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Clinical Study

Analysis of the Distribution and Temporal Trends of Grade and Stage in Urothelial Bladder Cancer in Northern New England from 1994 to 2004

Alan R. Schned,[1] Petra Lenz,[2,3] Lee E. Moore,[4] Alison Johnson,[5] Michael Jones,[6] Masatoshi Kida,[7] Debra T. Silverman,[4] Molly Schwenn,[8] Karl T. Kelsey,[9] Angeline S. Andrew,[10] Dalsu Baris,[4] and Margaret R. Karagas[10]

[1] *Department of Pathology, Dartmouth Medical School, Hanover, New Hampshire, NH 03756, USA*
[2] *Division of Cancer Epidemiology and Genetics, Science Applications International Corporation-Frederick, Inc., National Cancer Institute-Frederick, Frederick, MD 21702, USA*
[3] *Clinical Monitoring Research Program, Occupational and Environmental Epidemiology Branch, SAIC-Frederick, Inc., National Cancer Institute, 6120 Executive Plaza South, RM 8007, Rockville, MD 20852, USA*
[4] *Occupational and Environmental Epidemiology Branch, Epidemiology and Biostatistics Program, National Cancer Institute, NIH, DHHS, Bethesda, MD 20852, USA*
[5] *Vermont Cancer Registry, Burlington, Vermont, VT 05402, USA*
[6] *Department of Pathology and Laboratory Medicine, Maine Medical Center Portland, ME 04102, USA*
[7] *Department of Pathology, University of Vermont College of Medicine, Burlington, VT 05405, USA*
[8] *Maine Cancer Registry, Augusta, ME 04333, USA*
[9] *Department of Pathology and Laboratory Medicine, Brown University, Providence, RI 02912, USA*
[10] *Section of Biostatistics and Epidemiology, Dartmouth Medical School, Hanover, NH 03756, USA*

Correspondence should be addressed to Petra Lenz, plenz@mail.nih.gov

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We investigate the distribution of bladder tumor category and stage in Northern New England by geographic region, smoking status, and over time. 1091 incident bladder cancer cases from the New England Bladder Cancer Study (NEBCS), a large population-based case-control study carried out in Maine, New Hampshire, and Vermont (2001–2004) and 680 bladder cancer cases from previous case-control studies in New Hampshire (1994–2000) were used in the analysis. Of 1091 incident bladder cancer cases from the NEBCS, 26.7% of tumors were papillary urothelial neoplasms of low malignant potential (PUNLMP), 26.8% low-grade papillary urothelial carcinomas (PUC-LG), 31.3% high-grade papillary urothelial carcinomas (PUC-HG), 9.1% nonpapillary urothelial carcinomas (non-PUC), and 4.3% carcinoma in situ (CIS). Approximately 70% of cases were noninvasive (Tis/Ta), and all PUNLMP cases were of the Ta category. By contrast, half of all PUC-HG carcinomas were invasive. Short-term time trend analysis within the NEBCS (2001–2004) indicated an increase in the percentage of PUNLMP (P-trend <0.0001) paralleled by a decrease in PUC-LG (P-trend = 0.02) and for PUC-LG an increase in the percentage of non-invasive tumors (P-trend 0.04). Our findings suggest possible short-term trends with an increase in the percentage of PUNLMP and a change in the percentage of PUC-LG towards non-invasive disease.

1. Introduction

Urothelial carcinoma of the bladder accounted for 71,000 new cases and a prevalence of approximately 500,000 cases in the United States in the year 2009 (American Cancer Society, Cancer Facts and Figures 2009). Cigarette smoking is a well-established risk factor for bladder cancer resulting in a two- to threefold increased risk in smokers [1, 2]. In addition, in an earlier report, we observed a stronger association with cigarette smoking over time [2]. Tumor stage and grade

are highly correlated with disease recurrence, progression, and patient survival [3, 4]. They are thus the most important prognostic factors enabling better risk assessment and patient management. The 5-year disease-specific survival rates for muscle-invasive versus nonmuscle-invasive bladder cancers are 50% and 90%, respectively [4]. Studies of various urogenital carcinomas, including prostate cancer and renal cell carcinoma, have suggested a trend toward a lower tumor stage at diagnosis and a small survival improvement over time [5, 6]. Whether this has occurred for bladder cancer, however, is uncertain. Whereas one study reports an overall decrease in the incidence of bladder cancer and a minimal decrease in advanced stage disease [7], another study found no stage migration in bladder tumors [8].

Here we examine the tumor stage and grade distributions over time using large population-based series of bladder cancer cases from Northern New England. All slides were reviewed by a single urologic pathologist applying the World Health Organization (WHO)/International Society of Urologic Pathology (ISUP) classification system for maximum standardization and uniformity of diagnosis.

2. Materials and Methods

2.1. Study Population. The New England Bladder Cancer Study (NEBCS) is a population-based case-control study that was conducted in Maine, New Hampshire, and Vermont from 2001 to 2004 to identify factors contributing to the persistently elevated incidence and mortality rates for bladder cancer in Northern New England. The study, including tissue collection, was approved by the NIH Institutional Review Board. All patients between the ages of 35 and 79 years with primary bladder cancer newly diagnosed between September 1, 2001 and October 31, 2004 (Maine and Vermont) or between January 1, 2002 and July 31, 2004 (New Hampshire) were identified through hospital pathology departments, hospital cancer registries, and the state cancer registries. Details about the study have been published previously [2]. In brief, individuals who agreed to participate were interviewed at home by a trained interviewer using a detailed computer-assisted personal interview (CAPI). The interviewer obtained detailed information on demographics, use of tobacco products, occupational and residential histories, and other potential risk factors for bladder cancer. Of 1213 cases interviewed, 20 cases were excluded as noncancer subjects based on pathology review. Of the remaining 1193 cases (98.4%), 99 cases had cancer registry data only, but no material for pathology review by our study pathologist (A. S. Andrew), and were thus excluded. Three additional cases were excluded due to incomplete information to assign tumor category and stage, resulting in a total of 1091 cases (89.9%) included in our analysis. Short-term time trends were analyzed within the NEBCS over three time points (2001/2002, 2003, and 2004). Given that the year 2001 contained cases from Maine and Vermont beginning from September 1, 2001 with no cases from New Hampshire, cases for each state were combined from 2001 and 2002. Data for long-term time trend analysis was available for the state of New Hampshire only and was conducted using 377 cases from the New Hampshire component of the NEBCS (January 1, 2002 to July 31, 2004), as well as an additional 680 cases from two previous case-control studies (New Hampshire Phase I, July 1, 1994–June 30, 1998, 355 cases [9], and New Hampshire phase II, July 1, 1998–June 30, 2000, 325 cases [10]). The design of the New Hampshire studies was virtually identical to that of the subsequent larger NEBCS.

2.2. Pathology Review. All slides were reviewed by a single pathologist (A. S. Andrew) without knowledge of the submitted diagnosis and classified according to the World Health Organization (WHO)/International Society of Urologic Pathology (ISUP) consensus system into either carcinoma in situ (CIS), papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade papillary urothelial carcinoma (PUC-LG), high-grade papillary urothelial carcinoma (PUC-HG), nonpapillary urothelial carcinoma (nonPUC), or nonurothelial (other) [11, 12]. Tumor stage, which is determined by the total tumor burden and the extent of spread at the time of diagnosis [13], was designated according to the TNM criteria of the American Joint Committee on Cancer (AJCC). Using these definitions, carcinoma in situ, Tis, is a flat lesion that is a documented precursor to bladder cancer. Noninvasive bladder cancer comprises tumors that have not invaded into the lamina propria or beyond and is designated Ta. T1 tumors exhibit invasion into subepithelial connective tissue (lamina propria), T2 tumors into muscularis propria, T3 tumors into perivesical tissue, and T4 tumors into an adjacent organ. For all cases with registry *T* values of T2b (tumor invading greater than one-half of the muscle wall) or higher, the registry *T* values were used; otherwise histologic grade and tumor stage were assigned by the study pathologist (A. S. Andrew).

2.3. Information on Cigarette Smoking. For the NEBCS cases, smoking status was obtained from the CAPI. "Never smokers" were defined as patients who smoked less than 100 cigarettes over their lifetime. Patients who smoked more than one cigarette per day for at least 6 months were categorized as "current smokers" if they were smoking at the time of interview or quit within one year of the reference date and "former smokers" if they quit smoking one year or more before the diagnosis date [2]. Occasional smokers, defined as patients who smoked more than 100 cigarettes but never consumed cigarettes regularly (i.e., at least one cigarette per day for at least 6 months), were excluded from the analysis, thus smoking status was analyzed for a total of 1071 patients.

2.4. Statistical Analysis. Differences in the percentage and mean distribution of histologic and demographic variables were compared using chi-square and Students *t*-tests. We used the likelihood ratio test to evaluate trends in tumor stage distribution over time for grouped diagnosis years.

3. Results

Tumor classification data according to the WHO/ISUP criteria and stage distribution for the 1091 NEBCS cases are presented in Table 1. Low-grade papillary lesions, comprising

Table 1: Frequencies of WHO/ISUP classification and tumor stage by state in the NEBCS from 2001 to 2004.

State	All states	Maine		Vermont		New Hampshire		P-value*
Tumor category and stage	n (%)	Tis/Ta[§] n (%)	T1/≥T2[¶] n (%)	Tis/Ta n (%)	T1/≥T2 n (%)	Tis/Ta n (%)	T1/≥T2 n (%)	
PUNLMP[†]	291 (26.7)	137 (100)	—	54 (100)	—	100 (100)	—	—
PUC-LG	292 (26.8)	131 (92.3)	11 (7.7)	37 (86.0)	6 (14.0)	101 (94.4)	6 (5.6)	$P = 0.23$
PUC-HG	342 (31.3)	86 (51.2)	82 (48.8)	28 (49.1)	29 (50.9)	58 (49.6)	59 (50.4)	$P = 0.95$
CIS	47 (4.3)	16 (100)	—	11 (100)	—	20 (100)		—
NonPUC	99 (9.1)	—	50 (100)	—	22 (100)	—	27 (100)	—
Other	20 (1.8)	—	14 (100)	—	—	—	6 (100)	—
Total	1091 (100)[‡]	370 (70.2)	157 (29.8)	130 (69.5)	57 (30.5)	279 (74.0)	98 (26.0)	$P = 0.38$

[†] PUNLMP: papillary neoplasm of low malignant potential; PUC-LG: low-grade papillary carcinoma; PUC-HG: high-grade papillary carcinoma; CIS: carcinoma in situ; nonPUC: high-grade tumors without papillary component, other: non urothelial tumors.
[‡] Chi-square analysis showed that there was no significant difference in the distribution of tumor categories between the three states ($P = 0.15$).
[§] Tis: carcinoma in situ, Ta: non invasive papillary carcinoma; Tis and Ta cases were grouped together as noninvasive tumors.
[¶] T1: tumor invades subepithelial connective tissue, ≥T2: T2 (invasion into muscularis propria), T3 (invasion into perivesicular tissue); and T4 (invasion into an adjacent organ) tumors. T1 and ≥T2 cases were grouped together as invasive tumors, this category includes 106 cases with registry T values of T2b or higher.
* Chi-square test for the distribution of invasive versus on-invasive tumors for PUC-HG, PUC-LG and all tumors.

Table 2: Frequencies of WHO/ISUP classification and tumor stage by smoking status in the NEBCS from 2001 to 2004[†].

	Nonsmokers			Former Smokers			Current Smokers		
	All cases n (%)	Tis/Ta n (%)	T1/≥T2 n (%)	All cases n (%)	Tis/Ta n (%)	T1/≥T2 n (%)	All cases n (%)	Tis/Ta n (%)	T1/≥T2 n (%)
PUNLMP	46 (28.2)	46 (100)	—	144 (25.4)	144 (100)	—	97 (28.5)	97 (100)	—
PUC-LG	43 (26.4)	40 (93.0)	3 (7.0)	142 (25.0)	134 (94.4)	8 (5.6)	101 (29.7)	89 (88.1)	12 (11.9)
PUC-HG	51 (31.3)	28 (54.9)	23 (45.1)	190 (33.5)	102 (53.7)	88 (46.3)	92 (27.1)	38 (41.3)	54 (58.7)
CIS	10 (6.1)	10 (100)	—	24 (4.2)	24 (100)	—	12 (3.5)	12 (100)	—
NonPUC	9 (5.5)	—	9 (100)	57 (10.0)	—	57 (100)	33 (9.7)	—	33 (100)
Other	4 (2.5)	—	4 (100)	11 (1.9)	—	11 (100)	5 (1.5)	—	5 (100)
Total	163 (100)	124 (76.1)	39 (23.9)	568 (100)	404 (71.1) $P = 0.21$[‡]	164 (28.9)	340 (100)	236 (69.7) $P = 0.12$[§]	104 (30.6)

[†] Smoking data analyzed from a total of 1071 cases (see Section 2).
[‡] Chi-square test for invasive versus noninvasive tumors in former smokers as compared to nonsmokers.
[§] Chi-square test for invasive versus noninvasive tumors in current smokers as compared to nonsmokers.

PUNLMP and PUC-LG, accounted for 53.5% of all tumors. PUC-HG accounted for 31.3% of bladder cancer cases, whereas high-grade carcinomas without a papillary component (nonPUC) comprised another 9.1%. In addition, 4.3% of tumors were CIS, and 1.8% were of nonurothelial type. State-by-state comparison showed a similar distribution of tumor classifications across Maine, Vermont, and New Hampshire ($P = 0.15$). Tumors in the CIS, PUNLMP, and PUC-LG categories were >90% noninvasive (Tis or Ta) (Table 1). By contrast, approximately half of all PUC-HG lesions were invasive (T1–T4) and 15.8% of cases had a tumor stage of T2 or higher (data not shown). Nonpapillary and nonurothelial neoplasms had the highest percentage of T2 or higher tumors (73.3% and 90.0%, resp.). State-by-state comparison of the percentage of noninvasive versus invasive disease showed that there were no significant differences ($P = 0.38$) (Table 1).

Frequencies of tumor classifications and tumor stage by smoking status are presented in Table 2. Overall, smokers had a larger proportion of invasive bladder tumors, which comprised 23.9% of tumors in nonsmokers, 28.9% of tumors in former smokers, and 30.6% of tumors in current smokers. However, these differences were not statistically significant. When stratified by tumor classification, current smokers had a higher percentage of invasive tumors within the PUC-LG and PUC-HG categories, and current and former smokers had approximately twice as many nonpapillary high-grade tumors compared to nonsmokers.

To examine a possible shift in bladder cancer categories over time, we compared their distribution within the NEBCS across the study period (2001/2002, 2003, and 2004) (Table 3). We found an increase in the percentage of PUNLMP from 19.3% of bladder cancer cases in 2001/2002 to 32.0% in 2003 and 2004 (P-trend < 0.001). In contrast, the percentage of PUC-LG and PUC-HG tumors decreased over the study period in models that adjusted for gender, age and smoking status (P-trend = 0.02 and 0.05, resp., Table 3). We also compared the distribution of noninvasive versus invasive disease in all NEBCS cases and for tumors within the PUC-LG and PUC-HG categories as well as the distribution of Ta

Table 3: Time trend analysis of the frequencies of WHO/ISUP classifications and tumor stage in the New England Bladder Cancer Study (2001–2004).

Tumor category and stage	Study phase			Adjusted P-trend[‡]
	NEBCS 2001/2002[†] n (%)	NEBCS 2003 n (%)	NEBCS 2004 n (%)	
PUNLMP	89 (19.3)	122 (32.0)	80 (32.0)	<0.0001
PUC-LG	141 (30.7)	92 (24.1)	59 (23.6)	0.02
PUC-HG	160 (34.8)	108 (28.3)	74 (29.6)	0.05
Other	70 (15.2)	59 (15.5)	37 (14.8)	
PUC-LG				
Ta	126 (89.4)	85 (92.4)	58 (98.3)	
T1–T4	15 (10.6)	7 (7.6)	1 (1.7)	0.04
PUC-HG				
Ta	77 (48.1)	59 (54.3)	36 (48.6)	
T1–T4	83 (51.9)	49 (45.7)	38 (51.4)	0.6
All tumors				
Tis/Ta	315 (68.5)	282 (74.0)	182 (72.8)	
T1–T4	145 (31.5)	99 (26.0)	68 (27.2)	0.1
All tumors				
Ta	292 (63.5)	266 (69.8)	174 (69.6)	
T1	76 (16.5)	51 (13.4)	36 (14.4)	0.2[§]
Other	92 (20.0)	64 (16.8)	40 (16.0)	

[†]Included are cases from Maine and Vermont ascertained during September 1, 2001 and December 31, 2002 and cases from New Hampshire ascertained during January 1, 2002 and December 31, 2002.
[‡]P-trend adjusted for gender, age and smoking status.
[§]P-trend for Ta versus T1 tumors.

Table 4: Time trend analysis of the frequencies of WHO/ISUP classifications and tumor stage in New Hampshire during 1994–1998, 1998–2001, and 2002–2004.

Tumor category and stage	Study phase			Adjusted P-trend[¶]
	New Hampshire 1994–1998[†] n (%)	New Hampshire 1998–2000[‡] n (%)	New Hampshire 2002–2004[§] n (%)	
PUNLMP	105 (29.6)	84 (25.9)	100 (26.5)	0.6
PUC-LG	124 (35.9)	111 (34.2)	107 (28.4)	0.1
PUC-HG	99 (27.9)	74 (22.8)	117 (31.0)	0.7
Other	27 (7.7)	56 (17.2)	53 (14.1)	
PUC-LG				
Ta	110 (88.7)	104 (93.7)	100 (93.5)	
T1–T4	14 (11.3)	7 (6.3)	7 (6.5)	0.1
PUC-HG				
Ta	47 (47.5)	26 (35.1)	57 (48.7)	
T1–T4	52 (52.5)	48 (64.9)	60 (51.3)	0.9

[†]Cases from New Hampshire diagnosed during July 1, 1994 to June 30, 1998 [9].
[‡]Cases from New Hampshire diagnosed during July 1, 1998 to June 30, 2000 [10].
[§]Cases from the New Hampshire component of the NEBCS diagnosed during January 1, 2002 to July 31, 2004.
[¶]P-trends adjusted for gender, age and smoking status.

versus T1 tumors in early-stage disease (Table 3). For PUC-LG, we found an increase in the percentage of noninvasive versus invasive tumors over time from 89.4% in 2001/2002 to 92.4% in 2003 and 98.3% in 2004 (P-trend = 0.04).

Data for long-term time trend analysis was available from New Hampshire only (Table 4) and results for three time points spanning 1994 to 2004 show modest if any changes in the distributions of PUNLMP or PUC-HG. The percentage

of PUC-LG decreased over time from 35.9% in 1994–1998 to 34.2% in 1998–2000 and 28.2% in 2002–2004 ($P = 0.05$), but this trend was no longer statistically significant in models adjusting for age, gender, and smoking status ($P = 0.1$, Table 4). In addition, we observed no marked long-term time trends in the distribution of invasive versus noninvasive bladder cancer in New Hampshire (Table 4).

4. Discussion

In this large population-based series of bladder cancer conducted in Maine, New Hampshire, and Vermont, we studied the distribution of tumor category and stage by geographic region and smoking status and observed that smokers had a higher percentage of invasive disease. In addition, we examined short-term (NEBCS 2001–2004) and long-term (New Hampshire 1994–2004) time trends in the distribution of bladder cancer types and found an increase in the percentage of PUNLMP tumors and invasive disease among PUC-LG tumors within the NEBCS.

Cigarette smoking is a well-established risk factor for bladder cancer [1]. It is estimated that approximately 50–60% of urothelial carcinomas are directly attributable to smoking and that smokers have a three- to five-fold increased risk of developing bladder cancer [2]. Smokers also present with higher stage and grade tumors, and thus they have a higher bladder-cancer-specific mortality than nonsmokers [14, 15]. Overall, in the NEBCS we found a higher percentage of invasive (stage T1–T4) urothelial carcinoma in former (28.9%) and current smokers (30.6%) as compared to nonsmokers (23.9%). Within the PUC-LG and PUC-HG tumor categories, current smokers exhibited a higher percentage of invasive disease compared to nonsmokers, and they had approximately twice as many nonpapillary neoplasms, which by definition are high-grade tumors with a more aggressive clinical course. These findings suggest that high-grade bladder tumors may be a separate disease entity with differential association with cigarette smoking, but the exact molecular pathways involved in bladder carcinogenesis in smokers remain speculative [16–18]. It has been postulated that low-grade and high-grade urothelial carcinomas of the bladder arise and evolve through divergent molecular and phenotypic pathways in which low-grade noninvasive tumors are characterized by mutations in the *FGFR3* gene, whereas high-grade invasive tumors are characterized by mutations in tumor suppressor genes *p53* and *Rb* [19]. Further studies are needed to understand the molecular mechanisms underlying the observed heterogeneity by bladder cancer category associated with smoking.

Recent studies in various urogenital malignancies including prostate, renal pelvis, and ureteral carcinomas have suggested a trend toward a lower tumor stage at the time of diagnosis [5, 6, 8, 20]. This study was conducted to evaluate the distribution of bladder cancer over time, given that so far only a limited number of studies have investigated stage migration in bladder cancer. One study examined possible demographic changes associated with stage at the time of diagnosis and mortality of bladder cancer in Florida between the years of 1981 and 2004 [7]. Overall, there was a 1% increase of in situ cancer and local disease rates annually. This was paralleled by a 0.74% annual decrease in the percent of patients presenting with advanced disease ($P < 0.001$). Another study by David et al. [8] examined changes in stage, grade, and survival of urothelial carcinomas of the bladder and upper urinary tract between 1993 and 2005 and observed an increase in the proportion of Ta tumors and a decrease in the percentage of T1 tumors during the study period, but no changes in the overall proportion of invasive versus noninvasive tumors. Our results of the NEBCS show a trend toward an increase in the proportion of PUNLMP and an increase in noninvasive versus invasive tumors within the PUC-LG category, suggesting a possible shift to a more indolent phenotype. On the other hand, longer time trend analysis over a 10-year period limited to the state of New Hampshire did not corroborate these findings. Given that there was no difference in case ascertainment and all slides were reviewed by the same pathologist applying the same diagnostic criteria, this difference between short-term and long-term time trends cannot be attributed to differences in study design between the three studies. One possible explanation might be that time trends in the distribution of bladder cancer categories have only evolved in recent years. Unfortunately, short-term time trend analysis by individual state was not feasible due to case number constraints. Therefore, future studies will be necessary to better identify possible trends. Other explanations may include state-specific differences in medical practice, cancer registry criteria, or other factors in New Hampshire as well as the lower case numbers in the one-state analysis versus three states combined.

The present study has several advantages, including the population-based design. Incident cases for this analysis were collected through hospital pathology departments, hospital cancer registries, and the state cancer registries. Therefore, all biopsies reviewed were from the time of the initial diagnosis. The case ascertainment for this study occurred during a time when the adoption of the WHO/ISUP classification system was being phased in by pathologists in the three states. Underreporting of PUNLMP by the submitting institutions cannot be excluded due to inconsistencies in the terminology that pathologists used to describe borderline or noninvasive bladder malignancies. To maximize standardization and uniformity of diagnosis, all slides were reviewed again by a single urologic pathologist utilizing the WHO/ISUP criteria. The WHO/ISUP classifications system delineates detailed histologic criteria for each entity and identifies clinically and biologically distinct groups within the spectrum of urothelial neoplasms, and a number of studies have pointed to good reproducibility [11, 12, 21]. Using a single observer considerably decreases the likelihood of a drift in grading criteria as compared to the use of multiple observers in a study. Furthermore, we performed a small intraobserver reproducibility study, which showed good correlation (data not shown).

The data are derived from a geographic area in the United States with a predominantly Caucasian population. Although this uniformity reduces the variability of potential population-dependent modifiers, it may limit the generalization of the findings beyond these three states. A direct

comparison of our data with that of the Surveillance, Epidemiology and End Result Program (SEER) was not possible due to the fact that the two data sets used different classification systems. However, the distribution of tumor designations and pathological stage presented here are comparable to those of several other studies from different geographic areas and with different demographic characteristics [22].

5. Conclusion

This population-based series of bladder cancer conducted in Northern New England identified an increased percentage of PUNLMP and a higher percentage of noninvasive tumors with PUC-LG histology in the NEBCS (2001–2004), but no evidence of long-term time trends in the state of New Hampshire (1994–2004). Further monitoring will be necessary to better understand whether trends towards a more indolent phenotype of bladder cancer remain evident in Northern New England and elsewhere.

Authors' Contribution

A. R. Schned, P. Lenz, and D. Baris contributed equally to this work.

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