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Twenty-year trends in prostate cancer stage and grade migration in a large contemporary german radical prostatectomy cohort

Christoph Würnschimmel MD[1,2] | Mykyta Kachanov MD[1] | Mike Wenzel MD, BSc[2,3] | Philipp Mandel MD[3] | Pierre I. Karakiewicz MD[2] | Tobias Maurer MD[1,4] | Thomas Steuber MD[1,4] | Derya Tilki MD[1,4] | Markus Graefen MD[4] | Lars Budäus MD[1]

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

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

[3]Department of Urology, University Hospital Frankfurt, Frankfurt, Germany

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

Correspondence

Christoph Würnschimmel, MD, Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany.
Email: c.wuernschimmel@gmail.com

Abstract

Background: A trend towards inverse stage migration in prostate cancer (PCa) was reported. However, previous analyses did not take into account potential differences in sampling strategies (number of biopsy cores), which might have confounded these reports.

Material and Methods: Within our single-institutional database we identified PCa patients treated with radical prostatectomy (RP) between 2000 and 2020 (n = 21,646). We calculated the estimated annual percentage change (EAPC) for D'Amico risk groups, biopsy Gleason Grade Group (GGG), PSA and cT stage as well as postoperative RP GGG and pT stage relying on log linear regression methodology. Subsequently, we repeated the analyses after adjustment for number of cores obtained at biopsy.

Results: Absolute rates of D'Amico low risk decreased (−30.1%), while intermediate and high risk increased (+21.2% and +9.0%, respectively). Rates of GGG I decreased (−50.0%), while GGG II–V increased, with the largest increase in GGG II (+22.5%). This trend, albeit less pronounced, was also recorded after adjusted EAPC analyses (p < .05). Specifically, EAPC values for D'Amico low vs intermediate vs high risk were −1.07%, +0.37%, +0.45%, respectively, and EAPC values for GGG ranged between −0.71% (GGG I) and +0.80% (GGG IV). Finally, an increase in ≥cT2 (EAPC: +3.16%) was displayed (all p < .001). These trends were confirmed in EAPC calculations in RP GGG and pT stages (p < .001).

Conclusion: Our findings confirm the trend towards less frequent treatment of low risk PCa and more frequent treatment of high risk PCa, also after adjustment for number of biopsy cores.

KEYWORDS

biopsy cores, clinical stage, Gleason Grade Group, risk group, stage migration

1 | INTRODUCTION

Due to the introduction of prostate specific antigen (PSA) testing for early detection of prostate cancer (PCa), incidence rates increased since the late 1980s until the last decade.[1] However, the wide use and acceptance of PSA testing and opportunistic screening entailed a potential for over-detection of nonsignificant PCa and subsequently increased the risk of overtreatment. This was specifically important when considering invasive treatment options, such as radical prostatectomy (RP). For this reason, broad PSA testing was questioned and subsequently, a declining incidence of PCa was observed in the latest years, also within Germany.[2–4] On the other hand, when limiting PSA tests, the potential for inverse stage migration for PCa is evident.[5,6] In a recent report by Boehm et al.,[7] as well as within another report by Van den Bergh et al.,[8] the continuing trend of inverse stage and grade migration in PCa patients was confirmed, not only in Germany, but also throughout Europe.[7,8] This trend might be—on the one hand—explained by efforts to reduce overtreatment in low-risk PCa, but—on the other hand—might also be a worrisome indicator of deferred diagnosis and treatment, which may ultimately pose a detrimental effect on cancer-specific outcomes.

We aimed to provide a contemporary update on stage migration trends in German patients over the last 20 years within our large consecutive RP cohort from the Martini-Klinik database and hypothesized that the trend towards inverse stage migration continued since our last report.[5] Furthermore, as opposed to previous publications by Boehm et al as well as by Van den Bergh et al.,[8] we aimed to further adjust our analyses for the number of biopsy cores taken, since this approach has been proven to reduce potential confounding caused by differences in sampling techniques over time.[9]

2 | MATERIALS AND METHODS

2.1 | Study population

After institutional review board approval, we identified all non-metastatic PCa patients treated with RP at the Martini-Klinik between 2000 and 2020. We included only patients with complete clinical PCa variables including PSA, biopsy Gleason Grade Groups I–V (GGG) and biopsy core information (number of cores, number of positive cores) and clinical stage (cT1 vs cT2 or higher; cT3 was not assessed separately due to low sample size of 123 patients). Patients with fewer than 8 cores and more than 24 biopsy cores were excluded, to create a cohort of patients who were most likely to have received standardized sampling.[10–12] All patients were stratified according to D'Amico risk grouping.[13] Furthermore, we stratified the overall cohort by treatment years: the first era consisted of patients who were exclusively diagnosed by conventional ultrasound guided prostate biopsy (2000–2012) and the second era consisted of patients who were diagnosed by either conventional ultrasound guided prostate biopsy or magnetic resonance imaging (MRI)-guided prostate biopsy (2013–2020).

2.2 | Statistical analyses

First, we aimed to display the trends over time regarding clinical characteristics at diagnosis. In all tabulations, differences in rates over time were displayed using the estimated annual percent change (EAPC) approach that relied on previously described log linear methodology.[14] Using this approach, we displayed trends in D'Amico risk groups, biopsy GGG, PSA, and cT stages in a plain, unadjusted fashion. In the subsequent step of the analyses, we adjusted the EAPC values, where applicable, taking into account the number of cores taken at biopsy, as previously described.[9] Seperate analyses were performed for postoperative RP GGG and pT stages, as well as for patients who received MRI-guided biopsy, relying on the same methodology. Chi Square tested the difference in characteristics between year cohorts. All tests were two sided with a level of significance set at $p < .05$ and R software environment for statistical computing and graphics (version 3.4.3) was used for all analyses.[15]

3 | RESULTS

3.1 | Descriptive characteristics of the study population

Within the overall cohort of 21,646 patients, median age and PSA at diagnosis was 64 years and 7.0 ng/ml, respectively. Furthermore, 5548 (25.6%) patients exhibited low risk, 11,666 (53.9%) exhibited intermediate risk and 4432 (20.5%) exhibited high risk. When comparing the year cohorts 2000–2012 ($n = 4464$, "pre-MRI-era") versus 2013–2021 ($n = 17,000$, "MRI-era", with a 8.9% rate of MRI-guided biopsy), an increase in median PSA values (+0.8 ng/ml), positive biopsy core ratio (+0.1), D'Amico high risk groups (+10.4%) and aggressive biopsy GGG groups (IV–V, +9.9%) was exhibited (Table 1). Concerning tumor characteristics after RP (Table 2), the trend for more aggressive disease in the more contemporary cohort was confirmed, as evidenced by higher rates of pT3a (+4.4%) and pT3b/pT4 (+4.6%) and higher rates of GGG IV/V (+4.0%).

3.2 | Estimated annual percentage change in D'Amico risk groups

In unadjusted analyses (Figure 1A), incidence of D'Amico low risk decreased (EAPC: −5.73%), while conversely, the incidence of D'Amico intermediate risk (EAPC: +2.37%) and D'Amico high risk (EAPC: +6.70%) increased (all $p < .001$). In adjusted analyses (Figure 1B), the same EAPC trends were exhibited (EAPC low: −1.07%; EAPC intermediate: +0.37%; EAPC high: +0.45, all $p < .001$). Specifically, in adjusted analyses, the absolute rate differences between years 2000 and 2020 were −7.6% (from 31.7% to 24.1%) for D'Amico low risk, +5.0% (from 50.0% to 55.0%) for D'Amico intermediate risk and +2.6% for D'Amico high risk (from 18.3% to 20.9%).

TABLE 1 Patient and clinical tumor characteristics at the time of biopsy of 21,646 prostate cancer patients who received subsequent radical prostatectomy

Variable	Overall (*n* = 21,646)	2000–2012 (*n* = 4646)	2013–2020 (*n* = 17,000)	*p* Value
Age, years (median, IQR)	64 (59–69)	64 (59–68)	64 (59–69)	.002
PSA, ng/ml (median, IQR)	7.0 (5.0–10.4)	6.4 (4.7–9.6)	7.2 (5.1–10.7)	<.001
Prostate volume, ml (median, IQR)	30 (21–40)	30 (25–40)	29 (21–40)	<.001
Number of biopsy cores (median, IQR)	12 (10–12)	10 (9–12)	12 (10–13)	<.01
Positive biopsy core ratio (median, IQR)	0.3 (0.2–0.5)	0.2 (0.1–0.4)	0.3 (0.2–0.5)	<.001
Biopsy GGG (*n*, %)				<.001
I	7231 (33.4)	2248 (48.4)	4983 (29.3)	
II	7717 (35.7)	1449 (31.2)	6268 (36.9)	
III	3198 (14.8)	561 (12.1)	2637 (15.5)	
IV	1920 (8.9)	235 (5.1)	1685 (9.9)	
V	1580 (7.3)	153 (3.3)	1427 (8.4)	
Clinical stage (*n*, %)				<.001
T1	17,038 (78.7)	3920 (84.4)	13,118 (77.2)	
T2 or higher	4608 (21.2)	764 (15.6)	3882 (22.8)	
D'Amico risk group (*n*, %)				<.001
Low risk	5548 (25.6)	1822 (39.2)	3726 (21.9)	
Intermediate risk	11,666 (53.9)	2251 (48.5)	9415 (55.4)	
High risk	4432 (20.5)	573 (12.3)	3859 (22.7)	
Type of biopsy (*n*, %)				<.001
Conventional	20,132 (93.0)	4646 (100)	15,486 (91.1)	
MRI guided	1514 (7.0)	0 (0)	1514 (8.9)	

Note: Stratification was performed according to treatment years 2000–2012 (before introduction of magnetic resonance tomography MRI guided biopsy) and treatment years 2013–2020 (where MRI guided biopsy rate was 8.9%).

Abbreviations: GGG, Gleason Grade Group; IQR, interquartile range; MRI, magnetic resonance imaging; PSA, prostate specific antigen.

3.3 | Estimated annual percentage changes for biopsy GGG

In unadjusted analyses (Figure 2A), incidence of GGG I decreased (EAPC: −5.65%, $p < .001$), while the incidence of GGG II–IV increased (EAPC GGG II, III, IV: +3.07%, +4.37%, +7.66%, respectively; all $p < .001$). Finally, in absolute terms, also incidence of GGG V increased, but failed to reach significance (EAPC: GGG V: +0.29, $p = .05$). In adjusted analyses (Figure 2B), incidence of GGG I also decreased (EAPC: −0.71%, $p < .001$). Furthermore, incidence of GGG II also increased (EAPC: +0.43%, $p < .001$), GGG III now remained constant (EAPC: −0.15%, $p = .4$) and GGG IV also increased (EAPC: +0.80%, $p < .001$). Last, in contrast to unadjusted analyses, incidence of GGG V significantly increased in adjusted analyses (EAPC: +0.69%, $p = .001$). Specifically, in adjusted analyses, the absolute rate differences between years 2000 and 2020 were −4.8% (from 36.3% to 31.5%) for GGG I, +3.1% (from 33.7% to 36.8%) for GGG II, −1.5% (from 16.5% to 15.0%) for GGG III, +1.6% (from 7.2% to 8.9%) for GGG IV, and +1.5% (from 6.3% to 7.8%) for GGG V.

3.4 | Estimated annual percentage changes for PSA and clinical stage

When considering only nonadjustable variables like PSA (Figure 3A) and clinical stage (Figure 3B), decreased incidence of low PSA values (<5.0 ng/ml) at diagnosis was recorded (EAPC: −1.63%, $p = .04$), while the other categories (5.0–9.9 ng/ml; 10.0–19.9 ng/ml, and >20 ng/ml) remained constant ($p > .05$ for all). Furthermore, incidence of cT2 stages (or higher) increased (EAPC: +3.16%, $p < .001$), while incidence of cT1 stages decreased (EAPC: −0.69%, $p < .001$).

TABLE 2 Tumor characteristics after radical prostatectomy (RP) in 21,646 prostate cancer patients

	Overall (*n* = 21,646)	2000–2012 (*n* = 4646)	2013–2020 (*n* = 17,000)
pT stage, *n* (%)			
pT2	14191 (65.6)	3365 (72.4)	10826 (63.7)
pT3a	4737 (21.9)	857 (18.4)	3880 (22.8)
pT3b/pT4	2665 (12.3)	402 (8.7)	2263 (13.3)
pTx	53 (0.2)	22 (0.5)	31 (0.2)
Nodal status, *n* (%)			
pN0	15,159 (70.0)	2496 (53.7)	12,663 (74.5)
pN1	1966 (9.1)	174 (3.7)	1792 (10.5)
pNx	4521 (20.9)	1976 (42.5)	2545 (15.0)
RP GGG, *n* (%)			
GGG 1	2533 (11.7)	1121 (24.1)	1412 (8.3)
GGG 2	13,624 (62.9)	2752 (59.2)	10,872 (64)
GGG 3	3943 (18.2)	581 (12.5)	3362 (19.8)
GGG 4	187 (0.9)	37 (0.8)	150 (0.9)
GGG 5	1292 (6.0)	135 (2.9)	1157 (6.8)
Unknown	67 (0.3)	20 (0.4)	47 (0.3)

Note: Stratification was performed according to treatment years 2000–2012 (before introduction of magnetic resonance tomography MRI guided biopsy) and treatment years 2013–2020.

Abbreviation: GGG, Gleason Grade Group.

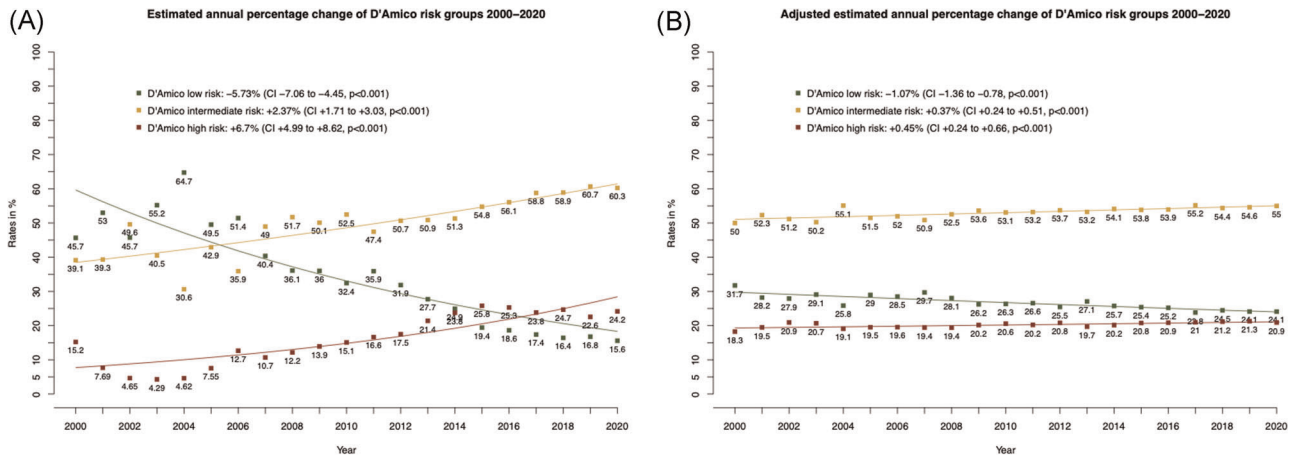

FIGURE 1 Unadjusted and adjusted trends over time for D'Amico low, intermediate and high-risk prostate cancer (PCa) between 2000 and 2020 within a German single-institutional radical prostatectomy cohort database. Log linear regression analyses were used to compute estimated annual percent change for (A) unadjusted observed rates between 2000 and 2020 and (B) rates adjusted for number of biopsy cores between 2000 and 2020. CI, confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

3.5 | Estimated annual percentage changes for RP outcomes

When considering only postoperative parameters, incidence of RP GGG I decreased (EAPC: −10.8%) while all other RP GGG increased (all $p < .05$, Figure 4A). The largest increase was exhibited for GGG III (EAPC: +5.48%), followed by GGG II (EAPC: +2.6%), GGG IV (EAPC: +0.80%), and GGG V (EAPC: +0.69%), in that order. For pT stages (Figure 4B), incidence of pT2 decreased (EAPC: −1.63%, $p < .001$), while pT3a and pT3b (or higher) increased (EAPC pT3a: +3.66%, EAPC ≥ pT3b: +4.34%, both $p < .001$).

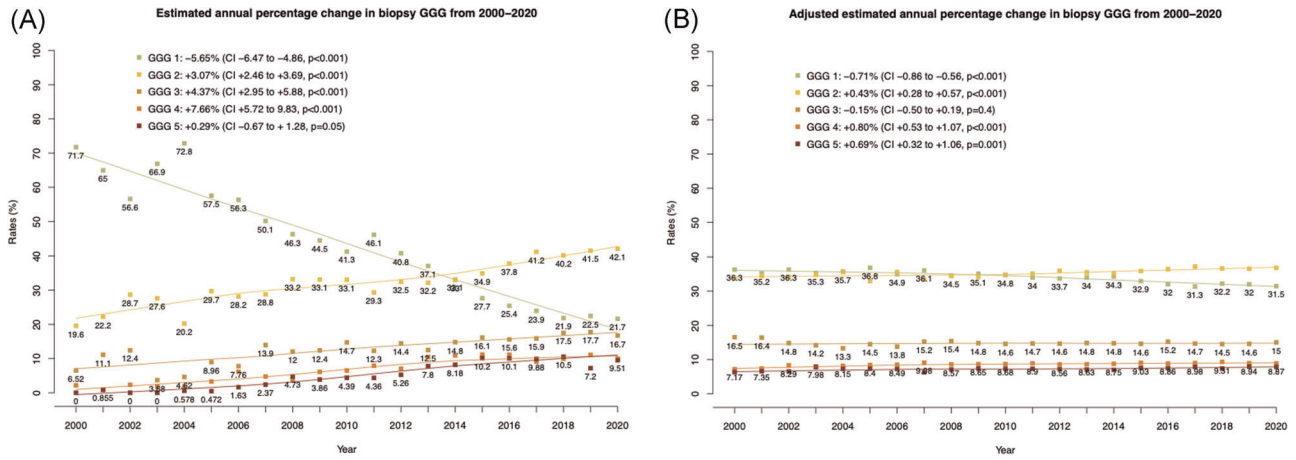

FIGURE 2 Unadjusted and adjusted trends over time for biopsy Gleason Grade Groups (GGG) between 2000 and 2020 within a German single-institutional radical prostatectomy cohort database. Log linear regression analyses were used to compute estimated annual percent change for (A) unadjusted observed rates between 2000 and 2020 and (B) rates adjusted for number of biopsy cores between 2000 and 2020. CI, confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

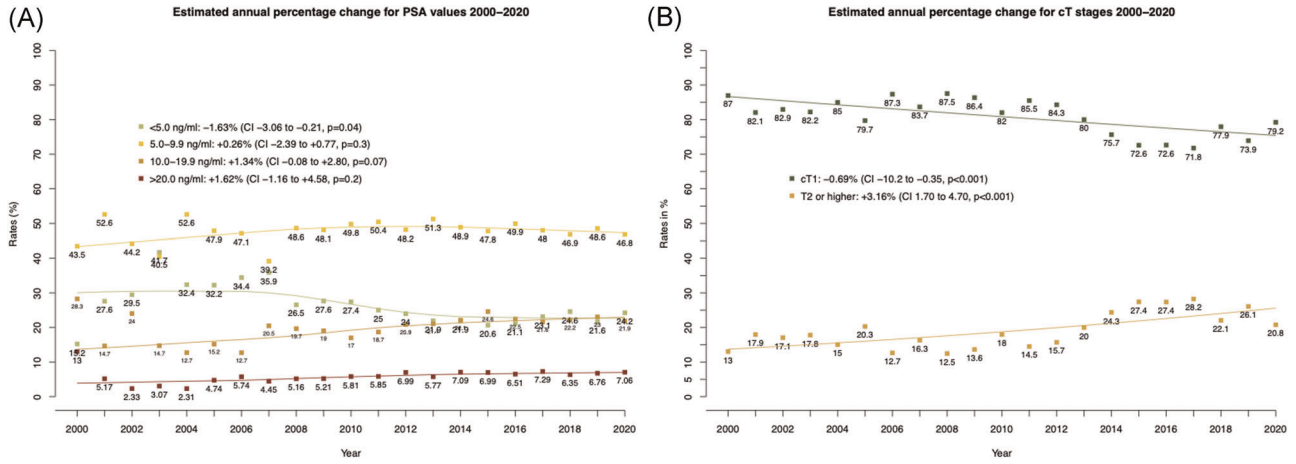

FIGURE 3 Trends over time for (A) prostate specific antigen (PSA) at diagnosis and (B) clinical stage at diagnosis (cT) between 2000 and 2020 within a German single-institutional radical prostatectomy cohort database. CI, confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

3.6 | Estimated annual percentage changes for GGG (MRI guided biopsy)

When considering only the subgroup of patients who received MRI guided biopsy ($n = 1487$), incidence rates for all GGG remained constant in both adjusted and unadjusted analyses (Figure S1A,B, all $p > .05$), except for GGG IV, where a decrease over time was exhibited in unadjusted analyses (EAPC: −31.66%, $p = .04$). When comparing GGG rates between the overall cohort and the MRI guided biopsy cohort in adjusted analyses, the latter always exhibited lower GGG I absolute rates (minimum 17.6%, maximum 20.9% for MRI guided biopsy vs. minimum 31.7%, maximum 33.5% for overall cohort).

4 | DISCUSSION

Due to the increasing awareness regarding the risk for overtreatment and subsequently, potentially provoking unnecessary complications and side-effects for patients harboring insignificant PCa, national and international urological guidelines promote active surveillance rather than treatment for these individuals.[16–18] Furthermore, on the example of the United States (U.S.), national health policy precautions were implemented to decrease the rate of insignificant PCa diagnosis. The most intensely discussed health policy approach in this regard was the "Update of the U.S. Preventive Service Task Force (USPSTF)" recommendation against a general PSA testing in 2012.[2] Thereafter, the incidence of nonsignificant PCa

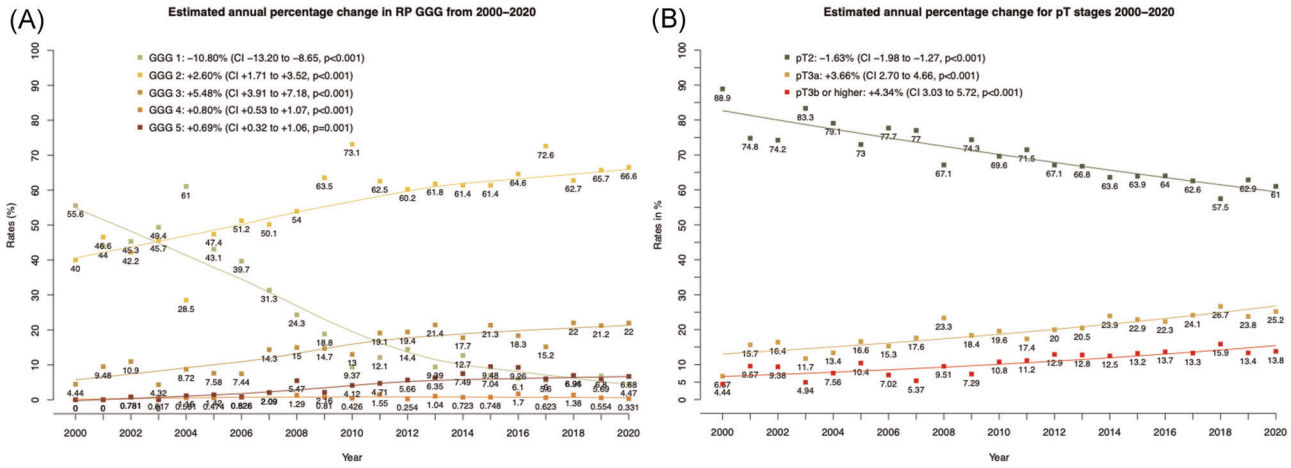

FIGURE 4 Trends over time for (A) radical prostatectomy (RP) Gleason Grade Groups (GGG) and (B) pathological T stages (pT) between 2000 and 2020 within a German single-institutional RP cohort database. CI, confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

decreased in the last decade in the U.S.[19] However, while this evolution appears welcomed, also the flipside of this approach needs to be discussed. The efforts to reduce overtreatment specifically by recommending against PSA testing also bears the potential to miss windows of opportunity for patients who would indeed require timely treatment. By neglecting these patients, it is inevitable that the incidence of high-risk PCa and advanced grades/stages increases, which may ultimately negatively impact cancer-specific outcomes for these individuals.[20] Therefore, the European Association of Urology (EAU), in contrast to the USPSTF recommendations from 2012, recently published a policy paper advocating PSA testing in a structured manner within the European Union.[21]

Based on previous observations by Boehm et al, who reported a continuing trend towards inverse stage migration in Germany, we hypothesized that similar trends might have occurred also within our institution. While this trend was already reported earlier on a European multiinstitutional scale, also incorporating data from our institution (Van den Bergh et al.,[8] years 2000–2015, $n = 28{,}572$) this report lacked the specificity for the German population and furthermore did not rely on the biopsy core adjusted EAPC approach, which decreases the confounding effect of differences in sampling techniques over time (i.e., number of biopsy cores).[8,9] Indeed, biopsy core adjustment has been proven as a powerful methodology to compensate for potential differences in sampling standards and differences in patient characteristics.[9] Furthermore, we assumed that a selection bias might be introduced when relying only on unadjusted rates, since it could be postulated that patients at risk of more aggressive PCa might also receive more aggressive sampling strategies, including higher numbers of biopsy cores taken. Therefore, the detection rate of high risk PCa might be artificially increased. Finally, we restricted our cohort to patients who were most likely to have received standardized sampling, by restricting number of biopsy cores to a range between minimum 8 and maximum 24.[10–12] Taken together, to the best of our knowledge, we provide the largest ($n = 21{,}646$) and most contemporary single-institutional analysis in this regard that accounts for the above-mentioned confounders. Our analyses yielded several noteworthy findings.

First, when considering the overall differences between the cohorts of years 2000–2012 and 2013–2020, the trend towards more aggressive disease in the contemporary cohort was confirmed. This was evidenced by an overall increase of 10.4% for the D'Amico high risk category and also by an overall increase of 9.9% for biopsy GGG IV–V. This increase was statistically significant in unadjusted and adjusted EAPC calculations. We first reported on this inverse stage migration trend in 2011, which now was confirmed to continue until 2020.[5]

Second, our hypothesis of decreasing GGG I rates was confirmed in both unadjusted and adjusted EAPC calculations and furthermore, in both biopsy GGG and RP GGG. This was evidenced by an absolute 4.8% decrease between 2000 and 2020 in biopsy GGG I after core adjustment, which also remained significant for EAPC values (−0.71%, $p < .001$) and was further strengthened by a noteworthy decrease in RP GGG I (EAPC: −10.8%, $p < .001$). Interestingly, in subgroup analyses relying only on patients who received MRI-guided biopsies, the EAPC values for all GGG subgroups remained largely constant before and after adjustment, hence also not displaying a GGG I decrease. This might be explained by the fact that patients who received MRI-guided biopsies already exhibited an absolute lower baseline rate of GGG I compared to the overall cohort (17.6%–20.9% vs. 31.7%–33.5%, respectively). Ultimately, this baseline difference indirectly validates the potential of MRI-guided biopsy to reduce rates of overdiagnosis and eventually, overtreatment.[22,23] Indeed, it appears conceivable that the implementation of MRI may further fuel the development of screening protocols that aim to reduce unnecessary biopsies, while still not missing of clinically significant PCa.[24,25] The implementation of MRI-based screening, rather than "PSA only" screening, could have a major impact on stage migration trends in the future and will be evaluated

within the next years within several ongoing prospective trials, such as the GÖTEBORG-2 (ISRCTN54449243), Re-IMAGINE (NCT04063566) or the IP1-PROSTAGRAM (NCT03702439) trials.

Last, we also reported EAPC values on nonadjustable variables like PSA and tumor stages. Here, we observed a significant trend towards less PSA values ≤5.0 ng/ml at diagnosis (EAPC: −1.63, $p = .04$). Furthermore, we observed generally higher tumor stages at diagnosis (≥cT2 EAPC: + 3.16%, $p < .001$) and also in RP pathology (EAPC pT3a: +3.66%, EAPC ≥pT3b: +4.34%, both $p < .001$).

Taken together, our analyses confirmed the hypothesis of continuing inverse stage migration also in a large contemporary German cohort. This trend was evidenced most strikingly by significantly decreased rates of D'Amico low risk and biopsy GGG I. Conversely, rates of D'Amico high risk PCa, higher clinical and pathological stages and aggressive GGG subgroups significantly increased.

Our findings should be interpreted based on the limitations that come along with single-institutional retrospective data samples. Therefore, our findings are hardly comparable with large epidemiological databases or multi-institutional reports.[6,8] Furthermore, as a tertiary referral center for PCa, not all patients received an in-house biopsy. Therefore, variations in sampling methods and biopsy assessment might have occurred despite adjustment for number of biopsy cores. However, since our reported trends are consistent with the further provided postoperative RP GGG and pT data, which were routinely assessed by dedicated uro-pathologists within our institution, we are of the opinion that our report remains valid. However, since we focused on RP treated patients only, it cannot reflect the overall population of diagnosed PCa patients and should ideally be complemented by other large contemporary series incorporating external beam radiotherapy, active surveillance and watchful waiting.

5 | CONCLUSION

Our findings confirm the trend towards less frequent treatment of low risk PCa and more frequent treatment of high risk PCa, also after adjustment for number of biopsy cores. This might be explained by the efforts to reduce overtreatment in clinically insignificant cancer.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conception and design: Christoph Würnschimmel, Mike Wenzel, Lars Budäus. *Acquisition of data*: Mykyta Kachanov. *Analysis and interpretation of data*: Christoph Würnschimmel, Mike Wenzel, Mykyta Kachanov. *Drafting of the manuscript*: Christoph Würnschimmel, Mike Wenzel. *Critical revision*: Markus Graefen, Tobias Maurer, Thomas Steuber, Derya Tilki. *Statistical analysis*: Christoph Würnschimmel, Zhe Tian. *Supervision*: Philipp Mandel, Pierre I Karakiewicz.

ORCID

Christoph Würnschimmel https://orcid.org/0000-0001-7891-4791
Mykyta Kachanov https://orcid.org/0000-0001-6543-0309
Mike Wenzel https://orcid.org/0000-0002-4338-0889
Derya Tilki https://orcid.org/0000-0001-7033-1380

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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