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Kidney Cancer

Life Expectancy of Renal Cell Carcinoma with Variant Histology

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Abstract

Background and objective: The effect of variant histology in renal cell carcinoma (vhRCC) on survival relative to age- and sex-matched population-based controls is unknown. This study aims to analyze the life expectancy of vhRCC patients.

Methods: In the Surveillance, Epidemiology and End Results (SEER) database (2004–2016), we identified 2928 patients with vhRCC, including mesenchymal, collecting duct, medullary, mucinous, and neuroendocrine RCC, as well as RCC of sarcomatoid and rhabdoid differentiation. Kaplan-Meier plots addressed overall survival relative to simulated life expectancy in population-based controls (Monte Carlo simulation), were derived from the Social Security Administration life tables.

Key findings and limitations: Of the 2928 vhRCC patients, 1905 (65%) harbored sarcomatoid, 404 (14%) mesenchymal, 318 (11%) collecting duct, 94 (3%) rhabdoid, 80 (3%) medullary, 68 (2%) mucinous, and 59 (2%) neuroendocrine RCC. Most vhRCC subtypes exhibit regional or metastatic stage at diagnosis, except for mucinous RCC. When diagnosed in metastatic stage, all vhRCC subtypes exhibited a decrease in survival rate ranging from –75% to –98% between controls and cases, except for mucinous and neuroendocrine RCC, with the least decrease in survival rate of –62% and –59%, respectively. In regional stage, all vhRCC subtypes exhibited a decrease in survival rate ranging from –68% to –41% between controls and cases, except for neuroendocrine RCC, with the least decrease in survival rate of –27%. Finally, in localized stage, all vhRCC subtypes

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exhibited a decrease in survival rate ranging from –56% to –22% between controls and cases, except for rhabdoid and mucinous RCC, with the least decrease in survival rate of –11% and –6%, respectively.

Conclusions and clinical implications: Most vhRCC subtypes reduce survival drastically relative to life expectancy of population-based controls, except for localized rhabdoid and mucinous RCC. Especially, medullary RCC leads to distinct reductions in life expectancy, irrespective of the stage at presentation.

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What does this study add?

The current study quantifies reduction of life expectancy in patients with variant histology renal cell carcinoma (vhRCC) according to stage at diagnosis and histological subtype. The novel findings enable clinicians to directly compare life expectancy of patients with vhRCC with that of age- and sex-matched population-based controls, and thus offers more comprehensive patient counseling at diagnosis. Particularly, patients with mucinous and rhabdoid RCC harbor the least reduction of life expectancy in localized stage, whereas patients with medullary RCC harbor distinct reduction of life expectancy compared with population-based controls, irrespective of the stage at diagnosis.

Patient Summary

In this study, we analyzed the life expectancy of renal cell carcinoma (RCC) patients with variant histology according to different disease stages. We found that RCC with the most variant histology presents with advanced or metastatic stages at diagnosis and that particularly medullary RCC harbors shortened life expectancy. Contrarily, patients with rhabdoid or mucinous RCC with localized stage have the least reduction of life expectancy among the variant histologies included in the study.

1. Introduction

Renal cell carcinoma (RCC) includes a diverse array of histological subtypes, with clear-cell RCC (ccRCC) representing the largest subgroup, accounting for approximately 70% of all diagnosed cases [1–3]. The remaining RCC cases consist of a heterogeneous group of histological variants, collectively referred to as non-ccRCC or variant histology RCC (vhRCC) [2]. Within this category, papillary (13–20%) and chromophobe RCC (5–10%) [4] are the predominant subtypes [2,5,6]. Further subgroups include collecting duct carcinoma, mesenchymal, neuroendocrine, medullary, and mucinous RCC as well as RCC with sarcomatoid and rhabdoid differentiation [7–10].

Previous reports indicated that vhRCC is associated with more advanced stage at presentation and poor survival outcomes [7–14]. However, previous analyses typically compared vhRCC with ccRCC, and no previous analyses contrasted the survival of vhRCC patients relative to age- and sex-matched population-based controls.

We addressed this knowledge gap and hypothesized that significant survival differences may distinguish vhRCC patients from simulated age- and sex-matched population-based controls. To test this hypothesis, we relied on the Surveillance, Epidemiology and End Results (SEER) database (2004–2016). According to guideline recommendations, population-based controls were simulated using the methodology employed previously (Monte Carlo simulation), based on the life expectancy data, derived from the life tables of the US Social Security Administration.

2. Patients and methods

2.1. Data source and study population

The SEER database provides cancer statistics for approximately 47.9% of the US population [15]. Within the SEER database (2004–2016), we identified histologically confirmed vhRCC patients (International Classification of Disease for Oncology [ICD-10] site code 64.9) aged ≥18 yr. Specifically, we included the following variant histologies (VHs): collecting duct (ICD-10 8319/3), medullary (8510/3), mucinous (8480/3), and neuroendocrine (8013/3, 8246/3, and 8574/3) RCC, as well as RCC with rhabdoid differentiation patterns (8963/3), RCC with sarcomatoid differentiation patterns (8318/3), and mesenchymal RCC. Within mesenchymal RCC, leiomyosarcoma (8890/3), fibrosarcoma (8810/3), angiomyoliposarcoma (8860/3), hemangiosarcoma (9120/3), rhabdomyosarcoma (8900/3), and synovial sarcoma of the kidney (9040/3) were included according to the updated 2022 World Health Organization classification [4]. Only patients with known SEER stage and survival data were included. Cases with autopsy or death certificate only were excluded.

2.2. Statistical analyses

Baseline characteristics of vhRCC patients were tabulated (Table 1). For continuous variables, medians and interquartile ranges (IQRs) were included, while frequencies and proportions were reported for categori-

Table 1 – Descriptive characteristics of 2928 patients with variant histology of renal cell carcinoma within the SEER database 2004–2016

Characteristic	Overall (n = 2928)[a]	Sarcomatoid (n = 1905, 65%)[a]	Mesenchymal (n = 404, 14%)[a]	Collecting duct (n = 318, 11%)[a]	Rhabdoid (n = 94, 3%)[a]	Medullary (n = 80, 3%)[a]	Mucinous (n = 68, 2%)[a]	Neuroendocrine (n = 59, 2%)[a]
Age	61 (51, 71)	63 (55, 72)	57 (39, 70)	61 (52, 72)	39 (18, 61)	27 (21, 34)	62 (53, 68)	67 (54, 80)
Sex								
Male	1913 (65)	1319 (68)	217 (52)	223 (70)	53 (56)	64 (79)	33 (48)	32 (53)
Female	1015 (35)	609 (32)	203 (48)	97 (30)	42 (44)	17 (21)	36 (52)	28 (47)
Stage								
Localized	597 (20)	289 (15)	142 (35)	83 (26)	17 (18)	6 (7.5)	51 (75)	9 (15)
Regional	860 (29)	548 (29)	132 (33)	112 (35)	25 (27)	15 (19)	9 (13)	19 (32)
Metastatic	1471 (50)	1068 (56)	130 (32)	123 (39)	52 (55)	59 (74)	8 (12)	31 (53)

SEER = Surveillance, Epidemiology and End Results.
[a] Values are presented as median (Q1, Q3) or n (%).

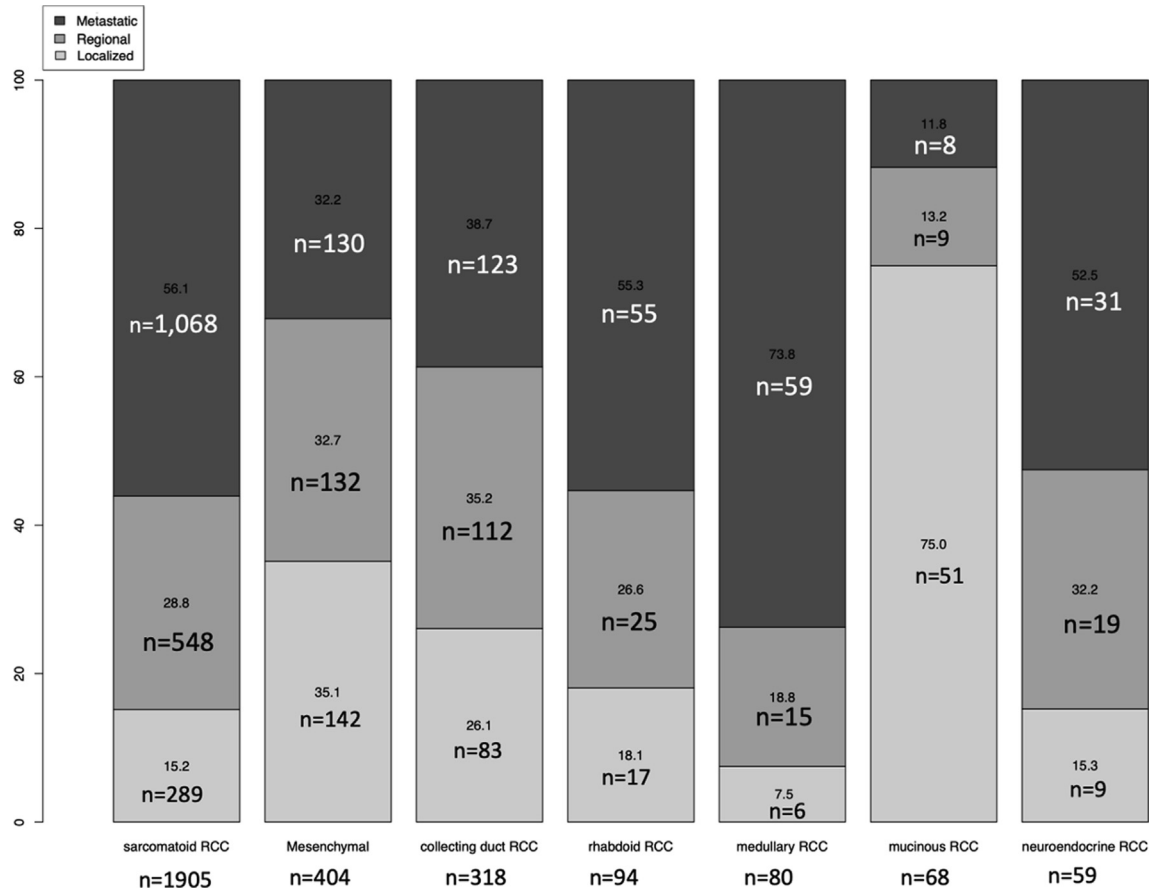

Fig. 1 – Stacked bar plots depicting proportions of stages within 2928 renal cell carcinoma patients with variant histologies within the SEER database 2004–2016. RCC = renal cell carcinoma; SEER = Surveillance, Epidemiology and End Results.

cal variables. Second, in vhRCC patients, Kaplan-Meier plots addressed overall survival (OS) according to localized versus regional versus metastatic stages (Fig. 1). Third, a Markov chain model representing the natural aging progression was constructed for each control based on the data from the US Social Security Administration life tables (2004–2021) [16] and matched to each RCC case (4:1). Fourth, a Monte Carlo simulation was applied in order to compute life expectancy, according to a previously used methodology [17–21]. Owing to small numbers of observations in vhRCC cases, controls were simulated in a 4:1 ratio for each vhRCC patient. Statistical tests were two sided, with a level of significance set at $p < 0.05$. R software environment (R version 4.4.0; The R Foundation for Statistical Computing, Vienna, Austria) was applied for graphics and statistical computing.

3. Results

3.1. *Descriptive characteristics of vhRCC patients*

Within the SEER database (2004–2016), we identified 2928 vhRCC patients. Of these patients, 1905 (65%) harbored

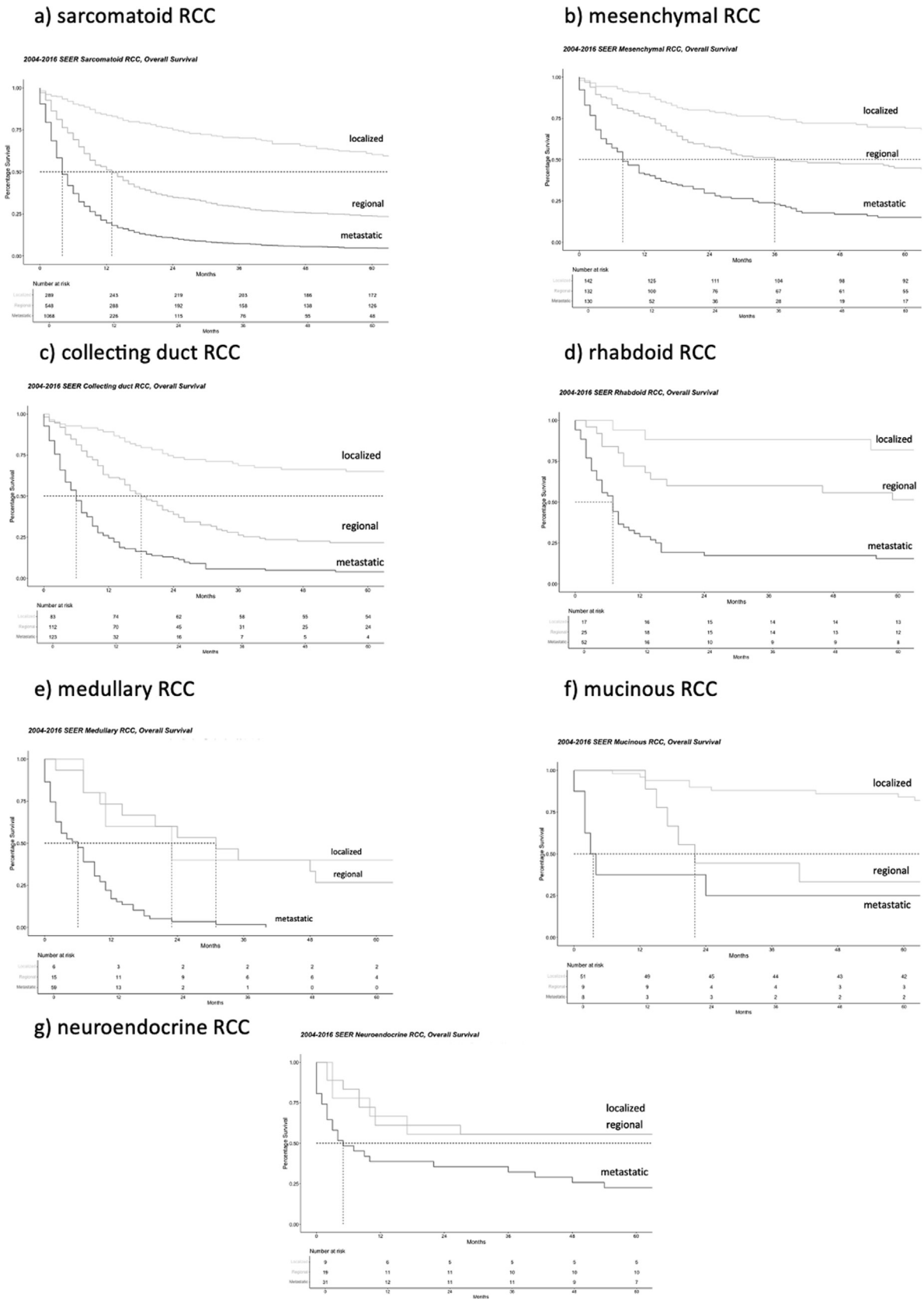

Fig. 2 – Kaplan-Meier plots depicting overall survival of variant histology subtypes in renal cell carcinoma patients according to stage (localized, regional, and metastatic): (A) sarcomatoid, (B) mesenchymal, (C) collecting duct, (D) rhabdoid, (E) Medullary, (F) mucinous, and (G) neuroendocrine RCC. RCC = renal cell carcinoma; SEER = Surveillance, Epidemiology and End Results.

sarcomatoid, 404 (14%) mesenchymal, 318 (11%) collecting duct, 94 (3%) rhabdoid, 80 (3%) medullary, 68 (2%) mucinous, and 59 (2%) neuroendocrine RCC (Table 1). After stratification according to VH subtype, the median age was 27 yr (IQR 21–34) in medullary, 39 (IQR 18–61) in rhabdoid, 57 (IQR 39–70) in mesenchymal, 61 (IQR 52–72) in collecting duct, 62 (IQR 53–68) in mucinous, 63 (IQR 55–72) in sarcomatoid, and 67 (IQR 54–80) in neuroendocrine RCC. After stratification according to stages, most vhRCC patients harbored metastatic or regional stage, except for those with mucinous RCC. Only mucinous RCC predominantly exhibited localized stage (Fig. 2).

3.2. OS in vhRCC according to stage

In stage-specific analyses, localized stage harbored more favorable OS than regional or metastatic stage in sarcomatoid, mesenchymal, collecting duct, and mucinous RCC (Fig. 3A–D and 3F). Median OS in localized stage was not reached within 5 yr of follow-up in all of the abovementioned vhRCC cases as well as in neuroendocrine and rhabdoid RCC cases. In all other variants, the median OS for regional and metastatic stage were 13 and 4 mo in sarcomatoid, 36 and 8 mo in mesenchymal, 18 and 6 mo in collecting duct, 31 and 6 mo in medullary, and 22 and 3 mo in mucinous RCC, respectively. The median OS for metastatic stage was 10 mo for rhabdoid and 6 mo for neuroendocrine RCC.

3.3. OS of vhRCC patients versus age- and sex-matched population-based controls

3.3.1. Localized staged vhRCC patients versus controls

In localized stage, 5-yr OS rates were 40% in medullary, 60% in sarcomatoid, 65% in collecting duct, 66% in neuroendocrine, 69% in mesenchymal, 82% in rhabdoid, and 84% in mucinous RCC patients (Fig. 3A–G). In the simulated controls, the corresponding rates were 96%, 87%, 89%, 86%, 91%, 93%, and 90%. The resulting differences in 5-yr OS rates between RCC patients and controls (Δ) were −56% in medullary, −31% in neuroendocrine, −27% in sarcomatoid, −23% in collecting duct, −22% in mesenchymal, −11% in rhabdoid, and −6% in mucinous RCC patients. Localized staged vhRCC patients invariably harbored worse survival than their controls, except for rhabdoid and mucinous RCC patients, in whom less pronounced differences were recorded.

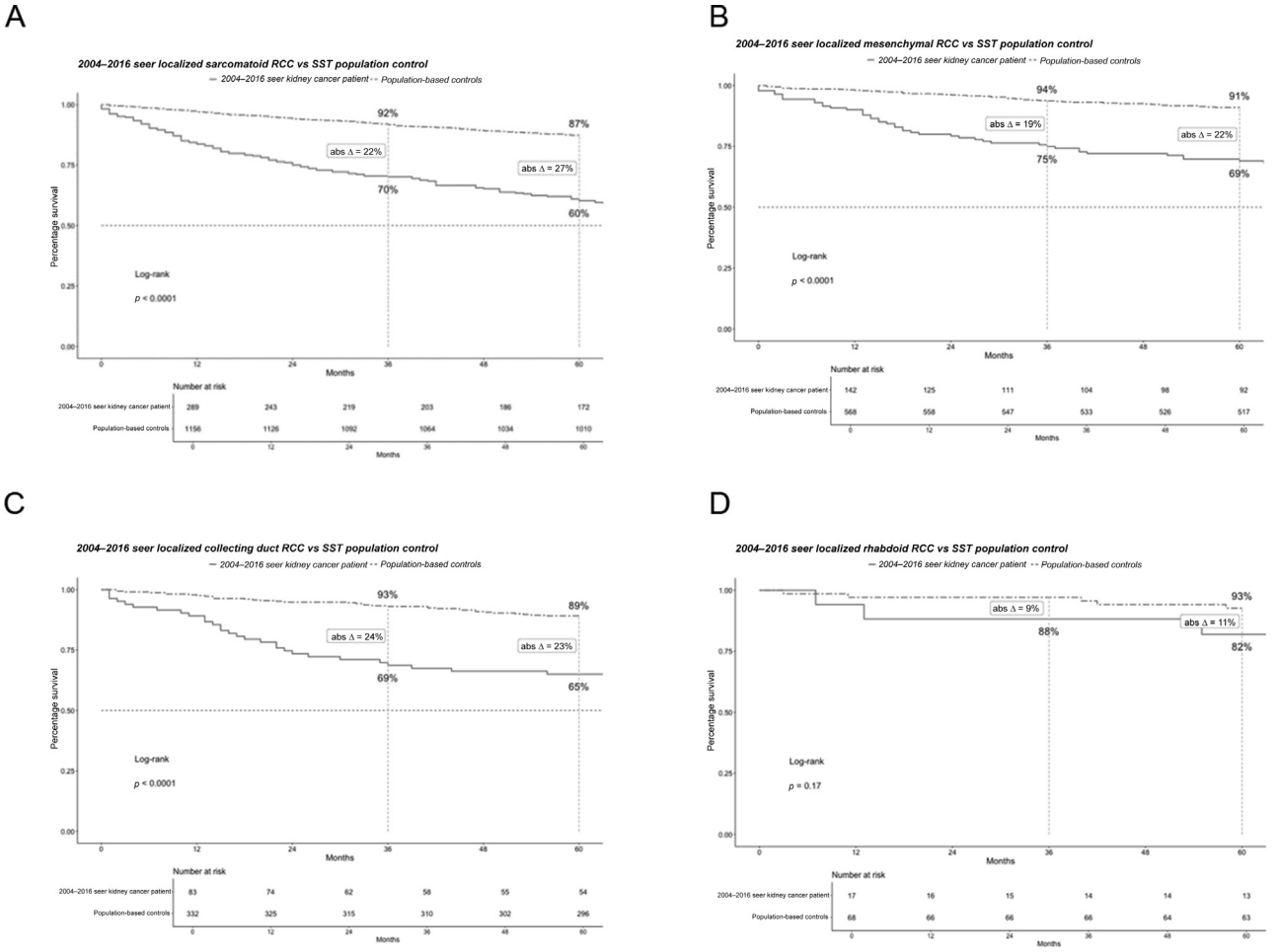

Fig. 3 – Kaplan-Meier plots depicting overall survival of localized staged patients with variant renal cell carcinoma subtypes relative to age- and sex-matched population-based controls: (A) Sarcomatoid, (B) mesenchymal, (C) collecting duct, (D) rhabdoid, (E) medullary, (F) mucinous, and (G) neuroendocrine RCC. abs = absolute; RCC = renal cell carcinoma; SEER = Surveillance, Epidemiology and End Results.

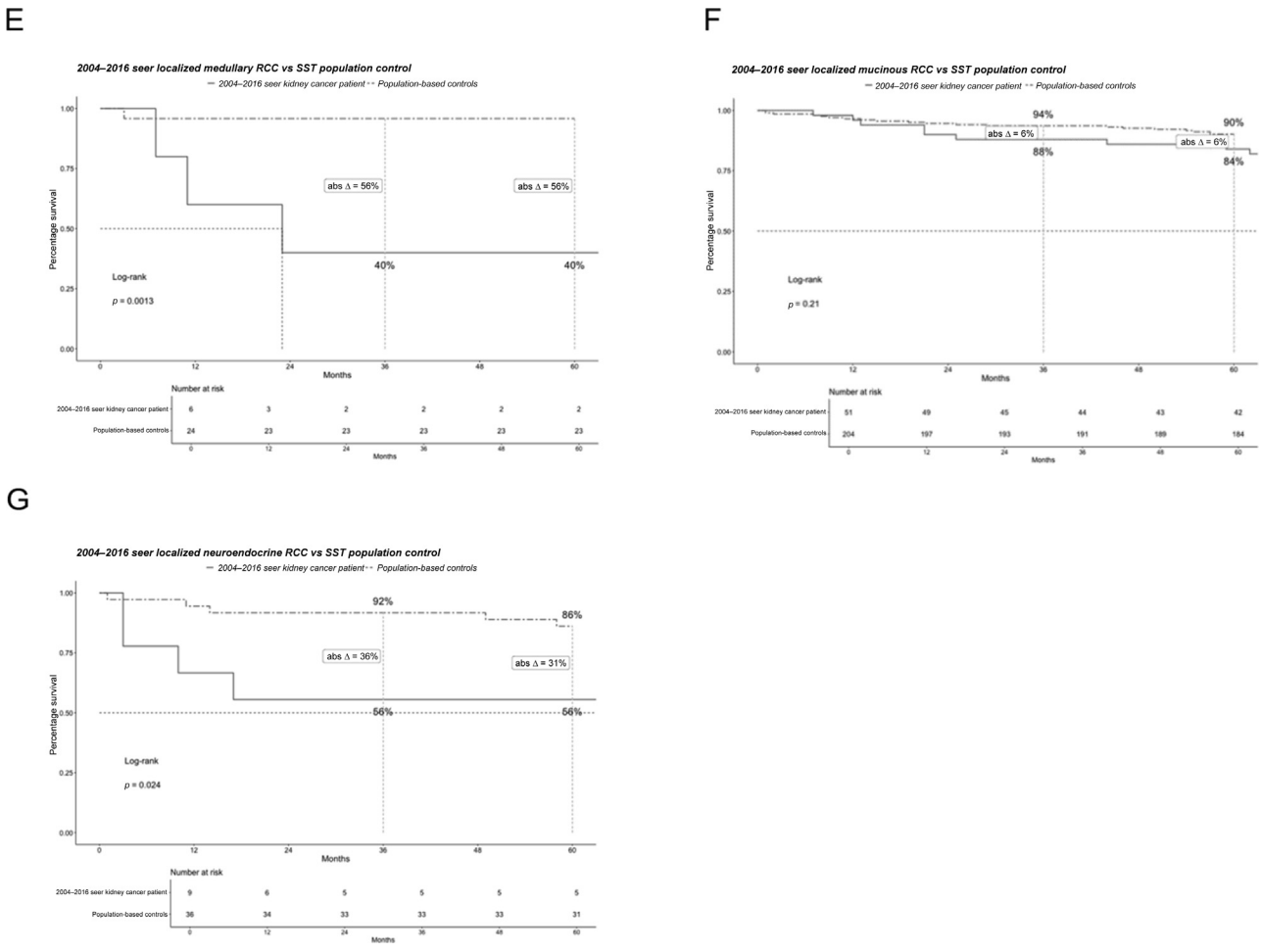

Fig. 3 (*continued*)

3.3.2. Regional staged vhRCC patients versus controls

In regional stage, 5-yr OS rates were 22% in collecting duct, 24% in sarcomatoid, 27% in medullary, 33% in mucinous, 45% in mesenchymal, 51% in rhabdoid, and 56% in neuroendocrine RCC patients (Fig. 4A–G). In the simulated controls, the corresponding rates were 87%, 86%, 95%, 81%, 90%, 92%, and 83%. The resulting differences in 5-yr OS rates between RCC patients and controls were –68% in medullary, –65% in collecting duct, –63% in sarcomatoid, –47% in mucinous, 45% in mesenchymal, 41% in rhabdoid, and –27% in neuroendocrine RCC patients. Regional staged vhRCC patients invariably harbored worse survival than their controls, except for rhabdoid and neuroendocrine RCC patients, in whom less pronounced differences were recorded.

3.3.3. Metastatic staged vhRCC patients versus age- and sex-matched population-based controls

In metastatic stage, 5-yr OS rates were 1% in medullary, 4% in collecting duct, 5% in sarcomatoid, 15% in mesenchymal and rhabdoid, 23% in neuroendocrine, and 25% in mucinous RCC patients (Fig. 5A–G). In the simulated controls, the corresponding rates were 99%, 88%, 89%, 90%, 93%, 81%, and 88%. The resulting differences in 5-yr OS rates between RCC patients and controls were –98% in medullary, –84% in sarcomatoid and collecting duct, –78% in rhabdoid, 75% in mesenchymal, –62% in mucinous, and –59% in neuroendocrine RCC patients. Metastatic staged vhRCC patients invariably harbored worse survival than their population-based controls, except for mucinous and neuroendocrine RCC patients, in whom less pronounced differences were recorded.

4. Discussion

Currently, it is unknown to what extent VH reduces life expectancy in RCC patients relative to their controls. We addressed this knowledge gap and tested for differences in OS between vhRCC and controls. We hypothesized that vhRCC patients would exhibit lower life expectancy, especially in metastatic stages. We tested these hypotheses using the current population of vhRCC patients in the SEER database (2004–2016) and made several noteworthy observations.

First, vhRCC cases are rare [1,4,7,8,12], as ccRCC, papillary RCC, and chromophobe RCC are the most prevalent subtypes in RCC, making up approximately >90–95% of all RCC cases [4,22]. Previous reports on vhRCC are based on

small cohorts within single- or multi-institutional databases as well as population-based databases (SEER) ranging from 27 to 1600 observations in sarcomatoid [23–27], 20 to 723 in rhabdoid [28–31], 21 to 273 in collecting duct [8,11,12,32], 52 to 100 in medullary [14,33], and one to eight in mucinous [34–37] RCC. For neuroendocrine and mesenchymal RCC, fewer data were available, including mainly case reports [38–41]. In the current study, we included 2928 vhRCC patients from the SEER database (2004–2016). Of them, 1905 (65%) harbored sarcomatoid, 404 (14%) mesenchymal, 318 (11%) collecting duct, 94 (3%) rhabdoid, 80 (3%) medullary, 68 (2%) mucinous, and 59 (2%) neuroendocrine RCC. The current study cohort of vhRCC patients represents the largest population ever reported. Within each vhRCC subtype, the sample size exceeded those of previous reports, except for rhabdoid and medullary RCC.

Second, all vhRCC patients were included within the same analyses, where the same methodology was used. Such an approach allowed a uniform assessment of the frequencies of rare vhRCC. Subsequently, it allowed systematic depiction of stage distribution within all examined vhRCC cases. Ultimately, stage-specific OS rates were depicted graphically using equally standardized and uniform methodology.

Third, distribution assessment of stage at diagnoses yielded important differences, where most vhRCC cases, except for mucinous RCC, were heavily weighted toward metastatic and regional stages. This methodological approach of displaying SEER stage distribution was not used previously. In consequence, the current study provides the first direct comparison of stage at presentation between vhRCC types including localized, regional, and metastatic stages.

Fourth, this study provides the first report of stage-specific survival for all included vhRCC types. In stage-specific stratification, localized stage was most prevalent in mucinous (75%) RCC, followed by mesenchymal (35%), collecting duct (26%), rhabdoid (18%), neuroendocrine and sarcomatoid (15%), and medullary (7%) RCC. Conversely, metastatic stage was most prevalent in medullary RCC (74%), followed by sarcomatoid (56%), rhabdoid (56%), neuroendocrine (53%), collecting duct (39%), mesenchymal (32%), and finally, mucinous (12%) RCC. Similar to the current study findings, previous reports indicated that medullary and neuroendocrine RCC, and RCC with sarcomatoid

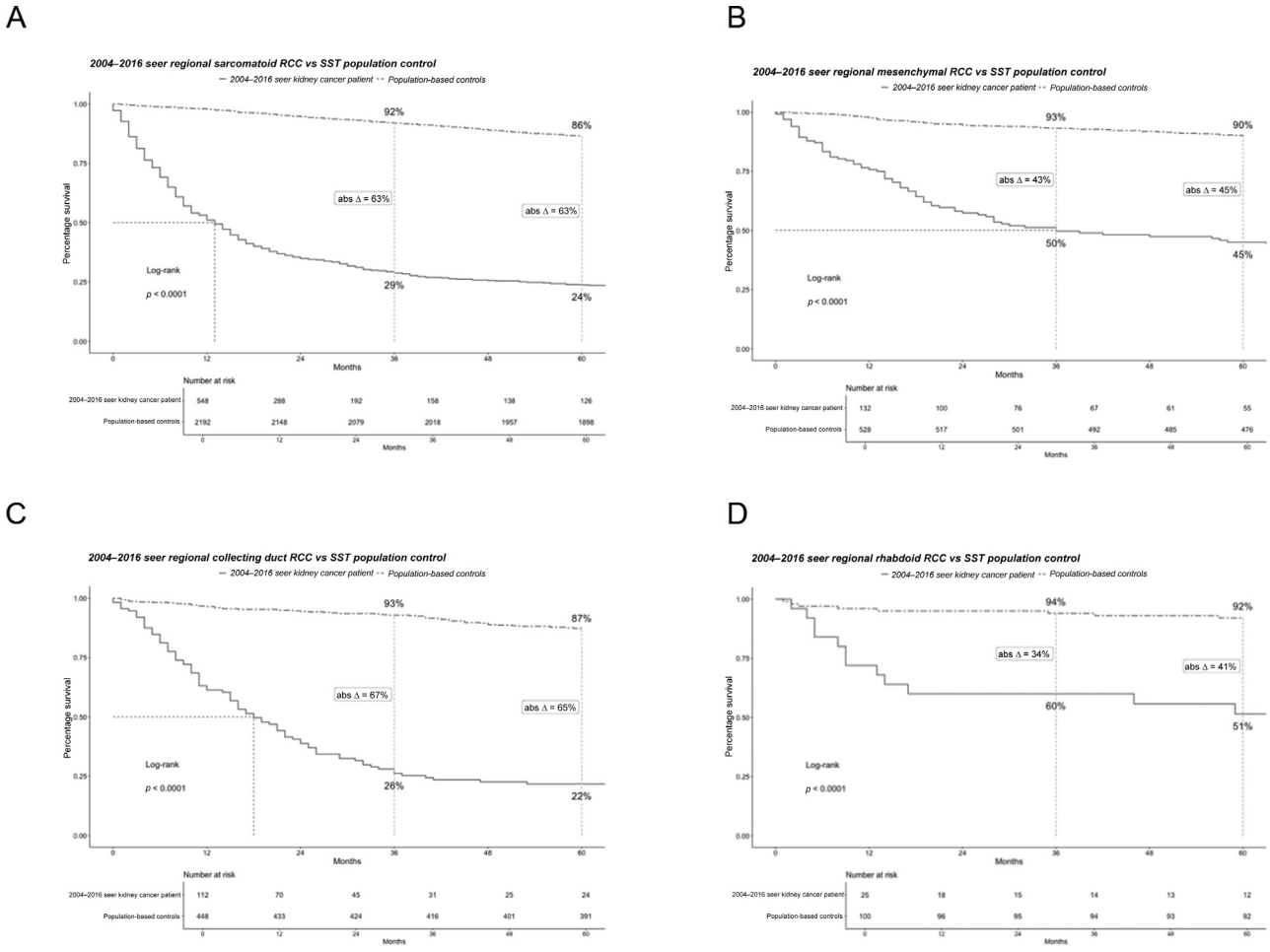

Fig. 4 – Kaplan-Meier plots depicting overall survival of regional staged patients with variant renal cell carcinoma subtypes relative to age- and sex-matched population-based controls: (A) sarcomatoid, (B) mesenchymal, (C) collecting duct, (D) rhabdoid, (E) medullary, (F) mucinous, (G) neuroendocrine RCC. abs = absolute; RCC = renal cell carcinoma; SEER = Surveillance, Epidemiology and End Results.

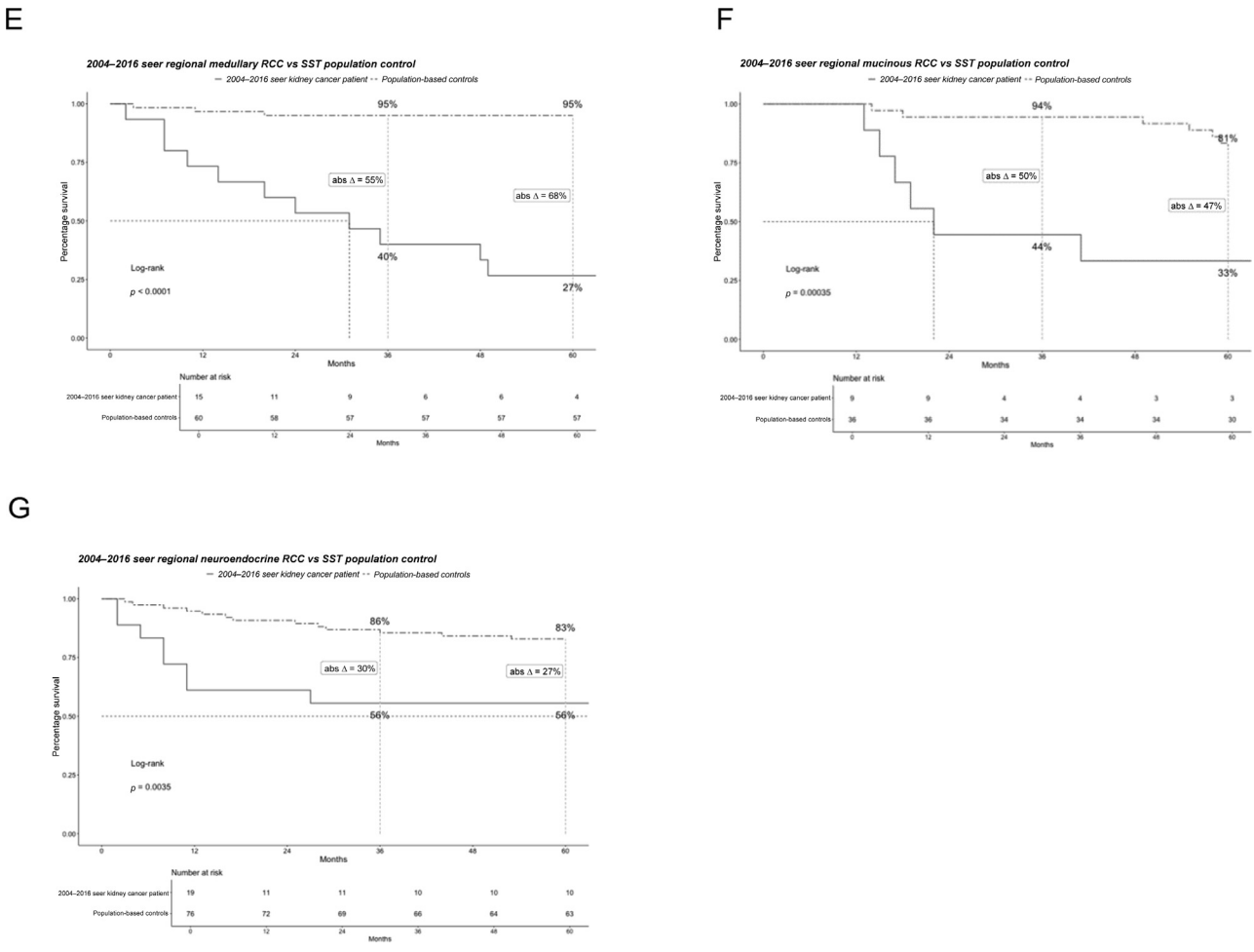

Fig. 4 (*continued*)

or rhabdoid differentiation often harbor advanced or metastatic stages at presentation [8,27,28,42].

Fifth, we focused on differences between vhRCC cases and those of simulated population-based controls. Most vhRCC cases exhibited dismal survival in metastatic and regional states, and some vhRCC cases exhibited dismal survival even in localized stages. In localized stage, 5-yr OS differences were most pronounced in medullary RCC patients (–56%), followed by neuroendocrine (–31%) and sarcomatoid RCC patients. In regional stage, 5-yr OS differences were most pronounced in medullary RCC patients (–68%), followed by collecting duct (–65%) and sarcomatoid RCC (–63%) patients. Finally, in metastatic stage, 5-yr OS differences were most pronounced in medullary RCC (–98%), followed by collecting duct and sarcomatoid RCC (–84%) patients. Conversely, mucinous (–6%) and rhabdoid RCC (–11%) patients harbored the least decrease in life expectancy in localized stage, neuroendocrine RCC (–27%) patients harbored the least decrease in regional stage, and finally, mucinous (–62%) and neuroendocrine (–59%) RCC patients harbored the least decrease in life expectancy in metastatic stage. However, despite mucinous and neuroendocrine RCC harboring least decreases within metastatic vhRCC, these subtypes still lead to a drastic reduction of OS. Based on the novelty of these results, the currently reported findings cannot be compared directly with any previous study since no studies addressed the life expectancy of vhRCC patients.

Taken together, vhRCC invariably presents at metastatic or regional stage and is associated with very poor if not dismal survival, virtually regardless of stage. Virtually all vhRCC cases exhibit a very pronounced difference in OS versus life expectancy in population-based controls, with minor exceptions in localized rhabdoid and mucinous RCC cases. These observations provide important clinical details for patient counseling at initial diagnosis to provide patients with the most unbiased estimates of their survival relative to life expectancy in individuals without vhRCC diagnosis. Such a comparison will illustrate a very discouraging scenario. However, it is essential that patients are aware of their severely undermined life expectancy relative to age- and sex-matched population-based controls. It is equally important that some vhRCC patients should be informed about substantially more favorable survival than some other vhRCC patients, for example, in localized staged rhabdoid and mucinous RCC.

Despite its novelty, this study has limitations due to its observational design and the retrospective nature of the SEER database. First and foremost, despite the large scale of the SEER database, the number of vhRCC patients, especially in stage-specified stratification, is limited due to low numbers of observations. Thus, 4:1 matching of cases and controls was necessary to provide a more accurate estimation of the life expectancy comparison. Second, our control group is based on a simulated population derived the Social Security Administration's life tables; hence, the OS of the control cohort represents an estimation. Third, the Social Security Administration's life tables do not provide data on race and ethnicity. These could not be accounted for in the current study. Last but not least, we included sarcomatoid (8318/3) and rhabdoid (8963/3) differentiation patterns of RCC without specification of the underlying histology, which could be ccRCC or non-ccRCC. However, the degree of differentiation of sarcomatoid or rhabdoid patterns could not be accounted for, since this detailed information is not provided within the SEER database.

5. Conclusions

Diagnosis of vhRCC reduces life expectancy in RCC patients drastically, proportionately to the stage at diagnosis, except for localized staged rhabdoid and mucinous RCC. Conversely, diagnosis of medullary RCC leads to distinct life expectancy reduction compared with population-based controls, regardless of stage at diagnosis.

Author contributions: Quynh Chi Le had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Le, Karakiewicz, Chun, Kosiba.
Acquisition of data: Le, Marmiroli, Longoni.
Analysis and interpretation of data: Le, Falkenbach, Catanzaro, Nicolazzini, Polverino, Goyal.
Drafting of the manuscript: Le, Karakiewicz, Saad, Goyal.
Critical revision of the manuscript for important intellectual content: Schiavina, Carmignani, Briganti, Longo, Graefen, Palumbo, Wenzel, Humke, Kosiba.

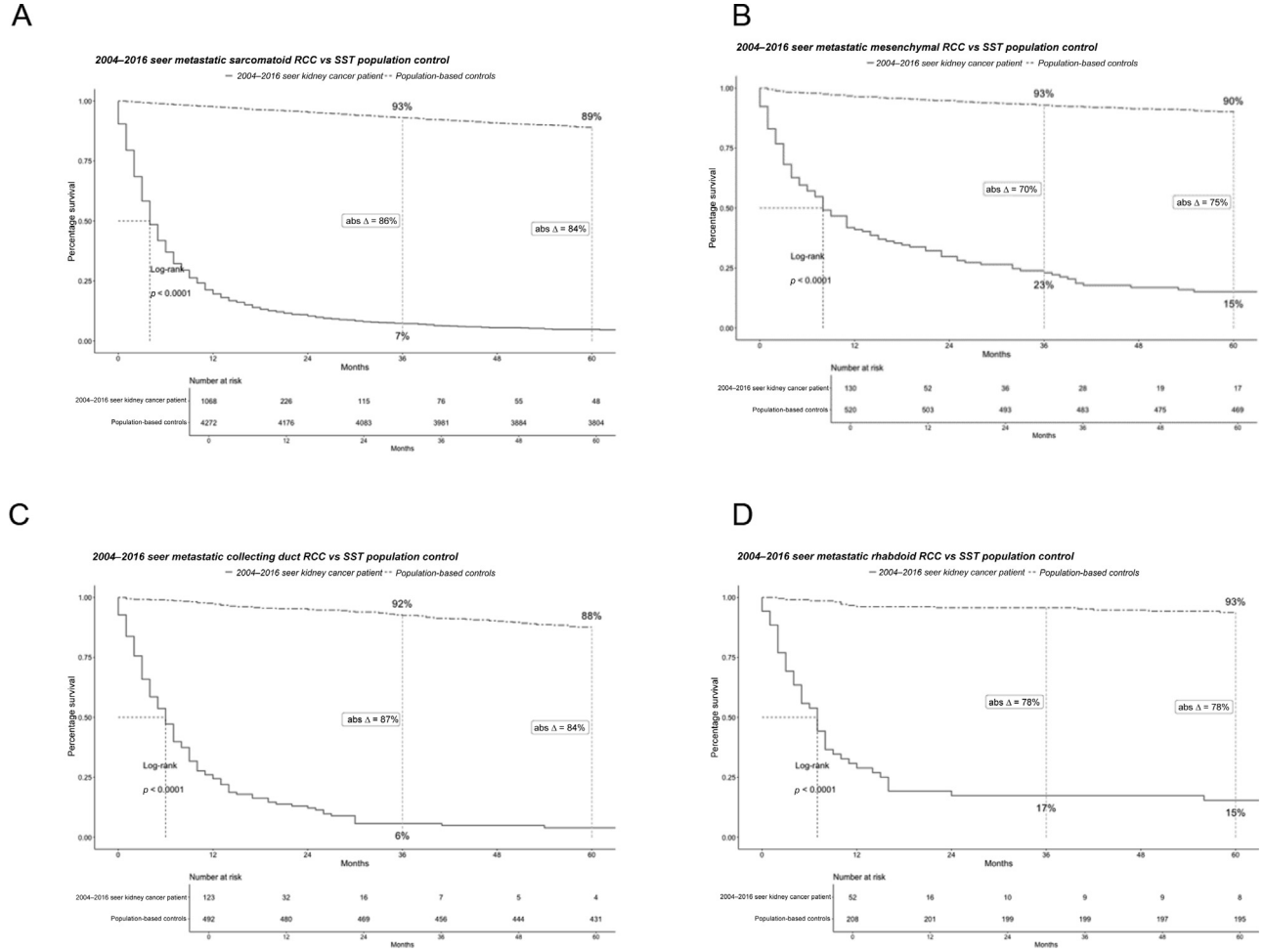

Fig. 5 – Kaplan-Meier plots depicting overall survival of metastatic staged patients with variant renal cell carcinoma subtypes relative to age- and sex-matched population-based controls: (A) sarcomatoid, (B) mesenchymal, (C) collecting duct, (D) rhabdoid, (E) medullary, (F) mucinous, and (G) neuroendocrine RCC. abs = absolute; RCC = renal cell carcinoma; SEER = Surveillance, Epidemiology and End Results.

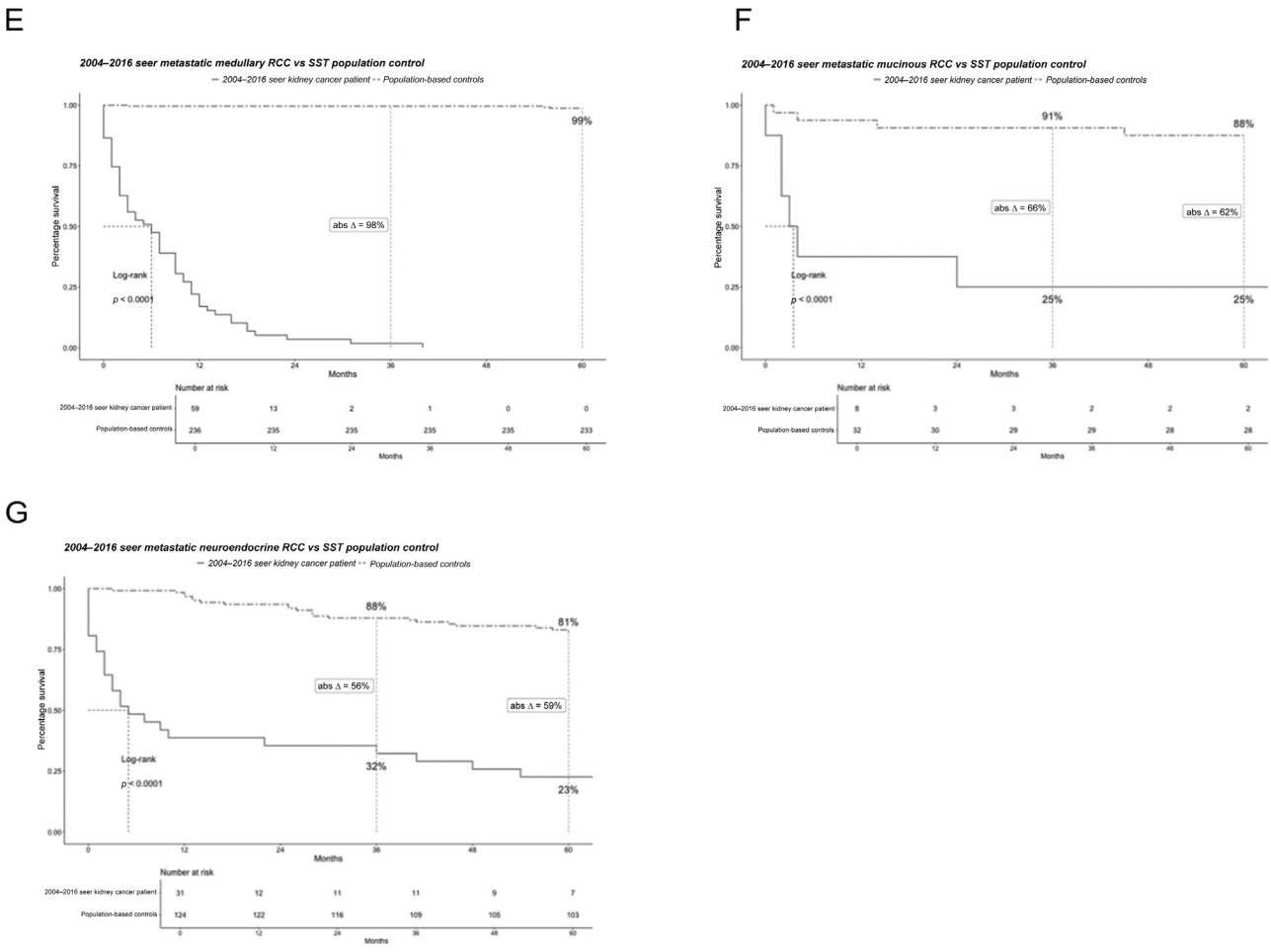

Fig. 5 (*continued*)

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