ORIGINAL ARTICLE

Factors affecting guideline adherence in the initial treatment of non-muscle invasive bladder cancer: Retrospective study in a French peripheral hospital

Facteurs influençant l’application des référentiels de traitement dans la prise en charge initiale des tumeurs de vessie n’envahissant pas le muscle : étude rétrospective d’un centre hospitalier régional français

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Clinical practice guidelines;
Treatment adherence;
Non-muscle invasive bladder cancer;
Intravesical therapy;
BCG therapy;
cystectomy

Summary
Objectives. — To assess whether the initial treatment of non-muscle invasive bladder cancer (NMIBC) was performed according to the guidelines, and to determine the reasons why initial treatment was not provided in nonadherence cases.

Materials and methods. — We retrospectively reviewed all patients with NMIBC who underwent their first transurethral resection of bladder tumor (TURBT) at a peripheral hospital, between 2007 and 2016. The treatment offered to the patient was compared to the European Association of Urology guidelines according to risk stratification. For each patient who did not receive the treatment according to the guidelines, one of the following reasons was identified: poor patient compliance, poor patient general health status, urologist’s decision, lack of resources.

Results. — One hundred fifty-nine patients were included with a mean age of 72.2 years at the time of NMIBC diagnosis. The low-risk patients were strictly treated according to the guidelines. Among the intermediate-risk patients, 14% received mitomycin C. Among the high-risk

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patients, 39% received intravesical Bacillus Calmette-Guerin. In the nonadherence cases (61%), the reasons were related to the patient in 44% of cases (poor compliance, 21%; poor patient general health status, 23%), urologist’s decision in 54% of cases, and lack of resources in 2% of cases. Thirty-seven percent of the high-risk patients underwent re-resection.

Conclusions. — Overall, adherence to NMIBC guidelines was low in all treatment types (intravesical therapy, re-resection, or cystectomy for very high-risk patients), but this finding was similar to that in previous studies. Reasons were mainly related to the urologist’s decision or to the patient condition (poor compliance or poor general health status).

**Level of evidence.** — 3.

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**MOTS CLÉS**
Référentiels de traitement ; Adhésion aux recommandations ; Tumeur de vessie non infiltrante ; Instillations intra-vésicales ; BCG thérapie ; Cystectomie

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**Introduction**

Non-muscle invasive bladder cancer (NMIBC) guidelines offer the highest level of evidence regarding the treatment of non-muscle invasive disease and are intended to optimize patient care [1–3]. Therefore, it would be expected to observe a high level of similarity between the guidelines and daily clinical practice [4].

No study has mainly investigated the reasons why adherence to the guidelines was hindered in NMIBC. However, the importance of those reasons has been highlighted by many studies [3–6]. A few studies regarding NMIBC guideline adherence have used surveys to investigate urologists’ treatment patterns [4,7–9]. Other studies have investigated the rate of adherence to NMIBC treatments (instillations and re-resections) [6,10–13]. Knowing the reasons implied with nonadherence to the guidelines would allow health care professionals to take action on the modifiable factors in order to improve the rate of NMIBC adherence.

The objectives of this study were to evaluate if the initial treatment of NMIBC was performed according to the NMIBC guidelines, and to determine the reasons why initial treatment was not provided in the cases of nonadherence.

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**Patients and methods**

We conducted a retrospective study of all consecutive charts of patients with NMIBC who underwent their first transurethral resection of bladder tumor (TURBT) at a single community hospital in France from January 2007 to May 2016. Patients with missing data; those who had undergone their initial TURBT outside of the community hospital; and those who had a pathology report of a condition other than NMIBC were excluded. Over that timeframe, the patients were operated by nine senior urologists.

At baseline, the following information was recorded: age at diagnosis, Charlson Comorbidity Index, Charlson 10-year
survival probability, and tumor characteristics according to the surgical and pathological reports.

**Classification of patients**

Patients were divided into four risk groups according to the EAU NMIBC guidelines [2].

Patients were stratified as low risk if the tumor was pTa, low grade, < 3 cm; intermediate risk if pTa, low grade, multifocal, or > 3 cm; high risk if pT1 and/or high grade and/or carcinoma in situ (CIS); and very high risk if pT1 and high grade, very large on the first TURBT or persistent on re-resection, pT1G3 and CIS, or an aggressive pathologic subtype.

The tumor was considered > 3 cm or multiple if described as such in the operative report written in the patient’s medical record, or if it was described as very large or to be multiple tumors.

**Treatments received**

If the patient was in the low-risk group, there was no indication for re-resection, intravesical therapy, induction, or maintenance therapy. Immediate postoperative instillation was not analyzed in our study. If the patient was in the intermediate group, there was an indication for intravesical therapy with induction by either Bacillus Calmette-Guerin (BCG) or mitomycin C. If mitomycin C was chosen, there was an indication for a minimum of eight instillations with no mandatory maintenance, since maintenance is not required by the guidelines. If BCG was chosen, there was an indication for six induction instillations followed by maintenance composed of three instillations for 3 months, followed by three instillations every 6 months for a minimum of 1 year. If the patient was in the high-risk group, there was an indication for intravesical BCG with induction identical to that in the intermediate group, followed by the same maintenance protocol used in the intermediate group but for a duration of 3 years, as recommended by the European Association of Urology (EAU) [2].

Regarding the patients who were eligible for intravesical therapy, we considered that intravesical therapy was started if the patient had received at least one instillation. If the patient was in the very high-risk group, there was an indication for cystectomy [2].

**Assessment and classification of protocol deviations**

Each case was analyzed to determine if re-resection or instillations were indicated. The indication for re-resection was present if one of the following criteria was met: incomplete resection, pT1 and/or high-grade tumor, and no muscle visible on the pathological report, except for low-grade pTa when the lamina propria was seen. For patients treated before 2013, according to the previous French guidelines regarding re-resection, the criteria were as follows: incomplete resection, pT1 and high-grade tumor [14].

For each patient, we noted if the treatment applied was according to his/her risk group, as recommended by the EAU guidelines. When the treatment guidelines (intravesical therapy [started and finished], re-resection, and cystectomy) were not applied, we reviewed the chart to determine the main reason for which the patient was not treated according to the guideline. Poor patient general health status was considered the main reason if the patient had an advanced age (> 80 years), major comorbidities (Charlson Comorbidity Index), a poor estimated Charlson 10-year survival probability defined as less than 10%, and if the chart indicated a known intolerance to the treatment. “Poor patient health status” was also considered the main reason if the patient stopped maintenance BCG for intolerance issues. Another main reason was considered poor patient compliance if the patient refused the treatment, did not show up for treatment, or was lost to follow-up. The lack of resources was considered the main reason if the guideline treatment could not be applied because of a lack in resources. This situation was only encountered because of the lack of supply of BCG. In cases when the urologist specified in his consult notes that he preferred a non-guideline treatment for reasons not related to the patients’ health; his compliance or for lack of resources, the reason was classified as the urologist’s decision. When the patient had a good general health status, was compliant, resources were available and still the recommended treatment was not provided, the reason was also classified as the urologist’s decision by default.

**Statistical analysis**

Our main purpose was to provide a detailed descriptive analysis of the treated population. Categorical variables are described using frequency tables. Cross tabulations were performed to describe our variables. For the descriptive analysis, quantitative variables are expressed as mean and standard deviations; qualitative variables are expressed as percentages. The Chi² test with the Yates correction for comparison was used to compare reresection for high risk at different time periods. We used SPSS software, version 12.0 (IBM Corp.) to perform the statistical analysis.

**Ethical statement**

All legal conditions for epidemiological surveys were respected, and the French national commission governing the application of data privacy laws (the “Commission Nationale Informatique et Libertés”) issued approval for both projects. Since the study was strictly observational and used anonymous data, in accordance to the laws that regulate “non-interventional clinical research” in France, namely articles L.1121-1 and R.1121-2 of the Public Health Code, we did not require the written informed consent from the participants or the authorization from any other ethics committee to conduct this survey.

**Results**

**Patient cohort**

Four hundred eleven NMIBC files were reviewed. The final cohort included 159 patients (130 [82%] men and 29 [18%] women). Patients’ mean age at the time of diagnosis was 72.2 years. The mean Charlson Comorbidity Index was 1.2, and the mean Charlson 10-year survival probability was
36.4%. The distribution of the tumor types was as follows: 70%, pTa; 26%, pT1; and 4%, CIS. The most frequent tumor type was a single, < 3 cm, pTa, low-grade urothelial carcinoma (49 patients [31%]). Table 1 shows the clinical and pathological characteristics of the cohort and different risk groups.

### Classification of patients

The 159 patients were stratified according to their EAU risk group: 49 (30%) were low risk, 28 (18%) were intermediate risk, 70 (44%) were high risk, and 12 (8%) very high risk (Fig. 1).

### Treatments received

Among the low-risk patients, all underwent surveillance. None received intravesical therapy or re-resection. Among the intermediate-risk patients, 14% started intravesical therapy, all with mitomycin C; none received BCG. In the high-risk group, 39% of patients started intravesical therapy, all with BCG; none received mitomycin C. Of the high-risk patients that started BCG, 15% (4/27) finished maintenance. Concerning the high-risk patients that started BCG, the average instillations/per patient was 8.1 (219 intravesical BCG for 27 patients). In the high-risk group, 37% of patients who had an indication for re-resection, underwent this procedure. In the very high-risk group, all the patients had an indication for radical cystectomy. In this subgroup, 8% (1/12) underwent radical cystectomy (Table 2).

### Protocol deviation

Among those who did not start intravesical therapy in the intermediate group, the reasons were related to the patient in 21.0% of cases (poor compliance) and urologist’s decision in 79.0% of cases.

Among those who did not start intravesical BCG in the high-risk group, the reasons were related to the patient in 44.2% of cases (poor compliance, 20.9%; poor general health status, 23.3%), urologist’s decision in 53.5% of cases, and lack of resources in 2.3% of cases.

Among the high-risk patients that started but did not finish BCG maintenance, the reasons were related to the patient in 56.5% of cases (poor compliance, 34.8%; poor general health status, 21.7%), urologist’s decision in 34.8% of cases, and lack of resources in 8.7% of cases.

Among those who did not undergo re-resection in the high-risk group, the reasons were related to the patient in 45.0% of cases (poor compliance, 15.0%; poor general health status, 20.0% and urologist’s decision in 65.0% of cases (Table 3). When stratifying by time period before and after the 2010 French guidelines (that mentioned clearly the need for re-resection), we found a resection rate for high risk not statistically different when comparing 2007–2010 and 2011–2016 (27% vs. 40%, P=0.54) (Table 4).

Among those that did not undergo radical cystectomy in the very high-risk group, the reasons were related to the patient in 81.8% of cases (poor compliance, 18.2%; poor general health status, 63.6%) and urologist’s decision in 18.2% of cases (Table 3).
Figure 1. Patient flow chart.

Table 2 Treatments received.

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Intravesical therapy</th>
<th>Re-resection</th>
<th>Cystectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indicated, n</td>
<td>Started, n (%) of patients who started MMC or BCG according to the guidelines</td>
<td>Re-resected, n (%) of patients re-resected according to the guidelines</td>
</tr>
<tr>
<td>Low-risk group, n=49</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate-risk group, n=28</td>
<td>28</td>
<td>4 (14%)</td>
<td>1</td>
</tr>
<tr>
<td>High-risk group, n=70</td>
<td>70</td>
<td>27 (39%)</td>
<td>63</td>
</tr>
<tr>
<td>Very high-risk group, n=12</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

MMC: mitomycin C; BCG: Bacillus Calmette-Guerin.

Discussion

Adherence to the guidelines concerning the treatment of NMIBC was low for re-resection, intravesical therapy, and radical cystectomy for very high-risk cases. The reasons were related to the patient, urologist’s decision, or lack of available resources. When stratifying by risk groups, we observed a higher guideline adherence for low-risk patients and a lower guideline adherence for intermediate-risk, high-risk, and very high-risk patients.
Factors affecting initial treatment of non-muscle invasive bladder cancer

**Table 3** Treatment deviation in comparison to guidelines.

<table>
<thead>
<tr>
<th>Deviation from guideline: No intravesical therapy</th>
<th>Deviation from Guideline: No re-resection</th>
<th>Deviation from guideline: No cystectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with an indication for intravesical therapy that did not start intravesical therapy</td>
<td>Patients with indication for re-resection that did not undergo re-resection</td>
<td>Patients with indication for cystectomy who did not undergo radical cystectomy</td>
</tr>
<tr>
<td>Proportion of each reason when not starting intravesical therapy</td>
<td>Proportion of each reason for not undergoing re-resection</td>
<td>Proportion of each reason for not undergoing radical cystectomy</td>
</tr>
<tr>
<td>Poor patient compliance</td>
<td>Poor patient compliance</td>
<td>Poor patient compliance</td>
</tr>
<tr>
<td>Poor general health status</td>
<td>Poor general health status</td>
<td>Poor general health status</td>
</tr>
<tr>
<td>Urologist’s decision</td>
<td>Urologist’s decision</td>
<td>Urologist’s decision</td>
</tr>
<tr>
<td>Lack of resources</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low-risk group n = 49</th>
<th>Intermediate-risk group n = 28</th>
<th>High-risk group n = 70</th>
<th>Very-high risk group n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>24 (86%)</td>
<td>43 (61%)</td>
<td>0</td>
</tr>
<tr>
<td>Poor patient compliance</td>
<td>5 (21.0%)</td>
<td>9 (20.9%)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>Poor general health status</td>
<td>0 (0.0%)</td>
<td>10 (23.3%)</td>
<td>2 (40.0%)</td>
</tr>
<tr>
<td>Urologist’s decision</td>
<td>19 (79.0%)</td>
<td>23 (53.5%)</td>
<td>2 (40.0%)</td>
</tr>
<tr>
<td>Lack of resources</td>
<td>0 (0.0%)</td>
<td>1 (2.3%)</td>
<td>3 (60.0%)</td>
</tr>
</tbody>
</table>

**Table 4** Re-resection for high risk by time periods.

<table>
<thead>
<tr>
<th>Patients n</th>
<th>Re-resection indicated n</th>
<th>Re-resected, n (% of patients re-rected according to the guidelines)</th>
<th>Deviation from Guideline: No re-resection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patients with indication for re-resection that did not undergo re-resection</td>
<td>P</td>
</tr>
<tr>
<td>2007—2010</td>
<td>17</td>
<td>15 (27%)</td>
<td>11 (73%)</td>
</tr>
<tr>
<td>2011—2016</td>
<td>53</td>
<td>48 (40%)</td>
<td>29 (60%)</td>
</tr>
<tr>
<td>2007—2016</td>
<td>70</td>
<td>63 (37%)</td>
<td>40 (63%)</td>
</tr>
</tbody>
</table>
Our results corroborate those in national studies where only 36% of urologists reported constantly following NMIBC guidelines [7]. Adherence to guidelines has been shown to also be low in Europe, Canada, the United States, and Brazil [3,4,6]. Additionally, low guideline adherence has been encountered in other specialties, such as gynecology (e.g., concerning the treatment of ovarian cancer) [15]. To our knowledge, this is the first worldwide study that mainly assessed the reasons for nonadherence to NMIBC guidelines. One of the strengths of our study was the inclusion of all the patients diagnosed as having NMIBC, which ruled out urologist selection bias that was found in other survey studies that tended to overestimate guideline adherence [5,7—9,16].

Poor general health status

In our cohort, the poor general health status contributed to a large part of the lack of guideline adherence, which is not surprising since bladder cancer tends to affect elderly individuals [17]. The ‘poor general health status’ factor explains why BCG was not started in 23.3% of the high-risk patients and why cystectomies were not performed in 63.6% of the very high-risk patients (Table 3).

Age over 75—80 years has already been considered a factor for BCG underuse [10,18,19]. Age more than 70 years and comorbidities have also been found to be a factor hindering guideline adherence in gynecological oncology [15]. A multidisciplinary approach involving the onco-gerontologist is essential in order to obtain the best outcomes for the elderly population [20].

Patient compliance

Poor compliance was also a major cause of nonadherence, accounting for 20.9% of cases when intravesical BCG was not started and 34.8% of cases when BCG was not finished. Since the high-risk patients in our series that started BCG, received an average of 8.1 instillations per patient (therefore slightly more than 6 instillations which corresponds to a BCG induction), it shows that our cohort received BCG induction followed by only a few maintenance instillations. According to Lamm et al., the patients’ poor compliance could have been related to their reluctance to side effects as well as their underestimation of its benefits [21]. Physicians should have better communication with the patient, first concerning the benefits of BCG and second concerning the possibility to prevent the minor side effects or treat them if they occur [7,21,22]. Psycho-educational support could also improve patients’ compliance to treatment and would reduce their fears [23].

Unfortunately, the management of side effects of BCG is not optimal among urologists because of inadequate prescription of antibiotics and premature protocol termination for minor side effects [7,22]. Complementary training on the side effects of BCG as well as regular updates on the free available best practice European and French guidelines concerning the prevention of these side effects could be the key to alleviating this problem [1,2].

Urologist’s decision

Only 39% of our patients started BCG, which is low but similar to a result found in a Swedish study without any urologist selection bias [10]. Lenis et al. reported that some urologists waited for multiple recurrences of an initially high-risk tumor before offering intravesical BCG, contrary to the guidelines, which corroborates with our findings that in more than half of the cases when BCG is not given for high-risk patients, it is because of the urologist’s decision [18]. Furthermore, urologists consider maintenance BCG as difficult to organize; therefore, they often diverge from Lamm et al.’s 3-year protocol [4,7].

We also found that underuse of mitomycin C mainly because of the urologist’s decision accounts for approximately 80% of cases, which corroborates with findings of other studies where more than half of the intermediate-risk patients did not receive any intravesical therapy [5]. Barcos et al. suggested that in order to reduce the gap between intravesical therapy and the guidelines, urologists must adhere more to the guidelines [24].

We found a relatively low re-resection rate for high-risk tumors (37%) mainly because of the urologist’s decision (65.0%), but this finding was similar to that in other retrospective studies (22—35%) [6,13,25—27]. Even though it was not statistically significant, we noted an increase in re-resection rates for high risk after 2010, when the French guidelines mentioning re-resection were published (27% vs. 40%, P = 0.54). The lack of statistical significance might be due to the small sample size and thus the lack of power. Larger studies might be necessary in order to explore our findings. Gotto et al. found that regional hospitals tend to re-resect less high-risk tumors than academic centers, which could be the case in our regional hospital [6]. In Canada, meetings to discuss best practice and review guidelines were organized, but the rate of participation of urologists working in a regional background was low [6]. It has been shown that discussing an oncology case in an uro-oncology multidisciplinary meeting (MDM) majorly alters the treatment in 26.7% of cases [13,27]. It should be noted that some cases of NMIBC that we analyzed lacked an MDM report.

Lack of resources

We found that 8.7% (2/23) of high-risk patients that started BCG were unable to complete BCG maintenance because of the worldwide BCG shortage. Both patients were diagnosed in 2013, which corresponds to the period of BCG shortage in France. For one of the patients, maintenance was not done, for the other it was done using mitomycin C. Gates et al. found a similar rate of 5% (2/41) for BCG not completed because of the worldwide shortage [12]. We only found one report of a high-risk patient where the urologist specified that he chose not to start BCG because of BCG shortage. The prevention of BCG shortage is obviously necessary.

Limitations

Since the study is performed at a single community center, we did not have any possibility of follow up for patients treated initially at the institution that later sought
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Care elsewhere, which might have overestimated the rate of 'non-compliance'. Another limitation is the retrospective nature of the study therefore making difficult to determine the exact reason for guideline deviation. Furthermore, the category "urologist’s decision" might have been overestimated, since if the urologist applied a non-guideline treatment without specifying the reason (health counter-indication, lack of resources, patient’s preference for a non-guideline treatment), the reason was classified erroneously as the urologist’s decision. We also possible wrongfully classified as "urologist’s decision" in cases when no consult notes were found by the investigator reviewing the files in order to find the real reason behind the non-guideline treatment. We remind that it is fundamental for a urologist opting for a non-guideline treatment to assure that the patient’s chart contains the elements of justification (patient’s decision, cardiologist’s counter indication, lack of BCG, etc). Other pitfalls of this study include the relatively small sample size due to the fact that the study is performed in a low-volume peripheral hospital.

Conclusions

The guidelines are rightfully established in order to optimize treatment, avoid protocol deviations, and favor optimal evidence-based health care for patients. Some of the measures to improve guideline adherence include a better onco-geriatric evaluation, improved doctor-patient communication, the use of a multidisciplinary team involving a psycho-educational approach, and prevention of the lack of resources. All urologists should be encouraged to (1) consult the guidelines freely available on the official EAU websites, (2) participate in uro-oncology MDMs, and (3) participate in meetings that discuss best practice and review guidelines [3]. Future multicentric studies should focus on the efficacy of the implementation of these measures in improving guideline adherence for treating NMIBC.

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Disclosure of interest

The authors declare that they have no competing interest.

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