





Intraductal carcinoma has a minimal impact on Grade Group assignment in prostate cancer biopsy and radical prostatectomy specimens

L. Lucia Rijstenberg,¹ Tim Hansum,¹ Eva Hollemans,¹  Charlotte F Kweldam,^{1,2} Intan P Kümmerlin,¹ Chris H Bangma,³ Theodorus H van der Kwast,⁴ Monique J Roobol³ & Geert J L H van Leenders¹ 

¹Department of Pathology, Erasmus MC, University Medical Centre, Rotterdam, ²Department of Pathology, Maastricht Hospital, Rotterdam, ³Department of Urology, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands, and ⁴Laboratory Medicine Program, University Health Network, Toronto, Ontario, Canada

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Aims: Intraductal carcinoma (IDC) is an adverse histopathological parameter for prostate cancer outcome, but is not incorporated in current tumour grading. To account for its dismal prognosis and to omit basal cell immunohistochemistry, it has been proposed to grade IDC on the basis of its underlying architectural pattern. The aim of this study was to determine the impact of IDC grade assignment on prostate cancer biopsy and radical prostatectomy tumour grading.

Methods and results: A cohort of 1031 prostate cancer biopsies and 835 radical prostatectomies were assigned a Grade Group according to the 2014 International Society of Urological Pathology guidelines, without incorporation of IDC in grading. Tumour grading was compared with a Grade Group in which IDC was graded on the basis of its underlying architecture. Of 1031 biopsies, 139 (13.5%) showed IDC. Grade assignment of IDC led to a Grade Group change in 17 (1.6%) cases: four of 486 (0.8%) Grade

Group 1 cases were reclassified as Grade Group 2, nine of 375 (2.4%) Grade Group 2 cases were reclassified as Grade Group 3, and four of 58 (6.9%) Grade Group 4 cases were reclassified as Grade Group 5. IDC was observed in 213 of 835 (25.5%) radical prostatectomies, and its grading led to a change in tumour grade in five of 835 (0.6%) patients, with upgrading in two of 207 (1.0%) patients with Grade Group 1 cancer, in two of 420 (0.5%) patients with Grade Group 2 cancer, and in one of 50 (2%) patients with Grade Group 4 cancer.

Conclusion: IDC grade assignment led to a Grade Group change in 1.6% of prostate biopsy specimens and in 0.6% of radical prostatectomy specimens. Although the inclusion of IDC in or the exclusion of IDC from the Grade Group might affect decision-making in individual patients, it has a minimal impact on overall prostate cancer management.

Keywords: Gleason score, Grade Group, intraductal carcinoma, prostate cancer

Address for correspondence: L. Lucia Rijstenberg, MD, Department of Pathology, Erasmus MC, University Medical Centre, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. e-mail: l.rijstenberg@erasmusmc.nl

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Introduction

The Gleason score/Grade Group system is one of the main parameters used to predict clinical outcome and to guide treatment in prostate cancer patients. For

instance, patients with Gleason score 6 (Grade Group 1) prostate cancer are often eligible for active surveillance, whereas those with Gleason score ≥ 7 (Grade Group ≥ 2) are usually offered active treatment. Apart from Gleason grading, additional pathological parameters have been identified with independent predictive value for disease behaviour, and these are increasingly being used for therapeutic decision-making.¹

Intraductal carcinoma (IDC) of the prostate is defined as a proliferation of malignant epithelial cells confined to acini and dilated pre-existing glands. In the vast majority of cases, IDC is accompanied by invasive prostate carcinoma, although rare cases of pure IDC have been reported.² IDC accompanied by invasive carcinoma in prostate biopsy and radical prostatectomy specimens has been associated with increased biochemical recurrence, metastasis, and disease-specific death.²⁻⁷ The 2014 International Society of Urological Pathologists (ISUP) consensus conference recommended that IDC without concomitant invasive carcinoma should be reported, with a comment stating that it was usually associated with aggressive disease, which was endorsed by the 2016 World Health Organization (WHO) classification of prostate carcinoma.^{1,8} Reporting of IDC admixed with invasive carcinoma, however, has been a matter of debate.

To better convey the aggressive nature of IDC and to omit basal cell immunohistochemistry for its distinction from invasive cribriform and solid fields, it has been proposed to include IDC associated with invasive carcinoma in prostate cancer grading.⁹ Furthermore, a recent publication highlighted problems and controversies regarding the systematic reporting of IDC, in part because of the current lack of guidelines, which might be overcome by including IDC in grading schemes.²⁶

Little is known about what impact grading of IDC associated with invasive carcinoma has on Grade Group assignment in prostate cancer patients. The objective of this study was to determine the effect on Grade Group assignment of IDC being graded on the basis of its underlying architectural pattern in a large prostate cancer biopsy and radical prostatectomy cohort.

Materials and methods

PATIENT SELECTION

This study included separate prostate cancer biopsy and radical prostatectomy cohorts, which have been reported on by our group previously.^{11,12} The biopsy

cohort consisted of 1031 patients from the Dutch part of the European Randomized Study of Screening for Prostate Cancer who had been diagnosed with prostate cancer between November 1993 and March 2000 in Erasmus MC, University Medical Centre, Rotterdam, The Netherlands. All patients underwent sextant biopsies, and one or two additional biopsies were also performed if a suspicious lesion was detected with transrectal ultrasound.^{13,14} The radical prostatectomy cohort consisted of 835 patients who had undergone surgery for prostate cancer without prior radiation or hormonal therapy at the same institute between 2000 and 2017. After fixation, the radical prostatectomy specimens were sectioned transversely and entirely embedded for diagnostic purposes. All slides were available for pathology review. Except for two cases, there was no overlap between the biopsy cohort and the prostatectomy cohort. The use of tissue samples for scientific purposes was approved by the institutional Medical Research Ethics Committee (MEC-2018-1614).

PATHOLOGICAL EVALUATION

The biopsies were reviewed in common sessions by three investigators (C.K., I.K., and G.v.L.), and the radical prostatectomy specimens were reviewed in common sessions by two investigators (E.H. and G.v.L.), who were all blinded to patient information and outcome. For each biopsy core, the following were recorded: Gleason score, cancer length in millimetres, percentages of Gleason patterns 3, 4 and 5, and the presence and percentage of IDC. Biopsy tumour length included both invasive carcinoma and IDC. For each patient, a global Gleason score was determined as follows. For each biopsy, the lengths (mm) of individual Gleason patterns 3, 4 and 5 and IDC were calculated by multiplying the percentage of each component by tumour length. The lengths of the individual components in different biopsies were added, and divided by the total tumour length from all positive biopsies, resulting in percentages of Gleason pattern 3, 4 and 5 and IDC for the entire case. These parameters were used to calculate the Grade Group according to the 2014 ISUP/2016 WHO recommendations.¹ IDC was incorporated in the Grade Group by adding its percentage to Gleason pattern 4 in cases of cribriform architecture and to pattern Gleason 5 in cases of solid architecture or comedo necrosis, before application of the same grading rules. This study included only IDC cases associated with invasive carcinoma, and not isolated IDC cases without invasive disease, which should not be graded.

The following features were recorded at review of radical prostatectomy specimens: Gleason score/Grade Group according to the 2014 ISUP/2016 WHO guidelines, pT stage according to the American Joint Committee on Cancer TNM 8th edition, surgical margin status, percentages of Gleason pattern 3, 4, and 5, and the presence and percentage of IDC. For incorporation of IDC in Grade Group assignment, its percentage was added to Gleason pattern 4 or 5, and the Grade Group was then determined. In radical prostatectomies, Gleason patterns 4 and 5 were considered to be a tertiary pattern if they occupied <5% of the tumour area.

Both the biopsy cohort and the radical prostatectomy cohort have been used for investigation of the added clinical value of invasive cribriform carcinoma and IDC.^{11,15–17} Particular effort was made to distinguish these entities. Invasive cribriform Gleason pattern 4 was morphologically distinguished from IDC on the basis of the following features. Invasive cribriform prostate cancer had an irregular outline, and showed anastomosing fields beyond pre-existing gland architecture or extension into periprostatic adipose tissue, ejaculatory ducts, or seminal vesicles. IDC was morphologically identified if cribriform structures were clearly continuous with pre-existing glands lined by basal epithelium or contained corpora amylacea. If invasive cribriform carcinoma and IDC could not be differentiated by the use of morphological criteria alone, additional immunohistochemical 34BE12 staining for the presence of basal cells was performed: this applied to 104 of 197 (52.8%) prostate cancer biopsies with cribriform or solid architecture, and to 189 of 417 (45.3%) radical prostatectomy specimens with these features.

STATISTICAL ANALYSIS

Differences between percentages of Gleason pattern 4 with exclusion and inclusion of IDC were analysed in Grade Group 2 and 3 patients by the use of Student's *t*-test. Statistical analyses were performed with SPSS version 24 (IBM, Chicago, IL, USA). Results were considered to be significant when the two-sided *P*-value was <0.05.

Results

PATIENT CHARACTERISTICS OF THE BIOPSY COHORT

The prostate biopsy cohort included 1031 patients with a median age of 66 years [interquartile range

(IQR) 62–71 years] and a prostate-specific antigen (PSA) level of 5.6 ng/ml (IQR 3.9–8.8 ng/ml). Sextant biopsies were performed in 649 (53.3%) patients, and one or two additional biopsies were performed in 460 (44.6%) and 22 (2.1%) patients, respectively. Four hundred and eighty-six (47.1%) patients had global Grade Group 1 cancer, 375 (36.4%) had Grade Group 2 cancer, 63 (6.1%) had Grade Group 3 cancer, 58 (5.6%) had Grade Group 4 cancer, and 49 (4.8%) had Grade Group 5 cancer.

IMPACT OF IDC INCORPORATION ON THE GRADING OF PROSTATE CANCER BIOPSIES

In total, 139 (13.5%) patients had IDC in one or more biopsies associated with invasive adenocarcinoma, of whom four (0.8%) had Grade Group 1 cancer, 70 (18.7%) had Grade Group 2 cancer, 22 (34.9%) had Grade Group 3 cancer, 19 (32.8%) had Grade Group 4 cancer, and 24 (9.0%) had Grade Group 5 cancer. Incorporation of IDC in the Grade Group by considering it as Gleason pattern 4 led to a change in the Grade Group in 17 cases (1.6%). None of the patients was reclassified by assignment of Gleason pattern 5 to IDC with solid growth or comedonecrosis. Four (0.8%) of 486 Grade Group 1 patients had IDC, and these were reclassified as Grade Group 2; nine of 375 (2.4%) patients with Grade Group 2 cancer were upgraded to Grade Group 3; and four of 58 (6.9%) patients with Grade Group 4 cancer were upgraded to Grade Group 5 (Table 1). The last four cases were all reclassified from Gleason score 3 + 5 = 8 with tertiary Gleason pattern 4 to Gleason score 4 + 5 = 9.

As the percentage of Gleason pattern 4 is an independent pathological parameter for prostate cancer outcome, we also assessed the influence of grade assignment of IDC on Gleason pattern quantity.^{18–20} When IDC was not assigned a grade and was quantified as a separate entity, the mean percentage of invasive Gleason pattern 4 in the 375 global Grade Group 2 patients was 17.8% [standard deviation (SD) 12.2%]. When IDC was incorporated in the grading system and quantified as Gleason pattern 4 in the reassigned 370 Grade Group 2 patients, the Gleason pattern 4 percentage was 18.5% (SD 12.8%; *P* = 0.44). The percentages of Gleason pattern 4 in Grade Group 3 patients without and with incorporation of IDC were 65.9% (SD 13.4%) in 63 patients and 67.6% (SD 11.8%) in 72 patients, respectively (*P* = 0.42). When only biopsies containing IDC were analysed, the percentage of Gleason pattern 4 increased from 21.9% (SD 10.8%) in 70 Grade Group

Table 1. Impact of Grade Group in prostate cancer biopsies ($n = 1031$) if intraductal carcinoma (IDC) is assigned a tumour grade as if it were invasive disease

Prostate biopsy		Grade Group with IDC grade assignment					Total
		1	2	3	4	5	
Grade Group without IDC grade assignment	1	482	4	–	–	–	486
	2	–	366	9	–	–	375
	3	–	–	63	–	–	63
	4	–	–	–	54	4	58
	5	–	–	–	–	49	49
	Total	482	370	72	54	53	1031

2 patients without IDC grade assignment to 26.2% (SD 12.4%) in 65 Grade Group 2 patients with IDC grade assignment ($P = 0.03$). Although the percentage of Gleason pattern 4 increased from 58.5% (SD 13.4%) in 22 Grade Group 3 patients to 64.7% (SD 11.3%) in 31 Grade Group 3 patients, this did not meet conventional measures of significance ($P = 0.08$) in this relatively small subset.

PATIENT CHARACTERISTICS OF THE RADICAL PROSTATECTOMY COHORT

The radical prostatectomy cohort consisted of 835 patients with a median age of 65 years (IQR 60–68 years) and a median PSA level of 8.2 ng/ml (IQR 5.7–13.0 ng/ml). Two hundred and seven (24.8%) patients had Grade Group 1 cancer, 420 (50.3%) had Grade Group 2 cancer, 101 (12.1%) had Grade Group 3 cancer, 50 (6.0%) had Grade Group 4 cancer, and 57 (6.8%) had Grade Group 5 cancer. Pathological stage was distributed as follows: 476 (57.0%) pT2, 263 (31.5%) pT3a, 93 (11.1%) pT3b, and three (0.4%) pT4. In total, 284 (34.0%) patients had a positive surgical margin.

IMPACT OF IDC INCORPORATION ON THE GRADING OF RADICAL PROSTATECTOMIES

IDC was observed in 213 of 835 (25.5%) patients, and was present in four of 207 (1.9%) with Grade Group 1 cancer, 103 of 420 (14.5%) with Grade Group 2 cancer, 51 of 101 (50.5%) with Grade Group 3 cancer, 20 of 50 (40.0%) with Grade Group 4 cancer, and 35 of 57 (61.4%) with Grade Group 5 cancer. Incorporation of IDC in Grade Group assignment led to a change in tumour grade in five of 835 (0.6%) patients: upgrading of two of 207 (1.0%) with

Grade Group 1 cancer, two of 420 (0.5%) with Grade Group 2 cancer, and one of 50 (2.0%) with Grade Group 4 cancer (Table 2). In these cases, upgrading resulted from the assignment of Gleason pattern 4 to cribriform IDC. No cases were upgraded as a result of grade assignment to IDC with a solid growth pattern or comedonecrosis.

When IDC was not assigned a grade and was quantified as a separate entity, the percentage of invasive Gleason pattern 4 was 20.7% (SD 11.4%) among 420 Grade Group 2 patients. The percentage of Gleason pattern 4 was 21.9% (SD 12.2%) among 419 Grade Group 2 patients in whom IDC was assigned a grade and quantified as Gleason pattern 4 ($P = 0.14$). When IDC was excluded from grade assignment and Gleason pattern 4 quantity among 101 Grade Group 4 patients, the percentage of Gleason pattern 4 was 68.5% (SD 11.2%), as compared with 71.4% (SD 11.7%; $P = 0.07$) among 104 patients with inclusion of IDC in grade and Gleason pattern 4 quantity. When only Grade Group 2 radical prostatectomies were included with IDC, the percentage of Gleason pattern 4 increased from 25.3% (SD 10.3%) in 103 patients without IDC grade assignment to 30.3% (SD 11.3%) in 103 patients with IDC grade assignment ($P = 0.001$). For Grade Group 3 patients with IDC, the percentage of Gleason pattern 4 increased from 66.9% (10.5%) in 51 patients to 72.6% (SD 11.6%) in 54 patients ($P = 0.01$).

Discussion

The independent adverse prognostic value of IDC has been well acknowledged. Because IDC is a lesion within pre-existing prostate glandular structures, it was not taken into account in prostate cancer

Table 2. Impact of Grade Group in radical prostatectomy specimens ($n = 835$) if intraductal carcinoma (IDC) is assigned a tumour grade as if it were invasive disease

Radical prostatectomy		Grade Group with IDC grade assignment					Total
		1	2	3	4	5	
Grade Group without IDC grade assignment	1	205	1	1	–	–	207
	2	–	418	2	–	–	420
	3	–	–	101	–	–	101
	4	–	–	–	49	1	50
	5	–	–	–	–	57	57
	Total	205	419	104	49	58	835

grading according to the 2014 ISUP and 2016 WHO guidelines. In recent years, several arguments have been raised in favour of incorporation of IDC in prostate cancer grading. In the current study, we investigated its impact on Grade Group assignment in a biopsy cohort and a radical prostatectomy cohort. We found that incorporation of IDC in tumour grading as if it were an invasive structure led to minor changes in Grade Groups, ranging from 1.6% in biopsy specimens to 0.6% in radical prostatectomy specimens. Although incorporation of IDC might affect decision-making in individual patients, it has, overall, a minimal impact on grading in prostate cancer populations.

Many groups have shown the independent predictive value of IDC in prostate cancer biopsy and radical prostatectomy cohorts.^{2–7} The 2014 ISUP consensus conference and WHO 2016 both recommended reporting of IDC without invasive disease, but the evaluation and reporting practices for IDC admixed with carcinoma are less clear.^{1,8} Recently, it has been debated whether IDC should be integrated in prostate cancer grading.⁹ The most important argument for not grading IDC associated with invasive carcinoma is that it is not an invasive lesion in itself. On the other hand, assigning a grade to IDC is easier in daily clinical practice. Morphologically, IDC can closely resemble invasive cribriform Gleason pattern 4, or solid and comedonecrosis pattern 5. In fact, two studies have shown that comedonecrosis is more frequent in IDC than in invasive Gleason pattern 5.^{21,22} Their distinction often requires basal cell immunohistochemistry, in which a complete lack of basal cells would favour invasive disease, whereas the presence of a local, scattered or continuous basal cell layer is more compatible with IDC. Although immunohistochemistry is helpful in many cases, it is

not conclusive in every case. For instance, it is well established that basal cells may be absent in some high-grade prostatic intraepithelial neoplasia glands, owing to sampling artefacts. As glands with IDC are, by definition, distended, the chance of there being basal cell sampling artefacts would be even larger in IDC, leading to a false diagnosis of invasive carcinoma. On the other hand, irregular cribriform fields substantially exceeding the pre-existing gland architecture but with sporadic basal cells should be considered to represent invasive carcinoma, as has also been observed for rare Grade Group 1 tumours.²³

In the current study, we found that inclusion of IDC associated with invasive carcinoma in tumour grading led to a change in Grade Group assignment in only 1.6% of all prostate cancer biopsy specimens and in only 0.6% of radical prostatectomy specimens. For distinction of IDC from invasive cribriform or solid carcinoma, we performed basal cell immunohistochemistry on one or more slides of 52.8% of prostate cancer biopsies and 45.3% of radical prostatectomies with these morphological features. In a recent prostate biopsy study, Chen-Maxwell *et al.* identified 123 cases of IDC admixed with invasive carcinoma in 4630 patients, of whom 2726 had a positive biopsy (personal communication).²⁴ After application of basal cell immunohistochemistry in 83% of these, they found a change in global Grade Group in 28 (23%) patients, representing 1.0% of their prostate cancer population, which is comparable to our 1.6% biopsy Grade Group change. In both studies, a significant number of immunohistochemical stains were used on samples with cribriform or solid architecture, ranging from 45% to 83%, to differentiate IDC from invasive disease, with a Grade Group change in a minority of cases. In the latest 2019 ISUP consensus meeting on prostate cancer grading in Nice, France,

it was agreed that IDC associated with invasive carcinoma should be graded on the basis of its underlying architectural pattern as if it were invasive disease.²⁵ The most important reasons for this recommendation were: (i) that it accounts for the adverse clinicopathological features associated with IDC, which is particularly important for men with Grade Group 1 cancers with IDC, who are at risk for undertreatment of their disease; and (ii) the omission of significant numbers of immunohistochemical stains, including those for which interpretation is arbitrary.²⁶ Our finding that exclusion of IDC from prostate cancer grading is associated with a Grade Group change in <2% of cases is supportive of this practical 2019 ISUP recommendation.

A recent interobserver study among 42 genitourinary pathologists highlights current practice on the utilisation of immunohistochemistry and reporting of IDC.¹⁰ This study reflects the 2016 WHO practices, with the majority of participants not incorporating IDC in Grade Group assignment in biopsy and radical prostatectomy specimens. Some of the current controversies also become clear in this study, as the majority included IDC in tumour volume assessment, and 88% rarely, if ever, employed immunohistochemistry in assigning Grade Group and/or Gleason pattern 4 or 5 quantification. Although Gleason pattern 4 quantification is recommended for all Gleason score 7 (Grade Groups 2 and 3) prostate cancers, it is not clear to what extent this estimate includes IDC.^{8,25} Grading practices of including IDC in tumour volume assessment and possibly Gleason pattern 4 quantification, but not in tumour grading, seem contradictory. The 2019 ISUP recommendation on grading of IDC associated with invasive adenocarcinoma is helping to overcome these inconsistencies.

The strength of this study is the use of large, well-characterised biopsy and radical prostatectomy cohorts, in which extensive immunohistochemistry had been used for distinction of IDC and invasive carcinoma. A disadvantage is that this study included sextant biopsies from the 1990s, whereas standard current practice is to obtain more biopsies with additional magnetic resonance imaging-targeted sampling. Furthermore, despite the use of extensive immunohistochemistry, it was not performed on each case for practical reasons. Although we interpreted cribriform lesions with basal cells as IDC, and those without as invasive carcinoma, definitive classification might be arbitrary in some cases.^{23,27} Finally, we compared global biopsy Grade Groups and did not study the effects of IDC grade incorporation in single biopsies with the worst Grade Group, which might

result in more pronounced changes in grading. Apart from investigating the effects of IDC grading on Grade Group assignment, we also wanted to obtain insights into the alteration in the Gleason pattern 4 percentage, which is more comprehensive for the entire case than for individual biopsy cores.

In conclusion, we have demonstrated that the incorporation of IDC in prostate cancer Grade Groups on the basis of its underlying architecture led to a change in Grade Group assignment in <2% of prostate cancer biopsies and radical prostatectomies. Given the minimal impact of excluding IDC from prostate cancer grading, this study supports the practical 2019 ISUP recommendations on grading of IDC associated with invasive carcinoma.

Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

LR, TH, EH, CK and IK performed the research; GvL designed the study; CB, Tvdk and MR contributed essential clinical tools; LR and GvL analysed the data, and wrote the manuscript.

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