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ORIGINAL ARTICLE

En bloc re-resection of high-risk NMIBC after en bloc resection: results of a multicenter observational study

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Abstract

Purpose To investigate the role of en bloc re-resection (EBRS) in patients who had undergone previous en bloc resection for high-risk non-muscle-invasive bladder cancer (NMIBC).

Methods An international, multicenter, observational retrospective analysis of prospectively collected data. Patients with a high-risk NMIBC who had previously undergone en bloc resection were scheduled for EBRS of the resected area after 40 days. The primary outcome was the presence of residual tumor or recurrence-free survival.

Results Overall, 78 patients underwent EBRS. Only five (6.41%) residual cancers were found: one patient had a pTa G3 (1.28%) cancer and four (5.13%) had a pTis. The detrusor muscle was preserved in all samples. Only one patient had a positive margin on EBRS. No procedure called for a conversion to traditional re-TURBT. No patient experienced bladder perforation or other intra-operative complications. The recurrence rate at the first follow-up cystoscopy (RRFF-C at 3 months) was 3.85% (three patients). The median follow-up period was 30.8 months (range 6.9–76.0 months). In univariate analysis, the only predictor of recurrence was grade. Overall we observed 11 recurrences. Only one tumor progressed to T2 MIBC.

Conclusions The low rates of residual tumor, recurrence, and progression seem to raise doubts about the efficacy of EBRS in patients who have previously undergone en bloc resection. EBRS appears to be a feasible and safe procedure with a low rate of complications. However, further data will be needed before EBRS can be used in clinical trials or recommended as a treatment modality.

Keywords Bladder cancer · NMIBC · En bloc resection · En bloc re-resection · Outcome

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Introduction

In patients with T1 non-muscle-invasive bladder cancer (NMIBC), the persistence of bladder disease ranges between 33 and 55%, and may reach 41.4% after resection of a TaG3 tumor [1, 2]. Guidelines suggest a re-staging resection. The likelihood of muscle-invasive disease detected by second resection of an initial T1 tumor ranges from 1.3 to 25%. When the pathological sample obtained at the time of primary resection did not contain detrusor muscle, the rate of MIBC may increase to 45% [3, 4]. According to a meta-analysis, the prevalence of residual tumors and up-staging to invasive disease remain high even in T1 tumors with muscle in the specimen. In the total population of 3556 patients with T1 tumors, disease persistence was detected in 61% and tumor understaging in 15% of cases, whereas in the subgroup of 1565 T1 tumors with the presence of muscle

the corresponding figures were 58% and 11%, respectively. However, the analysis revealed a significant diversity between studies [5]. From a clinical point of view, it has been found that a second TURB may prolong recurrence-free survival [1, 2], improve outcomes after BCG treatment [6], and provide prognostic information [7].

Recently en bloc resection has been described as a technique for improving the quality of resection, staging, and outcome. Hurle et al. showed that, in 90 en bloc resected tumors, the detrusor muscle (DM) was present in all cases and the recurrence rate after 3 months was 5.4% [8]. The traditional procedure of "piecemeal" re-resection was associated with the same limitation as standard TURBT: tumor cell scattering, risk of seeding and re-implantation, and the absence of DM in the histopathology report. According to literature, en bloc resection could partially avoid such drawbacks, although evidence remains poor [5, 9].

In the current series, we investigated the role of en bloc re-resection (EBRS) in patients who had undergone previous en bloc resection for primary high-risk NMIBC.

Here, we tested the hypothesis that en bloc re-resection is feasible and effective in a selected group of patients previously treated by primary en bloc resection.

Materials and methods

This is an international, multicenter, observational retrospective study of data collected prospectively at two tertiary hospitals, in patients who underwent EBRS for staging of high-risk NMIBC from September 2011 to April 2017. Patients older than 18 years of age with a first diagnosis or a primary recurrence of high-risk NMIBC according to the EAU guidelines [10], who had previously undergone en bloc resection for a single tumor of ≤ 3 cm and ≤ 4 lesions, were scheduled for EBRS of the resected areas within 40 days. Tumors located anteriorly, over the posterior wall, and all those cases where the cancer did not allow visualizing the ureteral ostium had been ruled out from primary en bloc resection. Furthermore, patients with a definitive histopathological diagnosis, which revealed a nonurothelial carcinoma, were excluded.

The local ethics committees and IRBs approved the study; patients consented in writing to data analysis. All patients were followed up according to the EAU Guidelines for NMIBC [9]. Patients underwent adjuvant instillation of bacillus Calmette–Guerin (BCG).

Techniques

The surgical procedure was performed by three experienced surgeons (RH, LL and ML) according to the standardized technique at our institution. A circular incision was made around the scar using any of five devices, depending on the surgeon's preference (J-electrode Collins loop: Storz 27040 L 24 CH; Collins loop bipolar Olympus; Thulium laser; Storz bladder round loop 27040 DB/EB; and bladder rectangular loop EG 714941), maintaining a distance of ~ 5–10 mm from the scar edge. The incision was made in macroscopically 'normal' mucosa surrounding the scar, and then extended through the subepithelial connective tissue, the muscularis mucosae, and the muscularis propria layers throughout the detrusor muscle (Fig. 1). During the procedure, the bladder was filled to low or medium capacity. The previously resected areas were dissected cautiously from the periphery to the center of the lesion base to avoid perforation. Finally, the tissue was detached from the bladder wall and extracted with an Ellick evacuator or a bladder syringe.

All patients received a transurethral catheter for postoperative bladder irrigation. The latter was started immediately after surgery and was continued for 18 h [11–13]. Each specimen was marked to facilitate the pathologist's analysis, and examined to determine its widest diameter, peripheral/circumferential and depth margins.

Pathological evaluation of specimens

All of the specimens were inked at the base. To avoid sample shrinkage due to formalin fixation, which is known to induce shrinkage of 1 mm in every 10 mm of tissue and sometimes mild distortion of lesions, all samples were measured in the operating room before fixation. Sample quality was based on the ability to assess the resected specimens from their

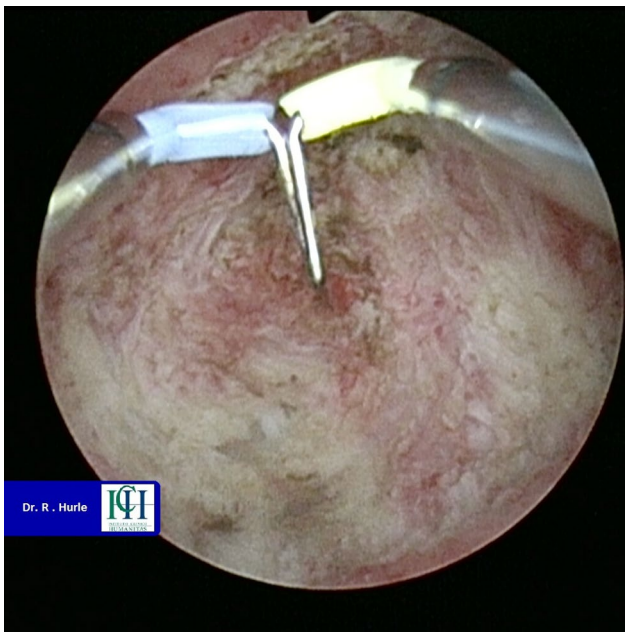

Fig. 1 Endoscopic view of en bloc re-resected area

surface to the deeper aspect, including the detrusor muscle wall. This systematic approach permitted complete microscopic evaluation of the basal surface of the sample over the lamina propria to assess or exclude foci of residual tumor, and identify the submucosal layer and the muscularis propria beneath the lamina propria.

This orientation also permitted the investigator to assess the surgical margins of the sample. Peripheral/circumferential resection margins were evaluated histologically. The pathological stage was determined for all samples, based on stepwise sectioning of the specimens for histological examination.

Two expert uropathologists (PC, MH) reviewed the samples according to the 2016 WHO classification. [14].

Outcome of interest

The primary outcome was the presence of residual tumor or recurrence-free survival. Secondary outcomes were feasibility defined by the rate of conversion to standard TURBT, safety defined intra-operatively by the occurrence of bladder perforation with bleeding and post-operatively by the Clavien–Dindo classification scale, and the quality of resection defined according to the presence/absence of detrusor muscle and whether or not the patient experienced a recurrence at 3 months.

Statistical analysis

Data are given in numbers and percentages, or means and standard deviations as appropriate. Pre- and post-resection data were compared using the Chi-square test with Fisher's correction where necessary. The time of recurrence was calculated from the date of surgery to the date of recurrence or last contact. We performed a univariate Cox regression to assess the impact of potential prognostic factors on recurrence-free survival. A p value of < 0.05 was considered significant. All analyses were performed using Stata13.

Results

A total of 78 patients, mean age 68 ± 9 years, underwent EBRS. Their clinical characteristics are summarized in Table 1.

The mean interval between primary resection and re-resection was 27 ± 13 days. No procedure required a conversion to traditional re-TURBT. Re-resection performed according to the en bloc technique revealed only five residual cancers: one patient had pTaG3 (1.28%), and four had pTis (5.13%). No malignant lesion was found in 73 patients. The detrusor muscle was present in all samples, and it was not infiltrated by the disease. Only one patient presented with a positive circumferential margin at en bloc re-resection. In 78 patients with NMIBC who underwent en bloc re-resection, the recurrence rate at the first follow-up cystoscopy (RRFF-C at 3 months) was 3.85% (three patients).

Table 1 Demographic and clinical characteristics of patients with NMIBC

N patients	78
Age	68 ± 9
M/F	51/27
N resected tumor	1 (1–4)
Primary tumor size (cm)	1.9 (1–3.5)
Primary	65
Ta	17 (21.79%)
T1 (1, 1a, 1b)	57 (73.08%)
Tis	4 (5.13%)
Grade (3)	72 (92.31%)
DET +	77 (98.72%)

Table 2 Univariable analysis for recurrence-free survival

	HR (95% CI)	p
Age	1.05 (0.97–1.14)	0.225
Interval 1°–2° TURBT (days)	0.98 (0.93–1.03)	0.363
T		
Ta	1	
T1	0.32 (0.07–1.43)	0.134
Tis	2.02 (0.33–12.22)	0.445
Grade (3)	0.28 (0.12–0.70)	0.006
Histology at 2nd TURBT (scar)	0.66 (0.08–5.22)	0.698

Neither age nor days between 1° and re-en-bloc resection were independent predictors of recurrence. The only predictor of recurrence was grade. Due to low sample size, no multivariate analysis was performed

The median duration of follow-up was 30.8 months (range 6.9–76.0 months). In univariate analysis performed to assess the impact of potential prognostic factors on recurrence-free survival, neither age nor the number of days between primary and second en bloc resection were independent predictors of recurrence (Table 2). The only predictor of recurrence was tumor grade. Multivariate analysis could not be performed because of the small sample size.

No patient experienced bladder perforation, uncontrollable bleeding, or any other intra-operative complication. Post-operatively, four (5.1%) patients developed a C–D Class 1 complication. The catheter was routinely removed on day 1 post-surgery and the patients were usually discharged the same day.

Overall, we observed 11 recurrences. Figure 2 shows the Kaplan–Meier curve for recurrence-free survival.

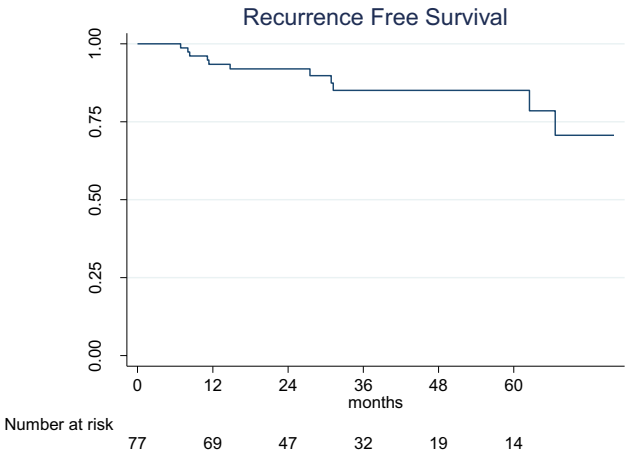

Fig. 2 Kaplan–Meier curve for recurrence-free survival

The first follow-up cystoscopy after 3 months did not reveal any significant scar, although we found two lateral retractions of normally ejaculating ureteral ostium.

We observed only one progression to T2 MIBC; the patient was treated with chemo-radiotherapy for several significant comorbidities. Two patients with Tis HG underwent cystectomy.

Discussion

We report the results of a first series of patients who routinely underwent a second en bloc resection after initial en bloc resection of a high-risk NMIBC. The investigators of the study considered re-resection by the en bloc technique a viable option for NMIBC. In the present series, we registered a very low rate of residual tumors, which supported the oncological efficacy of primary en bloc resection. Both, primary and re-resection procedures were feasible, safe, associated with low complication rates, and serve as acceptable options in the management of NMIBC.

The rate of persistent disease in T1 tumors is reported to be rather high and stable in a number of studies [5]. The pooled prevalence of persistent disease is about 50%. A meta-analysis published in 2011 reported similar findings; 2248 patients including 1432 cases of T1 disease were analyzed [15]. Interestingly, the authors observed similar pooled prevalence rates in patients with single and multiple primary lesions. We previously reported residual cancers in 55/130 (42%) patients, and up-staging of 5/130(3%) in a heterogeneous population. However, focusing on patients with detrusor muscle at the first resection, the rates dropped to 23/90(25%) and 1/9(1%) for residual cancer and DM, respectively. Based on the current series, it could be stated that en bloc resection of primary cancer and repeat en bloc resection may further improve the oncological outcome. In our series, we registered a recurrence rate of about 6.5% over a mean period of 31 days, and 3.85% after 3 months.

In general, the en bloc strategy appears to be superior to the standard TURBT approach. Nagele et al. proved the feasibility of waterjet hydrodissection for removing bladder tumors. In contrast to conventional TURB, this technique enabled the pathologist to assess the entire lamina propria and the resection margins because of the en bloc technique, and assess invasiveness as well as R0 versus R1 resection [15]. The principal objection to TURB is that it does not comply with basic oncological principles, i.e. respecting the margins of tumor resection and resection of the specimen in one piece. Basically re-TUR is the best available option to overcome the constraints of TURB, even if the first TUR is considered "complete" by the surgeon and the specimen includes the muscle. However, re-TUR has the same technical flaws as TURB. Thus, EBRS offers the intrinsic advantages of en bloc resection versus re-TUR, since the latter is subject to the same limitations as TUR. The use of technical innovations such as fluorescence [16] or narrow-band imaging [17] may further improve the management of non-muscle-invasive bladder cancer. Randomized studies show that fluorescence and narrow-band imaging may improve the detection of bladder cancer and reduce, but not avoid, R1 and/or disease recurrence [16, 17].

The present series would appear to fulfil an unmet clinical need by confirming the role of en bloc resection in urology [18, 19]. According to the EAU Guidelines of 2018, the results of repeat resection, the detection of residual tumors, and the definition of disease stage reflect the quality of initial TURB; the current investigation would appear to confirm this statement.

The small number of patients included in the present study was one of its major limitations. Furthermore, although the absolute number of patients with positive margins is low ($n=1$), it should be correlated with the rather large number of patients with residual cancer ($n=5$). As this is the first multinational/multi-institutional series, larger series will be needed for comparison. A second major limitation of the present study is the post hoc retrospective analysis of prospectively collected data, and no RCT vs. standard TURBT. Thus, it cannot be stated with any certainty that en bloc re-resection could replace re-TUR in the near future. Its appropriate place in clinical routine may be to assist both TURB and re-TUR in achieving maximum clarity about the tumor and its stage. Bladder cancer may recur due to seeding of cancer cells, which can be avoided to a large extent by standard TURB. Some recurrences can be partly explained by the "field cancerization" effect or the "clonal" origin of urothelial cancer; these phenomena have not been fully clarified yet. It may also progress to metastatic disease without recurring in the bladder. Obviously, the surgeon's expertise might play a role in preventing the biological consequences

of the disease. As en bloc resection in our series was performed by expert surgeons, this may have influenced the low complication rate. An additional limitation was given by us using more than one device. Finally, the MVA was not performed due to small sample size for such an analysis. In our series, we had a very few patients with non-G3 grade tumors. These patients happened to have risk factors for recurrence (working exposure and smoking). The negative outcome of these patients has probably biased the univariable analysis, making grade 3 a "protective factor" for recurrence.

Conclusions

Re-resection by the en bloc technique may be considered safe and effective after initial en bloc resection. The very low rates of residual tumor, recurrence, and progression seem to raise doubts about the efficacy of re-resection in patients who have previously undergone en bloc resection. These data appear to support the fact that the quality of primary en bloc resection is the key factor, and EBRS should be used selectively.

This raises the question as to whether re-ERBT—in contrast to re-TURBT—should be performed on a routine basis. Re-ERBT could serve as an alternative to standard/conventional re-TURBT in pathological T1 and high-grade tumors. EBRS appears to be a feasible and safe procedure with a low rate of complications. Further data will be needed before EBRS can be recommended as a treatment procedure or used in clinical trials.

Author contributions CP: data collection and management; CD: data collection and management; CP: data analysis; HM: data analysis; HTRW: protocol/project development; HR: protocol/project development; OD: data collection and management; KT: data collection and management; LM: manuscript writing/editing, supervision; LL: protocol/project development; MM: data collection and management; ME: statistical analysis; PM: manuscript writing/editing; SA: data collection and management.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, the 1964 Helsinki declaration and its later amendments, or comparable ethical standards.

Informed consent The IRB approved the study and patients consented to data analysis. Informed consent was obtained from all persons included in the study.

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