

Discrepancy between German S3 Guideline Recommendations and Daily Urologic Practice in the Management of Nonmuscle Invasive Bladder Cancer: Results of a Binational Survey

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Keywords

Survey · Bladder cancer · Nonmuscle invasive bladder cancer · Guideline adherence · Treatment management

Abstract

Introduction: Guideline recommendations are meant to help minimize morbidity and to improve the care of non-muscle invasive bladder cancer (NMIBC) patients but studies have suggested an underuse of guideline-recommended care. The aim of this study was to evaluate the level of adherence of German and Austrian urologists to German guideline recommendations. **Methods:** A survey of 27 items evaluating diagnostic and therapeutic recommendations (15 cases

of strong consensus and 6 cases of consensus) for NMIBC was administered among 14 urologic training courses. Survey construction and realization followed the checklist for reporting results of internet e-surveys and was approved by an internal review board. **Results:** Between January 2018 and

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June 2019, a total of 307 urologists responded to the questionnaire, with a mean response rate of 71%. The data showed a weak role of urine cytology (54%) for initial diagnostics although it is strongly recommended by the guideline. The most frequently used supporting diagnostic tool during transurethral resection of the bladder was hexaminolevulinate (95%). Contrary to the guideline recommendation, 38% of the participants performed a second resection in the case of pTa low-grade NMIBC. Correct monitoring of Bacille Calmette-Guérin (BCG) response with cystoscopy and cytology was performed by only 34% of the urologists. **Conclusions:** We found a discrepancy between certain guideline recommendations and daily routine practice concerning the use of urine cytology for initial diagnostics, instillation therapy with a low monitoring rate of BCG response, and follow-up care with unnecessary second resection after pTa low-grade NMIBC in particular. Our survey showed a moderate overall adherence rate of 73%. These results demonstrate the need for sharpening awareness of German guideline recommendations by promoting more intense education of urologists to optimize NMIBC care thus decreasing morbidity and mortality rates.

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Introduction

With a global incidence of over 550,000 new cases and 200,000 deaths in 2018, urothelial bladder cancer (BCa) is the second leading genitourinary malignancy worldwide, as well as in Germany, and it is a potentially lethal disease [1]. Approximately 70% of newly diagnosed BCa patients present with nonmuscle invasive BCa (NMIBC) [2]. Over a 5-year period, the probabilities of recurrent disease ranged from 31% to 78% and for progressive disease from <1% to 45%, depending on risk tables of the European Organization for Research and Treatment of Cancer [2]. A systematic review showed progression from NMIBC to muscle invasive BCa in 21% of patients with high-risk NMIBC after a mean follow-up of 48–123 months, with long-term survival rates of 35% of the patients [3]. This demonstrates that BCa is an aggressive disease and is associated with high morbidity and mortality rates if not treated optimally.

In November 2016, the German Society for Urology (DGU e.V.) renewed and published an evidence- and consensus-based (highest evidence level of S3) [4] The German guideline for diagnosis, therapy, and follow-up of BCa to help standardize treatment of BCa in Germany [5]. The guideline recommendations are meant to help minimize

morbidity and to improve the care of NMIBC patients, but studies have suggested an underuse of guideline-recommended care [6–8]. After all, patients who receive guideline-recommended care have been found to experience a significant survival benefit [7]. The aim of this study was to evaluate the level of adherence of German and Austrian urologists to German guideline recommendations.

Patients and Methods

A survey of 27 items evaluating diagnostic and therapeutic recommendations (15 cases of strong consensus and 6 cases of consensus) for NMIBC was administered among 14 urologic training courses in Germany and Austria sponsored by Ipsen Biopharm Ltd., the German Society of Residents in Urology e.V., the Professional Association of German urologists (BvDU e.V.), and urologic departments of University hospitals in Lübeck and Cologne. Survey construction and realization followed the checklist for reporting results of Internet e-surveys [9] and was approved by an internal review board consisting of members from the BCa research group of the young academics of the German Society of Residents in Urology e.V. Ethics approval was not required since this was an anonymous survey.

Participants received no reimbursement for completion of the survey. Baseline data and guideline knowledge rates are shown in Table 1. The strength level of recommendations and the items selected to test for adherence are summarized in the online suppl. Material (see www.karger.com/doi/10.1159/000518166) and in Table 2. The evidence classification system of the Scottish Intercollegiate Guidelines Network [10] was applied in the guideline, with a grading of grade 1++ (meta-analysis and systematic randomized controlled trials with a very low-risk of systematic bias) to grade 4 (expert opinion). This led to a recommendation classification grading from grade A (strong recommendation, “shall”) over grade B (recommendation, “should”) to grade 0 (open recommendation, “can”), with consensus grades of strong consensus (>95% of voters), consensus (>75–95% of voters), majority (>50–75% of voters), and dissent (<50% of voters). Descriptive statistical data are expressed in absolute numbers and percentages. All analyses were performed using SPSS Statistics software (version 26; IBM).

Results

Between January 2018 and June 2019, a total of 307 urologists from Austria ($n = 30$) and Germany ($n = 277$) responded to the questionnaire, with a response rate of 71%. The median age was 38 years (range of 24–66 years), and 284 (93%) of the respondents treated BCa patients on a regular basis several times a week. Baseline data and guideline knowledge rates are shown in Table 1.

Diagnostics for NMIBC

The diagnostic tools used for initial diagnosis of BCa are shown in Table 2, question 9. The data showed weak utiliza-

Table 1. Baseline data and guideline

Question and answer	Physicians, %	N	
Q1. Profession			
Resident	38.5	116	
Certified urologist	61.5	185	
Q2. Working place			
Hospital of basic care (up to 350 beds)	18.2	55	
Hospital of special care (at least 370 beds)	15.8	48	
Hospital of maximum care (>700 beds)	23.8	72	
University hospital	19.1	58	
Center of rehabilitation	0.0	0	
Ambulatory healthcare center	2.6	8	
Doctor's office	26.4	80	
Q5. Frequency of treatment of BCa patients			
Never	0.3	1	
Once a month	2.0	6	
Once a week	4.9	15	
Several times per week	92.8	284	
Q6. How well do you know the content of the S3 guideline for BCa?			
Very well	6.6	20	
Well	55.8	169	
Moderate	34.0	103	
Hardly	3.0	9	
Not at all	0.7	2	
Q7. Frequency of the S3 guideline use in daily practice			
Several times per week	33.0	98	
Once a week	21.9	65	
Once a month	25.9	77	
Less than once a month	17.9	53	
Never	1.4	4	
Q8. Which sources of information about BCa do you use? (8 = most frequently to 1 = less frequently)			
Answer choices (162 responses)	score 1–4	score 5–8	total
EAU guidelines	47	107	154
Other guidelines	67	68	135
Books	75	71	146
Medical databases/scientific journals (e.g., PubMed)	77	62	139
Congress attendance	65	81	146
Colleagues	44	106	150
Internet (e.g., Google or Bing)	81	66	147
Others	105	24	129

Question 8: 162 urologists answered to q8 and 145 skipped this question. These 162 urologists rated the use of other sources than the German S3 guideline from 1 (less frequently) to 8 (most frequently). One hundred and seven used EAU guidelines in a high frequency (vote 5 or higher). Q, question; n, number of participants; BCa, bladder cancer; S3, highest evidence level; EAU, European Association of Urology.

tion of urine cytology (54%), urine markers (15%), and fluorescence-based cystoscopy (29%) for initial diagnostic evaluation. The most frequently used primary diagnostic tools for NMIBC were white light (WL) cystoscopy in 92% of all cases followed by ultrasound in 91% of all cases.

Treatment of NMIBC

The participants were asked about resection techniques, pathologic reporting, the use of supporting diag-

nostic tools, and instillation therapies for low-, intermediate-, and high-risk NMIBC (see Table 2, questions 10–27). Apart from the German guideline, other frequently used sources for treatment recommendations were guidelines of the European Association of Urology (EAU) and discussion with colleagues. En bloc resection (ERBT) for tumors that were >1 cm in size was performed by 68% of the participants. The most frequently used supportive diagnostic tool during transurethral resection of the blad-

Table 2. Adherence to guideline recommendations for diagnostics and therapy of NMIBC

Question and answer	Physicians, %	N	Degree of consensus	Grade of recommendation	LoE	Guideline adherence (concordance score)
Q9. Which tools do you use for primary diagnostics in the case of clinical suspicion for BCa? (multiple selections)						
Ultrasound	90.5	275	Consensus	Experts	na	90.5
WL cystoscopy	91.5	278	Strong	Experts	na	91.5
Ambulant fluorescent cystoscopy	28.6	87	Consensus	Experts	na	28.6
Urine cytology	53.6	163	Strong	Experts	na	53.6
Urine markers	15.1	46	Strong	Experts	na	84.9
Other	4.0	12	na	na	na	na
Overall adherence rate (concordance score)						69.8
Q10. If technically feasible, do you try ERBT for tumors that are >1 cm in diameter?						
Yes	67.6	194	na	na	na	na
No	32.4	93	na	na	na	na
Q11. If feasible, do you try to include the detrusor muscle in the standard resection technique?						
Yes	95.5	275	Strong	B	2+	95.5
No	4.5	13	na	na	na	na
Q12. While performing a TURB, do you take extra probes from the tumor ground and resection margins?						
Yes	79.3	222	Consensus	0	2+	79.3
No	20.7	58	na	na	na	na
Q13. Do you mention tumor size in cm, tumor sites, and the number of tumors in the TUR report?						
Yes	98.9	281	Consensus	Experts	na	98.9
No	1.1	3	n.a	na	na	na
Q14. Do you report former therapies, tumor morphology, mucosal abnormalities, and concordant CIS to your local pathologist?						
Yes	79.2	221	Strong	Experts	na	79.2
No	20.8	58	na	na	na	na
Q15. Do you use supporting diagnostic tools for TURB, such as						
HAL, Hexvix®	95.3	245	na	na	na	na
NBI	16.3	42	na	na	na	na
SPIES	0.8	2	na	na	na	na
Other	5.1	13	na	na	na	na
Q16. In which cases do you use supporting diagnostic tools?						
Initial TURB	20.9	55	na	na	na	na
2nd look resection	18.6	49	na	na	na	na
Both	60.5	159	na	na	na	na
Q17. In which cases do you use Hexvix®? (multiple selections)						
Single tumor site	26.5	72	Consensus	Experts	na	73.5
Multiple tumor sites	67.7	184	Consensus	Experts	na	67.7
High-grade tumors in the patient's history	63.6	173	Consensus	Experts	na	63.6
Suspected CIS (e.g., positive urine cytology)	84.2	229	Consensus	Experts	na	84.2
None of the cases mentioned above	7.0	19	na	na	na	na
Overall adherence rate (concordance score)						72.2
Q18. Which patients receive a 2nd resection if not scheduled for cystectomy? (multiple selections)						
Ta, low-grade tumors without proof of detrusor muscle	37.7	106	na	na	na	62.3
Ta, low-grade tumors with proof of detrusor muscle	12.1	34	na	na	na	87.9
Incompletely resected NMIBC in 1st resection	89.7	252	Strong	A	1–	89.7
Missing detrusor muscle (except for Ta, low-grade)	66.6	187	Strong	A	1–	66.6
pT1 tumors	88.3	248	Strong	A	1–	88.3
High-grade tumors	87.2	245	Strong	A	1–	87.2
Primary CIS	50.9	143	na	na	na	49.1
Overall adherence rate (concordance score)						75.9
Q19. Do you perform early single intravesical instillation therapy when low-risk NMIBC is suspected and there is no sign of significant bleeding or perforation?						
Yes	80.4	225	Strong	0	1++	80.4
No	19.6	55	na	na	na	na
Q20. Do you continue intravesical instillations after initial TURB and early single instillation in cases of low-risk NMIBC?						
No further intravesical instillations	82.4	225	Strong	A	1++	82.4
Yes, mitomycin	12.8	35	n.a	n.a	n.a	n.a
Yes, BCG	2.6	7	na	na	na	na
Yes, gemcitabine	0	0	na	na	na	na
Yes, other (please specify)	2.2	6	na	na	na	na

Table 2 (continued)

Question and answer	Physicians, %	N	Degree of consensus	Grade of recommen- dation	LoE	Guideline adherence (concordance score)
Q21. Do you continue intravesical instillations after initial TURB and early single instillation in cases of intermediate-risk NMIBC?						
No further intravesical instillations	18.8	48	na	na	na	na
Yes, mitomycin	62.5	160	Strong	B	1++	62.5
Yes, BCG	15.2	39	Strong	B	1++	15.2
Yes, gemcitabine	1.2	3	na	na	na	na
Yes, other (please specify)	2.3	6	na	na	na	na
Overall adherence rate (concordance score)						77.7
Q22. Do you continue intravesical instillation therapy after initial TURB and early single instillation in cases of high-risk NMIBC, if cystectomy is not indicated?						
No further intravesical instillations	6.0	15	na	na	na	na
Yes, mitomycin	12.8	32	na	na	na	na
Yes, BCG	79.7	200	Consensus	A	1++	79.7
Yes, gemcitabine	0.8	2	na	na	na	na
Yes, other (please specify)	0.8	2	na	na	na	na
Q23. In case of complete remission after BCG induction therapy, do you apply BCG maintenance therapy in high-grade NMIBC? If yes, for how long?						
No intravesical BCG maintenance	6.5	17	na	na	n.a	na
Yes, <12 months	16.0	42	na	na	n.a	na
Yes, 1 to 3 years	74.8	196	Consensus	A	1++	74.8
Yes, >3 years	2.7	7	na	na	na	na
Q24. How do you monitor the response of intravesical BCG induction and maintenance therapy?						
Histological probes	28.8	82	na	na	na	na
Urine cytology	22.5	64	na	na	na	na
Histological probes + urine cytology	33.7	96	Strong	Experts	na	33.7
Visually via ambulant cystoscopy	56.1	160	na	na	na	na
No control	2.5	7	na	na	na	na
Q25. If yes, please indicate the timing of monitoring						
Immediately after induction	12.9	33	na	na	na	na
Every 3 months	72.9	186	Strong	B	1+	72.9
Every 6 months	12.2	31	na	na	na	na
Once a year	2.0	5	na	na	na	na
Q26. Do you apply prophylactic antibiotics accompanying BCG instillations?						
Yes	7.4	20	na	na	na	na
No	92.6	251	Strong	A	1–	92.6
Q27. In which cases of NMIBC do you see an indication for RC? (multiple selections)						
Initial diagnosis of single CIS	4.8	14	Strong	0	3	4.8
High-risk NMIBC	35.5	104	Strong	n.a	2+	35.5
Early recurrence or persistence of high-risk NMIBC after						
BCG instillations (BCG failure)	93.9	275	Consensus	A	2–	93.9
Endoscopically uncontrollable NMIBC	85.7	251	na	na	na	85.7

Q, question; n, number of participants; BCG, bladder cancer; LoE, level of evidence; CIS, carcinoma in situ; TURB, transurethral resection of the bladder; HAL, hexaminolevulinate; NBI, narrow band imaging; SPIES, Storz Professional Image Enhancement System; NMIBC, nonmuscle invasive bladder cancer; BCG, Bacille Calmette-Guérin; na, not applicable; WL, white light; RC, radical cystectomy; ERBT, en bloc resection.

der (TURB) is hexaminolevulinate (HAL) as indicated by 95% of the urologists, followed by narrow band imaging (16%). HAL was used particularly in cases of suspected carcinoma in situ (CIS), high-grade tumors, and multiple tumor sites. Over 60% used these tools for initial resection as well as for 2nd-look TURB.

Concerning recommendations for bladder instillation therapy, 80% of the participants performed early single instillation therapy when low-risk NMIBC was suspect-

ed, as recommended by the guideline; 78% continued with the instillations for intermediate-risk NMIBC; and 80% used Bacille Calmette-Guérin (BCG) instillations for high-risk NMIBC. The response to intravesical BCG induction and maintenance was monitored by 34% of the urologists. Of these, 73% monitor every 3 months.

Concerning early radical cystectomy (RC), the greatest number of urologists consider early RC in cases of recurrent high-risk NMIBC after BCG (BCG failure) (93%) or

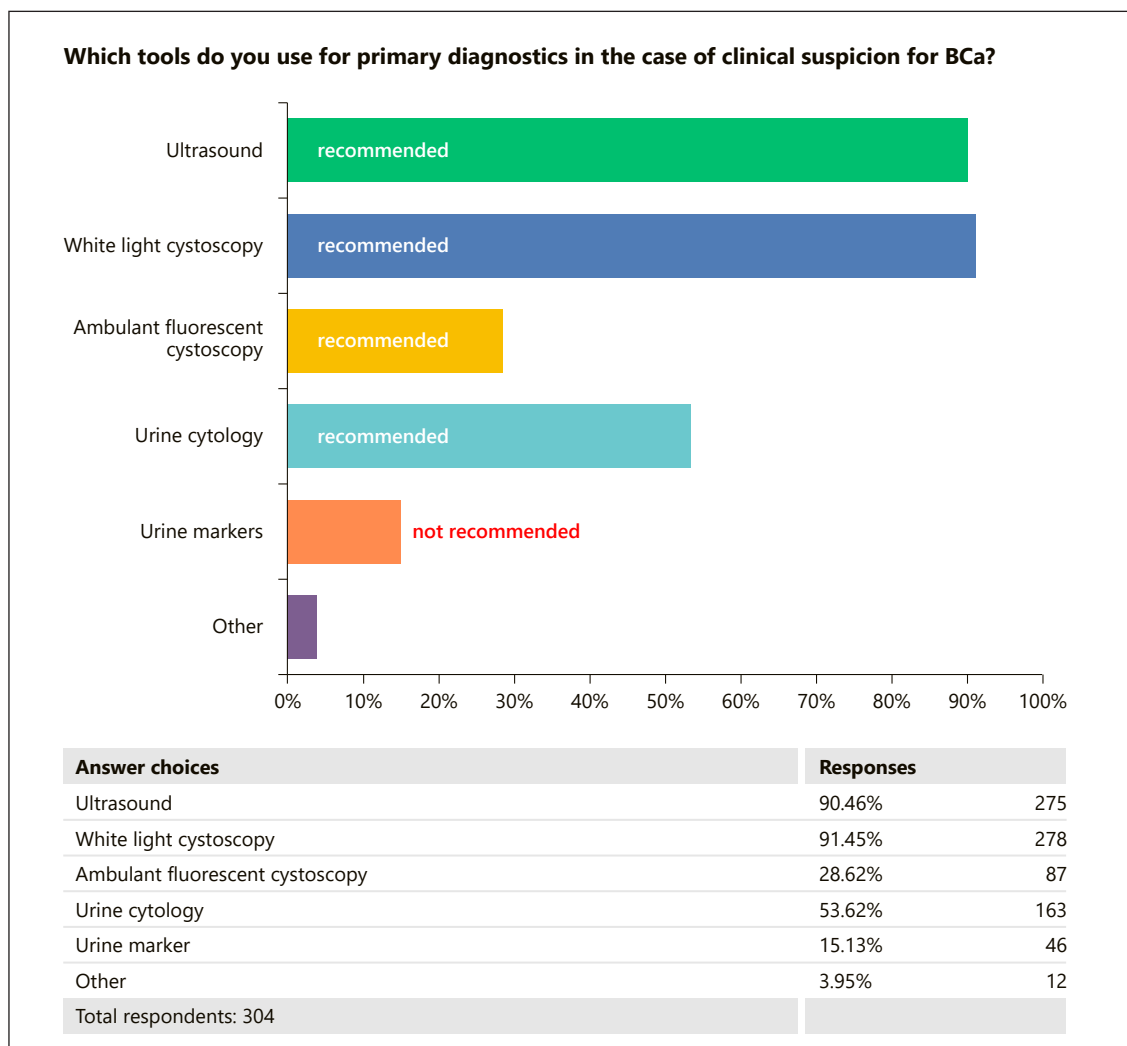


Fig. 1. Responses to question 9: Which tools do you use for primary diagnostics in the case of clinical suspicion for BCa? BCa, bladder cancer.

in cases of endoscopically noncontrollable NMIBC (86%). In the case of the first diagnosis of single CIS or high-risk NMIBC, 40% take early RC into consideration. The overall adherence analysis showed that 73% of the urologists followed strong consensus recommendations and 74% followed consensus recommendations.

Discussion/Conclusion

The introduction of German S3 guidelines for NMIBC points out the purpose of developing guidelines for diagnosis, therapy, and follow-up care, which should help to ameliorate patient-centered care, reducing morbidity

and mortality rates for NMIBC patients. In this survey, around 96% of the urologists claimed to know the content of the S3 guideline for NMIBC either “moderately” or “very well,” and at least 55% of them use the German guideline on a weekly basis. These numbers underline the importance of this guideline. Recent data show that non-adherence leads to overtreatment [11] as well as undertreatment [12, 13] and has a detrimental impact on patient outcomes [14]. Therefore, this survey will help to identify the key areas where national guideline adherence is low to further understand the factors that lead to discrepancies between guideline recommendations and routine management. This could help to address areas that could improve NMIBC patient care in the near future.

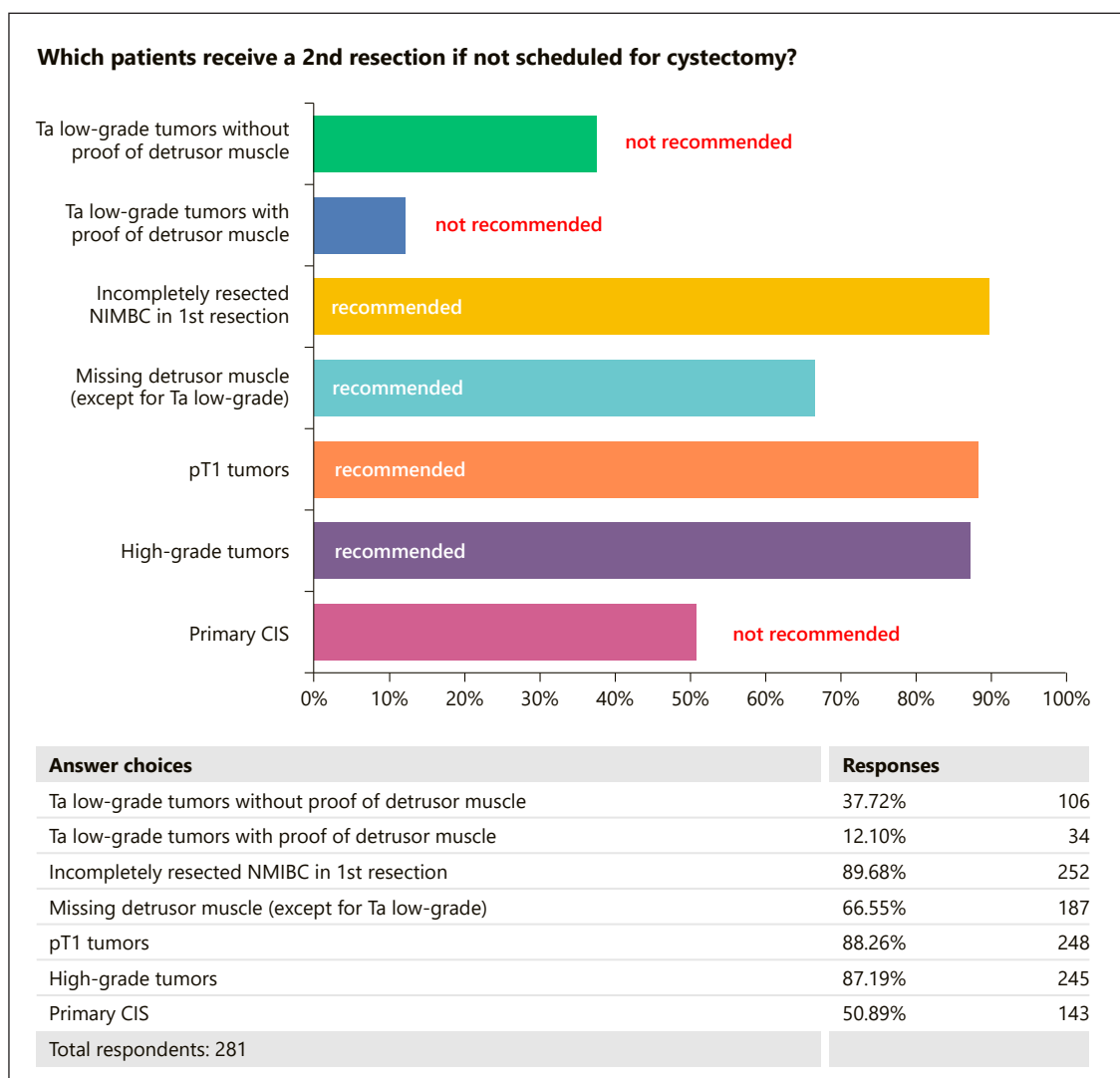


Fig. 2. Responses to question 18: Which patients receive a 2nd resection if not scheduled for cystectomy?

The most commonly used primary diagnostic tools for NMIBC in our study were WL cystoscopy in 92% of all cases followed by ultrasound in 91% of all cases. This is in line with recent findings in Europe [15]. Although the use of urine markers for primary diagnostics of NMIBC is not in line with German or EAU guideline recommendations, 15% of the urologists use them anyway. Despite the recommendation of utilizing urine cytology for primary diagnostic evaluation, a rather low number of the participants (54%) use this tool (Fig. 1). Comploj et al. [16] stated that even if cytology has low sensitivity, especially in low-grade bladder carcinomas, the high specificity and inexpensive nature of the equipment required justification performing it since the greatest value of cytology for

patients with NMIBC is the detection of high-grade urothelial carcinoma.

Different trials have revealed improved diagnosis accompanied by long-term recurrence rate reduction for the use of photodynamic diagnostics in NMIBC [17, 18], while coming along with high false-positive rates [19]. A meta-analysis by Gakis and Fahmy [20] on 294 studies with over 1,300 patients revealed a significant recurrence and survival benefit for NMIBC patients treated with HAL-based TURB instead of WL TURB. A meta-analysis by Kang et al. [21] on 274 studies with over 1,000 patients showed a significant recurrence risk reduction for narrow band imaging use in TURB. We found that round 29% of the participants reported the use of fluorescent cystos-

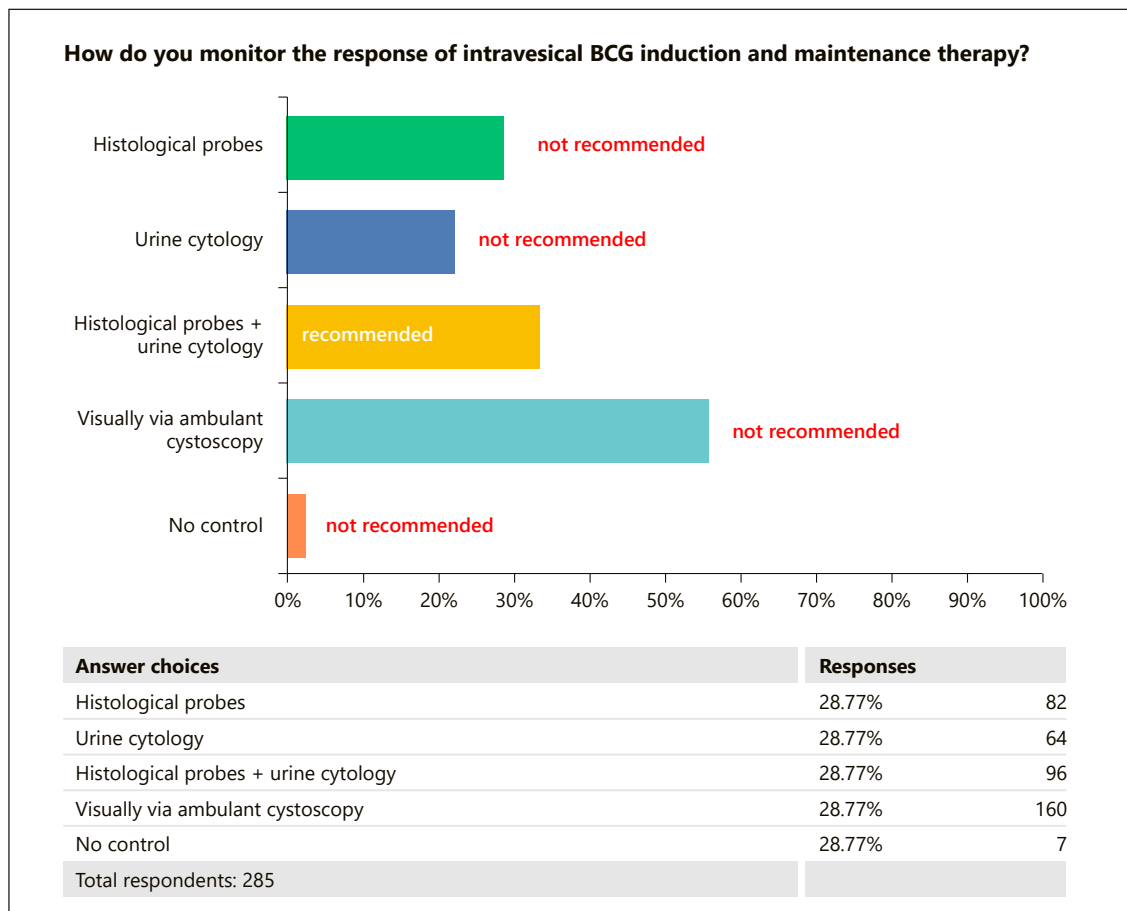


Fig. 3. Responses to question 24: How do you monitor the response of intravesical BCG induction and maintenance therapy? BCG, Bacille Calmette-Guérin.

copy in initial diagnostic workups, and 27% used fluorescence cystoscopy for single tumor sites, which might include a certain overdiagnosis for low-risk tumors. Based on the existing data, the additional use of any type of photodynamic diagnostics in initial TURB seems to be justified. Therefore, the reported 67% of HAL use for patient groups with a history of high-risk tumors seems to be rather low and results in a possible underdiagnosis for these patients.

Although the German and EAU guidelines recommend performing a second resection in cases of missing detrusor muscle, except for pTa low-grade NMIBC, only 67% of the participants follow this recommendation. Thirty-eight percent of the participants still perform a second resection in the case of pTa low-grade NMIBC (Fig. 2). This finding is in line with data in Europe that indicate re-TURB is performed in a relatively high percentage of patients with low-risk NMIBC (25–75%) [15]. This assumes potential undertreatment for patient groups

without inclusion of detrusor muscle in the first place, as well as overtreatment for low-risk tumors, and it suggests that inadequate first resection or other clinical or surgical factors influence this decision.

Adherence to recommendations concerning instillation therapy is contradictory. Whereas, 80% of the participants perform early single instillation therapy when low-risk NMIBC is suspected, as recommended by the guideline, 78% continue with the instillations for intermediate-risk NMIBC, and 80% use BCG instillations for high-risk NMIBC; only 34% monitor the response to BCG induction and maintenance by obtaining histological material including urine cytology (Fig. 3), and 73% monitor every 3 months. These findings are in line with previous studies showing significant nonadherence to EAU and American Urological Association guideline recommendations regarding BCG instillation therapy for intermediate- and high-risk NMIBC [12, 15, 22]. The efficacy of BCG for improving recurrence-free survival and

reducing progression risk for intermediate- and high-risk NMIBC is well-known [23, 24]. This adherence gap may be caused by possible side effects, cost, time, effort, BCG delivery shortages, and lack of patient compliance but it indicates once more how additional promotion of instillation therapy patterns in NMIBC is needed.

So far, no specific recommendations for ERBT of NMIBC with a size >1 cm have been implemented in the German guideline. We found that 68% of the participants already perform ERBT for tumors over 1 cm in size. A recent published study by our working group revealed that ERBT improves histopathologic evaluation of NMIBC, with complete preservation of en bloc integrity for tumors between 1 and 2 cm [25]. Prospective data, for example, of our ERBT of urothelial carcinoma trial, will be provided in the near future. Still, this finding shows the growing clinical importance of ERBT in daily urological practice.

The greatest number of urologists consider early RC in cases of recurrent high-risk NMIBC after BCG (BCG failure) (93%) or in cases of endoscopically noncontrollable NMIBC (86%). In the case of the first diagnosis of single CIS or high-risk NMIBC, 40% take early RC into consideration, which seems rather high. The existing data support imminent RC for T1G3 tumors with associated CIS due to the high-risk (around 55%) of the disease, which is already muscle invasive at the time of clinical diagnosis. Both are otherwise burdened by a high volume of recurrences and progressions. Conversely, for a single T1G3 tumor without associated CIS, a conservative bladder-preserving strategy with instillation therapy and close surveillance seems to be justified [26, 27]. Other groups have stated that the role of concomitant CIS for recurrence and progression rates remains unclear [28]. This demonstrates the urgent need for identification of new biological markers that are able to predict the behavior of NMIBC and to guide the decision-making process between conservative or aggressive treatment. For now, our data show no broad support for early cystectomy in daily German urological practice.

Although 96% of the German urologists claim to know the content of the S3 guideline for NMIBC either “moderately” or “very well,” and at least 55% of them use the German guideline on a weekly basis, the overall adherence analysis revealed that 73% of the participating urologists follow strong consensus recommendations and 74% follow consensus recommendations. Our findings are complemented by other data concerning guideline adherence toward diagnostics and therapy of BCa around Europe [6, 7, 13, 15]. This demonstrates the need for in-

creasing awareness of national guideline recommendations to improve the care of patients with NMIBC in the near future. More intense promotion and education of German and Austrian urologists by national urologic societies supported by modern social media platforms and applications for portable devices could be of use. However, our study is not devoid of limitations.

We did not assess the nationality of each participant in our anonymous survey. Judging from the participation records of the training courses, at least 30 Austrian urologists completed the survey which represents a minority of 10%. As mentioned in the result section, only 2 urologists stated that they do not know the German guideline recommendations at all. Nine urologists hardly knew them. That represents 3.7% of the participants, so to our opinion, the survey results are representative. An evaluation by Hendricksen et al. [15] among 69 German and 27 Austrian urologists showed that 52% of the German and still 22% of the Austrian urologists followed national (that means German S3) guideline recommendations, whereas 96% of the Austrians followed the EAU guideline. Additionally, Austrian urologists pass the European FEBU exam to get their urologic certificate. Assuming a low utilization of the German guideline among Austrian participants, this represents a limitation to our study.

Of the participants, 11% ($n = 34$) and 18% ($n = 56$) skipped several questions in the instillation therapy section, which could lead to a certain bias since it seems possible that only those participants who knew the guideline recommendations answered these questions. Furthermore, knowing the main reasons that led to discrepancies between guideline recommendations and daily urological practice is imperative. We did not; however, conduct follow-up interviews with nonadherent urologists since this was an anonymous survey. Understanding the factors that drive decision-making should; therefore, be a part of future inquiries.

We found a discrepancy between certain guideline recommendations and daily routine practice concerning the use of urine cytology for initial diagnostics, instillation therapy with a low monitoring rate of BCG response, and follow-up care with unnecessary second resection after pTa low-grade NMIBC in particular. Our survey resulted in a moderate overall adherence rate of 73% among German and Austrian urologists. These results demonstrate the need for increasing awareness of S3 guideline recommendations by promotion and more intense education of urologists to optimize NMIBC care, thereby decreasing morbidity and mortality rates.

Statement of Ethics

Ethics approval was not required since this was an anonymous survey.

Conflict of Interest Statement

This work was supported by Ipsen Biopharm Ltd., which was involved in the design and conduct of the study as well as the data collection and management. Additionally, the manuscript underwent a professional English proofreading by proof-reading-service.com. The authors have no other conflicts of interest to declare.

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Author Contributions

J.P.S. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; J.P.S., J.S., M.W.K., M.F., M.J.P.H., M.C.H., P.P., T.N., T.F., T.S.W., M.G., P.-F.P., S.D., S.L.H., C.K., A.M., M.P.B., L.-M.K., H.R., and F.F.D. were involved in the study concept and design; J.P.S., J.S., M.F., M.W.K., M.J.P.H., M.C.H., P.P., T.N., T.F., T.S.W., M.G., P.-F.P., S.D., S.L.H., C.K., A.M., M.P.B., L.-M.K., H.R., and F.F.D. were involved in the acquisition of the data; J.P.S., J.S., and M.W.K. analyzed and interpreted the data; J.P.S. drafted the manuscript; J.P.S., J.S., M.W.K., M.J.P.H., M.C.H., P.P., T.N., T.F., T.S.W., M.G., P.-F.P., S.D., S.L.H., C.K., A.M., M.P.B., L.-M.K., H.R., and F.F.D. critically revised the manuscript for important intellectual content; J.P.S. performed the statistical analysis; M.F. and Ipsen Ltd. provided administrative, technical, and material support; and J.S. and M.W.K. provided supervision.

Data Availability Statement

The datasets used and/or analysed during the current study are available from the corresponding author on request.

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