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

Exposure to multiple lines of treatment and survival of patients with metastatic renal cell carcinoma: a real-world analysis.

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CONFLICT OF INTEREST STATEMENT

Dr. Giuseppe Procopio reports receiving fees for serving on advisory boards from Bayer, Bristol-Myers Squibb (BMS), Ipsen, Novartis and Pfizer.

Dr. Elena Verzoni reports receiving fees for serving on advisory boards from Pfizer and Novartis.

Prof. Massimo Di Maio acted as a consultant for Merck Sharp & Dohme, Bristol Myers Squibb, Janssen, Amgen, AstraZeneca.

The other authors declare to have no conflicts of interest.

MICROABSTRACT

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.

ABSTRACT

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).

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

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).

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

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

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).

Until 2005, interferon alfa (IFN-α) 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).

Recently, a better understanding of the biological and molecular basis of kidney cancer has led to the development and approval of new targeted agents: many of them are directed against the vascular endothelial growth factor receptors (VEGFRs) (bevacizumab, sorafenib, sunitinib, pazopanib, axitinib and cabozantinib) (7-11), the mammalian target of rapamycin (mTOR) pathway (everolimus and temsirolimus) (12, 13) and the 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 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.

PATIENTS AND METHODS

Patient population and data sources

Data were retrospectively drawn from the Genitourinary Cancer Unit Database of the Istituto Nazionale dei Tumori of Milan (Italy). Patients were consecutively registered in the database. The data collected included 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 related to each treatment. Follow-up on each patient is conducted every six months to assess current vital status. We restricted our study to the advanced RCC cases only, and excluded localized disease cases, because systemic therapy is currently approved only in the locally advanced, unresectable, or metastatic 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).

Statistical analysis

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 received a specific treatment line by the number of patients who had progressed to the previous line. The c*onditional probability* (P) of 2L is the measure of the probability of receiving 2L at disease progression, given that the patient has received first line (1L): P(2L | 1L). The c*onditional probability* of 3L is the measure of the probability of receiving 3L at disease progression, given that the patient has received 2L: P(3L | 2L). The c*onditional probability* of 4L is the measure of the probability of receiving 4L at disease progression, given that the patient has received 3L: P(4L | 3L). The c*onditional probability* of 5L is the measure of the probability of receiving 5L at disease progression, given that the patient has received 4L: P(5L | 4L).

Consequently, the joint probability for a patient to receive each line was calculated as follows: joint probability (2L,3L) = P(2L) * P(3L | 2L); joint probability (2L,3L,4L) = P(2L) * P(3L | 2L) * P(4L | 3L); 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 assess the impact of treatment period along with the most relevant clinical characteristics (Heng score, ECOG performance status, synchronous or metachronous metastases, age, gender, liver metastases, lung metastases, lymphnodes metastases, bone metastases, brain metastases), multivariable analysis was performed, using the Cox regression model. In order to assess the potential interaction between treatment period and each clinical characteristic, a Cox model including that characteristic, treatment period and their interaction was performed.The chi square test or the Fisher exact test, as appropriate, were used to compare categorical variables among the groups. Wilcoxon test was used to compare continuous variables among the 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.

RESULTS

Patients characteristics

Five hundred patients with mRCC were included in the study: 274 started a treatment during the period 1 and 226 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 (75.2%) in period 2.

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

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).

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-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 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 period 2 respectively.

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 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 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 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).

DISCUSSION

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

With the approval of new targeted agents for mRCC, several questions raised about placement and the sequential 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.

Our analysis has some limitations: first of all the retrospective nature of the study, which sometimes led to incomplete or late entries of clinical data, or data input errors. Another limitation is the lack of some information regarding key laboratory values, as well as the lack of a standardization in imaging interpretations to define treatment outcomes. A small number of patients included in our database were enrolled into expanded access programs, but the impact on this analysis is negligible. Finally, the follow-up of patients is different between the two periods of time, so that a significantly lower absolute number of

patients in period 2 received subsequent lines of therapy at PD in comparison to period 1 and a relevant percentage of patients who started a therapy in period 2 are still on treatment: this represents a potential bias factor of the analysis.

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, changes in therapy and adverse events management).

Despite these limitations, we identified a positive trend in survival in mRCC, that seems to reflect the improvement in therapeutic strategies for this disease.

CONCLUSION

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.

CLINICAL PRACTICE POINTS

- 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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Table 1. Main characteristics of patients who started a treatment in period 1 (2004-2010) and period 2 (2011-2017).

	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)					
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

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

*Chi square

**out of patients metastatic at diagnosis

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

	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

Abbreviations: CI: Confidence Interval

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**

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

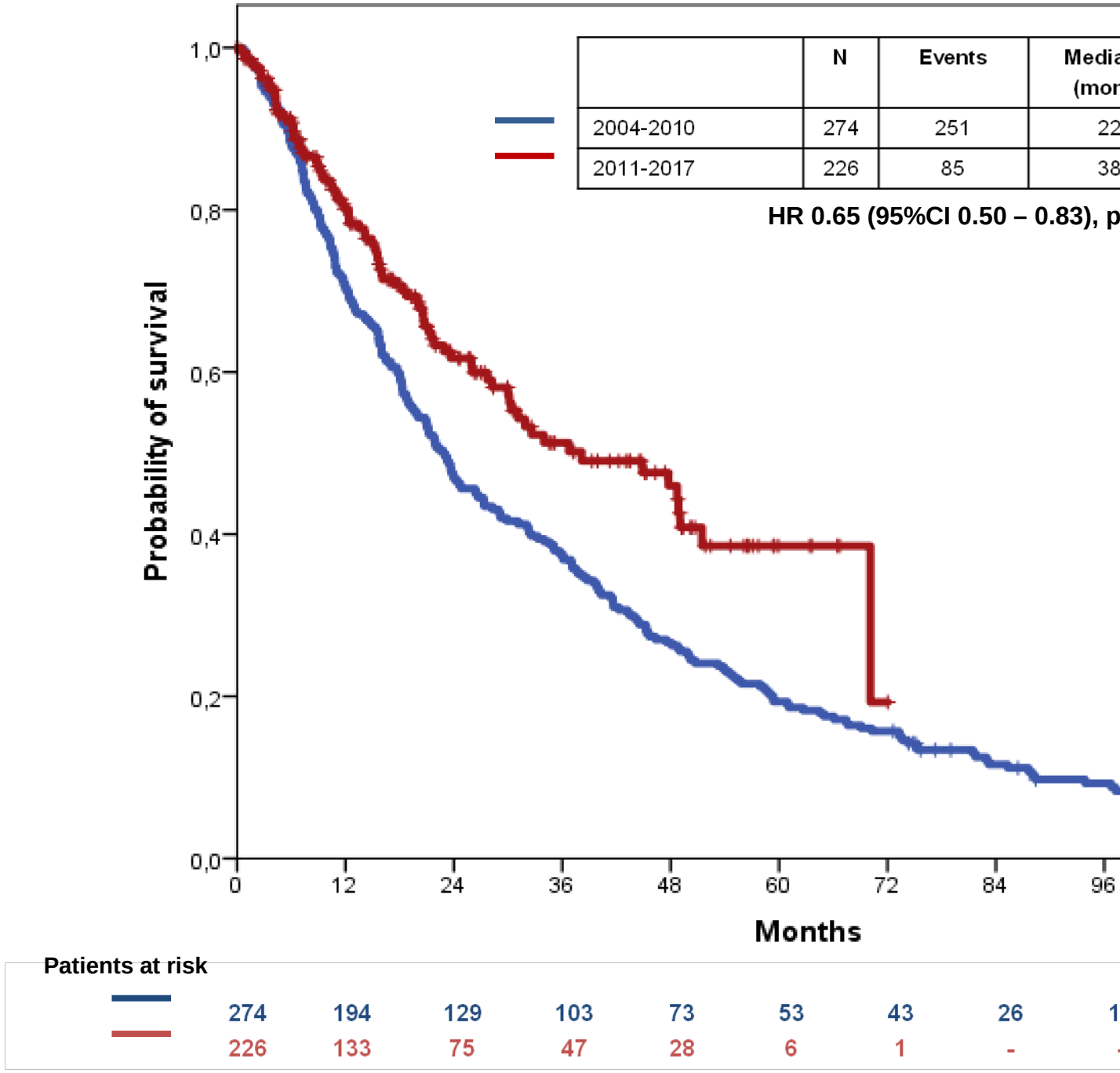


Figure 2. Kaplan-Meier estimates of overall survival according to ECOG PS in the whole population.

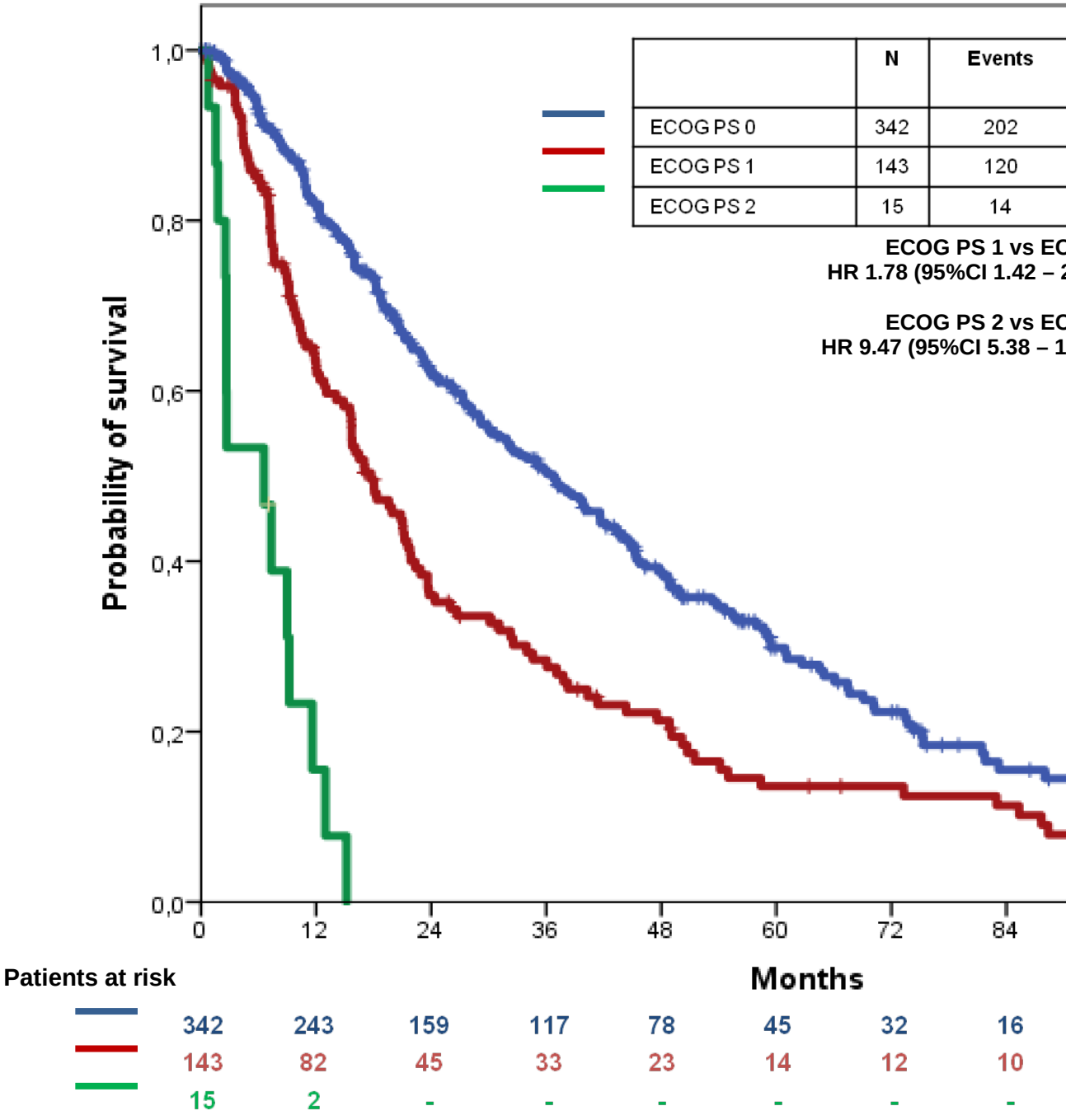


Figure 3. Kaplan-Meier estimates of overall survival according to Heng prognostic score in the whole population.

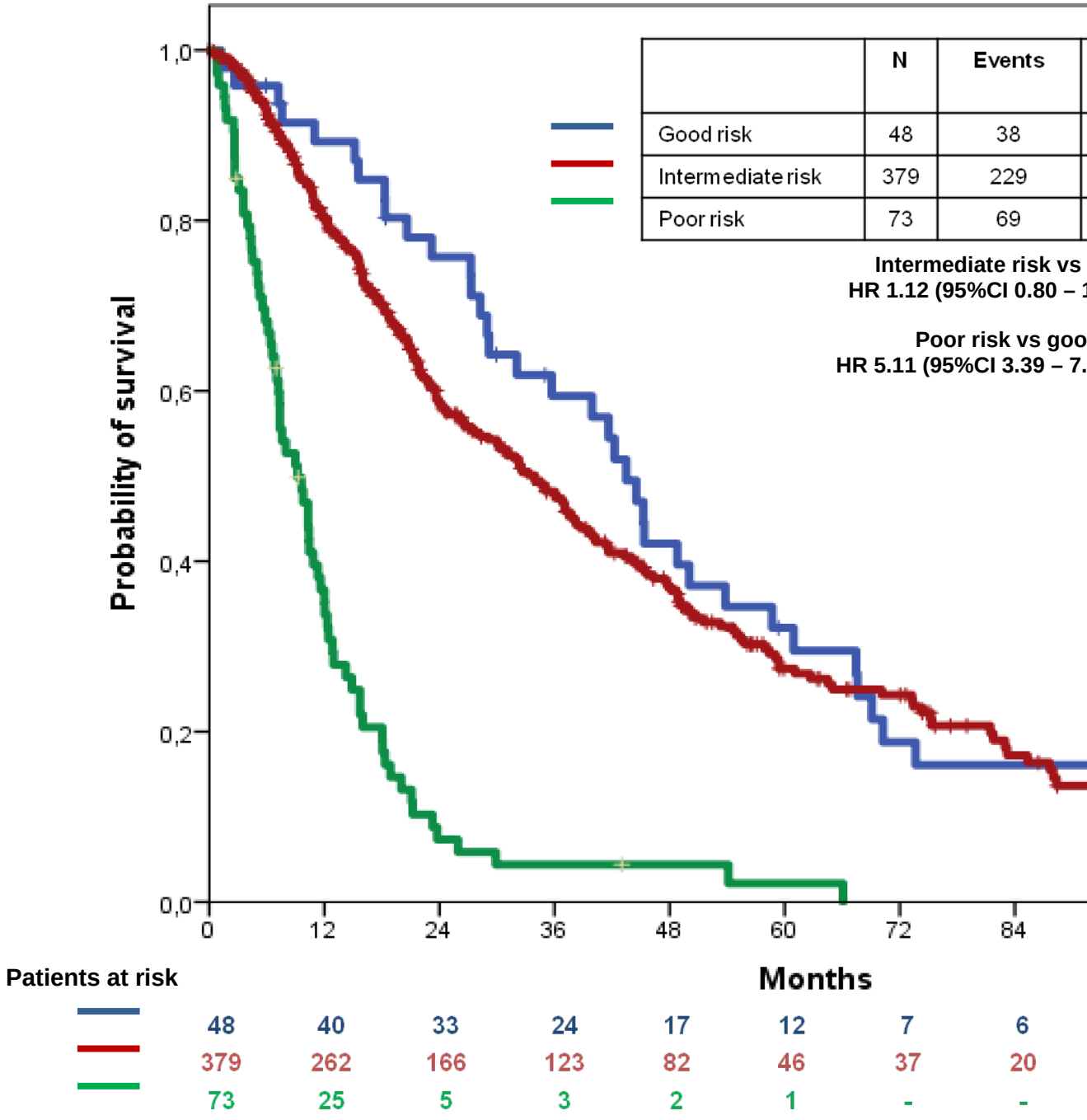
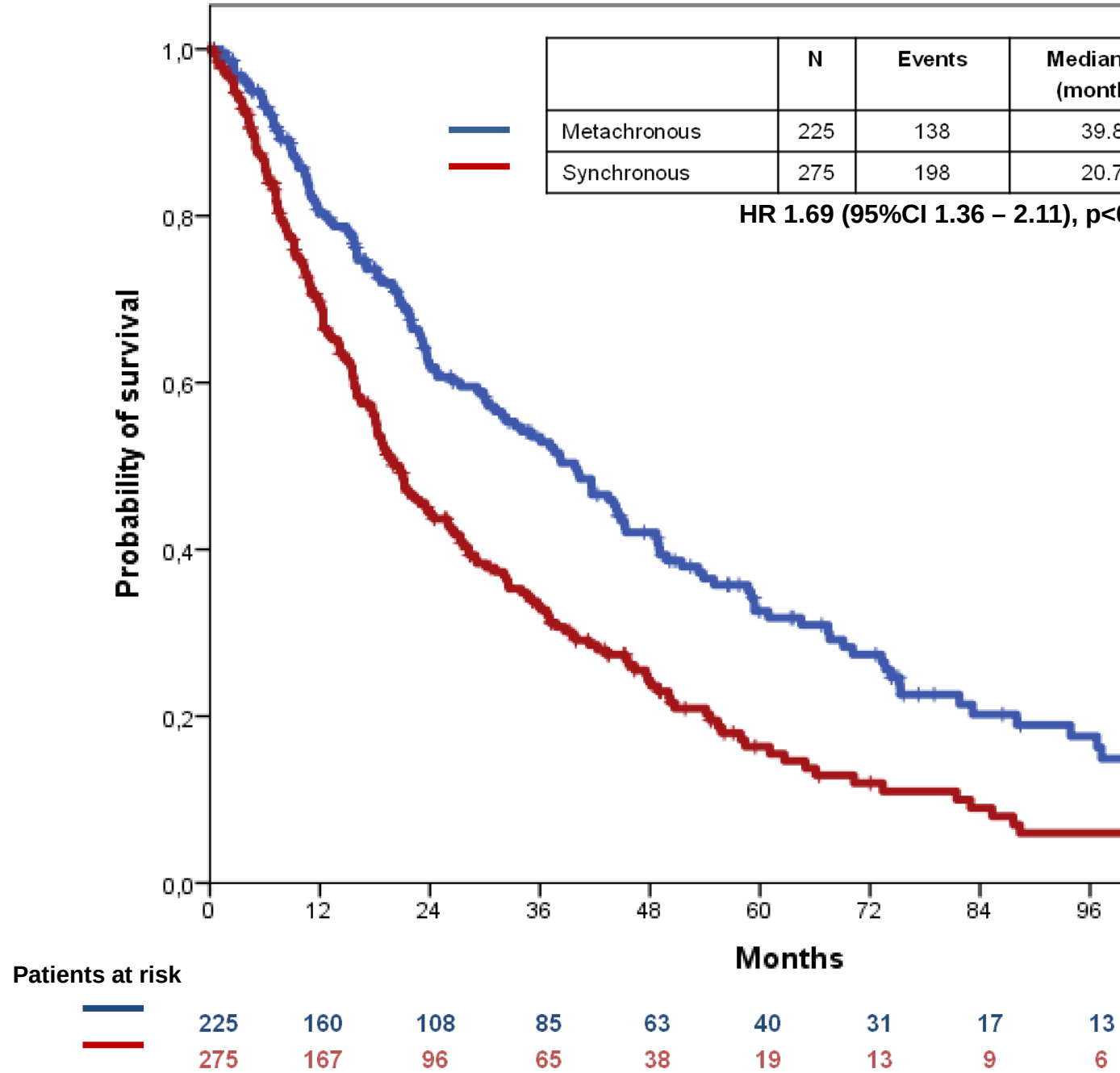


Figure 4. Kaplan-Meier estimates of overall survival according to synchronous or metachronous metastases in the whole population.


N
Events
Median (month
Metachronous
225
138
39.8
Synchronous
275
198
20.7
HR 1.69 (95%CI 1.36 – 2.11), p<
Probability of survival
1,0
0,8
0,6
0,4
0,2
0,0
0
12
24
36
48
60
72
84
96
Months
Patients at risk
225 160 108 85 63 40 31 17 13
275 167 96 65 38 19 13 9 6