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ORIGINAL ARTICLE

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Improvement in overall and cancer-specific survival in contemporary, metastatic prostate cancer chemotherapy exposed patients

Benedikt Hoeh MD[1,2] | Christoph Würnschimmel MD[2,3] | Rocco S. Flammia MD[2,4] | Benedikt Horlemann MD[2] | Gabriele Sorce MD[2,5] | Francesco Chierigo MD[2,6] | Zhe Tian MsC[2] | Fred Saad MD, PhD[2] | Markus Graefen MD, PhD[3] | Michele Gallucci MD, PhD[4] | Alberto Briganti MD, PhD[5] | Carlo Terrone MD, PhD[6] | Shahrokh F. Shariat MD, PhD[7,8,9,10,11,12] | Derya Tilki MD, PhD[3,13] | Luis A. Kluth MD, PhD[1] | Philipp Mandel MD, PhD[1] | Felix K. H. Chun MD, PhD[1] | Pierre I. Karakiewicz MD, PhD[2]

[1]Department of Urology, University Hospital Frankfurt, Goethe University Frankfurt am Main, Frankfurt am Main, Germany

[2]Division of Urology, Cancer Prognostics and Health Outcomes Unit, University of Montréal Health Center, Montréal, Québec, Canada

[3]Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany

[4]Department of Maternal-Child and Urological Sciences, Policlinico Umberto I Hospital, Sapienza Rome University, Rome, Italy

[5]Division of Experimental Oncology, Unit of Urology, Urological Research Institute, IRCCS San Raffaele Scientific Institute, Milan, Italy

[6]Department of Surgical and Diagnostic Integrated Sciences (DISC), University of Genova, Genova, Italy

[7]Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

[8]Department of Urology, Weill Cornell Medical College, New York, New York, USA

[9]Department of Urology, University of Texas Southwestern, Dallas, Texas, USA

[10]Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic

Abstract

Introduction: Over the last decade, multiple clinical trials demonstrated improved survival after chemotherapy for metastatic prostate cancer (mPCa). However, real-world data validating this effect within large-scale epidemiological data sets are scarce. We addressed this void.

Materials and Methods: Men with de novo mPCa were identified and systemic chemotherapy status was ascertained within the Surveillance, Epidemiology, and End Results database (2004–2016). Patients were divided between historical (2004–2013) versus contemporary (2014–2016). Chemotherapy rates were plotted over time. Kaplan–Meier plots and Cox regression models with additional multivariable adjustments addressed overall and cancer-specific mortality. All tests were repeated in propensity-matched analyses.

Results: Overall, 19,913 patients had de novo mPCa between 2004 and 2016. Of those, 1838 patients received chemotherapy. Of 1838 chemotherapy-exposed patients, 903 were historical, whereas 905 were contemporary. Chemotherapy rates increased from 5% to 25% over time. Median overall survival was not reached in contemporary patients versus was 24 months in historical patients (hazard ratio [HR]: 0.55, $p < 0.001$). After propensity score matching and additional multivariable adjustment (age, prostate-specific antigen, GGG, cT-stage, cN-stage, cM-stage, and local treatment) a HR of 0.55 ($p < 0.001$) was recorded. Analyses were repeated for cancer-specific mortality after adjustment for other cause mortality in competing

[11]Institute for Urology and Reproductive Health, I. M. Sechenov First Moscow State Medical University, Moscow, Russia

[12]Division of Urology, Department of Special Surger, Jordan University Hospital, The University of Jordan, Amman, Jordan

[13]Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany

Correspondence
Benedikt Hoeh, Cancer Prognostics and Health Outcomes Unit, University of Montréal Health Center; Department of Urology, University Hospital Frankfurt, Goethe University Frankfurt am Main, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany.
Email: benedikt.hoeh@kgu.de

risks regression models and recorded virtually the same findings before and after propensity score matching (HR: 0.55, $p < 0.001$).

Conclusions: In mPCa patients, chemotherapy rates increased over time. A concomitant increase in survival was also recorded.

KEYWORDS
chemotherapy, contemporary, metastatic prostate cancer, survival

1 | INTRODUCTION

Systemic treatment of metastatic prostate cancer (mPCa) has improved according tofindings from prospective randomized trials.[1–9] However, the magnitude of the improvement recorded in prospective randomized trials could not be validated in population-based analyses.[10,11] We addressed this void and embarked on a contemporary analysis of overall survival (OS) in contemporary patients exposed to chemotherapy relative to their historical counterparts within the Surveillance, Epidemiology, and End Results (SEER) database (2004–2016) in de novo mPCa. We hypothesized, that these most contemporary data will illustrate a more pronounced benefit in overall survival than was previously reported.[1–5]

2 | MATERIAL AND METHODS

2.1 | Study population

The current SEER database samples 34.6% of the US population and approximates it in demographic composition and cancer incidence.[12] Within the SEER database (2004–2016), we identified patients more than or equal to 18 years old with de novo metastatic, histologically confirmed adenocarcinoma of the prostate, diagnosed at biopsy (International Classification of Disease for Oncology [ICD-O-3] code 8140 site code C61.9). Chemotherapy status was ascertained. Patients with unknown M-stage status were excluded from further analyses. Furthermore, cases identified at autopsy or through death certificates, with unknown histology or non-primary prostate cancers were excluded. Prostate-specific antigen (PSA), age, and stage were defined at initial prostate cancer diagnosis. These selection criteria resulted in a cohort of 19,913 de novo mPCa patients, of which 1838 patients represented de novo mPCa patients exposed to chemotherapy. This subgroup represented the study population.

2.2 | Statistical analyses

The statistical analyses consisted of four steps. First, we examined chemotherapy rates between contemporary (2014–2016) versus historical (2004–2013) de novo mPCa patients.

Second, we addressed overall survival and cancer-specific survival without propensity score matching. We relied on Kaplan–Meier plots and Cox regression models to test for overall and cancer-specific survival differences according to contemporary versus historical groups. In multivariable Cox regression models, covariates consisted of age at diagnosis, PSA groups (≤20, 21–90, and ≥91 in ng/ml), Gleason Group Grading (GGG) at biopsy, clinical T-stage (cT0, cT1, cT2, cT3, cT4, and cTx), clinical N-stage (cN0, cN1, and cNx), clinical M-stage (cM1a, cM1b, cM1c, and cM1x), and type of local treatment (none, RP, RT, RP + RT, and unknown).

Third, we relied on propensity score matching to address potential differences between contemporary versus historical patients in age, PSA, GGG, cT-stage, cN-stage, cM-stage, and type of local treatment. Each contemporary patient was matched in a 1:1 fashion to one historical patient.

Fourth, we relied on the propensity score-matched cohorts. We repeated all Kaplan–Meier plots as well as multivariable Cox regression models to test for overall and cancer-specific survival differences according to contemporary versus historical groups.

Additionally, competing risk regression models addressed cancer-specific survival after adjusting for other cause mortality. In multivariable Cox regression models, covariates consisted of age at diagnosis, PSA groups (≤20, 21–90, and ≥91 in ng/ml), GGG at biopsy, clinical T-stage (cT0, cT1, cT2, cT3, cT4, and cTx), clinical N-stage (cN0, cN1, cNx), clinical M-stage (cM1a, cM1b, cM1c, and cM1x), and type of local treatment (none, RP, RT, RP + RT, and unknown).

All tests were two-sided with a level of significance set a $p < 0.05$ and R-software environment for statistical computing and graphics (version 3.4.3) was used for all analyses.[13]

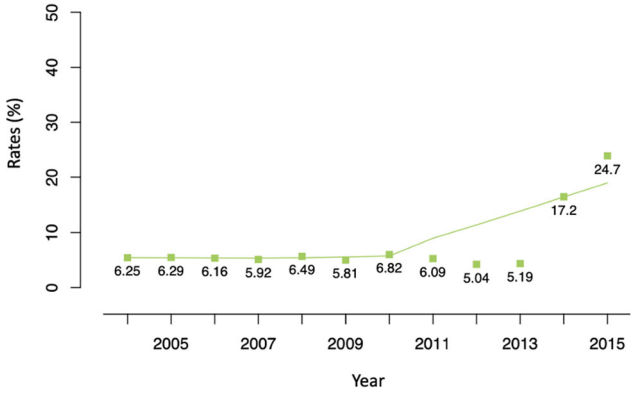

FIGURE 1 Trends of chemotherapy rates de novo in metastatic prostate cancer patients within the Surveillance, Epidemiology, and End Results database between 2004 and 2016. [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

3.1 | Descriptive characteristics of study population

Between 2004 and 2016 we identified 19,913 de novo mPCa patients, of whom 1838 represented de novo mPCa patients exposed to chemotherapy.

Rates of chemotherapy increased over time from between 5.0% and 6.3% ($p = 0.3$) between 2004 and 2013 to between 17.2% and 24.7% ($p = 0.04$) in 2014 and 2015, respectively (Figure 1). Of 1838 chemotherapy-exposed patients, 905 were contemporary, whereas 933 were historical. Contemporary patients differed from historical with respect to lower proportions of cT4 stage (14.2 vs. 18.2%, $p = 0.07$), lower proportions of cM1c stage (19.8 vs. 27.9%, $p = 0.02$), lower proportions of local treatment approaches (72.9 vs. 59.1%, $p = 0.002$) and lower proportions of radiotherapy treatment (19.8 vs. 31.3%, $p = 0.002$). Furthermore, more contemporary patients had lower proportions of unknown T-stage (19.5 vs. 17.7%, $p = 0.07$), unknown cN-stage (23.7 vs. 10.9%, $p = 0.06$), and unknown cM-stage (3.0 vs. 1.5%, $p = 0.02$). Contemporary patients differed from historical patients with respect to higher proportions of cN1-stage (44.5 vs. 30.0%, $p = 0.06$). Finally, no statistically significant differences were recorded in PSA distribution, GGG distribution, and median age at diagnosis (Table 1).

3.2 | Survival analyses without propensity score matching

Without propensity score matching, median overall survival was not reached in contemporary patients versus was 24 months (interquartile range [IQR]: 22–26) in historical patients. At 12 and 24 months, overall survival rates were 87.0 versus 75.4% and 68.8 versus 48.4% in contemporary versus historical patients, respectively (Figure 2A). In multivariable Cox regression models, contemporary de novo mPCa patients exhibited lower overall mortality (hazard ratio [HR]:0.54, confidence interval [CI]: 0.46–0.64, $p < 0.001$) compared with their historical counterparts (Table 2).

Consistently, median cancer-specific survival was not reached in contemporary versus was 25 months (IQR: 24–28) in historical patients (Figure 3A). In multivariable Cox regression models, contemporary mPCa patients exhibited lower cancer-specific survival (HR: 0.53, CI: 0.45–0.62, $p < 0.001$) compared with their historical counterparts (Table 2).

3.3 | Propensity score matching

Propensity score matching addressed 1838 patients with de novo mPCa. Of those, 708 of 905 contemporary and 708 of 933 historical patients could be matched in a 1:1 fashion. No statistically significant differences according to age at diagnosis, PSA, GGG, T-stage, lymph node stage, M-stage, and approach of local treatment existed between contemporary versus historical patients (all $p > 0.3$) (Table 1).

3.4 | Survival analyses after propensity score matching

After propensity score matching, 708 contemporary and 708 historical patients represented the focus of all propensity score-matched survival analyses. Median overall survival was not reached for contemporary patients versus was 25 months (IQR: 23–27) in historical patients. At 12 and 24 months, overall survival rates were 85.9 versus 76.3% and 69.0 versus 50.1% in respectively contemporary versus historical patients (Figure 2B). In multivariable Cox regression models, contemporary de novo mPCa patients exhibited lower overall mortality (HR:0.55, CI:0.46–0.65, $p < 0.001$) (Table 2).

Consistently, median cancer-specific survival was not reached in contemporary versus was 26 months (IQR: 24–28) in historical patients (Figure 3A). In competing risks regression analyses adjusting for other cause mortality, contemporary patients exhibited lower cancer-specific mortality (HR: 0.55, CI: 0.46–0.65, $p < 0.001$) than historical patients (Table 2).

4 | DISCUSSION

We hypothesized that a stronger survival benefit may be illustrated in contemporary versus historical de novo mPCa patients being exposed to chemotherapy than in previous large-scale epidemiological reports.[10,11] We tested this hypothesis and made several noteworthy findings.

First, the rates of chemotherapy use demonstrated a biphasic effect. Between 2004 and 2013, a plateau in chemotherapy use rates was recorded that ranged from 5% to 6%. Conversely, between 2014 and 2016 an important increase was noted, evidenced by

TABLE 1 Descriptive characteristics of de novo metastatic prostate cancer patients exposed to chemotherapy prior and after propensity score matching, grouped into contemporary (2014–2016) and historical (2004–2013) patients

	Before PSM			After PSM		
	2004–2013 (*n* = 933)	2014–2016 (*n* = 905)	*p* value	2004–2013 (*n* = 708)	2014–2016 (*n* = 708)	*p* value
Age, in years	64	64	0.3	64	63	0.3
median (IQR)	(58–71)	(58–70)		(57–71)	(57–70)	
PSA-groups in ng/ml, *n* (%)			0.08			1.0
Low (≤20)	211 (22.6)	167 (18.5)		141 (19.9)	141 (19.9)	
Intermediate (21–90)	217 (23.3)	219 (24.2)		169 (23.9)	167 (23.6)	
High (≥91)	505 (54.1)	519 (57.3)		398 (56.2)	400 (56.5)	
GGG biopsy, *n* (%)			0.04			1.0
I	23 (2.5)	8 (0.9)		9 (1.3)	8 (1.1)	
II	51 (5.5)	16 (1.8)		17 (2.4)	16 (2.3)	
III	61 (6.5)	51 (5.6)		42 (5.9)	47 (6.6)	
IV	148 (15.9)	153 (16.9)		111 (15.7)	113 (16)	
V	458 (49.1)	473 (52.3)		373 (52.7)	363 (51.3)	
Unknown	192 (20.6)	204 (22.5)		156 (22)	161 (22.7)	
cT-stage, *n* (%)			0.07			1.0
cT1	216 (23.2)	252 (27.8)		181 (25.6)	176 (24.9)	
cT2	267 (28.6)	260 (28.7)		205 (29)	212 (29.9)	
cT3	98 (10.5)	100 (11)		81 (11.4)	74 (10.5)	
cT4	170 (18.2)	133 (14.7)		114 (16.1)	114 (16.1)	
cTx	182 (19.5)	160 (17.7)		127 (17.9)	132 (18.6)	
cN-stage, *n* (%)			0.06			0.4
cN0	432 (46.3)	403 (44.5)		342 (48.3)	324 (45.8)	
cN1	280 (30)	403 (44.5)		259 (36.6)	286 (40.4)	
cNx	221 (23.7)	99 (10.9)		107 (15.1)	98 (13.8)	
M-stage, *n* (%)			0.02			1.0
M1a	54 (5.8)	51 (5.6)		44 (6.2)	41 (5.8)	
M1b	591 (63.3)	661 (73)		486 (68.6)	495 (69.9)	
M1c	260 (27.9)	179 (19.8)		165 (23.3)	158 (22.3)	
M1x	28 (3)	14 (1.5)		13 (1.8)	14 (2)	
Local treatment, *n* (%)			0.002			1.0
None	551 (59.1)	660 (72.9)		476 (67.2)	475 (67.1)	
RP	19 (2)	11 (1.2)		9 (1.3)	11 (1.6)	
RT	292 (31.3)	179 (19.8)		173 (24.4)	172 (24.3)	
RP + RT	54 (5.8)	38 (4.2)		35 (4.9)	34 (4.8)	
Unknown	17 (1.8)	17 (1.9)		15 (2.1)	16 (2.3)	

Note: All values are median (IQR) or frequencies (percentage).

Abbreviations: GGG, Gleason group grade; IQR, interquartile range; PSM, propensity score matching; RP, radical prostatectomy; RT, radiotherapy.

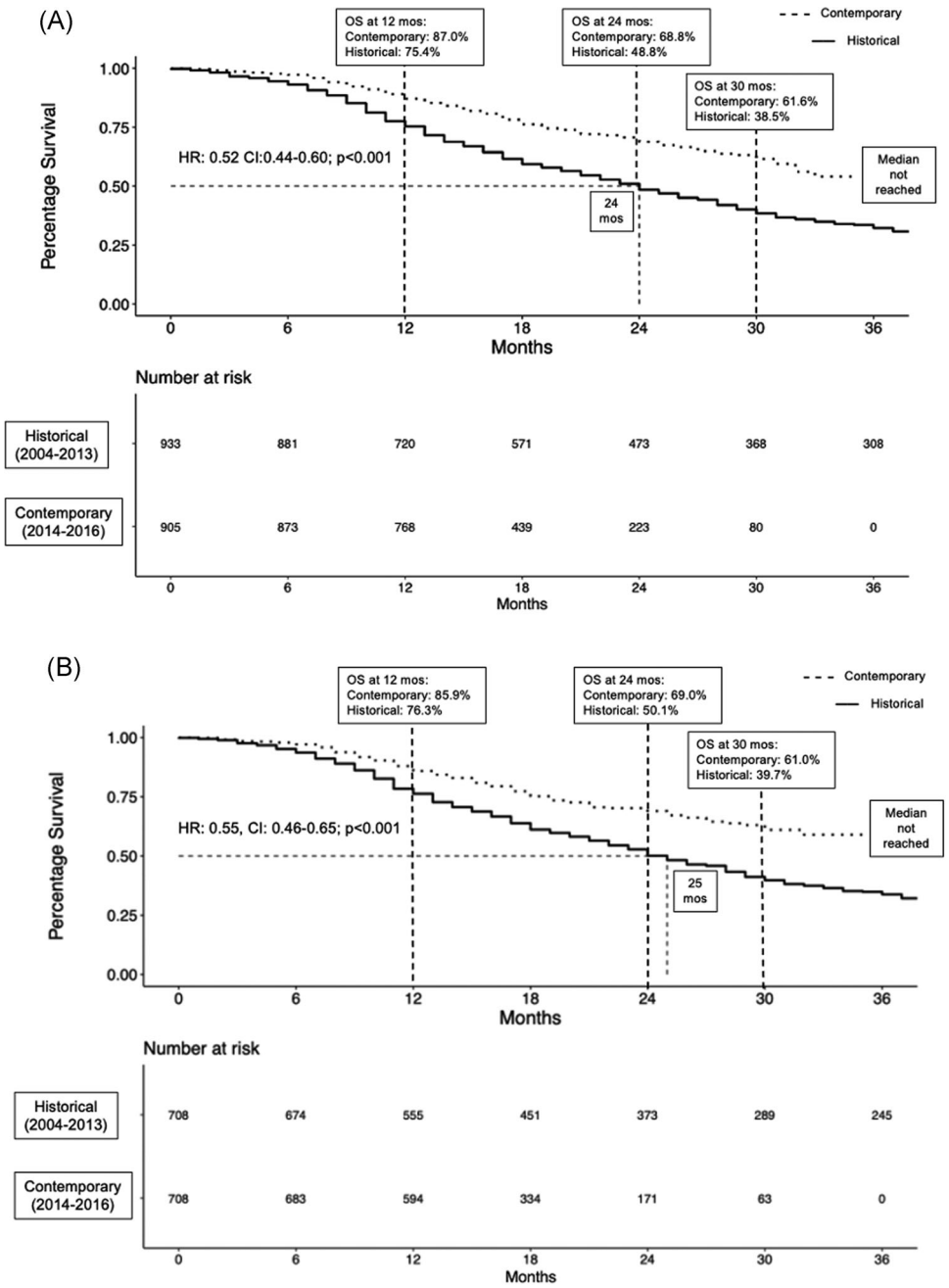

FIGURE 2 (A) and (B) Kaplan–Meier plots illustrating overall survival in 1838 metastatic prostate cancer patients (mPCa) before propensity score matching (A) and in 1416 mPCa patients after propensity score matching (B), exposed to chemotherapy. CI, confidence interval; HR, hazard ratio

chemotherapy use rates, that ranged from 17% to 25%. The very low, initial chemotherapy use rates are consistent with previously reported population-based data.[10,11,14–16] However, subsequent increases in chemotherapy use rates have not been reported until now. In consequence, the current observations regarding the increase in chemotherapy use rates demonstrate a very important change in practice patterns. Specifically, the initial lack of confidence in chemotherapy use in mPCa, evidenced by very low rates of use between 2004 and 2013, disappeared in more contemporary years. Moreover, contemporary rates were not only higher, but also further increased over time. These observations may be interpreted as a contemporary vote of confidence in chemotherapy use. The contemporary rates of chemotherapy use (17%–25%) closely correspond to chemotherapy rates increased after the presentation of CHAARTED study findings in 2014 and may be interpretated as directly motivated by CHAARTED results.[17,18]

Second, we also observed an important increase in overall survival in contemporary de novo mPCa patients relative to their historical counterparts (24 months: 68.8 vs. 48.4% overall survival rates). This observation was validated after propensity matching that

TABLE 2 Uni- and multivariable Cox regression models (CRM) predicting (a) overall mortality (OM) and (b) cancer-specific mortality (CSM) in metastatic prostate cancer patients exposed to chemotherapy before and after propensity score matching (PSM)

2a OM	Variable of interest	Univariable CRM for OM			Multivariable CRM for OM		
		Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Analyses before PSM	Contemporary versus historical	0.52	0.44–0.60	<0.001	0.54	0.46–0.64	<0.001
Analyses after PSM	Contemporary versus historical	0.55	0.46–0.65	<0.001	0.55	0.46–0.66	<0.001
2b CSM	**Variable of interest**	**Univariable CRM for OM**			**Multivariable CRM for OM**		
		Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Analyses before PSM	Contemporary versus historical	0.53	0.45–0.62	<0.001	0.55	0.47–0.65	<0.001
Analyses after PSM[a]	Contemporary versus historical	0.55	0.46–0.65	<0.001	0.54	0.45–0.65	0.001

Note: Cox regression models were adjusted for age, PSA, GGG, cT-stage, clymph node stage, cM-stage, and local treatment.

Abbreviations: CI, confidence interval; GGG, Gleason group grade; PSA, prostate-specific antigen.

[a]CSM was adjusted for OCM by using competing risks regression analyses.

adjusted for patient and/or tumor characteristics with the intent of controlling for more favorable case mix in more contemporary years. In consequence, our analyses indicate that the survival benefit in more contemporary chemotherapy exposed mPCa patients is related to more widespread use of chemotherapy and not to a stage migration of these individuals towards a more favorable phenotype irrespective of chemotherapy exposure status.

Third, we also made important observations regarding tumor characteristics of contemporary versus more historical metastatic chemotherapy exposed prostate cancer patients. Although, we demonstrated that a stage migration towards a more favorable prostate cancer phenotype was not a determinant of better survival, we did note a difference in contemporary patients with respect to lower proportion of cT4 stage, lower proportion of M1c stage, and lower proportion of radiotherapy treatment. Based on these differences a the use of propensity score matching should strongly be recommended in any further analyses. We applied this methodology in the current analyses. Interestingly, of 903 contemporary vs 905 historical patients, only 708 and 708 patients could be matched based on PSA, GGG, T-stage, N-stage, M-stage, and type of local treatment. This implies that important differences in PSA distributions, as well as stages and types of local treatment distinguished contemporary from historical patients.

Fourth, no previous studies compared chemotherapy benefits between contemporary versus historical patients in mPCa patients. However, previous studies examined overall survival in metastatic de novo prostate cancer regardless of chemotherapy exposure and demonstrated only marginal benefits in contemporary patients relative to their historical counterparts. Bandini et al. recorded a 3-month overall survival benefit between contemporary versus historical mPCa patients regardless of chemotherapy exposure status.[10] Similarly, Cattrini et al.[11] recorded a four-month overall survival benefit between contemporary versus historical mPCa patients regardless of chemotherapy exposure status. Our analysis is based on a different design, whereby chemotherapy exposure is analyzed in addition to comparisons between contemporary and historical patients. Our analysis exhibited striking differences in overall survival rates of 11.6% and 20.0% at 12 and 24 months, respectively.

Finally, several hypotheses may be proposed to explain the differences between overall survival between contemporary and historical patients. Customarily, the differences between contemporary and historical patients consist of a more favorable stage, age, and other cancer characteristics that invariably result in better overall survival.[19,20] Our analyses demonstrated that this effect did not account for the chemotherapy benefit, as outlined above. Instead, we did identify a very important overall survival benefit in contemporary patients that is most likely attributable to an intensification of systemic treatment lines in contemporary years relative to chemotherapy-exposed patients treated in historical years. Specifically, it is highly plausible that multiple systemic lines were offered to contemporary patients, but not to their historical counterparts. This hypothesis appears to represent the most plausible explanation for the observed findings. Nonetheless, the retrospective nature of our database does not allow us to firmly conclude the validity of this hypothesis. In consequence, it remains to be proven whether the same improvement in overall survival in more contemporary years will be recorded in other large-scale population based databases, such as CAPSURE or NCDB.

Despite the novelty and the very important absolute differences in overall survival between contemporary versus historical patients, that were observed in the current study, several limitations need to be acknowledged. First and foremost, our findings are limited by the non-randomized design of the current study. Although we applied the most stringent statistical methodology to attempt controlling for selection biases, these measures cannot fully eliminate the possibility of a selection bias that results in better survivals in contemporary patients, relative to their historical counterparts. Only a randomized design, that is secondarily stratified according to contemporary versus historical enrollment date could specifically answer this question. Second, the population-based nature of the study does not allow a detailed analysis of the number, duration, and type of systemic therapies that was administered to contemporary versus historical patients. Third, despite the availability of cT-, cN-, cM-stage, and tumor grade, the current population cannot be stratified between low and high tumor burden. This stratification represents a standard in all analyses of systemic therapy in newly diagnosed mPCa

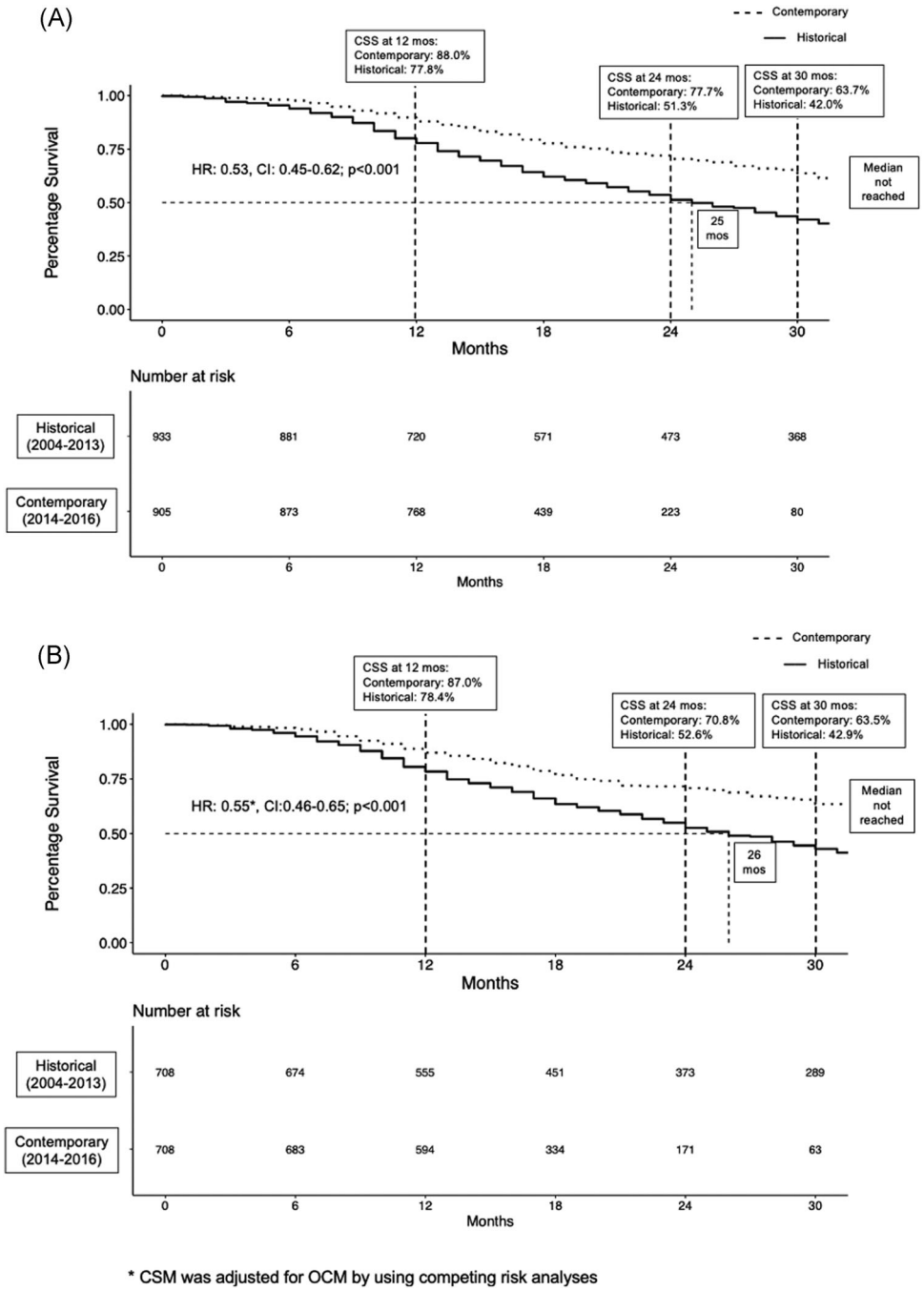

FIGURE 3 (A) and (B) Kaplan–Meier plots illustrating cancer-specific survival in 1838 metastatic prostate cancer (mPCa) patients before propensity score matching (A) and in 1416 mPCa patients after propensity score matching (B), exposed to chemotherapy

patients. Fourth, despite the population based, epidemiologically nature of the SEER database, the absolute number of contemporary, and historical prostate cancer patients are relatively low. In consequence, even though, the SEER database represents one of two most generalizable North American population-based cancer databases, the generalizability of chemotherapy exposed de novo metastatic cancer patients is more limited than that of all prostate cancer due to the relative rarity of this patient group. Fifth, the SEER database does not allow to assess variables that represent established indicators of tumor burden in prostate cancer, such as performance status or serum-derived markers others than PSA (lactate dehydrogenase and hemoglobin). Specifically, PSA values above 98 ng/ml could not precisely be recorded. Additionally, comorbidities are not available. To address this limitation, we repeated our analysis with cancer-specific mortality as an endpoint after adjustment for other cause mortality in competing risk regression models and recorded virtually the same findings (HR: 0.55, CI: 0.46–0.66, $p < 0.001$) as in overall mortality. In consequence, our findings were not confounded by lack of adjustments for comorbidities.

5 | CONCLUSIONS

To the best of our knowledge, this study provides the most recent evidence of significant improvement in overall survival in patients with de novo mPCa and chemotherapy exposition on a population-based approach.

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CONFLICT OF INTERESTS

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from SEER. Restrictions apply to the availability of these data, which were used under license for this study.

ORCID

Benedikt Hoeh http://orcid.org/0000-0002-4238-6584
Christoph Würnschimmel http://orcid.org/0000-0001-7891-4791
Derya Tilki http://orcid.org/0000-0001-7033-1380

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