 – 3.11)	
3 <sup>rd</sup> line / Failure of 2 <sup>nd</sup> line	74 / 154	55 / 79	2.48	0.002
	(48.1%)	(69.6%)	(1.40 - 4.40)	
4 <sup>th</sup> line / Failure of 3 <sup>rd</sup> line	22 / 61	15 / 35	1.33	0.51
	(36.1%)	(42.9%)	(0.57 – 3.11)	
5 <sup>th</sup> line / Failure of 4 <sup>th</sup> line	3 / 18	5 / 11	4.17	0.10
	(16.7%)	(45.5%)	(0.75 – 23.18)	

Abbreviations: CI: Confidence Interval 

## 451 Table 3. Multivariate analysis of factors predictive of overall survival in the whole population.

Variables		Hazard Ratio (95% CI)	p value
Study period	2011-2017 vs 2004-2010	0.77 (0.59 – 1.01)	0.06
Heng score	Intermediate vs. good	1.07 (0.75 - 1.53)	0.72
	Poor vs. good	3.20 (1.99 - 5.13)	<0.0001
ECOG performance status	PS1 vs PS 0	1.40 (1.09 - 1.80)	0.008
	PS2 vs PS0	3.45 (1.83 - 6.50)	<0.0001
Age	>70 vs <70	1.13 (0.87 – 1.48)	0.36
Gender	Female vs male	1.13 (0.88 – 1.46)	0.35
Liver metastases	Yes vs no	1.20 (0.88 - 1.62)	0.26
Brain metastases	Yes vs no	1.58 (0.91 – 2.73)	0.10
Lung metastases	Yes vs no	1.14 (0.90 – 1.44)	0.29
Lymphnode metastases	Yes vs no	1.20 (0.95 – 1.51)	0.14
Bone metastases	Yes vs no	1.03 (0.80 – 1.33)	0.82
Metastases at diagnosis	Yes vs no	1.33 (1.05-1.69)	0.02









487 Figure 4. Kaplan-Meier estimates of overall survival according to synchronous or metachronous

488 metastases in the whole population.



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