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RESEARCH PAPER

Accurate Determination of the Pathological Stage with Gross Dissection Protocol for Radical Cystectomy

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Abstract The current protocol for reporting urinary bladder cancer in radical cystectomies may exhibit limitations in the diagnostic accuracy, such as a risk of understaging, especially in cases with prostatic involvement. Difficulty can arise in the verification of stage pT0, and the assessment of surgical margins is suboptimal. We have developed a daily gross dissection protocol practice where radical cystectomies are totally embedded and evaluated histologically in whole-mount sections. We report here on the first 138 consecutive specimens from 2008 to the first quarter of 2012 inclusive. The incidence of the cancer stages was compared with data on 15,586 radical cystectomies from the literature. The differences were analyzed with the one-sample z-test ($p<0.05$). The following emerged from and our series and the literature data: pT0 8.7 % and 6.1 %; pTa 0.7 % and 2.9 %; pTis 2.9 % and 6 %; pT1 15.2 % and 15.5 %; pT2 21 % and 23.3 %; pT3 34.8 % and 34.3 %; and pT4 16.7 % and 11 %, respectively. Our findings closely reflected the means of the published statistical data based on a large number of cases. The differences were due to the more detailed processing: the case numbers in groups from pTis to pT2 were comparatively low, while those in groups pT3 and pT4 were higher. The difference in group pT4 was significant ($p=0.0494$). With this method, only those samples were regarded as pT0 in which the granulomatous area and the hemosiderin deposition indicative of the earlier intervention were observable and the entire preparation was tumor-free.

Keywords Cancer stage · Gross dissection · Pathology report · Radical cystectomy · Total embedding · Urinary bladder carcinoma · Whole mount section

Introduction

The incidence of bladder tumour has been rising during the past two decades. In 2002, 357,000 new cases were registered globally by WHO [1], making bladder tumour the fourth most common tumour type in men and the eighth in women. The treatment for the muscle-invasive tumour (T2–4) is radical cystectomy. One hundred seventy-two operations of this type were performed in Hungary in 2010.

The most important information for clinical decisions regarding advanced bladder tumour and the prognosis is the stage of the tumour [2]. In nearly half of the cases, the clinical stage does not match the post-surgical assessment based on histopathological examination [3]. However, the result of the pathological examination is at present decisive for the planning of the postoperative therapy and for the prognosis [2, 4, 5].

The most important step in the pathological examination is the selection of the areas to be processed for microscopic scrutiny, because these areas will be regarded as representative of the entire tumour, and will be studied in detail, subjected to immunohistochemistry and discussed in consultations. In striking contrast with the often traditional archivation requirement of embedded parts, tissue parts not deemed worthy of dissection are irrevocably destroyed.

The guidelines for the gross dissection of pathological samples are considerably more recent than microscopic examinations themselves. Consequently, their system of criteria

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Table 1 The distribution of 15,586 pathological staging data on 27,394 published radical cystectomies

Reference	May [14]		Hautmann [10]		Herrmann [11]		Vickers [21]		Tilki [19]		Rink [16]		Yu RJ [22]		Tollefson [20]		Stein [5]		Rodriguez [17]		Mateo [13]		van Dijk [9]		Madersbacher [12]		Takahashi [18]		Roupret [15]		
Interval	1989-2008		1986-2009		1986-2005		1969–2004		1979-2008		1979-2008		1971-2001		1980-1999		1971-1997		1978-2002		1988-2003		1989-2005		1985-2000		1991-1995		1990-2010		
Location	MI Germany		SI Germany		SI Germany		MI Inter-national		MI Inter-national		MI Inter-national		SI USA		SI USA		SI USA		SI Spain		SI Spain		MI The Netherlands		SI Switzerland		MI Japan		MI France		
No. of cystectomies	2403		1100		605		4462		3207		4335		1359		1177		1054		1114		420		375		507		518		4758	27394	
	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%
pT0	132	5.5	208	18.9	10	1.7	72	2							69	5.9	66	6	141	12.7	43	10.2	62	17					258	5.4	1061	6,1
pTa	77	3.2	30	2.72			111	2							38	3.2	42	4												298	2,9
pTis	104	4.3	133	12.09			124	3	117	3.64					237	20	100	9					17	4.5						832	6
pT1	389	16.2	127	11.54	126	20.8	765	17			585	13.5			194	17	194	18					20	5.3	77	15				2477	15,5
pT2	657	27.4	240	21.8	118	19.5	1035	23			1042	24	311	23	270	23	94	9							151	30	156	30.2		4074	23,3
pT3	796	33.1	256	23.26	269	44.5	1878	42			1371	31.6					233	21							184	36	152	29.4		5139	34,3
pT4	248	10.3	106	9.62	10.1	61	477	11			563	13					79	7							78	16	90	17.4		1702	11,36
Total stage data																														15583	100

The numbers highlighted in dark-gray are the highest, and those highlighted in light-gray are the lowest values in the various staging groups

Abbreviations: *MI* multi-institute, *SI* single institute

is not as mature as that of the latter. The first set of gross dissection guidelines concerning a urinary bladder removed because of cancer was printed 55 years ago [6]. A number of manuals have subsequently been published as the system has undergone development. These manuals are uniform in that they enumerate the areas of the preparation deemed important to be cut, but do not elaborate on the mode [7], whereas the mode of dissection and the positioning of certain organs, such as the uterus, cervix, fallopian tube, appendix and skin, have been meticulously regulated [8]. The objective of all such guidelines is to reduce the subjectivity of the pathologist.

The reported incidences of certain stages identified in cystectomy samples exhibit considerable variation [5, 9–22] (Table 1), and we consider that a major factor underlying this variation is the insufficient standardization of the pathological processing of the cystectomy samples.

In view of the importance of the pathological opinion [2, 4], we have developed a Gross Dissection Protocol for

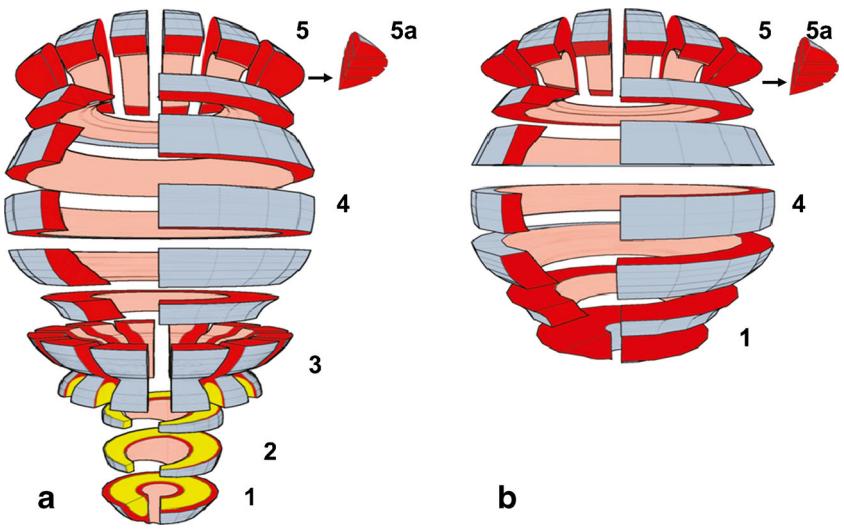

Fig. 1 Schematic representation of the Gross Dissection Protocol for Radical Cystectomy (GDPRC) for male (**a**) and female (**b**) cystectomies. 1: urethral resection line and prostatic apex. 2: prostate cross-sections with wider back part of lobes. 3: 12 radial cuts from the bladder-prostate basal block (BB). 4: bladder macro cross-sections. 5: sagittal sections of the dome. 5a: frontal processing of the lateral sagittal section in cases of dome involvement. Colour coding: *pink*: mucosa; *red*: muscle layer; *grey*: resection margin; *yellow*: glandular tissue

Fig. 2 Orientational incision and removal of the urethral resection level and prostate apex after side marking (*left side*: *blue*, *right side*: *black*) of a male cystoprostatectomy preparation

Radical Cystectomy (GDPRC) and introduced it into our daily routine. Our objective in this was to improve the European recommendation [7] by utilizing the potential of the commercially available macroblock technique. In this paper we describe the steps of dissection, embedding and microscopic evaluation in the processing of radical cystectomy samples.

We then compare our results with data reported in 15 publications on 15,586 stages identified in 27,394 cystectomies. We also comment on the financial and workload aspects of the procedure.

Patients and Methods

Patients

From 2008 to the first quarter of 2012, 138 radical cystectomies were performed at our Department of Urology. The consecutive samples were histologically processed whole, using macroblocks. The samples had been taken from 99 men to 39 women. The average age was 62.3 years; that of the men was 64.0 years (range 41–76), while that of the women was 60.6 years (range 49–71).

Pathological Evaluation with GDPRC

The steps of the processing and histological evaluation are described in detail in the Electronic Supplement. Briefly, the samples are fixed in 10 % formalin without dissection, for a minimum of 3 days. The cutting procedure of the cystectomy preparation is outlined schematically in Fig. 1. An anterior orientational incision is made (Fig. 2). Male and female bladders are further processed with different cutting steps (Figs. 3, 4, and 5):

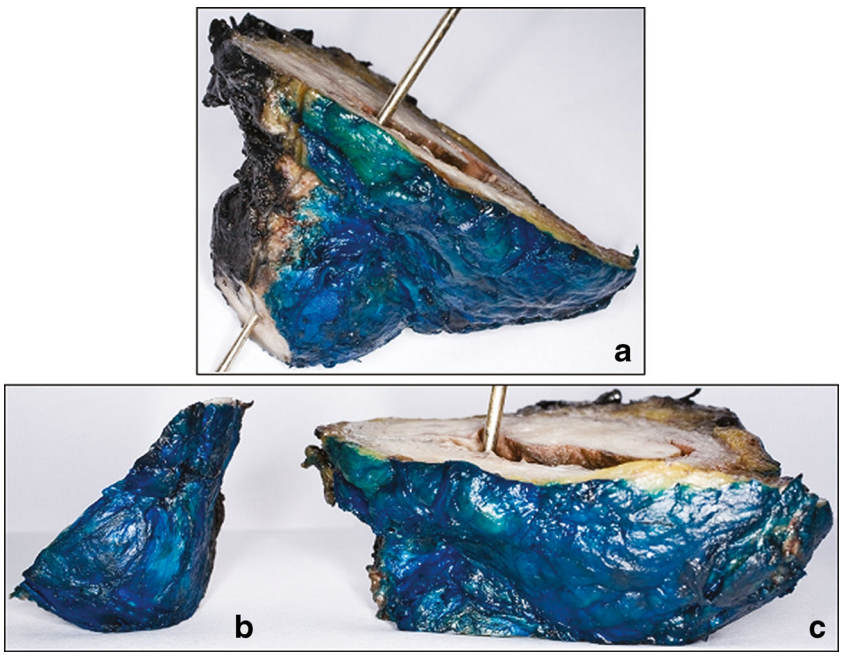

Fig. 3 Due to anteflexion of the axes of the prostate and the bladder the transverse resection level of the urethra and the bladder-prostate basal block (BB) are not parallel (**a**). The *wedge-shaped* cross section made from the prostate (**b**) yields a BB enclosed by *parallel* planes (**c**)

Male bladder

1. A cross-section of a urethral resection line
2. Wedge-shaped section of the prostate
3. Construction of a bladder-prostate basal block (BB), including the bladder base and the prostate base
4. 12 radial sections from the BB
5. Cross-sections above the BB
6. The bladder dome in sagittal parallel levels
7. Seminal vesicle embedding

Female bladder

1. The uterus, appendages and vaginal wall are separated
2. Cross-sections of the urethral resection level and the bladder
3. The bladder dome in sagittal parallel levels
4. The uterine cervix below the peritoneal pouch in cross-sections
5. The uterine cervix, corpus and bilateral appendages according to the current internationally applied procedural protocol.
6. The vaginal stump in parallel sections

The GDPRC is implemented in a flexible fashion. The most frequent modification is visualization (reflection), in two cutting levels, of the lesion observed on the cutting surface (Fig. 5). Lymph node regions are generally embedded whole; the larger ones are halved.

Histological evaluation is carried out by using a standardized report form (Fig. 6) and presented in a written form.

Statistical Analysis

Stages were determined with the AJCC/UICC TNM system as revised in 2002 [23]. The frequencies of the individual stages were expressed as percentages. Differences were evaluated using the one-sample z-test. A p value<0.05 was considered to indicate a significant difference between groups.

Results

Data of Staging and Dimensions

The GDPRC has been applied as the daily routine processing procedure for all radical cystectomy specimens in our Department of Pathology since 2008. Up to March 2012, a total of 138 examinations were completed. The results are shown in Table 2. Obturator lymph nodes were removed in 126 cases (91.3 %). The distributions of removed lymph nodes by stage and of metastastatic lymph nodes are presented

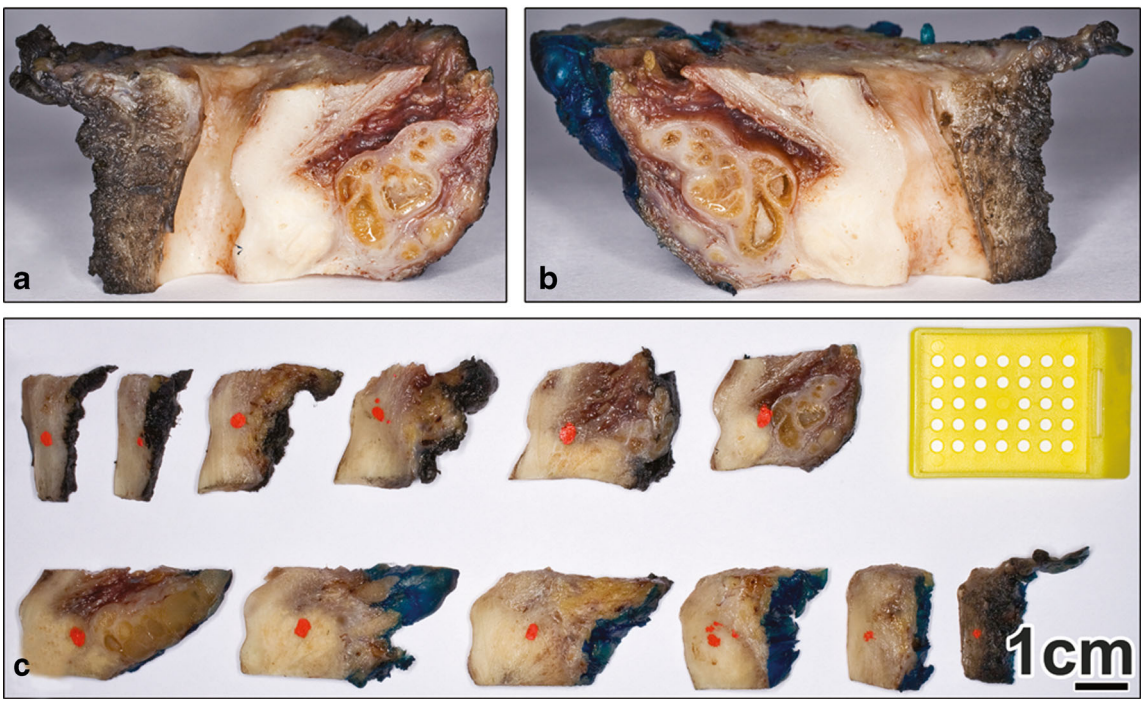

Fig. 4 Processing of the BB. The *right* (**a**) and the *left* (**b**) portions are shown after completion of the orientational incision. The orientational incision entering all the way to the urethra is greatly distorted and coloured blackish by *black ink* marking; this ensures orientation in the sections. The 12 radial cut-offs can be placed into standard cassettes. **c** *Red* staining indicates the surface to be micro-sectioned

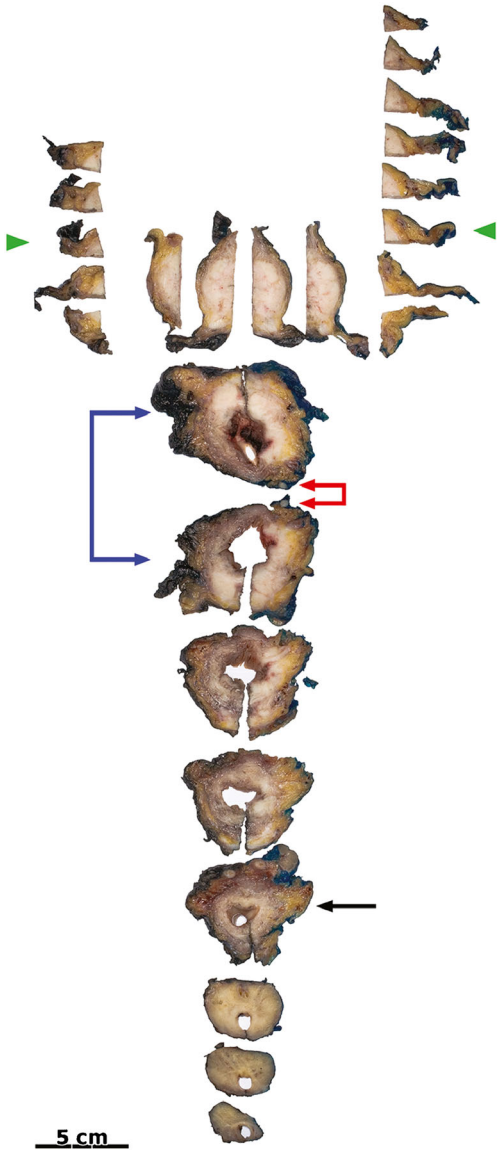

Fig. 5 Male cystoprostatectomy with GDPRC. The *arrow* indicates the BB from which 12 radial cut-outs serve for the evaluation of the bladder base and the prostate base. The *arrowheads* show the frontal processing of the sagittal cross-sections serving for the evaluation of the lateral portion of the dome. The *blue double arrow* shows a reflective cutting surface on which there is foreign tissue (*red double arrow*) in the posterior surgical margin

in Table 2. In two cases, an unevaluable lymph node conglomerate was not included.

The average sizes of the 124 preparations were: supero-inferior 101.6 mm (range 40–170 mm); medio-lateral 92.7 mm (range 40–140 mm); and antero-posterior 75.7 mm (range 35–130 mm). The average mass of 119 specimens was 308 g (range 46–680 g).

The macroblock allowed the preparation of bladder wall sections 7 mm in thickness and prostate sections 5 mm in maximum thickness.

Material Input and Costs

On average, 9.2 macroblocks and 14 standard blocks were used for the processing of the radical cystectomy samples. In cases of cystoprostatectomy, an average of 9.8 macroblocks and 16.3 standard blocks were prepared. In cases of cystectomy of female patients, 8.8 macroblocks and 9.6 standard blocks were used. The cost of the consumables used for the preparation of a macrosection was €1.88, whereas that of a standard histological section was €0.25.

The average cost of the consumables and chemicals used up for the GDPRC processing of a male radical cystectomy specimen was €21.8, and that of a female one was €18.2. A necessary one-time purchase was that of a macro head for the rotating microtome (Thermo Shandon Finesse ME+ Code Nr: 77510167): Ł 182.76.

Dissecting with photographic documentation took 2 h and microscopic examination 2 additional hours of the pathologist's time.

Discussion

The current international gross dissection guidelines for radical cystectomy list the anatomic site deemed sufficiently important to be examined and leave it to the pathologist to select (somewhat at random) the areas that may be expected to contain microscopic lesions. When only minimally required samples are considered, at least 27 cuts have to be made on a male bladder; however, only three of these will originate from the tumour. The urethra and its resection line are not even mentioned in the list. This method is of only limited value, especially in the case of formalin-fixed samples [24]. The GDPRC performs the examination on macrosections (Fig. 7), eliminating the subjectivity originating from dissection, the most critical step of pathological processing; the procedure is adapted to the conditions of the daily routine, with the possibility of intervention kept open.

The GDPRC Allows the Determination of Stage pT0

In the absence of suspicious macroscopic signs or data regarding the localization of earlier interventions, there is no guidance as to how to make the gross dissection. If the first gross dissection showing tumour negativity was made in a non-oriented fashion, subsequent cuttings can only be incidental and no guidance whatsoever is available as concerns their mode, extent or number. In the course of the GDPRC, only those samples were regarded as pT0 resections in which the granulomatous area and the haemosiderin deposition indicative of the earlier intervention were observable and the entire preparation was tumour-free.

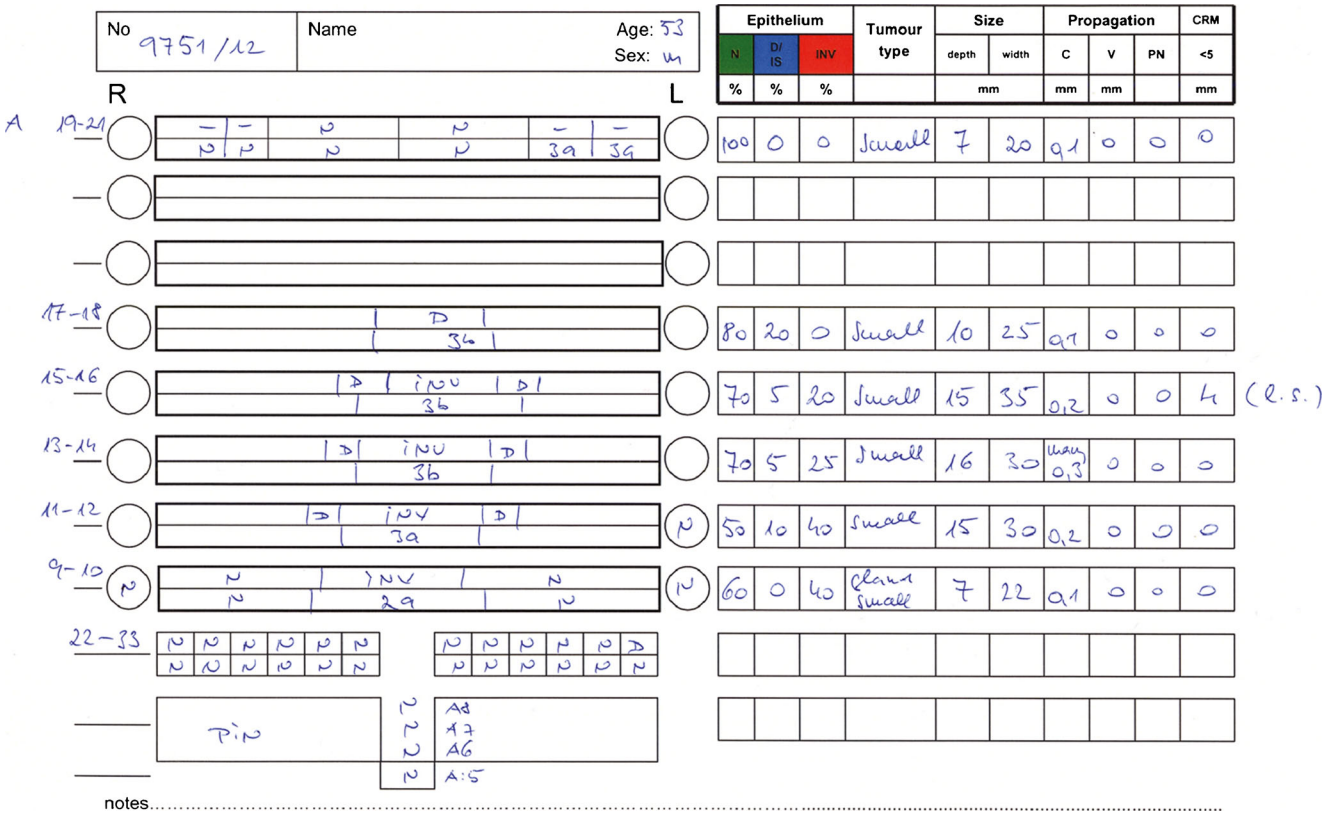

Fig. 6 An example of the report form relating to the evaluation of macro slides. The *left side* serves for schematic information and the *right side* for the recording of numerical data (see Electronic Supplement)

The GDPRC Allows the Precise Determination of pT2 Subcategories

The practicability of pT2 subcategories has recently been at the focus of intensive debate. Jewett based his classification of muscle-invasive tumours into internal and external layers on autopsies of 107 patients who had died as a consequence of bladder cancer, and the TNM system adopted that classification [25]. In contrast, American authors who followed up 123 muscle-invasive tumours failed to observe any difference between the suggested pT2 subcategories, and therefore suggested their elimination [26]. A recent international study based on 565 cases, however, evaluated the TNM system as practicable [27]. The settlement of the dispute is made more difficult by the fact that the aggressively infiltrating tumours that exhibit tentacular spread cannot be perceived visually or by palpation. Nor can imaging techniques be applied, since they do not offer microscopic resolution. A non-oriented cut therefore makes an evaluation of the infiltration depth uncertain. In the course of the GDPRC, simultaneous preservation of the localization and dimensions of the infiltrating area and its relationships with the surrounding tissues are ensured.

The GDPRC Identifies Stage pT3a with Certainty

Even theoretically, the current dissection procedure performed with the naked eye can detect extra-organ expansion only incidentally. This circumstance may have contributed to the failure of numerous reports to find differences between stages

Table 2 The pathological stage distribution in 138 radical cystectomy assessments with the GDPRC, and the lymph node involvement per stage

	pT0	pTa	pTis	pT1	pT2	pT3	pT4
No. of cases (%)	12 (8.7)	1 (0.7)	4 (2.9)	21 (15.2)	29 (21)	48 (34.8)	23 (16.7)
Total no. of lymph nodes	240	13	64	398	517	840	327
Average no. of lymph nodes average	20	13	16	21	39.4	39	29.5
No. of metastatic lymph nodes	13 (1.5 %)	0	0	2 (0.5 %)	18 (8.1 %)	123 (28.7 %)	58 (23.3 %)

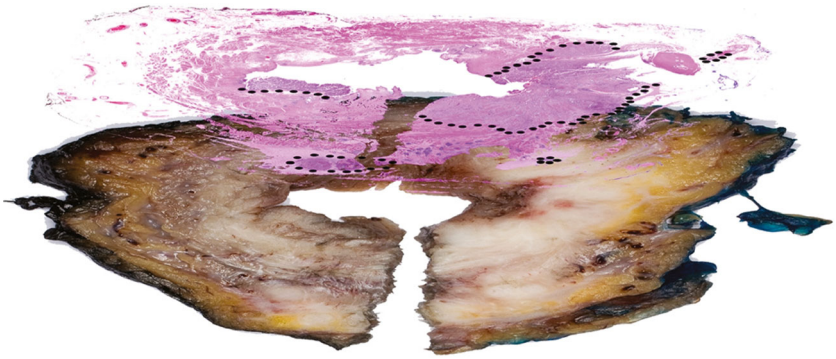

Fig. 7 Macro cut-out with the projection of the macro slide made from it; the extent of the tumour is indicated by *dots*

pT2 and pT3a or pT3b. The validity of the subcategorization of stage pT3 has been verified on the basis of a large number of cases (n=2,388), supporting the practicability of the present TNM system [28]. The GDPRC permits the identification and localization of the extravesical spread and the measurement of its dimensions.

The GDPRC Allows the Precise Identification of Stage pT4a and the Route of Prostate Infiltration

In consequence of the formalin fixation, tumour infiltration into the dense tissue of the prostate (stage pT4a) is most often invisible to the naked eye. The route of infiltration, which may occur by breaking through the entire thickness of the bladder wall or via the urethra is of prognostic significance, but no guidance is available as to the method of examination of prostate infiltration. Donat et al. studied specimens cut into 3-mm-thick sagittal sections [29]. However, in this way the urethra can be represented in only one or two levels, whereas this organ may be not only a route of infiltration, but also a primary tumour site. Another possibility is the separation of bladder and prostate, and the processing of both according to the protocol corresponding to the primary cancer of the given organ [30]. The GDPRC offers the possibility of the microscopic study of both organs in one section. On the 12 radial cuts of the BB, the 3D measurements and circumferential resection distance can also be determined. This is important, because this is regarded as the nearest resection margin.

Processing of the Prostate and the Urethra by GDPRC

The entire prostate below the BB is studied in macrosections, in compliance with the literature recommendation [31]. However, since the prostatic urethra runs in an anteriorly open angle, the cross-section plane of the urethral resection margin and the plane of the BB form a triangular section (Fig. 4b). In order to retain all surgical edge markings in the sections, further cuttings were also performed at an angle. (The reason why this is not the case in prostatectomy specimens is that the urethral resection lines are not taken into consideration during

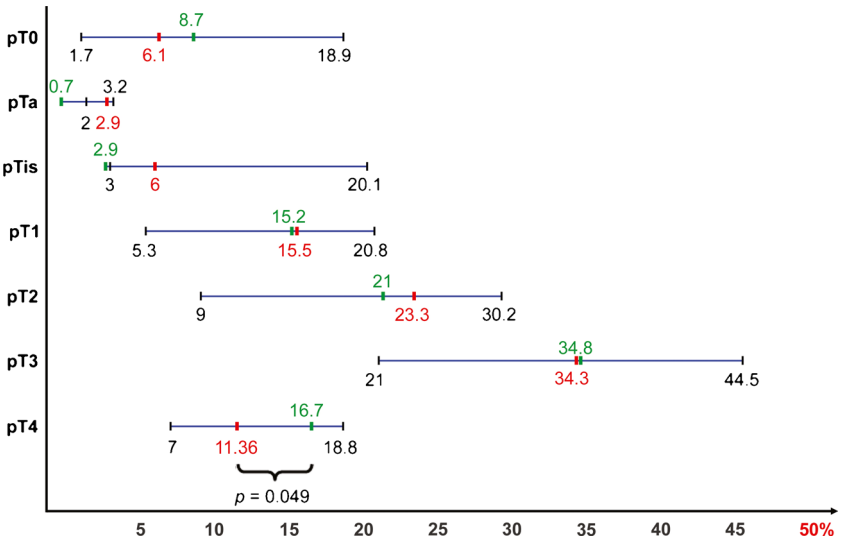

Fig. 8 The incidences of the various pathological stages in radical cystectomy. *Red numbers* denote the averages of the literature data. *Black numbers* are the extremes of the published data. *Green numbers* denote the incidence data as assessed with the GDPRC. The difference between the published data and those determined with the GDPRC for stage pT4 is statistically significant

the preparation, because it is not our aim to obtain complete cross-sections of those parts.) When the urethral stump was involved, we assessed the resection margin distance in sagittal cross-sections after re-embedding.

Comparison of the Stage Distribution as Assessed by the GDPRC with the Literature Data

The incidences of the pathological stages of cystectomies exhibit significant differences even within the same geographical region and time interval, even when the tests performed prior to cystectomy and the surgical indications are nearly identical. Nevertheless, the incidence determined on the basis of a large number of cases must reflect the actual incidence. We therefore carried out determinations by using the data on 15,586 stages of 27,394 cystectomies presented in 15 publications from the period between 1971 and 2010 (Table 1) [5, 9–22].

The relatively small number of cases processed with the GDPRC quite accurately reflected the statistical data based on a large number of cases (Fig. 8). The differences observed are due to the more detailed processing: the case numbers in the pTis-pT2 groups were found to be lower, while those in groups pT3 and pT4 were higher. In the case of pT4, the difference was significant (11.36 % vs. 16.6 %, p=0.0494). We consider that the more frequent occurrence of cases in the highest stage may provide a partial explanation for the inaccurate prognosis of cystectomies.

The incidence of pT0 among the cases we studied was higher than the average of the published data (8.7 % vs. 6.1 %). The reason for this may be that the histological examination of preoperative TUR cannot provide a reliable evaluation of the completeness of tumour removal, and the resolution of imaging techniques is at its worst with small tumours. The surgical indications for this stage are therefore more uncertain, and are unsuitable for a well-founded comparison.

Further Possibilities in the GDPRC

The GDPRC may be additionally utilized to evaluate further prognostic factors, such as:

1. microscopically measured tumour dimensions and surgical margins;
2. vascular and perineural infiltrations;
3. accompanying urothelial dysplasia/in situ carcinoma;
4. tumour heterogeneity and infiltration pattern.
5. The GDPRC opens the way to the digital processing of data and to comparison with the findings of imaging techniques.

Limitations of the GDPRC

The GDPRC is more labour-intensive and more expensive than the present protocol. Current processing requires 27 standard cassettes with a minimum cost of €6.75 (27×€0.25). The cost of consumables applied in the GDPRC for male bladders are therefore 3.5 times higher and for female bladders three times higher.

Macro slide preparation requires practice for the preparation of 4–6-μm thick sections. The staining is not automatized. The GDPRC is labour-intensive for the pathologist. Gross dissection with photographic documentation takes 2 h, and histological evaluation an additional 2 h.

The 7-mm-thick macroblock cross-section is a reasonable compromise in exchange for not having to inflate the bladder before fixation, or to submit it to special preparative procedures under clinical conditions.

The GDPRC is not suitable for the processing of atypically resected samples.

In summary, use of the GDPRC can minimize the level of subjectivity during pathological examinations of radical cystectomies. The definition of pT0 is unambiguous and assessments of the higher stages become more certain. Stage pT4 proves to be more frequent than currently believed.

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