



Digital versus light microscopy assessment of extraprostatic extension in radical prostatectomy samples

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Abstract

Focal or non-focal/extensive extraprostatic extension of prostate carcinoma is an important pathologic prognostic parameter to be reported after radical prostatectomy. Currently, there is no agreement on how to measure and what are the best cutoff points to be used in practice. We hypothesized that digital microscopy would potentially provide more objective measurements of extraprostatic extension, thus better defining its clinical significance. To further our knowledge on digital prostate pathology, we evaluated the status of extraprostatic extension in 107 consecutive laparoscopic radical prostatectomy samples, using digital and conventional light microscopy. Mean linear and radial measurements of extraprostatic extension by digital microscopy significantly correlated to pT status ($p = 0.022$ and $p = 0.050$, respectively) but only radial measurements correlated to biochemical recurrence ($p = 0.042$) and grade groups ($p = 0.022$). None of the measurements, whether conventional or digital, were associated with lymph node status. Receiving operating characteristic analysis showed a potential cutoff point to assess linear measurements by conventional ($< vs. > 24.21$ mm) or digital microscopy ($< vs. > 15$ mm) or by radial measurement ($< vs. > 1.6$ mm). Finally, we observed an association between the number of paraffin blocks bearing EPE with pT ($p = 0.041$) status (digital microscopy), and linear measurements by conventional ($p = 0.044$) or digital microscopy ($p = 0.045$) with lymph node status. Reporting EPE measurements by digital microscopy, both linear and radial, and the number of paraffin blocks with EPE, might provide additional prognostic features after radical prostatectomy.

Keywords Prostate cancer · Radical prostatectomy · Extraprostatic extension · Digital microscopy · Digital pathology · Biochemical recurrence

Introduction

Extraprostatic extension (EPE) status is an important parameter to be reported in radical prostatectomy specimens [1–20];

recording the presence or absence and extent of EPE are required elements in virtually all internationally validated cancer reporting initiatives [2]. The identification of any EPE is important, since both focal and non-focal extraprostatic

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extension are associated with a significantly higher risk of recurrence and disease progression after radical prostatectomy, at 5 and 10 years [3–7].

On the other hand, the development and application of whole slide imaging (WSI) has profoundly affected the field of digital pathology. In the past years, digital pathology was more successfully used for education, quality assurance, archiving, research, and image analysis, but the importance of WSI in the process of rendering histopathologic diagnoses is nowadays increasing. Validation recommendations have been given by the College of American Pathologists and, in countries like Canada, official licensure has been given for the use of digital pathology for routine diagnoses [21–27]. Some devices have received approval for diagnostic purposes from the European Medicament Agency (EU) and the FDA (USA).

The systems show good concordance between digital and light microscopy; the reliability of advanced digital microscopy technologies has increased and they are nowadays widely available, as shown by several recent studies [21–29]. One potential application of digital pathology in clinical practice is the assessment of radical prostatectomy (RP) samples; in particular, positive surgical margin and EPE assessment would potentially benefit from more objective measurement, and this might be better provided by digital microscopy [1]. Positive surgical margin and EPE extension reported as focal or non-focal/extensive is an important pathologic parameter, shown in some studies to be predictive of biochemical recurrence [1]. There is, however, limited or no agreement on the method of measurement and the best cutoff points to be used in practice [1]. We hypothesized that EPE assessment by digital microscopy may be able to provide more objective measurements, which could be of potential diagnostic and prognostic relevance. In this report, therefore, we present the assessment of EPE by digital microscopy, compared with the results obtained by conventional light microscopy, in a large sequential series of radical prostatectomy specimens.

Materials and methods

The study was based on 107 consecutive laparoscopic radical prostatectomies performed by two urologists experienced (> 15 years) in laparoscopic prostatectomy, which were evaluated at our hospital from March 2014 to March 2017. None of the patients had preoperative radiotherapy or androgen deprivation treatment. Radical prostatectomy specimens were inked, sliced serially, and examined by an experienced urologic pathologist (ALB). The entire prostate was embedded in all cases. We used the 2014 modified Gleason scoring system (GS) and grade groups (GGs) [30–33]. For the purpose of the study, GG was retrospectively assigned to some earlier cases and AJCC/pTNM adjusted to the 2017 8th edition [4].

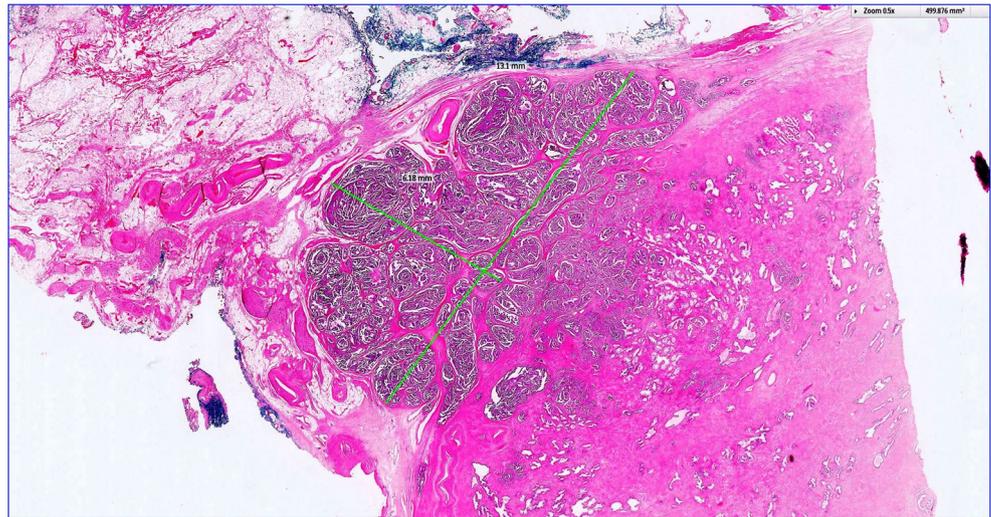
The clinic-pathological variables were prospectively collected and reviewed for the purpose of this paper. Information included age at surgery, Gleason score and grade group at radical prostatectomy, pathological stage [4], and follow-up data on biochemical recurrence. Patients were followed after surgery according to the accepted guidelines, with PSA levels being typically checked at 3-month intervals for the first year and every 6 months for the subsequent 2 years. Biochemical recurrence following surgery was considered to be a PSA measurement > 0.2 ng/mL [34]. Follow-up of at least 3 months was expressed in months, as was the time to biochemical recurrence.

From pathology reports, we retrieved data on the presence of EPE, defined as an extension of the tumor beyond the confines of the gland, into the periprostatic soft tissue. Since the assessment of EPE can be difficult, because the prostate is not surrounded by a discrete, well defined fibrous capsule [2, 10], we further assessed EPE in the following situations: (i) the presence of neoplastic glands abutting on or within the periprostatic fat or beyond the adjacent fat plane in situations in which no fat is present; (ii) neoplastic glands surrounding nerves in the neurovascular bundle; (iii) the presence of a nodular extension of tumor, bulging beyond the periphery of the prostate or beyond the compressed fibromuscular prostatic stroma at the outer edge of the gland; and (iv) extraprostatic glands seen in fibrous tissue, rather than in fat, in the case of a desmoplastic reaction in the vicinity of EPE.

Longitudinal measurements by ocular micrometer, aggregated to produce the total length (LM) in millimeters, and the number of paraffin blocks with EPE were recorded. Radial EPE was defined as the distance that the tumor protrudes perpendicularly beyond the outer margin of the capsule [6, 13]. For the purpose of the study, radial EPE was assessed by digital microscopy only due to the difficulties in reliably assessing this parameter by light microscopy. In addition, all slides were scanned using the Philips Ultrafast Scanner 1.6 device (Philips Digital Pathology Solutions, Philips Electronics Nederland BV, PC Best, The Netherlands). This scanner has received international clearance for diagnostic purposes. WSIs were examined for the presence and extent of EPE by another experienced urologic pathologist (MV), who performed all the digital measurements. Digital measurement was found easy to assess and not particularly time consuming, taking about the same time as that required for conventional light microscopy measurement.

In the scanned images, areas in which the tumor showed EPE were manually traced out and measured using Philips Image Management System 2.4.2.2. Since only linear measurement is possible with the aforementioned system, the measurements were taken between the start and end points of the EPE (Fig. 1). These measurements were recorded by the software and then aggregated to produce the total length

Fig. 1 Extraprostatic extension in a case of prostate adenocarcinoma following radical prostatectomy. Green lines identify linear and radial measurements (HE, $\times 0.5$)



(DM) in millimeters. The number of positive blocks resulting from the digital assessment was also recorded.

After a “washout period” of 2 weeks [25], all digital measurements were simultaneously reviewed a second time and agreed by two dedicated pathologists (MV and ALB).

The current project received institutional review board approval.

Statistical analysis

The endpoint of the study was to compare EPE measurements obtained by conventional and digital microscopy. Categorical variables were presented as frequencies and percentages and were compared using the chi-square test. Continuous variables were expressed as mean \pm standard deviation. The Kolmogorov-Smirnov test was used for normality analysis, and nonparametric tests were used accordingly.

The association between continuous variables and study variables was compared using Mann–Whitney/Kruskal–Wallis/Anova. For each parameter investigated, an optimal cutoff value was determined in order to maximize the sum of sensitivity and specificity using ROC (receiver operating characteristic) curves. All statistical analyses were performed using standard statistical software SPSS 17.0 version (SPSS, Inc., IL, USA). A p value of ≤ 0.05 was considered to be significant.

Results

The demographic and clinicopathological characteristics of the 107 patients in the study are summarized in Table 1. After patient follow-up of 3 to 36 months (range), 24 of them had biochemical recurrence (2 to 33 months after surgery). Table 2 shows the characteristics of patients with EPE. The second examination using digital microscopy detected no

additional case with EPE. As seen in Table 3, mean linear measurements by digital microscopy and radial measurements significantly correlated to pT status ($p = 0.022$ and $p = 0.050$, respectively) but only radial measurements were related to biochemical recurrence ($p = 0.042$) and the grade groups ($p = 0.022$). None of the measurements were associated with lymph node status.

Receiving operating characteristic analysis also showed a potential cutoff point for assessing linear measurements by conventional (\leq vs. > 24.21 mm) or digital microscopy (\leq vs. > 15 mm) or by radial measurement (\leq vs. > 1.6 mm) (Fig. 2).

Finally, we observed an association between the number of paraffin blocks bearing EPE with pT ($p = 0.041$) status (digital microscopy), and linear measurements by conventional ($p = 0.044$) or digital microscopy ($p = 0.045$) with lymph node status (Table 4).

Discussion

Extraprostatic extension status is an important parameter to be assessed after radical prostatectomy. Recording the presence or absence and extent of extraprostatic extension is in fact required in reporting radical prostatectomy specimens by the ICCR international initiative of cancer reporting [2]. The identification of any EPE is important, since both focal and non-focal EPE are associated with a significantly higher risk of recurrence at both 5 and 10 years [3–7]. Following radical prostatectomy, the 10-year progression-free probability for node negative patients with uninvolved seminal vesicles is 85–89% for organ confined disease, falling to 67–69% for focal EPE and to 36–58% for extensive EPE [1–20].

Our study deals with EPE assessment in a sequential series of 107 laparoscopic radical prostatectomies in order to assess its predictive value after definitive therapy. In our study, 38%

Table 1 Clinicopathological characteristics of 107 patients who underwent radical prostatectomy for prostate cancer

Characteristic (<i>n</i> = 107)	<i>n</i> (%); or min-max (mean ± SD); or median
Age (years)	47–75 (61.23 ± 5780)
Gleason score/grade group	
3 + 3/GG1	4 (3.7%)
3 + 4/GG2	75 (70.1%)
4 + 3/GG3	21 (19.6%)
4 + 4/GG4	5 (4.7%)
4 + 5; 5 + 5/GG5	2 (1.9%)
Pathological stage	
pT2	66 (61.7%)
pT2Nx	47 (43.9%)
pT2N0	18 (16.8%)
pT2N1	1 (0.9%)
pT3a	29 (27.1%)
pT3aNx	6 (5.6%)
pT3aN0	17 (15.9%)
pT3aN1	6 (5.6%)
pT3b	12 (11.2%)
pT3bNx	1 (80.9%)
pT3bN0	9 (8.4%)
pT3bN1	2 (1.9%)
Follow-up (months)	
Range (mean + SD), median	3–36 (11.68 ± 8.012), median 10
Biochemical recurrence <i>n</i> (%)	24 (26.7%)
Time to biochemical recurrence (months)	
Range (mean + SD), median	2–33 (7.00 ± 7.413); median 7
Extraprostatic extension (EPE)	
Negative	66 (61.7%)
Positive	41 (38.3%)
Extraprostatic extension LM (<i>n</i> = 41)	
Length LM (aggregate of measurements/cumulative length)	
Range (mean + SD), median	0.90–26.0 (6.8976 ± 6.32058); median 5
Length LM single (greatest single EPE/case)	0.9–16.0 (5.020 ± 3.1935); median 4
No of positive blocks/case	1–7 (2.39 ± 1.481); median 2
Extraprostatic extension DIG (<i>n</i> = 41)	
Length DIG (aggregate of measurements/cumulative length)	0.314–89.180 (18.07683 ± 19.697034); median 11.4
range (mean + SD), median	
Length DIG single (greatest single EPE/case)	0.314–22.200 (7.32220 ± 5.840048); median 5.98
range (mean + SD), median	
No of positive blocks/case	1–10 (3.1295 ± 2.20801); median 3
Radial extraprostatic extension (greatest single radial EPE/case)	0.118–9.560 (2.05956 ± 2.124814); median 1.35
range (mean + SD), median	
SM and EPE status <i>n</i> = 107	
SM neg, EPE neg	51 (47.7%)
SM pos, EPE neg	15 (14.0%)
SM neg, EPE pos	27 (25.2%)
SM pos, EPE pos	14 (13.1%)

LM (length of extraprostatic extension in mm, determined by light microscopy; EPE LM); DIG (length of extraprostatic extension in mm, determined digitally on whole slide images, EPE DIG); SM (surgical margins); radial extraprostatic extension (greatest single radial length of extraprostatic extension in mm, determined digitally on whole slide images, EPE DIG R)

Table 2 Patient and tumor characteristics for each patient with extraprostatic extension in radical prostatectomy specimen

No.	Age	pT status	EPE LM	EPE LM single	LM block no.	EPE DIG	EPE DIG single	EPE DIG R	DIG block no.	FU	BR	BRt	GS	GG
1	64	pT3aN0	6	4	3	16.27	5.63	2.69	3	34	1	33	7	3
2	63	pT3a	11	10	3	39.21	12.5	4.14	3	28	0		8	4
3	66	pT3aN0	1	1	1	0.545	0.545	0.601	1	18	0		7	2
4	67	pT3aN0	16	10	6	41.56	10.5	1.35	6	19	0		7	3
5*	50	pT3aN0	16	3	3	6.26	2.94	0.961	3	20	1	6	7	3
6	63	pT3aN0	1	1	1	0.314	0.314	0.251	1	16	0		7	3
7	56	pT3aN1	26	15	4	43.80	15.3	5.98	5	17	1	3	8	4
8*	58	pT3bN0	6	5	2	36.85	22.2	2.76	5	16	1	9	7	3
9*	56	pT2cN0	4	4	2	3.27	2.57	0.1442	2	15	0		7	2
10	64	pT3aN1	4	4	2	13.8	7.07	2.8	3	16	1	3	7	2
11	67	pT3bN0	18	16	7	89.18	19.5	9.56	7	16	1	9	7	2
12*	57	pT3a	8	7	3	18.95	7.42	1.85	4	15	0		7	2
13	62	pT3aN0	4	4	1	6.04	6.04	0.328	1	14	1	5	7	3
14	65	pT3a	3	3	1	3.02	3.02	0.67	1	14	1	5	7	3
15*	65	pT3b	6	6	3	51.5	51.5	4.22	7	12	0		7	2
16	68	pT3a	1	1	1	0.77	0.77	0.358	1	14	0		7	2
17	57	pT3bN1	17	15	4	35.87	35.87	8.12	3	11	1	3	8	4
18	57	pT3a	0.9	0.9	1	0.571	0.571	0.118	1	5	0		7	2
19*	58	pT3aN0	24	10	3	41.93	10.4	2.51	4	10	0		8	4
20*	54	pT3bN0	7	6	3	60.36	18.4	2.04	9	11	1	3	7	3
21	50	pT3aN1	0.9	0.9	2	7.37	4.79	2.49	3	11	0		7	2
22	62	pT3aN0	15	5	5	16.27	3.71	1.24	5	10	0		7	2
23*	53	pT3bN0	2	2	1	9.26	1.17	0.894	2	8	1	4	7	2
24	64	pT2bN0	3	3	1	1.21	1.21	0.336	1	7	0		7	2
25	61	pT3aN0	1	1	1	1.14	1.14	2.02	1	6	1	2	8	4
26	62	pT3bN0	3	3	2	24.21	11.5	1.34	4	3	0		7	2
27*	57	pT3aN0	2	2	1	4.16	3.16	1.18	3	3	0		7	3
28	62	pT3bN0	2	2	1	2.37	1.96	0.355	2	5	0		7	2
29	61	pT3aN0	6	6	1	11.4	11.4	0.669	1	5	0		7	2
30*	75	pT3a	2	2	1	1.35	1.35	0.464	1	3	1	3	7	2
31	54	pT3aN1	6	5	2	14.65	11.45	2.29	3	4	0		7	3
32	64	pT3aN0	8	6	4	10.18	5.29	3.46	4	6	0		7	3
33	62	pT3aN0	6	5	2	11.43	5.98	1.81	3	3	1	3	7	2
34	50	pT3aN1	5	4	2	9.82	4.59	0.54	4	4	0		7	2
35*	67	pT3aN0	5	4	3	19.42	16.4	0.773	2	4	0		7	2
36*	60	pT3bN1	11	10	4	14.18	7.57	1.4	5	3	0		7	3
37	64	pT3aN0	3	3	1	10.19	6.84	1.38	2	6	0		7	3
38*	63	pT3bN0	9	7	4	39.59	6.9	6.18	10	3	1	3	7	2
39	50	pT3aN0	7	5	3	14.38	12.7	1.32	3	3	0		7	3
40*	62	pT3bN0	5	4	2	4.33	3.26	1.26	2	3	0		7	2
41	59	pT3aN0	1	1	1	5.51	5.51	1.59	1	3	0		7	2

pTN (pathological T and N stage, according to UICC/TNM 2017); EPE LM (length of extraprostatic extension in mm, light microscopy); EPE LM single (greatest single extraprostatic extension/case in mm, determined by light microscopy); LM block No (number of paraffin blocks with extraprostatic extension, light microscopy); EPE DIG (longitudinal length of extraprostatic extension in mm, determined digitally on whole slide images); EPE DIG single (greatest single extraprostatic extension/case in mm, determined digitally on whole slide images); EPE DIG R (radial length of extraprostatic extension in mm, determined digitally on whole slide images; per definition single largest measurement); DIG block no. (number of paraffin blocks with extraprostatic extension, determined digitally); follow-up (in months); BR (biochemical recurrence, no = 0, yes = 1); BR time (time to biochemical recurrence, in months); GS (Gleason score); GG (grade group)

*Positive surgical margins

Table 3 Mean extraprostatic extension measurement compared to aggressive disease features after radical prostatectomy

	EPE LM (mm)	<i>p</i> value	EPE LM single (mm)	<i>p</i> value	EPE DIG (mm)	<i>p</i> value	EPE DIG single	<i>p</i> value	EPE DIG radial (mm)	<i>p</i> value
pT; (<i>n</i>) mean ± SD		0.608#		0.348#		0.074#		0.022†		0.050†
pT3a	(29) 6.778 ± 6.828		(29) 4.421 ± 3.443		(29) 13.225 ± 13.161		(29) 6.333 ± 4.639		(28) 1.636 ± 1.332	
pT3b	(12) 7.818 ± 5.528		(12) 6.909 ± 4.846		(12) 33.330 ± 26.702		(12) 16.348 ± 15.696		(11) 3.466 ± 3.149	
LN status; (<i>n</i>) mean ± SD		0.418#		0.383#		0.330#		0.167#		0.138#
N0	(26) 6.730 ± 6.115		(26) 4.538 ± 3.373		(26) 18.274 ± 21.541		(26) 7.353 ± 6.310		(26) 1.815 ± 2.031	
N1	(8) 9.487 ± 8.278		(8) 7.362 ± 5.333		(8) 18.865 ± 13.339		(8) 11.577 ± 10.464		(8) 3.178 ± 2.554	
Nx	(7) 4.557 ± 3.882		(7) 4.271 ± 3.466		(7) 16.481 ± 21.052		(7) 11.018 ± 18.373		(7) 1.688 ± 1.789	
Biochemical recurrence; (<i>n</i>) mean ± SD		0.221*		0.383*		0.239*		0.461*		0.042*
No	(26) 5.992 ± 5.592		(26) 4.415 ± 3.031		(26) 14.123 ± 14.510		(26) 8.016 ± 9.977		(26) 1.429 ± 1.155	
Yes	(15) 8.466 ± 7.356		(15) 6.133 ± 5.012		(15) 24.948 ± 25.565		(15) 10.167 ± 10.019		(15) 3.151 ± 2.915	
Grade group; (<i>n</i>) mean ± SD		0.036#		0.069#		0.211#		0.205#		0.022#
GG 2	(22) 4.900 ± 4.409		(22) 4.036 ± 3.325		(22) 15.502 ± 20.955		(22) 7.712 ± 11.037		(22) 1.799 ± 2.261	
GG 3	(14) 6.857 ± 4.671		(14) 4.785 ± 2.636		(14) 17.243 ± 17.243		(14) 8.289 ± 6.202		(14) 1.577 ± 0.951	
GG 4	(5) 15.800 ± 10.183		(5) 10.200 ± 5.718		(5) 32.390 ± 17.722		(5) 15.042 ± 12.797		(5) 4.554 ± 2.525	

EPE LM—cumulative length of extraprostatic extension in mm, determined by light microscopy; EPE LM single—greatest single extraprostatic extension in mm, determined by light microscopy; EPE DIG—cumulative length of extraprostatic extension in mm, determined digitally on whole slide images; EPE DIG single—single greatest extraprostatic extension in mm, determined digitally on whole slide images; EPE DIG R—greatest single radial length of extraprostatic extension in mm, determined digitally on whole slide images; LN status—lymph node status; GG—grade group

#Kruskal–Wallis test

*U de Mann–Whitney test

†ANOVA test

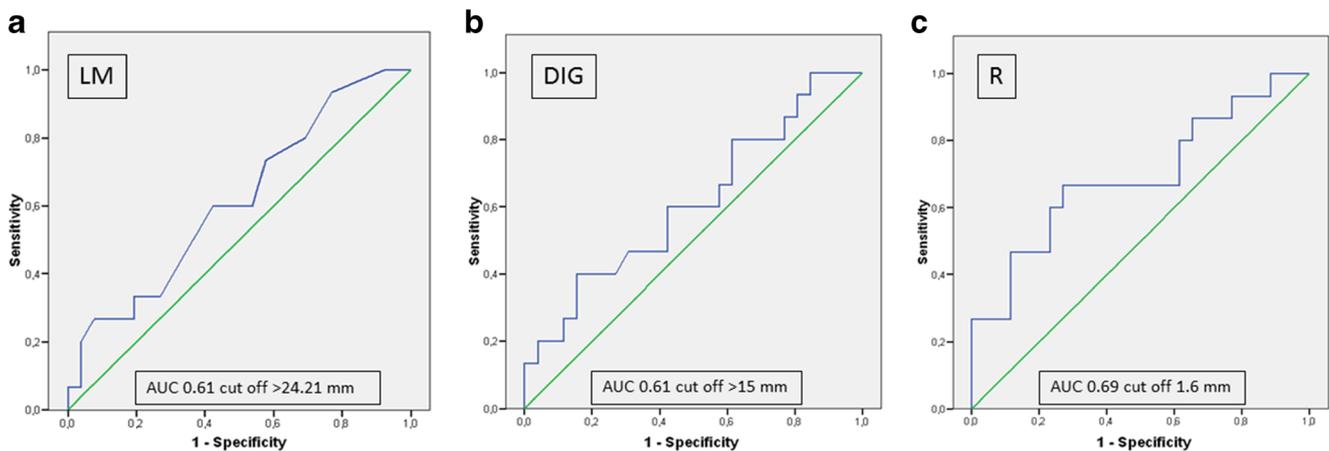


Fig. 2 Receiver operating characteristic (ROC) analysis showed potential cutoff points to assess linear measurements by conventional (EPE *LM*) (>24.21 mm) or digital microscopy (EPE *DIG*) (>15 mm) as well as measurement of radial distance (EPE *DIG R*) (1.6 mm)

of patients experienced EPE, a finding similar to the reported range (15–60%) in series using open radical prostatectomy or robotic-assisted laparoscopic radical prostatectomy [18, 28]. The incidence of EPE declines largely among lower Gleason grade patients, in whom it can be <1%.

In the era of digital microscopy, there is only limited data on the assessment of EPE by digital means and its comparison with EPE detected by conventional microscopy [21–27]. In our study, EPE status was assessed by dedicated uropathologists using linear extent assessed by conventional microscopy and then re-assessed using digital microscopy as a second examination. The EPE extension measurement also included the number of paraffin blocks having EPE, in addition to linear extension.

Our study showed that there was high agreement on EPE status between dedicated urologic pathologists, with no inter-observer variability, using both conventional and digital microscopic approaches. In fact, none of the cases showed additional EPE on digital microscopic assessments that were not seen with conventional microscopic evaluation. The lack of a clearly definable prostatic capsule and crush/thermal artifacts frequently seen after laparoscopic prostatectomy might be behind the minimal measurement variability observed in our study [29]. Likewise, missing small foci of EPE during the light microscopy reading might also be a potential explanation of the observed differences. In fact, no significant differences were seen between conventional and digital microscopy results in assessing EPE. This finding raises the question of

Table 4 Quantification of extraprostatic extension according to number of positive blocks and disease characteristics

	Overall	EPE LM blocks		<i>p</i> value*	EPE DIG blocks		<i>p</i> value*
pT	<i>N</i> = 41 (100%)	1 block	≥ 2 blocks	0.222	1 block	≥ 2 blocks	0.041
pT3a	28 (100.0%)	12 (42.9%)	16 (57.1%)		10 (35.7%)	18 (64.3%)	
pT3b	11 (100.0%)	2 (18.2%)	9 (81.8%)		0 (0.0%)	11 (100.0%)	
LN status				0.044			0.045
N0	26 (100.0%)	11 (42.3%)	15 (57.7%)		7 (26.9%)	19 (73.1%)	
N1	8 (100.0%)	0 (0.0%)	8 (100.0%)		0 (0.0%)	8 (100.0%)	
Nx	7 (100.0%)	4 (57.1%)	3 (42.9%)		4 (57.1%)	3 (42.9%)	
Biochemical recurrence				0.743			0.986
No	26 (100.0%)	10 (38.5%)	16 (61.5%)		7 (26.9%)	19 (73.1%)	
Yes	15 (100.0%)	5 (33.3%)	10 (66.7%)		7 (26.9%)	19 (73.1%)	
Grade group				0.679			0.739
GG 2	22 (100.0%)	9 (40.9%)	13 (59.1%)		7 (31.8%)	15 (68.2%)	
GG 3	14 (100.0%)	5 (35.7%)	9 (64.3%)		3 (21.4%)	11 (78.6%)	
GG 4	5 (100.0%)	1 (20.0%)	4 (80.0%)		1 (20.0%)	4 (80.0%)	

EPE LM blocks—number of paraffin blocks with extraprostatic extension, light microscopy; EPE DIG blocks—number of paraffin blocks with extraprostatic extension, determined digitally on whole slide images; LN status—lymph node status; GG—grade group

*Chi-square test

whether it is worth applying DM to assess EPE, given that the observed differences with LM were strictly limited to certain measurements that by definition should be more objectively done by digital microscopy.

The answer to this question probably needs further investigation and validation studies, but our data indicate an additional advantage of applying digital microscopy in assessing EPE in radical prostatectomy specimens. Our results on digital microscopy for the assessment of EPE also correlate with the most recent publications on the positive use of digital microscopy in the assessment of prostate pathology samples, both in an uropathology setting and in more general practice [21–27].

An additional observation in our series is related to the prognostic utility of so-called radial EPE assessment, which in our series was associated with pT status, biochemical recurrence, and grade groups. Our study there supports greater prognostic use of digitally assessed radial EPE (AUC 0.69) with a cutoff of \leq vs. $>$ 1.6 mm. The potential prognostic-predictive value of radial EPE was first identified by Davis et al. [6]. Sung et al. [13] later performed a comparative study for 8 different EPE quantitative methods and concluded that the radial distance of EPE is an independent prognostic factor for pT3 prostate adenocarcinomas. In this particular study, radial assessment was shown to be superior in predicting biochemical recurrence in comparison to other methods, including both Epstein's and Wheeler's criteria for focal versus established EPE. Radial EPE measurements were shown to have superior statistical value as a predictive factor in a study involving 1051 patients that had undergone RP [28]. Again, our results are in line with similar reported studies on radial EPE performed with conventional microscopy. Our data concerning radial EPE might be considered a digital update on the criteria reported by Sung et al. [13]. Our study also showed an association between EPE and positive surgical margins. Although methodologically novel in terms of using digital microscopy, it is already known that positive surgical margins correlate with EPE; in fact, cases with positive surgical margins are more frequently seen in prostatectomies with extraprostatic extension [1–20].

In view of the results presented in this paper, our study supports a digital microscopy approach as an appropriated method ready to be implemented in prostate specimen evaluation [1, 26]. In fact, our study shows that conventional and digital microscopy have overlapping features and are therefore both suitable methods for evaluating EPE in radical prostatectomy specimens. Also, the use of digital pathology could potentially investigate other parameters such EPE area and other morphometric measurements, approach that awaits investigation in future research. In addition, it is our experience that performing measurements on digitalized slides is simple and takes approximately the same amount of time as conventional microscopy.

Another important feature analyzed in our study was the distribution and significance of the number of paraffin blocks with EPE. This is a topic not well covered in the current literature and is therefore an original contribution of our study. Our study shows that none of the cases showing a single paraffin block with EPE had pT3b or N1 disease. Our results demonstrate that this is a simple and reproducible method for assessing EPE in radical prostatectomy specimens, since it probably represents an indirect assessment of EPE extension.

In conclusion, our study confirms that EPE evaluation is an important component of the pathologic report in prostate pathology. It also confirms that minor measurement differences of EPE between conventional and digital microscopy are of limited relevance in practice. In relation to digital microscopy, it is our experience that it produces similar data to that of conventional microscopy but has more accurate measurements than conventional microscopy and therefore seems to be an important tool in evaluating radical prostatectomy specimens. Reporting EPE presence and extension, and radial EPE, is an element of good pathology practice. A score for the number of blocks with EPE 1 vs. 2 or more might also provide additional prognostic data in prostate pathology.

Authors' contributions ALB, MV, and VH conceived and designed the study and wrote, edited, and reviewed the manuscript. AB performed the statistical analysis and reviewed the manuscript. AC, MRR, NV, VH, FP, and ALB collected and analyzed data and reviewed the manuscript. RM and LC critically read and edited the final manuscript. All authors gave final approval for publication.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Competing interests The authors declare that they have no conflict of interest.

Informed consent Written informed consent was obtained from all patients included in the study.

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