

"Nephrectomy improves overall survival in patients with metastatic renal cell carcinoma in cases of favorable MSKCC or ECOG prognostic features"

Mathieu, Romain ; Pignot, Géraldine ; Ingles, Alexandre ; Crepel, Maxime ; Bigot, Pierre ; Bernhard, Jean-Christophe ; Joly, Florence ; Guy, Laurent ; Ravaud, Alain ; Azzouzi, Abdel Rahmene ; Gravis, Gwenaëlle ; Chevreau, Christine ; Zini, Laurent ; Lang, Hervé ; Pfister, Christian ; Lechevallier, Eric ; Fais, Pierre-Olivier ; Berger, Julien ; Vayleux, Bertrand ; Roupret, Morgan ; Audenet, François ; Descazeaud, Aurelien ; Rigaud, Jerome ; Machiels, Jean-Pascal ; Staehler, Michael ; Salomon, Laurent ; Ferriere, Jean-Marie ; Kleinclauss, Francois ; Bensalah, Karim ; Patard, Jean-Jacques

Abstract

OBJECTIVES: The role of cytoreductive nephrectomy (CN) in the treatment of patients harboring metastatic renal cell carcinoma (mRCC) has become controversial since the emergence of effective targeted therapies. The aim of our study was to compare the overall survival (OS) between CN and non-CN groups of patients presenting with mRCC in the era of targeted drugs and to assess these outcomes among the different Memorial Sloan-Kettering Cancer Center (MSKCC) and The Eastern Cooperative Oncology Group (ECOG) performance status subgroups. **METHODS AND MATERIALS:** A total of 351 patients with mRCC at diagnosis recruited from 18 tertiary care centers who had been treated with systemic treatment were included in this retrospective study. OS was assessed by the Kaplan-Meier method according to the completion of a CN. The population was subsequently stratified according to MSKCC and ECOG prognostic groups. **RESULTS:** Median OS in the entire cohort was 37.1 months. Median OS was significantly impro...

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Original article

Nephrectomy improves overall survival in patients with metastatic renal cell carcinoma in cases of favorable MSKCC or ECOG prognostic features

Romain Mathieu, M.D.^a, Géraldine Pignot, M.D., Ph.D.^{b,*}, Alexandre Ingles, M.D.^b,
 Maxime Crepel, M.D.^a, Pierre Bigot, M.D.^c, Jean-Christophe Bernhard, M.D.^d,
 Florence Joly, M.D., Ph.D.^e, Laurent Guy, M.D., Ph.D.^f, Alain Ravaut, M.D., Ph.D.^d,
 Abdel Rahmene Azzouzi, M.D., Ph.D.^c, Gwenaelle Gravis, M.D., Ph.D.^g,
 Christine Chevreau, M.D., Ph.D.^h, Laurent Zini, M.D., Ph.D.ⁱ, Hervé Lang, M.D., Ph.D.^j,
 Christian Pfister, M.D., Ph.D.^k, Eric Lechevallier, M.D., Ph.D.^l, Pierre-Olivier Fais, M.D.^l,
 Julien Berger, M.D.^m, Bertrand Vayleux, M.D., Ph.D.ⁿ, Morgan Roupret, M.D., Ph.D.^o,
 François Audenet, M.D.^o, Aurelien Descazeaud, M.D., Ph.D.^m, Jerome Rigaud, M.D., Ph.D.ⁿ,
 Jean-Pascal Machiels, M.D., Ph.D.^p, Michael Staehler, M.D., Ph.D.^q, Laurent Salomon,
 M.D., Ph.D.^r, Jean-Marie Ferriere, M.D., Ph.D.^d, Francois Kleinclauss, M.D., Ph.D.^s,
 Karim Bensalah, M.D., Ph.D.^a, Jean-Jacques Patard, M.D., Ph.D.^b

^a Department of Urology, Pontchaillou Hospital, Rennes University, Rennes, France

^b Department of Urology, Bicêtre Hospital, Paris XI University, Le Kremlin Bicêtre, France

^c Department of Urology, Angers University Hospital, Angers, France

^d Departments of Urology and Oncology, Bordeaux University, Bordeaux, France

^e Department of Oncology, Centre François Baclesse, Caen, France

^f Departments of Urology, Clermont-Ferrand University, Clermont-Ferrand, France

^g Department of Oncology, Institut Paoli-Calmettes, Marseille, France

^h Department of Oncology, Institut Claudius Regaud, Toulouse University, Toulouse, France

ⁱ Department of Urology, Huriez Hospital, Lille Nord de France University, Lille, France

^j Department of Urology, Strasbourg Hospital, University of Strasbourg, Strasbourg, France

^k Department of Urology, Rouen University Hospital, Rouen, France

^l Department of Urology, La Conception Hospital, Marseille University, Marseille, France

^m Department of Urology, Dupuytren Hospital, Limoges University, Limoges, France

ⁿ Department of Urology, Hôtel Dieu Hospital, Nantes University, Nantes, France

^o Department of Urology, Pitié Salpêtrière Hospital, Paris VI University, Paris, France

^p Department of Oncology, Cliniques Universitaires St-Luc, Louvain University, Brussels, Belgium

^q Department of Urology, Ludwig-Maximilian-University of Munich, Munchen, Germany

^r Department of Urology, Henri Mondor Hospital, Paris XII University, Créteil, France

^s Department of Urology, Besancon University, Besancon, France

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Abstract

Objectives: The role of cytoreductive nephrectomy (CN) in the treatment of patients harboring metastatic renal cell carcinoma (mRCC) has become controversial since the emergence of effective targeted therapies. The aim of our study was to compare the overall survival (OS) between

¹Equally contributing author.

* Corresponding author. Tel.: +33-1-45-21-3698; fax: +33-1-45-21-2170.

E-mail addresses: geraldine.pignot@bct.aphp.fr, gg_pignot@yahoo.fr (G. Pignot).

CN and non-CN groups of patients presenting with mRCC in the era of targeted drugs and to assess these outcomes among the different Memorial Sloan-Kettering Cancer Center (MSKCC) and The Eastern Cooperative Oncology Group (ECOG) performance status subgroups.

Methods and materials: A total of 351 patients with mRCC at diagnosis recruited from 18 tertiary care centers who had been treated with systemic treatment were included in this retrospective study. OS was assessed by the Kaplan-Meier method according to the completion of a CN. The population was subsequently stratified according to MSKCC and ECOG prognostic groups.

Results: Median OS in the entire cohort was 37.1 months. Median OS was significantly improved for patients who underwent CN (16.4 vs. 38.1 months, $P < 0.001$). However, subgroup analysis demonstrated that OS improvement after CN was only significant among the patients with an ECOG score of 0 to 1 (16.7 vs. 43.3 months, $P = 0.03$) and the group of patients with good and intermediate MSKCC score (16.8 vs. 42.4 months, $P = 0.02$). On the contrary, this benefit was not significant for the patients with an ECOG score of 2 to 3 (8.0 vs. 12.6 months, $P = 0.8$) or the group with poor MSKCC score (5.2 vs. 5.2, $P = 0.9$).

Conclusions: CN improves OS in patients with mRCC. However, this effect does not seem to be significant for the patients in ECOG performance status groups of 2 to 3 or poor MSKCC prognostic group. © 2015 Elsevier Inc. All rights reserved.

Keywords: Carcinoma; Renal cell; Nephrectomy; Survival

1. Introduction

Cytoreductive nephrectomy (CN) is still considered standard of care for patients with metastatic renal cell carcinoma (mRCC) [1]. There are 2 prospective randomized trials that have proven the overall survival (OS) benefit of CN in patients with mRCC in the era of immunotherapy [2,3]. In a pooled analysis of both the trials, CN was associated with a decreased risk of death and a mean increased OS of 6 months [4].

Since the completion of these studies, new treatments have emerged. Targeted therapies (vascular endothelial growth factor monoclonal antibodies, tyrosine kinase inhibitors, and mammalian target of rapamycin inhibitors) have been validated and proven superior to immunotherapy by several phase 3 clinical trials [5–8]. Since then, these treatments have become cornerstones in the therapeutic strategies for patients with mRCC [1]. Even if these molecules have been evaluated in patients who previously underwent nephrectomy, their efficacy has also been reported on primary tumors [9]. Consequently, interest of CN is now debated in the era of targeted therapies. It has been reported that CN has already declined since the approval of antiangiogenic treatments [10].

We thought to assess the effect of CN on OS for patients with mRCC treated with systemic drugs including targeted therapies and to analyze this effect among the different Memorial Sloan-Kettering Cancer Center (MSKCC) and the Eastern Cooperative Oncology Group (ECOG) performance status prognostic subgroups.

2. Methods and materials

2.1. Data collection

The study included patients having mRCC from 18 academic centers from 1999 to 2009.

Patients received systemic drugs alone or after CN. Systemic drugs included oral sunitinib or sorafenib, temsirolimus, interferon, bevacizumab, or interleukin-2 according to ongoing expert guidelines. The CN procedure was performed by open access or laparoscopically. If CN was not performed,

histological confirmation of RCC was performed by biopsies from primary or metastatic lesions or both. Patient records were retrospectively extracted from each institutional database to obtain information regarding age, body mass index, ECOG–performance status (ECOG-PS), American Society of Anesthesiologists score, MSKCC score, TNM category, tumor size, histology, Fuhrman grade, and survival outcomes.

Tumor category was determined according to the 2002 Union Internationale Contre le Cancer revised TNM classification [11]. Malignancy on histology was reported according to the Heidelberg classification, and tumor grading was assessed according to the Fuhrman grading scheme by the pathologists of each institution [12,13]. ECOG-PS, American Society of Anesthesiologists, and MSKCC scores were determined according to the original criteria [14–16].

2.2. Statistical analysis

The population was subsequently stratified according to ECOG and MSKCC prognostic groups. Clinicopathological variables were compared by using the chi-square test or Fischer exact test for qualitative values and the Student *t* test for quantitative values. All *P* values were 2 sided, and a $P < 0.05$ was considered significant. OS was estimated in different prognostic groups according to the completion of a nephrectomy using the Kaplan-Meier method and compared with the log-rank test. All data analysis was processed through the SPSS 12.0 statistical software (Chicago, IL).

3. Results

3.1. Patients and tumors characteristics

A total of 351 patients with mRCC at diagnosis were included in this retrospective study. Main patient and tumor characteristics, especially TNM category, nuclear grade, and histology, are described in Table 1. The patient cohort included 252 men (71.8%) and 99 women (28.2%). Median age at diagnosis was 60.2 years [19–91] and median tumor size was 8.5 cm. ECOG-PS of 2 to 3 and poor MSKCC prognosis were

Table 1
Patients and tumors characteristics

Median age at diagnosis, y (range)	60.2 (19–91)
Sex, n (%)	
Males	252 (71.8)
Females	99 (28.2)
ASA score, n (%)	
1	91 (25.9)
2	173 (49.3)
≥3	87 (24.8)
ECOG score before nephrectomy, n (%)	
0	128 (36.4)
1	155 (44.2)
2	54 (15.4)
3	14 (4.0)
MSKCC risk group before nephrectomy, n (%)	
Good	88 (25.0)
Intermediate	227 (64.7)
Poor	36 (10.3)
Median tumor size, cm (range)	8.5 (3–14)
Histological subtype, n (%)	
Clear cell carcinoma	306 (87.2)
Papillary carcinoma	25 (7.1)
Other	20 (5.7)
T category, n (%)	
T1	38 (10.8)
T2	43 (12.3)
T3-4	270 (76.9)
Fuhrman grade, n (%)	
1	7 (2.0)
2	67 (19.1)
3	177 (50.4)
4	100 (28.5)
Number of metastatic sites at diagnosis, n (%)	
1	109 (31.1)
2	126 (35.9)
3 Or more	116 (33.0)

ASA = American Society of Anesthesiologists.

noted in 19.4% and 10.3% of the patients, respectively. Most of the patients (67%) presented with 1 or 2 metastatic sites at diagnosis.

3.2. Treatment strategies

CN was performed in 298 patients (84.9%). First-line systemic treatment was initiated with a median time of 3 months (range: 0–164) after CN and included antiangiogenic drugs for 69.4% of patients (sunitinib, 39.0%; sorafenib, 18.5%; temsirolimus, 7.1%; and bevacizumab, 4.8%). Details of first-line systemic treatment are presented in Table 2.

3.3. Comparison of CN and non-CN groups

Table 3 shows patient and disease characteristics according to nephrectomy status. Patients who underwent nephrectomies were significantly younger than patients who did

not (59.0 vs. 65.5 years respectively, $P < 0.0001$). Median tumor size was higher in the CN group (9.3 vs. 7 cm, $P = 0.01$). Patients with systemic treatment alone (without prior nephrectomy) had significantly worse MSKCC and ECOG performance status scores ($P = 0.05$ and $P = 0.01$, respectively). Sex ratio, histological subtype, T category, Fuhrman grade, and number of metastatic sites at diagnosis were not significantly different between both the groups.

3.4. Follow-up and survival

Considering the entire cohort, median OS was 37.1 months. Median OS was significantly improved in patients who underwent CN from 16.4 to 38.1 months ($P < 0.001$) (Fig. 1). However, considering the ECOG score, CN was associated with a significant increase of OS only in patients with an ECOG score of 0 to 1 (16.7 vs. 43.3 months, $P = 0.04$) (Fig. 2). In patients with an ECOG score of 2 to 3, there was no significant difference in OS according to nephrectomy status, despite a median increase in OS of 4.6 months in the CN group (8.0 vs. 12.6 months, $P = 0.8$). Similarly, in patients with good and intermediate MSKCC risk score, median OS was significantly increased among the nephrectomy group (16.8 vs. 42.4 months, $P = 0.02$) (Fig. 3). In poor-risk patients, median OS was similar in both the groups (5.2 months, $P = 0.9$).

The number and location of metastases also have a prognostic effect. OS was significantly better in case of isolated lung metastases ($P = 0.04$) and when the number of metastases did not exceed 2 ($P < 0.001$). Finally, patients treated with antiangiogenic therapies had better median OS than patients treated with cytokines did (39.8 vs. 24.1 months, $P = 0.03$).

Multivariate analysis confirms the positive effect of CN in the group with good and intermediate MSKCC risk score and in patients with ECOG score of 0 to 1, regardless of the metastatic status and the kind of therapy.

4. Discussion

Immunotherapy has been the single systemic treatment in mRCC for many years. During this era, 2 prospective randomized studies have demonstrated the survival benefit

Table 2
Treatment strategies

Cytoreductive nephrectomy, n (%)	298 (84.9)
First-line systemic treatment, n (%)	
Sunitinib	137 (39.0)
Sorafenib	65 (18.5)
Temsirolium	25 (7.1)
Interferon	57 (16.2)
Bevacizumab + interferon	17 (4.8)
Interferon + IL2	20 (5.7)
Others	30 (8.7)

IL2 = interleukin-2.

Table 3
Comparison of CN and non-CN groups.

	CN (n = 298)	Non-CN (n = 53)	P value
Median age at diagnosis, y (range)	59.0 (19–82)	65.5 (28–91)	<0.0001^a
Median BMI	26.5	26.7	0.86 ^a
Sex, n (%)			0.74 ^b
Males	215 (72.1)	37 (69.8)	
Females	83 (27.9)	16 (30.2)	
ECOG score before nephrectomy, n (%)			0.01^b
0	122 (40.9)	6 (11.3)	
1	123 (41.3)	32 (60.4)	
2	43 (14.4)	11 (20.8)	
3	10 (3.4)	4 (7.5)	
MSKCC risk group before nephrectomy, n (%)			0.05^b
Good	84 (28.2)	4 (7.5)	
Intermediate	186 (62.4)	41 (77.4)	
Poor	28 (9.4)	8 (15.1)	
Median tumor size, cm (range)	9.3 (4–14)	7 (3–12)	0.01^a
Histological subtype, n (%)			0.42 ^b
Clear cell carcinoma	261 (87.6)	45 (84.9)	
Papillary carcinoma	22 (7.4)	3 (5.7)	
Other	15 (5.0)	5 (9.4)	
T category, n (%)			0.39 ^b
T1	35 (11.7)	3 (5.7)	
T2	37 (12.4)	6 (11.3)	
T3-4	226 (75.9)	44 (83.0)	
Fuhrman grade, n (%)			0.17 ^b
1	4 (1.3)	3 (5.7)	
2	56 (18.8)	11 (20.8)	
3	150 (50.3)	27 (50.9)	
4	88 (29.6)	12 (22.6)	
Number of metastatic sites (%)			0.13 ^b
1	98 (32.9)	11 (20.8)	
2	107 (35.9)	19 (35.8)	
3 Or more	93 (31.2)	23 (43.4)	

Bold values are significant p-value with $p < 0.05$.

BMI = body mass index.

^aStudent *t* test.

^bChi-square test.

of associative CN and interferon-alfa [2,3]. Since a decade, new drugs have emerged to become standard treatment of mRCC. Currently, the association of CN with these new targeted molecules is still recommended based on former data with immunotherapy. Most of the patients in the pivotal targeted therapy studies had undergone nephrectomy. However, when considering the safety and efficacy of presurgical antiangiogenics, some authors are calling into question the time schedule and even the relevance of such a procedure. There are 2 phase 3 randomized studies that are ongoing to partially answer these questions [1]. Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer (SURTIME; European Organisation for Research and Treatment of

Cancer [EORTC] 30073) trial is a randomized phase 3 trial that compares progression-free survival in case of immediate vs. deferred (after 3 complete cycles of sunitinib) CN in mRCC. In addition, tumoral tissue and serum are collected to identify molecular profiles predictive of response and resistance. The Clinical Trial to Assess the Importance of Nephrectomy (CARMENA) trial is a phase 3 randomized noninferiority study that evaluates OS with nephrectomy followed by sunitinib vs. sunitinib alone. Together CARMENA and SURTIME complement one another, and both will address the role of CN and the optimal sequence in the targeted therapy era. Unfortunately, no result is expected before 2016.

There are retrospective studies that have investigated the benefit of CN in patients with mRCC treated exclusively with targeted therapies. Warren et al., in a Canadian population-based study, identified CN as an independent factor of OS improvement in patients with mRCC treated with tyrosine kinase inhibitors [17]. Choueiri et al. reported OS of 314 patients with mRCC according to their CN status [18]. CN was associated with a significant increase in OS (19.8 vs. 9.4 months), even after adjusting for established prognostic risk factors. More recently, Heng et al. retrospectively reported a series of 1,658 patients with mRCC from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and defined a new prognostic tool using 9 clinical factors to model survival in the era of targeted therapy. They found that most patients benefited from tumor removal, except for those with 4 or more IMDC risk factors [19]. Finally, in a Surveillance, Epidemiology, and End Results (SEER) database analysis including 7,143 patients with mRCC treated between 2005 and 2009, among whom 37% underwent CN, CN was significantly associated with improved OS on multivariate analysis [20]. Our results are concordant, as we report that CN performed before targeted treatments was associated with a significant increase of OS in the entire cohort.

If global benefit of CN has been demonstrated, one question remains worthwhile: Does every patient with mRCC take advantage from this surgery? Pivotal studies in the era of immunotherapy (Southwest Oncology Group [SWOG] trial 8949 and EORTC trial 30947) only enrolled patients with PS 0 or 1 [2,3]. Schuch et al. suggested that surgery in patients who have a poor performance (ECOG 2/3 patients) may serve a palliative function, but it should be performed with caution because of the poor outcome of such patients [21]. Indeed, 42.5% of these patients did not proceed to receive systemic therapy and presented a median OS of 6.6 months. Recent studies focusing only on targeted therapies suggested that CN might not benefit every patient with mRCC. In the study of Choueiri et al., the benefit was marginal for patients within a poor prognostic group, as determined by the MSKCC risk model ($P = 0.06$) [18]. Heng et al. also concluded to the absence of benefit in patients with 4 or more risk factors, as determined by the IMDC [19]. Further retrospective data showed that CN was

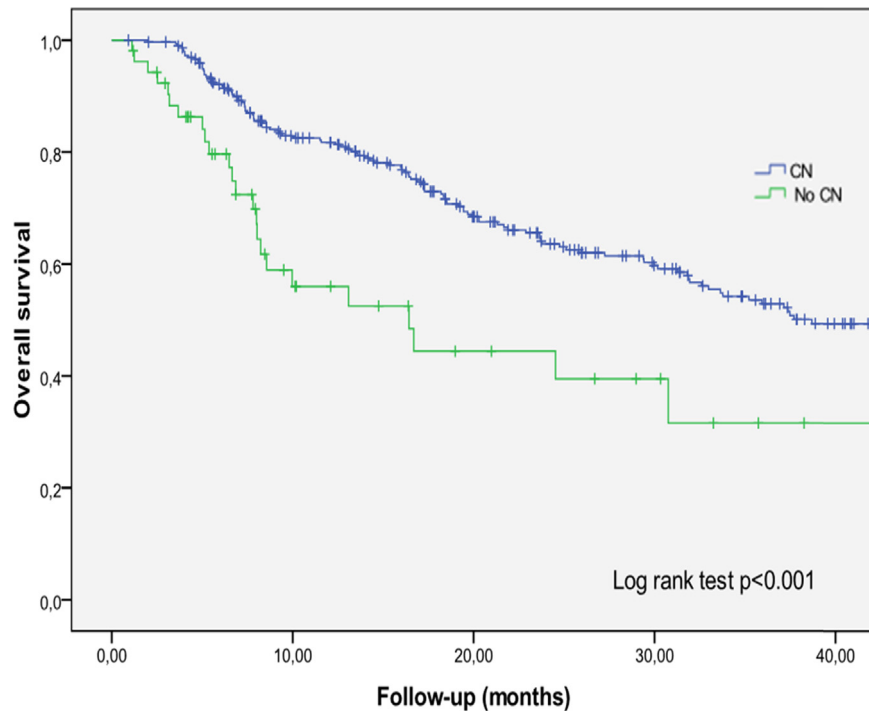


Fig. 1. Overall survival according to the completion of a CN in the entire cohort. (Color version of figure is available online.)

of most benefit in those patients where primary renal tumor accounts for most of the volume of the disease [22] and those with the non-clear cell histological subtype [23]. Recently, Ohno et al. suggested that patients with neutrophil-to-lymphocyte ratio ≥ 4.0 and ECOG-PS ≥ 1 might not benefit from immediate CN after initial diagnosis [24]. Culp et al. identified other poor prognostic

factors such as high lactate dehydrogenase level, low albumin level, symptoms at presentation caused by a metastatic site, liver metastasis, retroperitoneal adenopathy, supradiaphragmatic adenopathy, and clinical tumor classification $\geq T3$ [25]. Together, these retrospective data suggest that CN might have a role in some well-selected individuals [26].

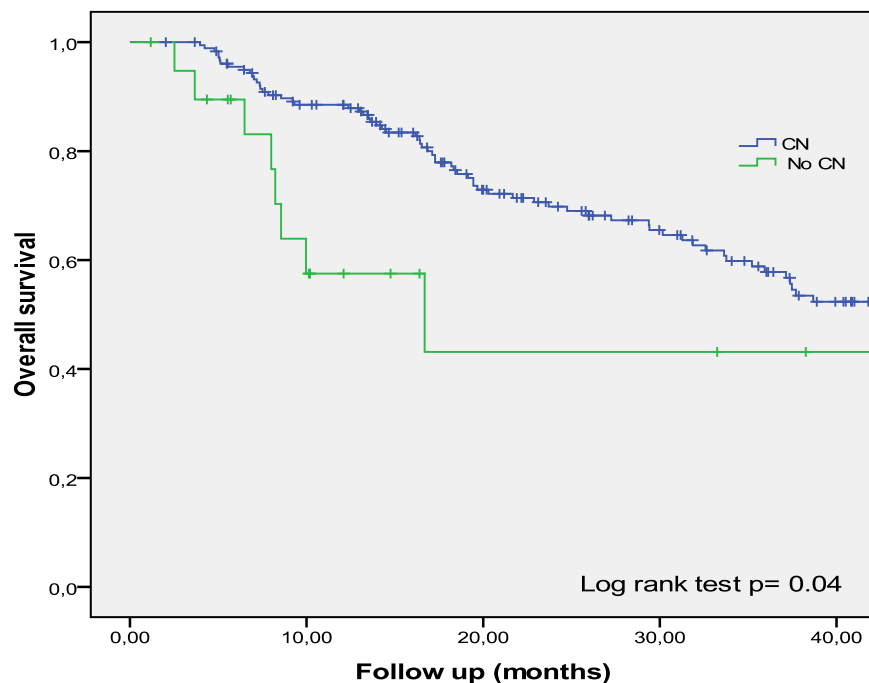


Fig. 2. Overall survival according to the completion of a CN in the group of patients with ECOG 0-1 score status. (Color version of figure is available online.)

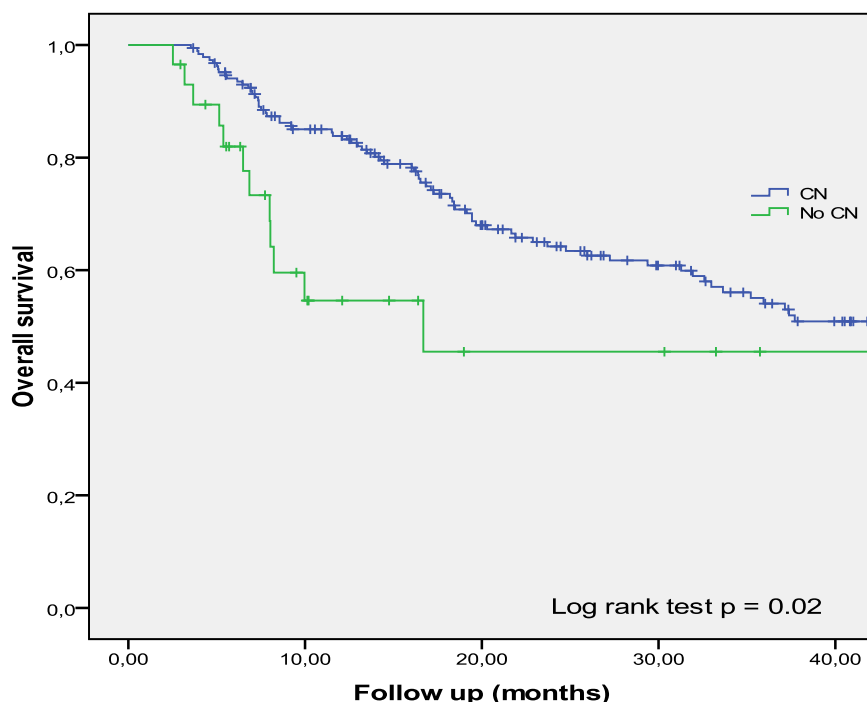


Fig. 3. Overall survival according to the completion of a CN in the group of patients with good and intermediate MSKCC score status. (Color version of figure is available online.)

In the present study, we demonstrated that only patients with ECOG score of 0 to 1 or good/intermediate MSKCC prognostic score had a benefit from CN. On the contrary, patients with ECOG score of 2 to 3 or poor MSKCC score did not take advantage from CN. There are several theoretical reasons why CN might not be beneficial in the era of targeted therapies. Unlike immune therapy, it is possible that targeted therapy alone controls the disease, particularly at the primary tumor site, at the point that nephrectomy is no more necessary. This might avoid the morbidity and mortality associated with surgery. In addition, the delay in starting systemic treatment associated with the postoperative period might allow further progression of aggressive disease and, consequently, be counterproductive. The frequent occurrence of disease progression (approximately 33% by the Response Evaluation Criteria In Solid Tumors [RECIST] criteria) during a surgery-related treatment break of approximately 3 to 4 weeks in the neoadjuvant strategies argues in favor of surgical abstention [27]. This is particularly suitable for patients with poor prognostic factors, such as those with an ECOG score of 2 to 3 and in the poor MSKCC score group. Targeted therapy might be proposed as the first-line treatment to these patients, and CN should be considered only after an objective response to the systemic treatment. Indeed, in some cases, delayed nephrectomy could probably be a good option. Apart from the theoretical advantage of downsizing of the primary renal tumor, which seems to be quite modest (2%–6% by the RECIST criteria) and probably does not facilitate surgery [27–29], the major concern is to quickly start effective systemic therapy without the delay associated

with planning, performing, and recovering from nephrectomy. Moreover, patients with primary refractory disease would be accurately identified and therefore might have an opportunity to promptly switch to another targeted agent. Finally, it should be noted that approximately 30% of patients do not go on to have the planned nephrectomy [27–29].

Our study confirms the results of previous retrospective series and provides interesting results that need to be taken into account in the management of mRCC. It suggests that careful clinical consideration is required before planning CN in all untreated patients with mRCC, especially for patients with risk for poor prognosis, as defined by the MSKCC score and for those with an ECOG score of 2 or 3. We concede that our study has some limitations owing to the retrospective and multicentric design. Some biases are expectable from the variability of systemic treatments and the time frame between surgery and the beginning of the adjuvant treatment. Furthermore, there is a selection bias as patient and tumor characteristics may affect the surgeon's choice. Indeed, it is noteworthy that patients in the non-CN group are older and are more likely to have worse ECOG and MSKCC scores. The debate regarding the place of CN in the era of targeted therapies is likely to continue until the ongoing prospective trials report their findings [30].

5. Conclusion

Nephrectomy improves OS in patients with mRCC preferentially treated with targeted therapies. However, this

effect is limited to patients with good and intermediate MSKCC prognostic score and to patients with ECOG performance status of 0 to 1. We consider that CN might not be proposed to patients with poor prognosis before systemic treatment and without an objective response to these drugs. This information may help in patient selection as we await results from randomized controlled trials.

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