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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 **CONFLICT OF INTEREST STATEMENT**

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.

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79 **MICROABSTRACT**

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

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86

87 **ABSTRACT**

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89 *Background:* The purpose of this retrospective analysis was to describe trends in exposure to multiple lines
90 of treatment and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC) who started
91 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.

97

98 *Results:* 500 patients were included into the study: 274 started a treatment in period 1 and 226 in period 2.
99 Out of those patients who stopped first-line treatment due to PD, patients in period 2 had a higher conditional
100 probability to receive second- and third-line treatment as compared to patients of period 1 (77.2% vs 63.7%,
101 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,
102 95% CI 1.40-4.40, p=0.002, respectively). Median OS improved from 22.8 months for patients of period 1 to
103 38.2 months for patients of period 2 (univariate analysis Hazard Ratio [HR] 0.65, 95% CI 0.50-0.83,
104 p=0.001).

105

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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111 **Keywords:** metastatic renal cell carcinoma, overall survival, targeted therapy, VEGF, mTOR

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118 **INTRODUCTION**

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

123 In the last decade, the introduction of new therapeutic agents has improved survival of patients with
124 metastatic RCC (mRCC). Specifically, the 5-year survival for RCC has improved from 52% in 1975 to 74%
125 in 2014 (3).

126 Until 2005, interferon alfa (IFN- α) and high-dose interleukin-2 (HD IL-2) were the standard of care for the
127 treatment of mRCC (4, 5); however they showed a limited impact on immune-escape mechanisms, resulting
128 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
134 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).

136 Considering the evolution of the standard of care in the treatment of mRCC, do these changes directly
137 translate into survival benefit in clinical practice? We tried to clarify whether improvements in mRCC
138 survival also exist in a “real world” cohort of patients.

139 The aim of this study was to examine the difference in trends exposure to multiple lines of treatment and OS
140 between patients who started therapy for mRCC in two different time periods (time period 1: 2004-2010 and
141 time period 2: 2011-2017) in a real-world setting.

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157 **PATIENTS AND METHODS**

158 **Patient population and data sources**

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

167 Patients were divided into two groups, on the basis of the time period when they started treatment for
168 metastatic disease. Patients of the time period 1 started a treatment for mRCC between 2004 and 2010 (n=
169 274) 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
173 probability of receiving a specific treatment line was calculated dividing the total number of patients who
174 received a specific treatment line by the number of patients who had progressed to the previous line. The
175 *conditional probability* (P) of 2L is the measure of the probability of receiving 2L at disease progression,
176 given that the patient has received first line (1L): $P(2L | 1L)$. The *conditional probability* of 3L is the
177 measure of the probability of receiving 3L at disease progression, given that the patient has received 2L:
178 $P(3L | 2L)$. The *conditional probability* of 4L is the measure of the probability of receiving 4L at disease
179 progression, given that the patient has received 3L: $P(4L | 3L)$. The *conditional probability* of 5L is the
180 measure of the probability of receiving 5L at disease progression, given that the patient has received 4L:
181 $P(5L | 4L)$.

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) = $P(2L) * P(3L | 2L) * P(4L | 3L) * P(5L | 4L)$.

185 OS curves were plotted using the Kaplan-Meier method and compared using the log-rank test. In order to
186 assess the impact of treatment period along with the most relevant clinical characteristics (Heng score,
187 ECOG performance status, synchronous or metachronous metastases, age, gender, liver metastases, lung
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.

194 All statistical tests were two-tailed and p-values less than 0.05 were considered statistically significant.

195 All statistical computations were performed using SPSS for Windows Version 24.0.

196 **RESULTS**

197 **Patients characteristics**

198 Five hundred patients with mRCC were included in the study: 274 started a treatment during the period 1 and
199 226 during the period 2.

200 In the whole study population, the median age was 60 years. Approximately two-thirds of the patients were
201 men (72.8% vs 27.2%) and the predominant histology was clear-cell type (88.3% in period 1 and 87.2% in
202 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.

205

206 **Clinical outcomes**

207 We evaluated the conditional probability of patients for period 1 and period 2 to receive a subsequent
208 treatment line after failure of the previous treatment due to PD, defined as per Response
209 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
211 one therapeutic line vs. 31 patients (22%) in period 2. In fact, patients in period 2 had a higher conditional
212 probability to receive second-line treatment as compared to patients of period 1 (77.2% vs 63.7%, odds ratio
213 [OR] 1.93, 95% Confidence Interval [CI] 1.20-3.11, p=0.0065). Similarly, out of those patients who stopped
214 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).
216 Out of those patients who stopped third-line treatment due to PD, patients in period 2 had a higher
217 conditional probability to receive a fourth-line in comparison to patients treated in the period 1, although
218 difference was not statistically significant (42.9% vs 36.1%, OR 1.33, 95% CI 0.57-3.11, p=0.51). Finally,
219 out of those patients who stopped fourth-line treatment due to PD, patients in the period 2 had a higher
220 conditional probability of receiving a fifth-line in comparison to patients of the period 1, although the
221 difference was not statistically significant (45.5% vs 16.7%, OR 4.17, 95% CI 0.75 – 23.18, p=0.10).

222 For all the lines of treatment beyond first-line, the joint probability of receiving a treatment was higher in
223 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).

225 Median follow-up (mFUP) in the overall population was 59.9 months (95% CI, 48.52-71.33) with a mFUP
226 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.

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

231 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

235 ECOG PS and treatment period (interaction p value = 0.017), mainly driven by a better outcome of PS0
236 patients in the more recent period. In detail, median OS was 29.1 months in ECOG PS0, 17.7 months in
237 ECOG PS1 and 6.6 months in ECOG PS2 patients treated between 2004 and 2010, versus 70.1 months in
238 ECOG PS0, 21.5 months in ECOG PS1 and 1.8 months in ECOG PS2 patients treated in the second period.
239 Patients with a good Heng prognostic score had a mOS of 43.5 months, patients with an intermediate
240 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
241 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
242 3), without significant interaction with treatment period (interaction p value = 0.49). Patients who presented
243 with synchronous metastases at diagnosis had a mOS of 20.7 months, while patients who did not present
244 metastases at diagnosis had a mOS of 39.8 months (HR 1.69, 95% CI 1.36-2.11, p<0.0001) (Figure 4),
245 without significant interaction with treatment period (interaction p value = 0.30).
246 Patients with liver metastases at diagnosis had a mOS of 15.7 months, while patients without liver metastases
247 had a mOS of 30.3 months (HR at univariate analysis 1.84, 95% CI 1.39-2.42, p<0.0001), without significant
248 interaction with treatment period (interaction p value = 0.19). Patients with lung metastases had a mOS of
249 24.7 months, while patients without lung metastases had a mOS of 29.0 months, and the difference was not
250 statistically significant at univariate analysis (HR 1.19, 95% CI 0.95 – 1.19, p=0.14), without significant
251 interaction with treatment period (interaction p value = 0.38).
252 Patients who presented with lymphnodes involvement at diagnosis of metastatic disease had a shorter mOS
253 in comparison with patients without nodal metastases (mOS was 21.1 and 34.0 months respectively). At
254 univariate analysis, the presence of metastases at lymphnodes was significantly associated with a worst
255 survival (HR 1.33, 95% CI 1.07-1.65, p=0.01). There was no significant interaction between lymphnode
256 metastases and treatment period (interaction p value = 0.32).
257 Brain metastases were associated with a shorter survival (median OS was 12.3 vs 27.7 months; HR at
258 univariate analysis 1.96, 95% CI 1.17-3.29, p=0.01), without significant interaction with treatment period
259 (interaction p value = 0.06), while the presence of bone metastases was not significantly associated with
260 mOS (mOS was 23.3 for patients with bone metastases vs. 28.3 months for patients without, HR 1.25, 95%
261 CI 0.98 – 1.60, p=0.07), without significant interaction with treatment period (interaction p value = 0.59).
262 At multivariate analysis (Table 3): Heng prognostic score, ECOG PS, presence of metastases at diagnosis
263 were significantly associated with survival while the difference between the 2 time periods did not reach
264 statistical significance (HR for period 2 vs period 1 0.77, 95% CI 0.59 – 1.01, p=0.06).

265

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- α) and has greatly improved patient outcomes including
272 overall survival (18).

273 With the approval of new targeted agents for mRCC, several questions raised about placement and the
274 sequential use into the algorithm in the real-world setting .

275 The restrictive inclusion criteria of randomized clinical trials limit the generalizability of the results to the
276 broader population of mRCC patients in the real world setting (19). Expanded access trials have provided
277 insights into real-world outcomes before the approval of the new drugs, but detailed data on practice patterns
278 and outcome across sequential lines of therapy are still limited (20).

279 We retrospectively collected data from 500 mRCC patients treated at Istituto Nazionale dei Tumori of Milan
280 (Italy). Patients were divided into two time periods on the basis of the beginning of treatment for metastatic
281 disease: patients of period 1 started a treatment between 2004 and 2010, while patients of period 2 started a
282 treatment between 2011 and 2017. We aimed to make an overview of real-world clinical practice for mRCC
283 and investigate difference in OS and trends in exposure to multiple lines of treatment between patients who
284 started first-line therapy in the two periods.

285 In our analysis, a significant improvement in OS occurred during the recent years in the mRCC population:
286 from a mOS of 22.8 months (2004-2010) to 38.2 months (2011-2017), although the difference did not reach
287 statistical significance at the multivariate analysis. We also described an increase, in the period 2, of the
288 number of patients who received more therapeutic lines at PD in comparison to patients treated in period 1.

289 This improvement over the years may be explained by the intensified medical and surgical strategies in a
290 multidisciplinary approach, aiming to provide the optimal treatment to patients during the course of the
291 disease (21). The increase of locoregional treatments in addition to surgery (in particular radiotherapy and
292 innovative ablation techniques, including radiofrequency ablation, microwave ablation or cryoablation) has
293 been highlighted in our report and the difference in the use of different therapeutic approaches in the period 2
294 in comparison to the period 1 was statistically significant ($p < 0.0001$). The role of cytoreductive nephrectomy
295 remains debated and should be carefully considered according to patients' and disease characteristics (22).

296 Second, for patients who started a treatment between 2011 and 2017, 4 new therapeutic agents for the
297 treatment of mRCC were available in Italy (axitinib, pazopanib, nivolumab and cabozantinib): the
298 availability of new drugs has increased the lines of treatment received by patients. As a consequence,
299 survival of patients receiving more therapeutic agents has increased. A significant association between
300 increased survival and treatment beyond first-line therapy has been highlighted (23). In our analysis we
301 showed that patients treated in period 2 were more likely to receive different therapeutic lines compared to
302 those treated in the period 1 at PD.

303 Third, in view of an increased number of drugs available, therapy and adverse events (AEs) management has
304 also improved: new schedules have allowed to tailor treatment on patient characteristics (24), allowing to
305 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 PD in comparison to period 1 and a relevant
313 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
316 understanding of possible factors able to influence the outcome (ie, improved number of therapies, changes
317 in 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.

320

321 **CONCLUSION**

322 These real-life data support and confirm the positive impact of novel therapies and multimodal approach for
323 mRCC. Prognosis of mRCC patients will likely to improve with either the optimization of current targeted
324 therapy and the approval of novel agents with different mechanisms of action.

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326 **CLINICAL PRACTICE POINTS**

- 327 • In the last decade, the introduction of novel targeted agents has revolutionized the treatment of
328 mRCC improving overall survival.
- 329 • We retrospectively collected data from 500 patients with mRCC treated at Istituto Nazionale dei
330 Tumori of Milan, which were divided in two time periods on the basis of the start of the first-line
331 therapy (period 1 2004-2010 and period 2 2011-2017 respectively). The aim of our analysis was to
332 describe trends in exposure to multiple lines of treatment and analyze differences in survival
333 between period 1 and period 2.
- 334 • Our real-world study described a relevant improvement in OS during the recent years in the mRCC
335 population. We also described an increase, in the last 5 years, of the number of patients who received
336 more therapeutic lines at PD in comparison to patients treated between 2004 and 2010.
- 337 • These results may help physicians in daily practice to manage patients with mRCC in order to
338 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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Characteristics	Period 1		Period 2		P value*
	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)					
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
Chemotherapy	1	0.4	6	2.7	0.03
Cytokines	44	16.1	0	0.0	<0.0001

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 431 Abbreviations: TKIs: tyrosine kinase inhibitors; VEGF: Vascular Endothelial Growth Factor; mTOR:
 432 mammalian target of rapamycin
 433 *Chi square
 434 **out of patients metastatic at diagnosis
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438 **Table 2. Conditional probability of receiving a subsequent therapeutic line at failure of the previous**
 439 **line because of disease progression (PD).**
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	Period 1 (2004-2010) n=274	Period 2 (2011-2017) n=226	Odds ratio (95% CI)	p value (Chi square)
1st line	274 (100%)	226 (100%)	n.a.	n.a.
2nd line / Failure of 1st line	163 / 256 (63.7%)	105 / 136 (77.2%)	1.93 (1.20 – 3.11)	0.0065
3rd line / Failure of 2nd line	74 / 154 (48.1%)	55 / 79 (69.6%)	2.48 (1.40 – 4.40)	0.002
4th line / Failure of 3rd line	22 / 61 (36.1%)	15 / 35 (42.9%)	1.33 (0.57 – 3.11)	0.51
5th line / Failure of 4th line	3 / 18 (16.7%)	5 / 11 (45.5%)	4.17 (0.75 – 23.18)	0.10

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442 Abbreviations: CI: Confidence Interval

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

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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

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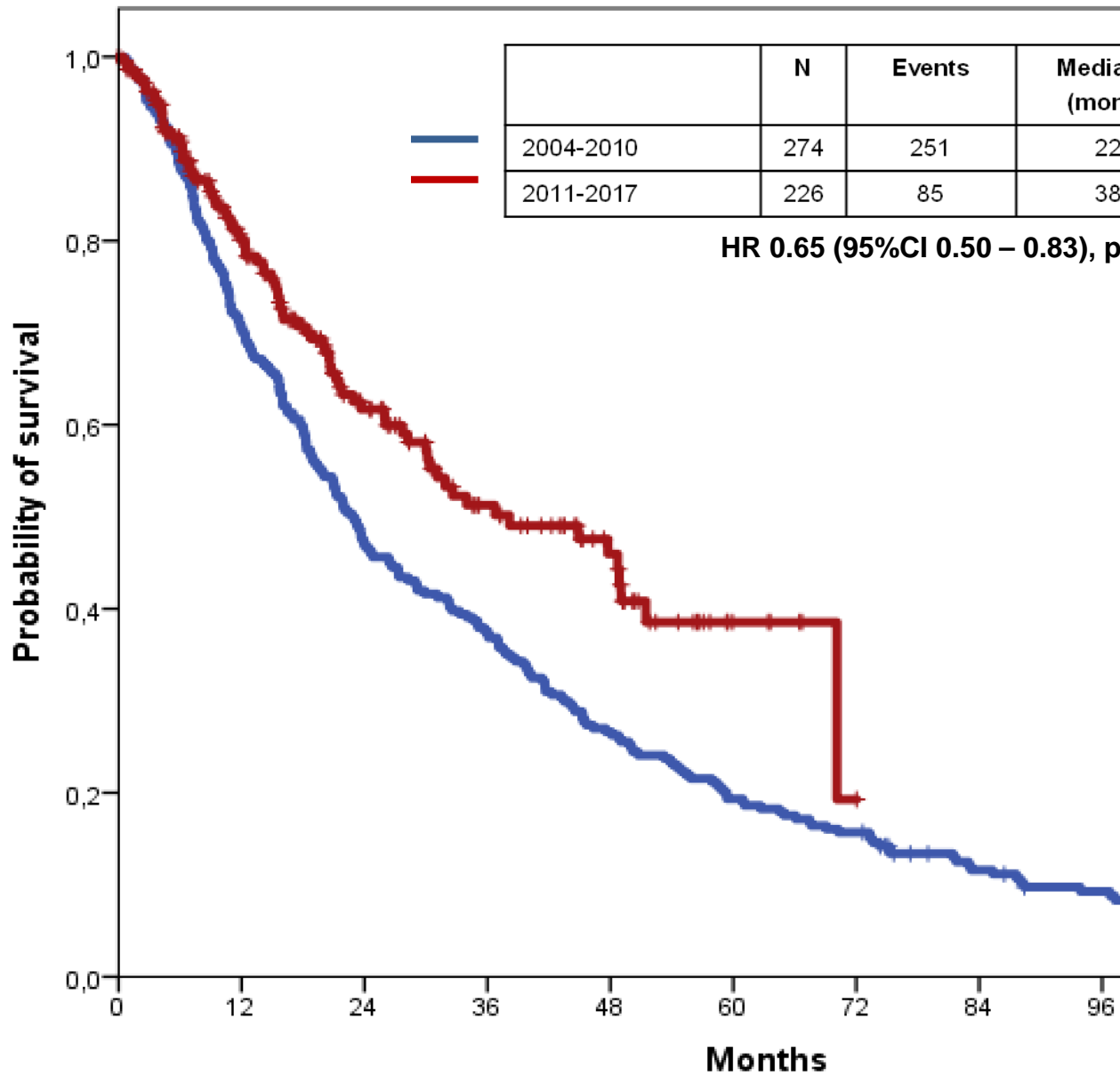
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472 **Figure 1. Kaplan-Meier estimates of overall survival for patients treated in Period 1 and Period 2.**

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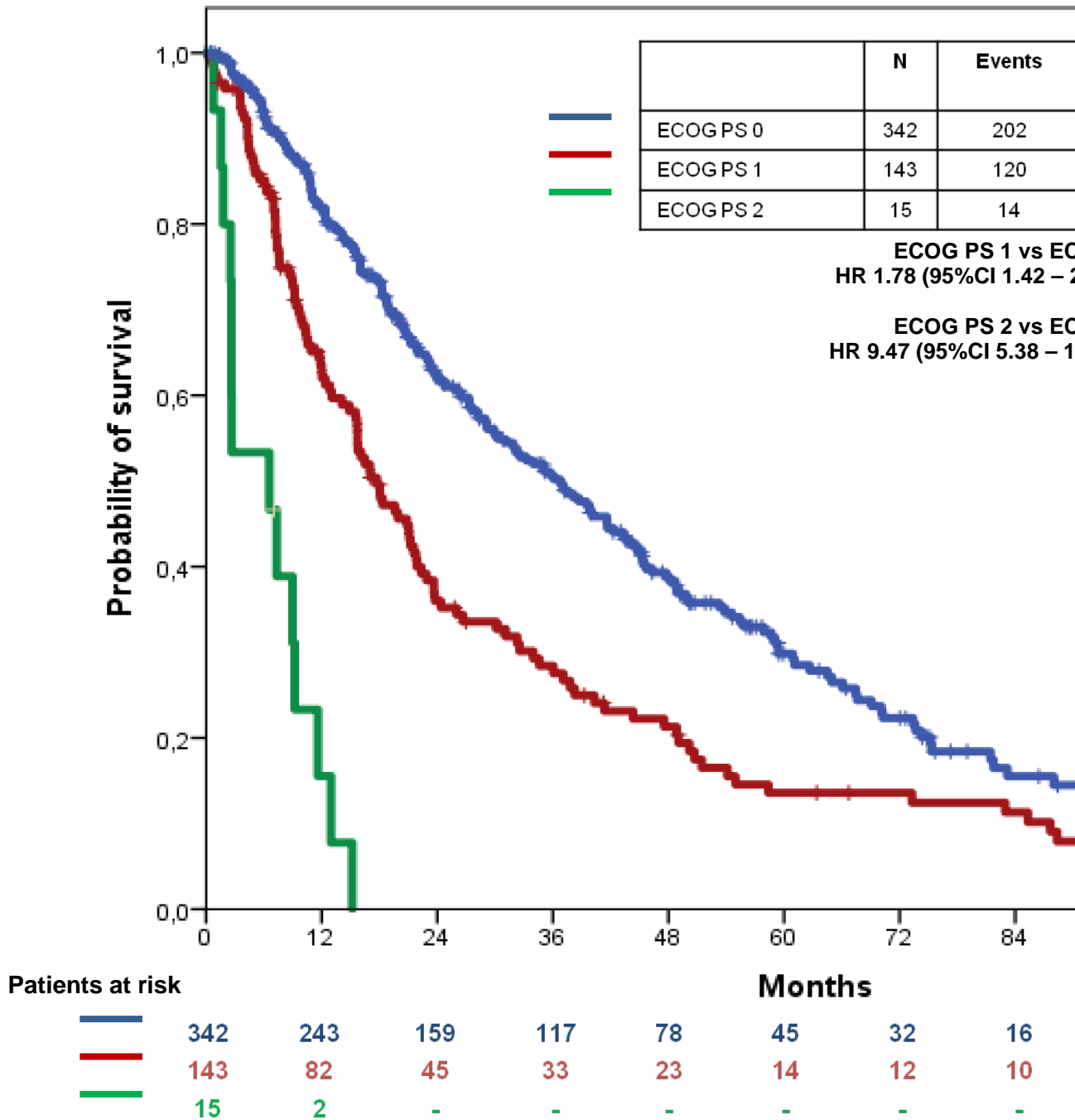


Patients at risk		0	12	24	36	48	60	72	84	96
—	274	194	129	103	73	53	43	26	1	0
—	226	133	75	47	28	6	1	-	-	-

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476 **Figure 2. Kaplan-Meier estimates of overall survival according to ECOG PS in the whole population.**



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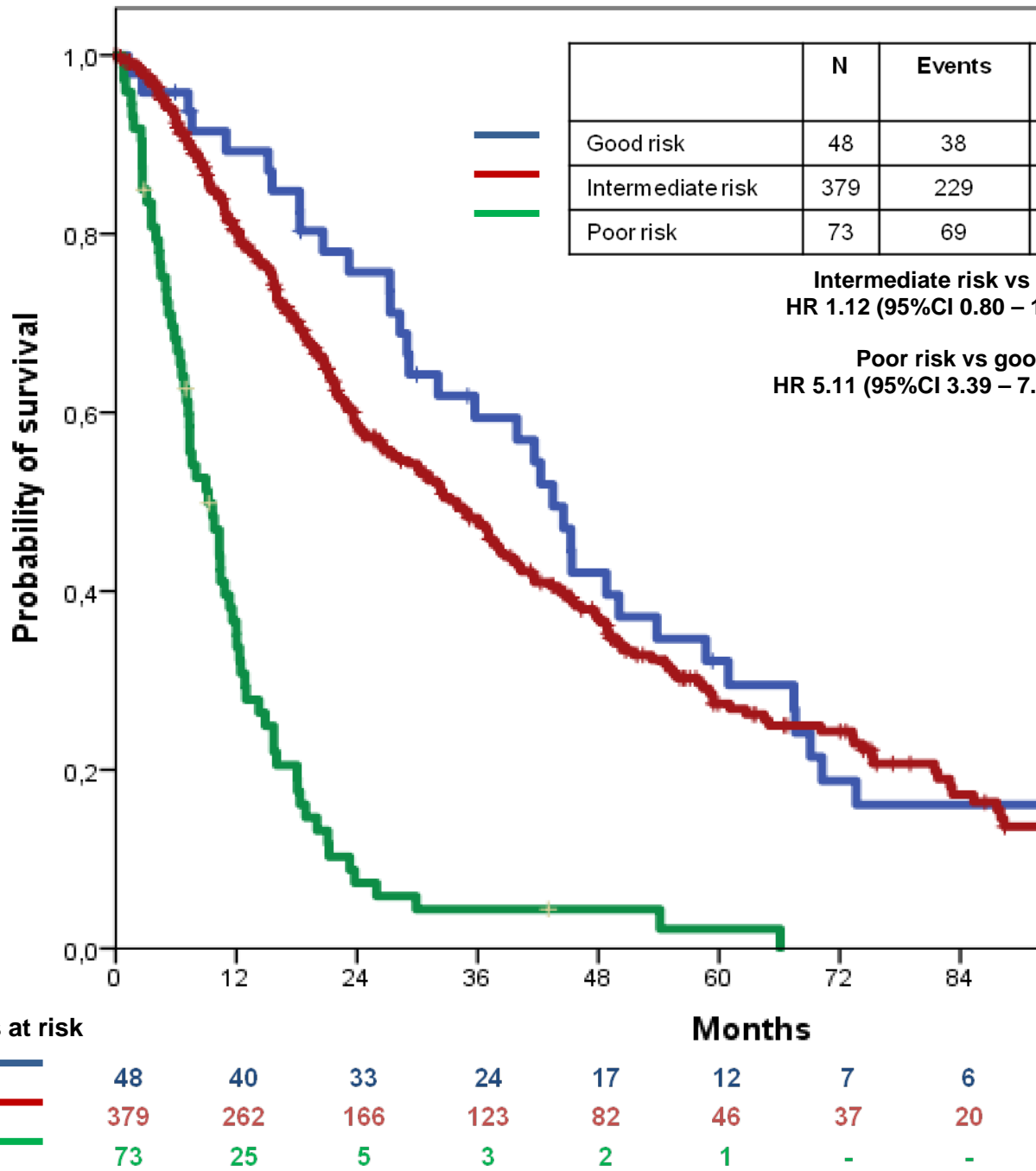
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482 **Figure 3. Kaplan-Meier estimates of overall survival according to Heng prognostic score in the whole**
 483 **population.**

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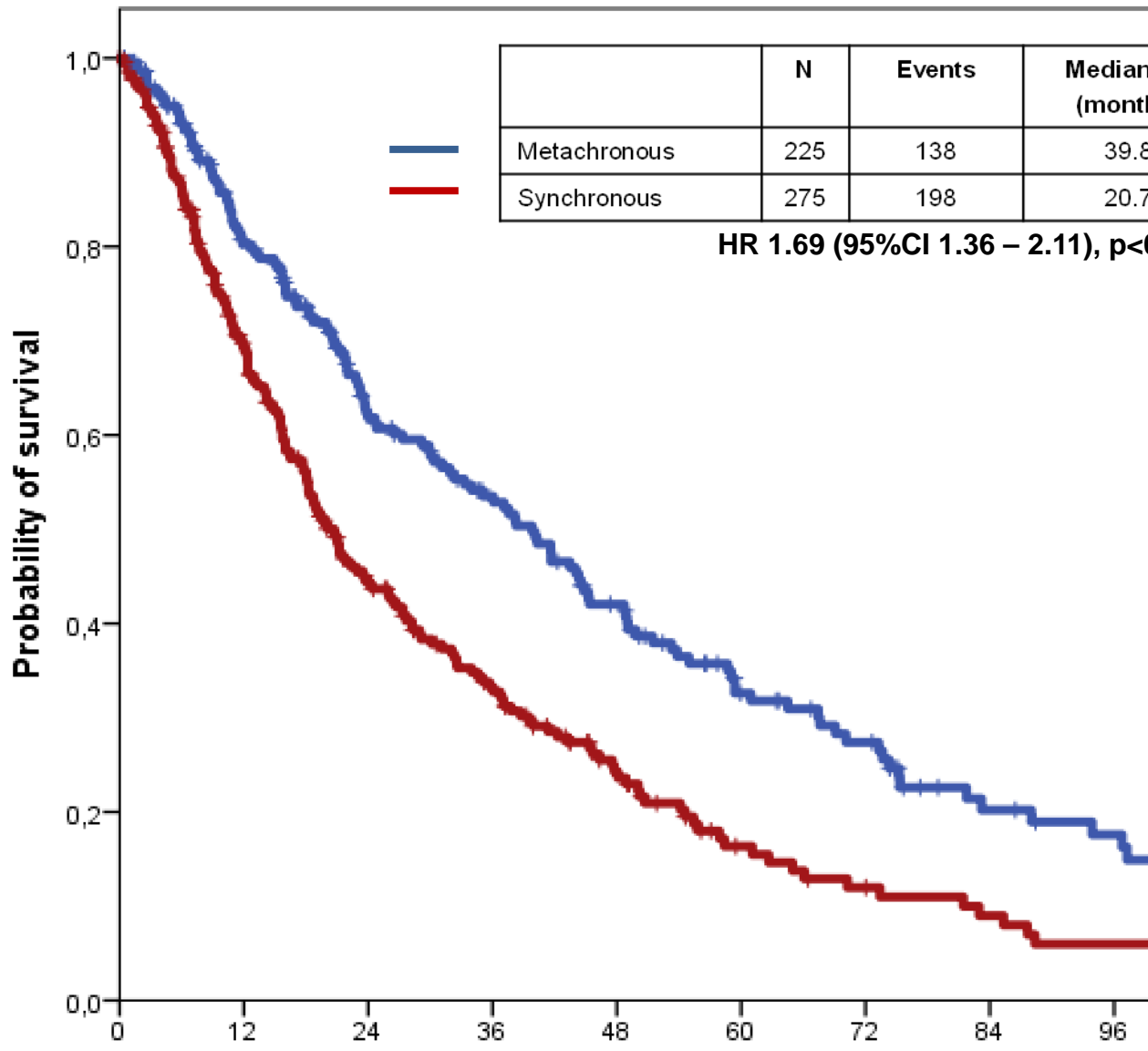


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487 **Figure 4. Kaplan-Meier estimates of overall survival according to synchronous or metachronous**
 488 **metastases in the whole population.**

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Patients at risk

	0	12	24	36	48	60	72	84	96
Metachronous	225	160	108	85	63	40	31	17	13
Synchronous	275	167	96	65	38	19	13	9	6

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