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The association of the type and number of D'Amico high-risk criteria with rates of pathologically non-organ-confined prostate cancer

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Introduction The aim of this study was to assess the association between the type and number of D'Amico high-risk criteria (DHRCs) with rates of pathologically non-organ-confined (NOC) prostate cancer in patients treated with radical prostatectomy (RP) and pelvic lymphadenectomy (PLND).

Material and methods In the Surveillance, Epidemiology, and End Results database (2004–2016), we identified 12961 RP and PLDN patients with at least one DHRC. We relied on descriptive statistics and multivariable logistic regression models.

Results Of 12 961 patients, 6135 (47%) exclusively harboured biopsy Gleason score (GS) 8–10, 3526 (27%) had clinical stage ≥T2c, and 1234 (9.5%) had prostate-specific antigen (PSA) >20 ng/mL. Only 1886 (15%) harboured any combination of 2 DHRCs. Finally, all 3 DHRCs were present in 180 (1.4%) patients. NOC rates increased from 32% for clinical T stage ≥T2c to 49% for either GS 8–10 only or PSA >20 ng/mL only and to 66–68% for any combination of 2 DHRCs, and to 84% for respectively all 3 DHRCs, which resulted in a multivariable logistic regression OR of 1.00, 2.01 (95% CI 1.85–2.19; p <0.001), 4.16 (95% CI 3.69–4.68; p <0.001), and 10.83 (95% CI 7.35–16.52; p <0.001), respectively.

Conclusions Our study indicates a stimulus-response effect according to the type and number of DHRCs. Hence, a formal risk-stratification within high-risk prostate cancer patients should be considered in clinical decision-making.

Key Words: high-risk prostate cancer ‹› prostatectomy ‹› non-organ-confined ‹› staging ‹› SEER

INTRODUCTION

The D'Amico risk stratification system, proposed by D'Amico et al. in 1998, classifies patients into low-, intermediate-, and high-risk (HR) groups based on prostate-specific antigen (PSA) level, clinical tumour stage (cT), and Gleason score (GS) at diagnosis [1]. It has become the standard

of care in risk stratification of newly diagnosed localized prostate cancer (PCa) patients. Other classification systems represent modified versions of the original D'Amico classification and include the European Association of Urology (EAU), National Institute for Health and Care Excellence (NICE), Genito-Urinary Radiation Oncologists of Canada (GUROC), American Urological Association (AUA), and National Comprehensive Cancer Network (NCCN)] [2–6].

According to the D'Amico classification, 30% of newly diagnosed, clinically localized PCa are defined as high risk (biopsy GS sum 8–10, or PSA >20 ng/ml, or clinical stage ≥T2c, or any combination of the above) [7–11].

Despite the use of D'Amico high-risk criteria to identify HR patients among all newly diagnosed PCa, no further stratification according to the number and type of specific D'Amico HR criteria is either recommended or has been evaluated within the HR category. We hypothesized that the type and/or number of D'Amico HR criteria can further risk-stratify within the high-risk PCa category according to rates of pathologically non-organ-confined (NOC) PCa at radical prostatectomy (RP) and pelvic lymphadenectomy (PLND). We tested these hypotheses within the Surveillance, Epidemiology, and End Results database (SEER).

MATERIAL AND METHODS

Study population

The SEER database samples 26% of the United States population and approximates the United States in terms of demographic composition, as well as cancer incidence [12]. Within the SEER database 2004−2016, we identified all patients ≥18 years old with histologically confirmed non-metastatic adenocarcinoma of the prostate, diagnosed at biopsy (International Classification of Disease for Oncology [ICD-O-3] code 8140 site code C61.9), which fulfilled high-risk D'Amico PCa criteria (defined as Gleason sum 8–10, or PSA >20 ng/ml, or clinical stage ≥T2c), treated with RP and PLND. Patients with unknown clinical or pathological stage, clinical T4 stage, unknown biopsy Gleason grade group (GGG), unknown PSA or PSA >50 ng/mL, as well as autopsy/death certificate-only cases were excluded.

NOC PCa was defined as the presence of one of the following: extra-prostatic extension (ECE, pT3aN0), positive seminal vesicle involvement (SVI, pT3bN0), or lymph node involvement (LNI, pTany pN1).

Statistical analyses

In the first part of the analyses, we tabulated the relationship between D'Amico high-risk criteria and NOC. In the second part of the analyses, we fitted logistic regression models relying on individual positive D'Amico HR criteria, as well as combinations of 2 or 3 positive D'Amico HR criteria, to identify NOC patients. For all statistical analyses, tests were 2-sided with a level of significance set at $p < 0.05$, and the R software environment for statistical computing and graphics (version 3.4.3) was used [13].

RESULTS

We identified 12961 patients who underwent RP+PLDN who fulfilled D'Amico high-risk criteria (Table 1). Of those, 6135 (47%) exclusively harboured biopsy GS 8–10, 3526 (27%) exclusively harboured clinical stage ≥T2c, and 1234 (9.5%) exclusively exhibited PSA >20 ng/mL. Only 1886 (15%) harboured 2 positive HR criteria. Specifically, 1121 (8.7%) harboured biopsy GS 8–10 with cT stage

Table 1. *Descriptive characteristics of 12961 non-metastatic D'Amico high-risk prostate cancer patients treated with radical prostatectomy and pelvic lymphadenectomy within the Surveillance, Epidemiology, and End Results (2004–2016) database*

	Overall
Characteristics	N = 12961[1]
Age at diagnosis	63 (58–68)
PSA (ng/mL)	8 (5, 14)
Biopsy GGG	
1	1242 (9.6%)
2	2397 (18%)
3	1340 (10%)
4	4799 (37%)
5	3183 (25%)
cT Stage	
T1	4979 (38%)
T2a	765 (5.9%)
T2b	2171 (17%)
T2c	3690 (28%)
T3	1356 (10%)
Pathological stage	
ECE	3028 (23%)
LNI	1639 (13%)
OC	6785 (52%)
SVI	1509 (12%)
Non-organ-confined	
No	6785 (52%)
Yes	6176 (48%)

cT – clinical stage; GGG – biopsy Gleason grade group; PSA – prostate-specific antigen, ECE – extra-prostatic extension; LNI – lymph node involvement; OC – organ-confined; SVI – seminal vesicle involvement; n – number of patients

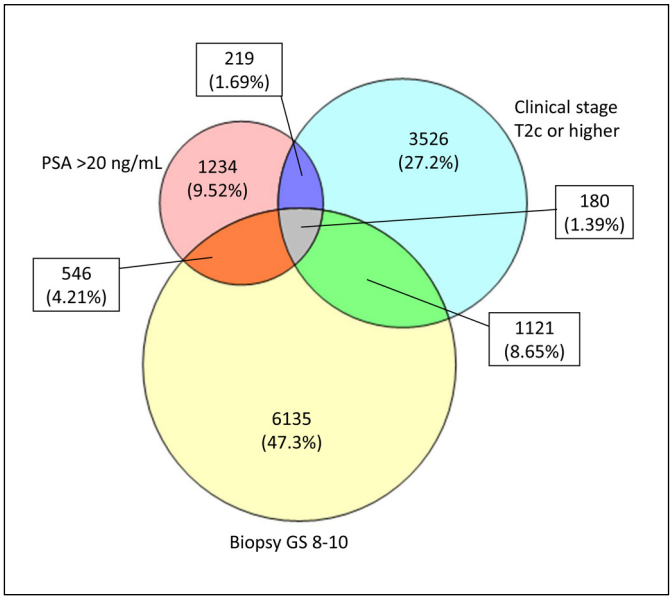

Figure 1. *Venn diagram illustrating the distribution of high-risk criteria in 12 961 D'Amico high-risk patients who underwent RP+LND between 2004 and 2016 within the Surveillance, Epidemiology, and End Results database.*

≥T2c, 546 (4.2%) had PSA ≥20 ng/mL with biopsy GS 8–10, and 219 (1.7%) had cT stage ≥T2c with PSA ≥20 ng/mL. The presence of all D'Amico HR criteria was recorded in 180 (1.4%) patients (Figure 1).

The observed rates of NOC (Table 2) were the lowest in presence of an individual HR criterion. Specifically, NOC rates for any individual positive HR criterion were the lowest (32%; 95% CI 31–34%) for cT stage ≥T2c, followed by 49% (95% CI 47–52%) for PSA >20 ng/mL alone, and 49% (95% CI 48–50%) for GGG 4–5 alone. NOC rates were higher in the presence of any combination of 2 HR criteria and ranged from 66 to 68%. Specifically, NOC rates of 66% (95% CI 63–69%), 68% (95% CI 61–74%), and 68% (95% CI 64–72%) were respectively recorded for the combination of GGG 4–5 with cT stage ≥T2c, of ≥cT2c with PSA >20 ng/mL, and of GGG 4–5 with PSA >20 ng/mL. Finally, the highest NOC rate (84%; 95% CI 78–89%) was recorded with the combination of all 3 D'Amico high-risk criteria.

In multivariable logistic regression models (Table 3) testing the association between NOC and the number of positive D'Amico HR criteria, in which the reference represented cT stage ≥T2c with the lowest NOC rate, all D'Amico HR criteria alone or in combinations revealed independent predictor status. The relative magnitude of the association between each risk factor and NOC increased in a highly similar manner to the observed rates of NOC. Specifically, relative to cT stage ≥T2c alone, any individual positive HR criteria (GGG 4–5 alone or PSA >20 ng/mL alone) exhibited an OR of 2.01 (95% CI 1.85–2.19; p <0.001), whereas any combination of 2 positive D'Amico HR criteria exhibited an OR of 4.16 (95% CI 3.69–4.68; p<0.001), and the combination of 3 positive HR criteria exhibited an OR of 10.83 (95% CI 7.35–16.52; p <0.001).

DISCUSSION

We hypothesized that the type and/or number of D'Amico HR criteria can further risk-stratify

Table 2. *Tabulation of non-organ-confined pathological stage at radical prostatectomy according to type and number of clinical D'Amico high-risk criteria in D'Amico high-risk prostate cancer patients treated with radical prostatectomy and lymph node dissection from 2004 to 2016 within the Surveillance, Epidemiology, and End Results database*

Type and number of positive D'Amico high-risk criteria		Rate (95% CI) of pathologically NOC PCa
Individual	cT ≥cT2c	32% (31–34)
	GGG 4–5	49% (48–50)
	PSA >20 ng/mL	49% (47–52)
Combination of any 2 criteria	GGG 4–5 + cT ≥cT2c	66% (63–69)
	cT ≥ cT2c + PSA >20 ng/mL	68% (61–74)
	GGG 4–5 + PSA >20 ng/mL	68% (64–72)
Combination of 3 criteria	cT ≥cT2c + GGG 4–5 + PSA >20 ng/mL	84% (78–89)

cT – clinical stage; GGG – biopsy Gleason grade group; CI – confidence interval; PSA – prostate-specific antigen; NOC – non-organ-confined; PCa – prostate cancer

Table 3. *Logistic regression analyses predicting pathologically non-organ-confined prostate cancer at radical prostatectomy according to according to the type and number of clinical D'Amico high-risk criteria in D'Amico high-risk prostate cancer patients treated with radical prostatectomy and lymph node dissection from 2004 to 2016 within the Surveillance, Epidemiology, and End Results database*

Clinical D'Amico high-risk criteria	OR	95% CI	p-value
cT ≥T2c only	reference	—	
Any individual positive criterion (GGG 4–5 or PSA >20 ng/mL only)	2.01	1.85–2.19	<0.001
Any 2 positive criteria (GGG 4–5 + PSA >20 ng/mL or GGG 4–5 + cT ≥T2c or PSA >20 + cT ≥T2c)	4.16	3.69–4.68	<0.001
Three positive criteria (GGG 4–5 + PSA >20 ng/mL + cT ≥T2c)	10.83	7.35–16.52	<0.001

cT – clinical stage; GGG – biopsy Gleason grade group; OR – odds ratio; CI – confidence interval

within the high-risk PCa category according to rates of pathologically NOC PCa. We tested this hypothesis within a large epidemiological dataset of contemporary HR patients treated with RP+PLND between 2004 and 2016. We made several noteworthy observations.

First, within D'Amico HR patients, the vast majority (83.5%) harboured only one HR criterion. Most frequently, this consisted of biopsy GS 8–10 (47%), followed by clinical stage ≥T2c (27%) and PSA >20 ng/mL (9.5%). Interestingly, a smaller fraction (15%) of HR patients harboured 2 HR criteria, and the smallest fraction (1.4%) of patients harboured all 3 HR criteria. To the best of our knowledge, we are the first to report on the prevalence and distribution of individual and combined D'Amico HR criteria in HR PCa patients. Similarly, no previous study that addressed the distribution of D'Amico HR criteria within clinical characteristics of their study population also systematically examined NOC rates or focused on NOC rates according to the number and/or the type of D'Amico HR criteria. Consequently, no previous study tested for the presence of a stimulus-response effect from the number and/or type of positive HR when NOC represented the endpoint of interest [9, 11, 14].

We addressed this void in the second part of our analyses. Here, we tabulated the rates of NOC according to 7 possible combinations of D'Amico HR criteria. These combinations were as follows: 1) cT stage ≥T2c; 2) PSA >20 ng/mL; 3) GGG 4–5; 4) the combination of cT stage ≥T2c with GGG 4–5; 5) the combination of cT stage ≥T2c with PSA >20 ng/mL; 6) the combination of GGG 4–5 with PSA >20 ng/mL; and 7) the presence of all 3 D'Amico HR criteria. The rates of NOC demonstrated the expected results. Specifically, the lowest NOC rates were recorded in the presence of one out of 3 positive D'Amico HR criteria and ranged from 32% (cT stage ≥T2c) to 49% (GGG 4–5 and PSA >20 ng/mL). Intermediate rates of NOC were recorded for the presence of 2 D'Amico HR criteria, ranging from 66% (combination of GGG 4–5 and cT stage ≥T2c) to 68% (combination of PSA >20 ng/mL and cT stage ≥T2c or GGG 4–5). Finally, the highest rates of NOC (84%) were recorded for the presence of all 3 D'Amico HR criteria.

Moreover, within the logistic regression model testing the association between D'Amico HR criteria and NOC, a stimulus-response within a multivariable setting was recorded. Relative to cT stage ≥T2c, the presence of any individual positive D'Amico HR criteria (either GS 8–10 only or PSA >20 ng/mL only) was associated with an OR of 2.01 (95% CI 1.85–2.19, p <0.001), whereas any combination of 2 positive D'Amico HR criteria was associated with an OR of 4.16 (95% CI 3.69–4.68, p <0.001), and the combination of 3 positive HR criteria was associated with an OR of 10.83 (95% CI 7.35–16.52, p <0.001). This finding provides evidence for an independent stimulus-response effect that originates from an increasing number of positive HR criteria, and where each increment results in at least a doubling of the magnitude of ORs for NOC with respect to the previous level.

To the best of our knowledge, these relationships were never previously described. From a clinical perspective, its interpretation validates the established clinical interpretation of multiple positive D'Amico HR criteria, where clinicians invariably consider patients with 2 out of 3 positive D'Amico HR criteria to be at higher risk of unfavourable oncological outcomes than those with a single criterion. Similarly, clinicians invariably consider patients with 3 D'Amico HR criteria to be at highest risk of unfavourable outcomes. However, the validation of the clinical perception of the relative importance of the D'Amico HR criteria has never been completed, and the current analyses fill this void. Pending further validation of this concept, it may be postulated that an additional level of risk stratification is of value for treatment intensification, according to the number of positive D'Amico high-risk criteria, within HR localized PCa patients.

Our study has some limitations. The first is represented by the specific selection of RP+PLND patients. Unfortunately, patients treated with other modalities could not be included because their pathological stage was unknown. Second, in accordance with American Joint Committee on Cancer systems and TNM classification, the T category still relies on digital rectal examination (DRE). However, previous studies have shown that multiparametric magnetic resonance imaging (mpMRI) outperforms DRE for local staging and reduces the risk of underestimation and undertreatment of patients with ≥T3a nonpalpable PCa [15, 16, 17]. These changes have led to questions regarding the conceptual framework with use of DRE as the most important tool for local staging. Therefore, it is possible that when using mpMRI for local staging, the rate of patients harbouring T2c or higher diseases would increase, potentially reducing the impact of PSA and GGG in predicting NOC disease, especially concerning ECE. However, a magnetic resonance imaging-based T-staging will be applied, as recently proposed [18], and DRE remains the standard for risk stratification in guideline recommendations, clinical trials, and patient counselling. Future studies are needed to understand if a change in TNM classification would affect our current results. Third, we could not assess cancer

control outcomes such as biochemical recurrence, metastatic progression, or cancer-specific mortality (CSM), because PSA progression and metastatic progression are not available in the SEER database and the data are too immature to reliably assess the association between D'Amico HR criteria and CSM. Moreover, lack of central pathology for the assessment of biopsy GGG and pathological stages at RP represent a further limitation. However, the nature of the data reflects community practice patterns, where central pathology assessment of biopsy and RP specimens is usually not applicable. Finally, the data are retrospective, with all the inherent limitations that affect the current analyses, as well as all other large-scale analyses of the SEER database, the National Cancer Database, or similar data repositories.

CONCLUSIONS

Our study indicates a stimulus-response effect according to the type and number of D'Amico HR criteria. Specifically, the effect size doubles from the weakest individual D'Amico HR criterion (cT stage ≥T2c) to stronger individual D'Amico HR criteria (either GS 8–10 only or PSA >20 ng/mL only), it doubles again in presence of any 2 D'Amico HR criteria, and doubles again in the presence of all 3. Hence, a formal risk-stratification within high-risk PCa patients should be considered in clinical decision-making.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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