Inverse stage migration patterns in North American patients undergoing local prostate cancer treatment: a contemporary population-based update in light of the 2012 USPSTF recommendations

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ORIGINAL ARTICLE

Inverse stage migration patterns in North American patients undergoing local prostate cancer treatment: a contemporary population-based update in light of the 2012 USPSTF recommendations

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Abstract

Purpose Recent studies demonstrated ongoing inverse stage migration in prostate cancer (PCa) patients towards more advanced and unfavorable tumors. The USPSTF grade D recommendation may impact this trend in North American patients. We assessed contemporary stage migration and treatment trends in a large North American cohort diagnosed with PCa 2009–2014.

Methods Time-trend analyses were performed in patients within the Surveillance, Epidemiology, and End Results database, with complete data of clinical tumor stage, biopsy Gleason score, and validated PSA values, resulting in 211,645 assessable patients. Patients were stratified according to their different treatment methods [radical prostatectomy (RP), radiotherapy (RT), and no local treatment (NLT)] and according to clinical and pathological risk stratification (D'Amico and CAPRA-S score).

Results Over time, proportions of D'Amico low-risk (LR) decreased, with an increase in intermediate-to-high-risk (IR/HR) patients. These trends were more distinct in men ≥ 70 years. NLT proportions increased, most notably in D'Amico LR and/or older patients. Conversely, RP proportions remained stable in younger HR and increased in older HR patients. Similar patterns were demonstrated in the RP-treated subgroup: D'Amico HR, pT3, and/or lymph-node invasion or CAPRA-S HR proportions increased from 23.5 to 30.8, 24.3 to 32.9, and 10.7 to 16.3% (each $p \leq 0.015$).

Conclusions Inverse stage migration with increase of unfavorable PCa continues in most contemporary North American patients. However, a paradigm shift to treat LR patients with less invasive methods (NLT) was demonstrated. Contrary, HR patients increasingly undergo LT. Future studies with long-term follow-up might answer if inverse stage migration vs. treatment trends translate into different PCa metastases/mortality rates vs. proposed NLT benefits, particularly related to USPSTF-recommended reduced PSA screening.

Keywords Radical prostatectomy · Active surveillance · University of California San Francisco (UCSF) cancer of the prostate risk assessment-surgical score (CAPRA-S) · Surveillance, Epidemiology, and end results (SEER)

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Abbreviations

AJCC	American Joint Committee on Cancer
CAPRA-S	Cancer of the Prostate Risk Assessment-S
EAPC	Estimated annual percentage change
GS	Gleason score
HR	High risk
IR	Intermediate risk
LR	Low risk
NCCN	National Comprehensive Cancer Network
NLT	No local treatment

PCa	Prostate cancer
PSA	Prostate-specific antigen
RP	Radical prostatectomy
RT	Radiation therapy
SEER	Surveillance, epidemiology, and end results
UCSF	University of California, San Francisco
USPSTF	United States Preventive Services Task Force

Introduction

Prostate-specific antigen (PSA)-based screening initially resulted in a stage migration towards clinical organ-confined prostate cancers (PCa) at diagnosis [1]. However, follow-up series demonstrated the phenomenon of inverse stage migration, where an increasing proportion of patients harbored non-organ-confined PCa at diagnosis or after radical prostatectomy (RP) [2]. Specifically, North American [2–4] and European [3, 5, 6] studies recently showed an inverse trend towards locally advanced tumors in RP-treated patients during the last decade.

These findings are related to multiple evolving factors, such as less invasive treatment methods, e.g., active surveillance (AS), which are based on the protracted natural history of PCa and the favorable impact on quality of life [7, 8]. Conversely, RP is increasingly used in multidisciplinary fashion, e.g., complemented by radiotherapy and/or androgen deprivation, in high-risk, locally advanced, or metastatic PCa patients [9, 10]. Moreover, in 2012, the United States Preventive Services Task Force (USPSTF) released a highly controversial recommendation against PSA screening in men regardless of age [11, 12]. This recommendation caused a paradigm shift in PCa screening with subsequent changes in PCa incidence [11] and tumor patterns [13]. However, the existing series were limited by either exclusively focusing on PCa incidence patterns in the overall population without consideration of treatment method [14] or on a specific treatment subgroup such as RP without the superordinate context of population-based PCa incidence. Therefore, it remained unclear if overall incidence patterns simply translated to a specific treatment method or were related to a specific treatment choice.

Based on these multifaceted considerations, we hypothesized that inverse stage migration patterns continue until today. Therefore, we performed a most contemporary update of overall clinical PCa characteristics patterns in North American patients. These were complemented with analyses of pathological PCa patterns in RP patients, to estimate translation and differences between clinical and pathological PCa characteristics. Moreover, to account for potential USPSTF-associated effects on PCa patterns and the fact that PCa grade and stage varies by age [15], we compared age groups < 70 vs. ≥ 70 years. For that purpose, we relied on most contemporary North American Surveillance, Epidemiology and End Results (SEER) database patients, who were diagnosed with PCa between 2009 and 2014.

Materials and methods

Patient selection

Within the SEER database (18 cancer registries, accounting for about 28% of the US population), 314,573 patients diagnosed with adenocarcinoma of the prostate [International Classification of Disease for Oncology (61.9); histological code: 8140] between years 2009–2014 were identified. Only patients with complete data of clinical tumor stage, PSA value at time of PCa diagnosis, and biopsy Gleason score (GS) were included. PSA data were revised in the SEER release from April 2017, which was used for our analyses. Exclusion criteria consisted of metastatic disease at diagnosis (i.e., SEER field "CS Mets at DX") and stages M1a-c (6th edition of American Joint Committee on Cancer Staging Manual, $n = 12{,}112$). These selection criteria yielded 211,645 patients. Patients were stratified according to treatment type: (1) RP (surgery site codes 50 and 70) with or without radiation therapy (RT), (2) local treatment (LT) other than RP with or without RT, (3) RT without surgery, and (4) no local treatment (NLT). Within 79,834 RP patients, only patients with complete pathological data (pathological tumor stage, nodal stage, and GS) were included, resulting in 63,406 assessable patients between the time period 2010–2014.

Patients were clinically risk-stratified according to D'Amico classification [5]. RP patients were risk-stratified according to organ confinement (pT2 vs. $\geq$ pT3 and/or pN1) [5], as well as to the University of California, San Francisco (UCSF) Cancer of the Prostate Risk Assessment-S (CAPRA-S) score [16, 17], consisting of (points indicated in brackets): PSA ≤ 6 (0), 6.1–10 (1), 10.1–20 (2) or > 20 ng/ml(3), Gleason patterns $\leq 3+3$ (0), $3+4$ (1), $4+3$ (2) and $\geq 4+4$ (3), positive surgical margin (2), presence of extracapsular extension (1), seminal vesical invasion (2), and lymph-node invasion (1). The assigned points resulted in possible scores from 0 to 12. A CAPRA-S score of 0–2 would indicate low-risk (LR), 3–5 intermediate-risk (IR), and ≥ 6 high-risk (HR) PCa, respectively.

Statistical analysis

Descriptive statistics included frequencies and proportions, as well as using the Chi-square test, for categorical variables. Medians, interquartile ranges, and the *t* test were used for continuously coded variables. Annual rates of PCa, the respective treatment methods, and clinical characteristics

were analyzed over the 6-year study period of 2009–2014. Similarly, analyses over time were repeated within patients that were treated with RP. The estimated annual percentage change was calculated using squares log linear regression to compare changes in proportions over time [18].

For purpose of testing the robustness of our results to these patients that were excluded due to missing data, we reanalysed the results with missing data imputed via Bayesian imputation. The difference in the estimated probabilities and accuracies was negligible, when compared to the results using non-imputed data [19, 20].

All tests were two-sided with a statistical significance set at $p < 0.05$. Analyses were performed with the statistical package for R (the R foundation for Statistical Computing, version 3.2.2).

Results

Clinical characteristics of the PCa patient population ($n = 211{,}645$) are shown in Table 1. Median age of 65 years at PCa diagnosis remained virtually unchanged over time ($p = 0.5$). Similarly, proportions of clinical tumor stages cT1c vs. T2 vs. ≥ T3 also remained virtually unchanged over time with 77.1–76.8, 19.9–19.6 and 3–3.6%, respectively (Supplemental Table). However, proportions of PSA ranges < 10, 10–20 and > 20 ng/ml changed from 77.2 to 72.5, 13.5 to 16.4, and 9.2 to 11.1%. Similarly, proportions of biopsy GS 6, 7, 8, and ≥ 9 changed from 42.9 to 36.6, 40.8 to 41.5, 9.3 to 12.4, and 7.0 to 9.4%, respectively, driving following D'Amico risk group proportions over time: LR PCa patients initially increased from 35.0 to 37.6% between 2009 and 2011, but overall decreased to 29.6% ($p = 0.069$) in 2014 (Fig. 1a). Conversely, IR and HR patients increased from 38.0 to 39.7% ($p = 0.08$; Fig. 1a) and 27.1 to 30.7% ($p = 0.13$), respectively. In younger men < 70 years, changes over time according LR vs. HR were 38.4–34.0% ($p = 0.26$) vs. 23.0–25.5% ($p = 0.16$), respectively (Fig. 1b). Conversely, corresponding changes were more distinct in older men ≥ 70 years (Fig. 1c), with 27.5–19.3% ($p < 0.001$) and 35.9–42.8% ($p = 0.013$). Patterns were similar after stratification according to ethnicity (African American vs. Caucasian; data not shown).

Based on these findings, the treatment modalities NLT, RT, and RP were stratified according to the combination of D'Amico risk classification and age group < 70 vs. ≥ 70 years (Fig. 2a–d). First, overall NLT proportions clearly increased over time, from 19.9 to 27.1% ($p = 0.002$). Specifically, in younger patients < 70 years, NLT proportions clearly increased in D'Amico LR (23.2–45.0%, $p < 0.001$) and IR (9.4–15.9%, $p < 0.001$) patients, but only slightly increased in HR patients (12.2–15.3%, $p = 0.3$). In patients ≥ 70 years, NLT proportions also clearly increased in D'Amico LR (35.5–51.2%, $p < 0.001$) patients, but remained stable in IR (23.4%, $p = 0.4$) patients and even decreased in HR patients (32.3–27.3%, $p = 0.065$).

Second, overall RT proportions decreased over time, from 36.6 to 32.1% ($p = 0.002$). In younger patients < 70 years, RT proportions clearly decreased in D'Amico LR patients (33.3–18.2%, $p < 0.001$), but only slightly in IR (27.7–30.2%, $p = 0.67$) and HR patients (32.6–30.9%, $p = 0.037$). In older patients ≥ 70 years, RT proportions also clearly decreased, in D'Amico LR (45.7–26.6%, $p < 0.001$), but remained stable in IR (53.1–51.6%, $p = 0.16$) and HR patients (47.9–48.6%, $p = 0.7$).

Third, overall RP patients showed a similar pattern as RT patients. Specifically, RP proportions slightly decreased over time, from 39.4 to 36.3% ($p = 0.010$). In younger patients < 70 years, RP proportions clearly decreased in D'Amico LR (40.4–32.7%, $p = 0.042$) and IR (61.3–52.1%, $p = 0.041$) patients, but remained stable in HR patients (52.4–51.6% $p = 0.3$). In older patients ≥ 70 years, RP proportions did not decrease, but remained low and stable in D'Amico LR (8.3%, $p = 0.8$) and IR (18.1–18.3%, $p = 0.5$) patients, but increased in HR patients (12.1–15.6%, $p = 0.003$).

Radical prostatectomy patients

Clinicopathological characteristics of RP patients are shown in Table 2. Median age was 62 years (IQR 56–66), with only 11.7% of the RP cohort being ≥ 70 years. During the study period, proportions of D'Amico LR patients decreased from 37.8 to 22.8% ($p < 0.001$), whereas proportions of IR and HR patients increased from 38.7 to 46.4% ($p = 0.003$) and 23.5 to 30.8% ($p = 0.015$), respectively (Fig. 3). Based on RP pathology, proportions of patients that harbored pT2 and GS 6 decreased from 29.1 to 16.8% ($p < 0.001$). However, those with pT2 and ≥ GS 7 showed a slight increase (46.6–50.3%, $p = 0.004$) and those with unfavorable non-organ-confined disease an even greater increase with 24.3–32.9% ($p < 0.001$). Finally, based on UCSF CAPRA-S, a similar pattern emerged. Specifically, proportions of CAPRA-S LR, IR, and HR patients ranged from 64.1 to 52.3, 25.2 to 31.4, and 10.7 to 16.3% (each $p \leq 0.002$) over time, respectively. This pattern is virtually identical to younger RP patients < 70 years ($n = 55{,}964$). In RP patients ≥ 70 years ($n = 7442$), CAPRA-S proportions of LR, IR, and HR patients ranged from 49.9 to 38.3% ($p = 0.004$), 34.8 to 38.9% ($p = 0.08$), and 15.3 to 22.9% ($p = 0.014$), respectively.

Discussion

Based on the increasing diversity of treatment options, we hypothesized that inverse stage migration patterns continue in North American PCa patients. Our analyses yielded following important findings.

Table 1 Descriptive characteristics of 211,645 prostate cancer patients, who were diagnosed with prostate cancer within the Surveillance, Epidemiology and End Results (SEER) database, stratified according to time periods 2009–2011 vs. 2012–2014

	Overall ($N=211,645$)		2009-2011 ($n=116,514$, 55.1%)		2012-2014 ($n=95,131$, 44.9%)	
Age, years, median, IQR	65 (59–71)		65 (59–71)		5 (59–71)	
Age interval, years, *n*, %						
< 70	147,338	69.6%	80,532	69.1%	66,806	70.2%
≥ 70	64,307	30.4%	35,982	30.9%	28,325	29.8%
Race, *n*, %						
Caucasian	161,913	76.5%	89,983	77.2%	71,930	75.6%
African American	34,270	16.2%	18,345	15.7%	15,925	16.7%
Oher/unknown	15,462	7.3%	8186	7.0%	7276	7.7%
Marital status, *n*, %						
Married	141,917	67.1%	79,118	67.9%	62,799	66.0%
Divorced/widowed/separated	24,398	11.5%	13,456	11.6%	10,942	11.5%
Single/unmarried	21,919	10.4%	11,562	9.9%	10,357	10.9%
Unknown	23,411	11.1%	12,378	10.6%	11,033	11.6%
Year of diagnosis, *n*, %						
2009	38,381	18.1%	38,381	32.9%	na	–
2010	38,660	18.3%	38,660	33.2%	na	–
2011	39,473	18.7%	39,473	33.9%	na	–
2012	33,490	15.8%	na	–	33,490	35.2%
2013	32,348	15.3%	na	–	32,348	34.0%
2014	29,293	13.8%	na	–	29,293	30.8%
Clinical tumor stage, *n*, %						
T1c	164,972	78.0%	90,794	77.9%	74,178	78.0%
T2	40,390	19.1%	22,414	19.2%	17,976	18.9%
≥ T3	6283	3.0%	3306	2.8%	2977	3.1%
PSA, ng/ml, median, IQR	6.4 (4.7–9.9)		6.2 (4.7–9.6)		6.6 (4.9-10.3)	
PSA intervals, ng/ml, *n*, %						
≤ 10.0	160,261	75.7%	89,701	77.0%	70,560	74.2%
10.1-20	31,336	14.8%	16,349	14.0%	14,987	15.8%
≥ 20.1	20,048	9.5%	10,464	9.0%	9584	10.1%
Biopsy Gleason score, *n*, %						
6	90,455	42.7%	52,418	45.0%	38,037	40.0%
7	82,898	39.2%	44,631	38.3%	38,267	40.2%
8	22,377	10.6%	11,497	9.9%	10,880	11.4%
≥ 9	15,915	7.5%	7968	6.8%	7947	8.4%
D'Amico risk classification, *n*, %						
Low	73,924	34.9%	42,867	36.8%	31,057	32.7%
Intermediate	80,165	37.9%	42,968	36.9%	37,197	39.1%
High	57,556	27.2%	30,679	26.3%	26,877	28.3%
UCSF active surveillance eligible**	26,207	12.4%	11,464	9.8%	14,743	15.5%
Treatment method, *n*, %						
RP (with/without RT)	79,834	37.7%	45,351	38.9%	34,483	36.3%
RT (without RP)	74,017	35.0%	42,546	36.5%	31,471	33.1%
Other local treatment	8478	4.0%	4481	3.9%	3997	4.2%
No local treatment	49,316	23.3%	24,136	20.7%	25,180	26.5%

RP radical prostatectomy, *RT* radiotherapy, *IQR* interquartile range, UCSF active surveillance eligible: clinical stage ≤ cT2a, PSA < 10 ng/ml, Gleason score of 6 or less, ≤ 33% positive biopsy cores

First, in the overall PCa population, the proportion of D'Amico LR patients continuously decreased, particularly in patients ≥ 70 years. Such rates indicate the proper selection for less invasive treatment options (i.e. AS, focal therapy) and awareness of potential overtreatment and complications associated with RP and/or RT. Such notions were essentially

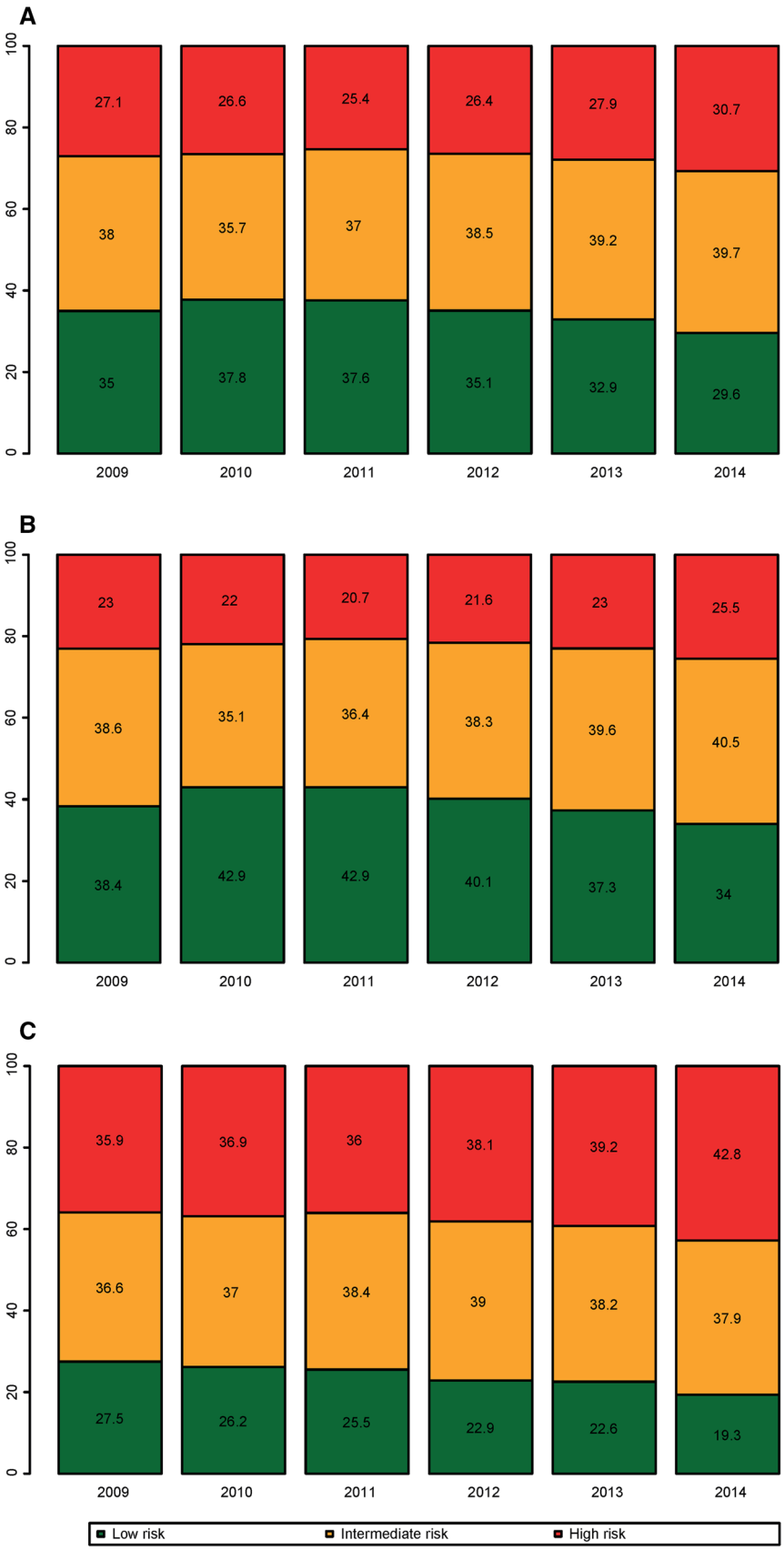

Fig. 1 **a**–**c** Proportions of newly diagnosed prostate cancer patients stratified according to D'Amico risk classification scheme (low- vs. intermediate- vs. high-risk) within the Surveillance, Epidemiology and End Results (SEER) database over the time period 2009–2014 (**a**), in men aged < 70 years (**b**) and in men aged ≥ 70 years (**c**)

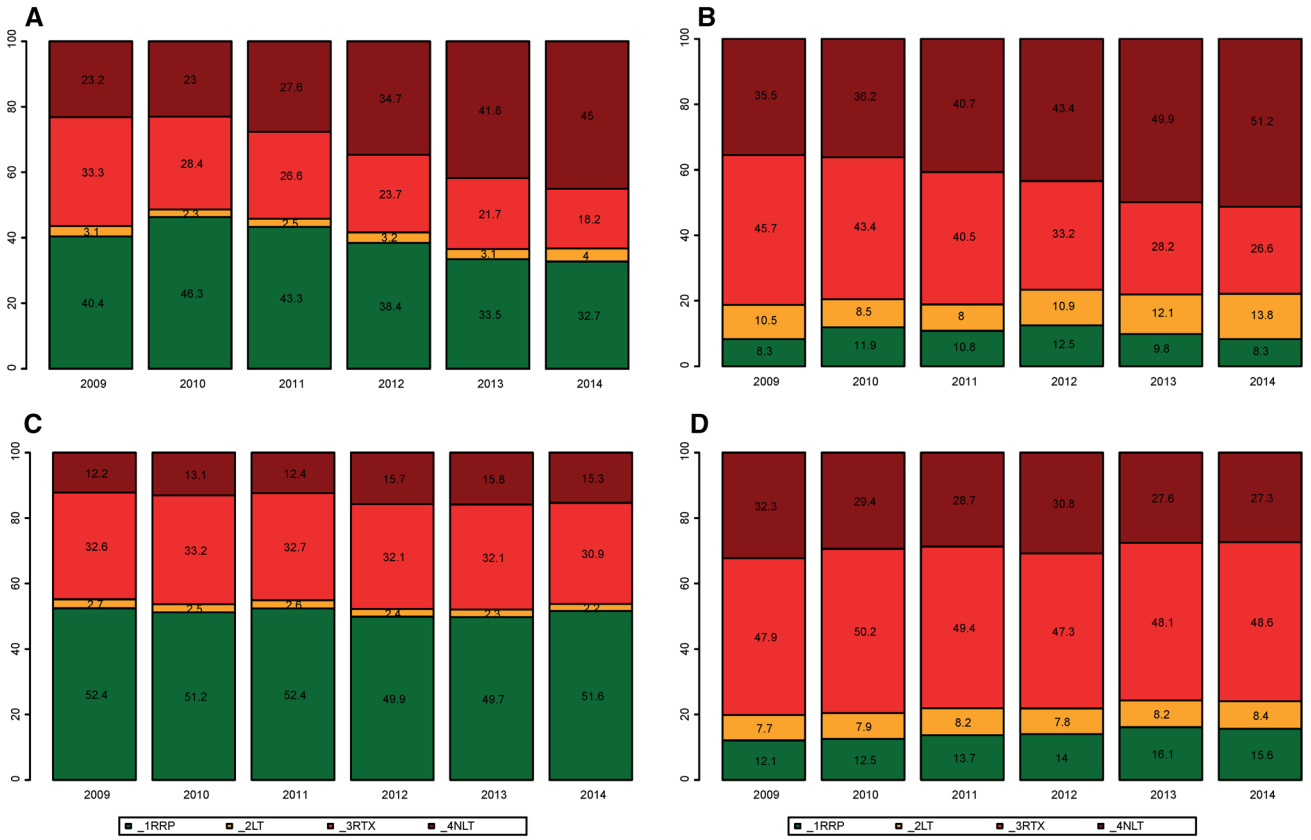

Fig. 2 **a**–**d** Proportions of newly diagnosed prostate cancer patients stratified according to treatment method [radical prostatectomy (RP) with or without additional radiotherapy vs. radiotherapy without surgery (RT) vs. other local treatment (LT) vs. no local treatment (NLT)] within the Surveillance, Epidemiology and End Results (SEER) database over the time period 2009 to 2014, within D'Amico groups low-risk and < 70 years (**a**) vs. low-risk and ≥ 70 years (**b**), and high-risk and < 70 years (**c**) vs. high-risk and ≥ 70 years (D)

confirmed by increased NLT proportions in D'Amico LR and IR patients, regardless of age group. Moreover, there was a concomitant decrease in RP or RT rates in LR/IR patients. These results corroborate European [3, 5, 6] and North American stage migration pattern findings [21, 22]. Finally, our findings in older patients indicate that life expectancy is considered at treatment selection, which is in agreement with current National Comprehensive Cancer Network guideline recommendations (V3.2016) [23].

Second, in the overall PCa population, the proportion of D'Amico HR patients continuously increased, particularly in individuals ≥ 70 years (35.9–42.8%, $p = 0.013$). Our findings demonstrate the continuation of clinical inverse stage migration in most contemporary PCa patients [21] However, it is of note that LR and HR proportions initially increased in 2009–2011 and then decreased in 2012–2014. This observation may be influenced by the 2012 USPSTF grade D recommendation against systematic PSA screening. The latter result in a complete reversal of clinical risk characteristics in patients with localized PCa [13]. Moreover, this is consistent with two recently published studies, where a decreased rate of PCa diagnoses after the release of the USPSTF recommendations was reported, but an encouraging trend towards lower rates of LR PCa diagnoses was observed [19, 20]. Conversely, increased HR proportions as demonstrated in our study were associated with potentially missing the window of opportunity for cure, by delaying diagnosis and subsequent treatment. Interestingly, when examining the underlying treatment patterns in elderly HR patients, the proportion of NLT patients decreased (32.3–27.3%, $p = 0.065$), whereas patients treated locally with RP increased over time (12.1–15.6%, $p = 0.003$). At first, this observation appears counterintuitive, since an increase of NLT HR patients could be expected after USPSTF recommendations were introduced. However, it is important to point out that our analyses included only patients that had a positive biopsy PCa diagnosis. In turn, there are a decreasing proportion of NLT patients in our SEER cohort over time, but most likely an increasing estimated number of unknown NLT patients 2011 onwards in the overall US population [24]. Information of preceding PSA screening behavior (e.g., decision-making between physician and patient, initiation, interval and termination of screening in relation to patient age, comorbidity, life expectancy, and PSA threshold), which led to positive

Table 2 Clinicopathological characteristics of 63,406 prostate cancer patients, who were treated with radical prostatectomy within the Surveillance, Epidemiology and End Results (SEER) database, stratified according to time periods 2010–2011 vs. 2012–2014

	Overall ($n=63,406$)		2010–2011 ($n=29,562$, 46.6%)		2012–2014 ($n=33,844$, 53.4%)	
Age, years, median, IQR	62 (56–66)		61 (56–66)		62 (57–67)	
Age interval, years, *n*, %						
< 70	55,964	88.3%	26,321	89.0%	29,643	87.6%
≥ 70	7442	11.7%	3241	11.0%	4201	12.4%
Race, *n*, %						
Caucasian	50,915	80.3%	23,975	81.1%	26,940	79.6%
African American	8490	13.4%	3797	12.8%	4693	13.9%
Other/unknown	4001	6.3%	1790	6.1%	2211	6.5%
Marital status, *n*, %						
Married	47,704	75.2%	22,443	75.9%	25,261	74.6%
Divorced/widowed/separated	5563	8.8%	2521	8.5%	3042	9.0%
Single/unmarried	6221	9.8%	2788	9.4%	3433	10.1%
Unknown	3918	6.2%	1810	6.1%	2108	6.2%
Year of diagnosis, *n*, %						
2010	14,689	23.2%	14,689	49.7%	na	–
2011	14,873	23.5%	14,873	50.3%	na	–
2012	12,191	19.2%	na	–	12,191	36.0%
2013	11,211	17.7%	na	–	11,211	33.1%
2014	10,442	16.5%	na	–	10,442	30.9%
Clinical tumor stage, *n*, %						
T1c	48,803	77.0%	22,750	77.0%	26,053	77.0%
T2	12,869	20.3%	6094	20.6%	6775	20.0%
≥ T3	1734	2.7%	718	2.4%	1016	3.0%
PSA, ng/ml, median, IQR	5.9 (4.6–8.6)		5.7 (4.4–8.1)		6.1 (4.7–9.0)	
PSA intervals, ng/ml, *n*, %						
≤ 10.0	51,795	81.7%	24,828	84.0%	26,967	79.7%
10.1-20	8214	13.0%	3423	11.6%	4791	14.2%
≥ 20.1	3397	5.4%	1311	4.4%	2086	6.2%
Biopsy Gleason score, *n*, %						
6	24,761	39.1%	13,388	45.3%	11,373	33.6%
7	28,473	44.9%	12,266	41.5%	16,207	47.9%
8	6592	10.4%	2569	8.7%	4023	11.9%
≥ 9	3580	5.7%	1339	4.5%	2241	6.6%
D'Amico risk classification, *n*, %						
Low	20,113	31.7%	10,876	36.8%	9237	27.3%
Intermediate	27,040	42.7%	11,762	39.8%	15,278	45.1%
High	16,253	25.6%	6924	23.4%	9329	27.6%
UCSF active surveillance eligibility**	7177	11.3%	3711	12.6%	3466	10.2%
Pathological tumor stage, *n*, %						
T2	46,241	72.9%	22,375	75.7%	23,866	70.5%
T3	16,940	26.7%	7094	24.0%	9846	29.1%
T4	225	0.4%	93	0.3%	132	0.4%
Surgical margin positivity, *n*, %	12,309	19.4%	5398	18.3%	6911	20.4%
Pathological Gleason score, *n*, %						
6	16,121	25.4%	8887	30.1%	7234	21.4%
7	39,462	62.2%	17,560	59.4%	21,902	64.7%
8	3449	5.4%	1414	4.8%	2035	6.0%
≥ 9	4374	6.9%	1701	5.8%	2673	7.9%

Table 2 (continued)

	Overall ($n=63,406$)		2010–2011 ($n=29,562$, 46.6%)		2012–2014 ($n=33,844$, 53.4%)	
Pathological nodal stage, *n*, %						
NX/N0	61,139	96.4%	28,757	97.3%	32,382	95.7%
N1	2267	3.6%	805	2.7%	1462	4.3%
Organ confinement, *n*, %						
pT2 and GS6	15,212	24.0%	8378	28.3%	6834	20.2%
pT2 and ≥ GS7	30,673	48.4%	13,872	46.9%	16,801	49.6%
≥ pT3 and/or LNI	17,521	27.6%	7312	24.7%	10,209	30.2%
CAPRA-S classification, *n*, %						
Low	37,581	59.3%	18,817	63.7%	18,764	55.4%
Intermediate	17,621	27.8%	7543	25.5%	10,078	29.8%
High	8204	12.9%	3202	10.8%	5002	14.8%

RP radical prostatectomy, *RT* radiotherapy, *IQR* interquartile range

** UCSF active surveillance eligibility is defined as: clinical stage ≤ cT2a, PSA < 10 ng/ml, Gleason score of 6 or less, ≤33% positive biopsy cores

biopsy PCa diagnosis, is not provided in the SEER database. In consequence, considerations that led to an eventual positive prostate biopsy and subsequent treatment or NLT could not be defined.

Third, we confirmed that clinical inverse stage migration trends indeed translate into pathological inverse stage migration patterns. Proportions of unfavorable pathological characteristics such as non-organ-confined PCa or CAPRA-S HR statistically significantly increased over time, opposed by decreased proportions of organ-confined GS 6 or CAPRA-S LR PCa patients. These findings confirm the previous series from Europe [3, 5, 6, 25] and North America [2–4]. Specifically, a recent update of a large European tertiary care center reported a decrease of favorable PCa characteristics (AS eligibility, GS 6 PCa, and/or organ confinement) within RP-treated patients, which is highly indicative for adequate patient selection [25].

To our knowledge, this study is the first to present temporal trends of clinical and pathological characteristics in most contemporary North American patients, who were treated with RP. Moreover, our study is the first to put RP migration patterns in overall context of PCa incidence in the SEER population and in context to other treatment methods. Finally, widely accepted and externally validated, contemporary, multivariate clinical, and pathological risk stratification tools such as D'Amico or CAPRA-S were used, [16, 17] as well as newly validated PSA data in SEER patients.

However, our study is not devoid of limitations. First, the SEER database does not contain the specific type of NLT [26]. Specifically, the SEER database provides no information on rates of AS prior to active therapy. In consequence, we could neither stratify, nor adjust according to this unreported variable. However, we are unaware of any data that would indicate differences in the rates of AS, prior to any of the examined active treatment modalities. In consequence, we do not believe that any potential biases originating from the previous AS apply differentially to any of the examined treatment modalities. Second, the SEER database does not contain data on comorbidities or performance status, which are used as treatment selection criteria in clinical practice and would have allowed assessing differences between respective treatment rates more appropriately [21]. However, within patients treated locally, RP and RT, similar temporal trends were observed suggesting a negligible effect of comorbidity profile on overall temporal trends. Moreover, it is important to acknowledge that other changes were taking place in parallel, for example, such as more judicious use of prostate biopsies [27], changes in diagnostics, e.g., preoperative MRI imaging, and treatment [28] and changes of referral patterns by primary care physicians [29]. Specifically, preoperative imaging information was missing and would have allowed to further account for discrepancies between pre- and post-operative risk profile and treatment choice. Third, the SEER database relies on a population sample and does not represent an exhaustive repository of patients with biopsy diagnosed PCa in the United States. Therefore, results of our study may not be generalized to all North American institutions. Fourth, the SEER database does not provide information on rates of screening for PCa. In consequence, we could not adjust for that effect in our analyses. However, we are unaware of any reasons why the rates of screening should apply differently according to examined treatment modalities.

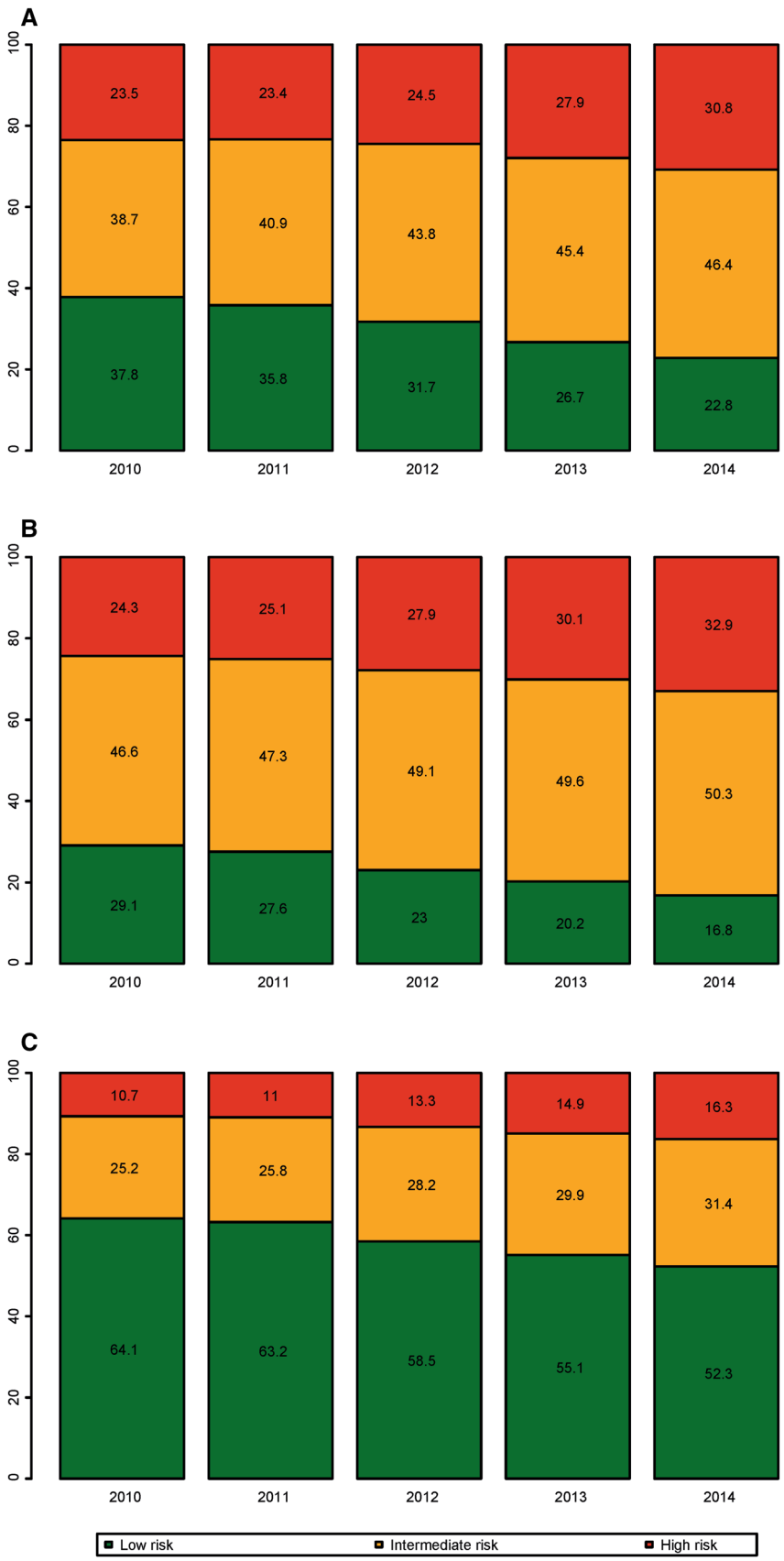

Fig. 3 **a–c** Proportions of prostate cancer patients, who were treated with radical prostatectomy, within the Surveillance, Epidemiology and End Results (SEER) database over the time period 2010–2014 stratified according to **a** D'Amico risk classification scheme (low- vs. intermediate- vs. high-risk), **b** organ confinement (pT2 and Gleason score 6 vs. pT2 and Gleason score = 7 vs. ≥ pT3 and/or lymph-node invasion) and **c** CAPRA-S score (low- vs. intermediate- vs. high-risk)

Conclusions

Inverse stage migration continues in most contemporary North American patients. In addition, a paradigm shift to treat LR patients with less invasive methods, whereas HR patients increasingly undergo LT, such as RP or RT, can be observed. However, it appears that USPSTF recommendations serve as catalyst, which further increase the gap between LR vs. HR and younger vs. elderly patients. In consequence, they might add to the potential benefit in terms of avoiding overtreatment, but at expense of detrimental effects such as missing the opportunity of correct diagnosis and curative treatment. Future studies with intermediate-to-long--term follow-up will answer the question if USPSTF-associated, reduced PSA screening and inverse stage migration lead to increased PCa mortality and metastases rates.

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Compliance with ethical standards

Conflict of interest The authors have no actual or potential conflicts of interest to declare.

Informed consent All patients provided written informed consent.

Ethical approval All authors of this research paper have directly participated in the planning, execution, or analysis of the study. All authors of this paper have read and approved the final version submitted. The contents of this manuscript have not been copyrighted or published previously. The contents of this manuscript are not under consideration for publication elsewhere.

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