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Substitution Urethroplasty with Closure Versus Nonclosure of the Buccal Mucosa Graft Harvest Site: A Randomized Controlled Trial with a Detailed Analysis of Oral Pain and Morbidity

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Abstract

Background: Optimal surgical management of the buccal mucosa harvest site in patients with urethral stricture disease during buccal mucosa graft urethroplasty (BMGU) remains controversial.
Objective: To analyze in detail intensity and quality of pain as well as oral morbidity following closure (C) versus nonclosure (NC) of the donor site.
Design, setting, and participants: Randomized controlled trial on 135 patients treated with BMGU between October 15, 2014 and December 18, 2015.
Intervention: Following computer-based randomization, 63 and 72 patients, respectively, received C and NC of the donor site at the inner cheek. Preoperatively, on days 1, 5, and 21 as well as at 3 and 6 mo postoperatively, patients completed standardized questionnaires, including validated questions on intensity and quality of pain as well as oral morbidity.
Outcome measurements and statistical analysis: The coprimary end points were intensity and quality of oral pain. Secondary end points included oral morbidity and intensity of pain of the perineogenital region. Generalized linear mixed models evaluated the effect of various covariates on intensity and quality of oral pain, oral morbidity, as well as intensity of pain of the perineogenital region.
Results and limitations: There was noninferiority for NC versus C in intensity and affective quality of oral pain at every time point following BMGU. Oral morbidity and complications included pain, bleeding, swelling, numbness, alteration of salivation and taste, as well as impairment of mouth opening, smiling, whistling, diet, and speech. Time from BMGU had significant effects on intensity ($p < 0.001$) and quality of oral pain (sensory pain: $p < 0.001$, affective pain: $p < 0.001$, total pain: $p < 0.001$). Length of buccal mucosa graft had significant effects on intensity ($p = 0.001$) and quality of oral pain (sensory pain: $p = 0.020$, total pain: $p = 0.042$).
Conclusions: NC is noninferior to C of the donor site in intensity and quality of oral pain, and offers a treatment alternative. Time from BMGU and length of the buccal mucosa graft have effects on oral morbidity and complications.
Patient summary: We investigated pain, morbidity, and complications following closure (C) versus nonclosure (NC) of the buccal mucosa harvest site in patients undergoing buccal mucosa graft urethroplasty (BMGU). We found that NC is not worse than C regarding oral pain. In addition, time from BMGU and length of the buccal mucosa graft have effects on oral morbidity and complications.

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1. Introduction

Substitution urethroplasty is the gold standard treatment for long primary and recurrent urethral strictures [1]. Currently, autologous buccal mucosa represents the most frequently used transplant for substitution urethroplasty [1,2], due to its favorable availability, simple processing, and durable integration in the urethra [3]. Although tissue-engineered grafts have been introduced, none has succeeded in routine clinical use for urethral reconstructive surgery [4]. Buccal mucosa graft urethroplasty (BMGU) offers excellent functional treatment outcomes [5,6]. However, donor site complications following BMGU may cause relevant pain and morbidity, including difficulties with mouth opening and perioral numbness [7–9].

Still, optimal surgical management of the buccal mucosa harvest site during BMGU remains a matter of controversial debates [8,10–13]. Previous findings suggest that closure (C) or nonclosure (NC) of the donor site may be advantageous, particularly in the early postoperative phase [10–13]. However, previous studies focused on intensity of oral pain, and morbidity mainly considered effects on mouth opening, salivation, diet, or perioral numbness [10–13], whereas quality of oral pain, swelling, impairments of speech, taste perception, or smiling has not been evaluated in detail. In addition, data on perioperative analgesic medication and pain in the perineogenital region have not been presented [10–13].

Therefore, the aim of the present randomized controlled prospective trial was to analyze in detail the intensity and quality of oral pain as well as morbidity in patients with urethral stricture disease treated with BMGU with C versus NC of the donor site.

2. Patients and methods

2.1. Patient cohort

The local ethics committee approved this randomized controlled, two-treatment-arm study (No. PV4827). Male patients ≥18 yr of age with urethral stricture disease were eligible. Exclusion criteria were any previous treatment with BMGU, known or suspected concomitant oral diseases (gingivitis and caries), psychiatric disorders or cognitive impairment, chronic pain, bilateral buccal mucosa graft harvest, and non–German-speaking patients. Power analysis indicated that 50 patients per group were required to achieve 96% power at a significance level of 0.05 to show noninferiority of NC versus C, assuming a noninferiority margin of a one point difference in pain intensity on an 11-point numeric rating scale (NRS). A noninferiority approach was used, since NC represents a less invasive procedure for a patient with fewer sutures compared with C of the donor site. A narrow noninferiority margin of a one point difference was chosen based on the findings of other authors, who reported that a reduction of 1.5 or 2 points on an 11-point NRS is clinically significant and that the change that defines a clinical significant difference decreases over time [14–16]. Based on previous withdrawal rates in questionnaire-based outcome studies of our institution [17,18], 163 patients were enrolled between October 15, 2014 and December 18, 2015 after written informed consent.

2.2. Surgical procedure and randomization

BMGU has previously been described in detail [19]. In brief, dorsal inlay or ventral onlay single-stage BMGU was performed depending on the location of the urethral stricture [20–23]. Buccal mucosa graft harvest at the inner check has extensively been described earlier [11,19]. In brief, the mouth was covered in a sterile manner in all patients. For exposure of the buccal mucosa at the inner cheek, two 3-0 monofil sutures were placed at the inferior and superior lip. The buccal mucosa was infiltrated with 2% lidocaine with adrenaline and harvested in an ovoid shape from the inner cheek [24]. The width of the buccal mucosa graft was consistently 15 mm. Before harvesting, the length of the buccal mucosa graft was measured in all patients. Bipolar electrocautery was used for hemostasis of the donor site. When eligibility criteria were met, physicians of the special consultation hour for reconstructive urology of our department enrolled patients in the trial. Afterward, participating patients were randomized to the C group or NC group in a 1:1 ratio using a computer-based randomization list containing consecutive numbers. Within the process of patient information on the surgical procedure on the day prior to the surgical intervention, all participating patients received a number, which was recorded on the written informed consent for BMGU. For concealment, neither physicians nor patients knew which number coded for C or NC before the buccal mucosa harvest. Only the statistician and the surgical nursing staff could know which number coded for C or NC. The surgical nursing staff kept the randomization list with the specific coding for C versus NC in a locked drawer in a separate nursing-staff room in the OP wing. Only during the buccal mucosa harvest, the surgical nursing staff revealed whether the number encoded for C or NC of the donor site. In the C group, the donor site was closed with interrupted 4-0 monofil sutures. In contrast, the donor site was not closed in the NC group. One piece of cottonoid gauze was placed at the harvest site in both groups and was removed at the end of the surgical procedure. In total, six surgeons dedicated to urethral reconstructive surgery performed BMGU in all patients.

2.3. Postoperative management

Postoperative management has been outlined in detail previously [19]. In brief, patients received analgesics according to the World Health Organization Analgesic Ladder consisting of nonsteroidal anti-inflammatory drugs (NSAIDs; ie, novalgin) and paracetamol, combined with weak opioids (ie, tramadol) according to the needs of patients [25]. According to institutional standards, all patients performed daily oral rinsing with chamomile and cooling of the cheek from postoperative days 1–5. All patients were routinely discharged on postoperative day 5. On postoperative day 21, all patients received a cystourethrogram at our institution.

2.4. Questionnaire

The standardized questionnaire comprised validated questions on intensity and quality of pain as well as nonvalidated questions on oral morbidity. The intensity of pain of the oral cavity and the perineogenital region, respectively, were assessed using a unidimensional single 11-point NRS [16]. The quality of pain of the oral cavity was evaluated using the multidimensional Short-Form McGill Pain Questionnaire (SF-MPQ), consisting of a sensory and an affective pain subscale with 11 and four items, respectively [16]. Questions on oral morbidity evaluated mouth opening, perception of taste, salivation, oral sensation, diet, oral bleeding, use of analgesics, smiling, whistling, oral swelling, speech, and burden in daily life due to oral morbidity. Questions on oral morbidity were scale rated on a five-stage scale, that is, “not at all” (=0), “a bit” (=1), “moderately” (=2), “much” (=3), and “very much” (=4).

Patients completed the questionnaires preoperatively, on postoperative days 1, 5, and 21, as well as at 3 and 6 mo postoperatively.

2.5. Statistical analysis

The coprimary end points were intensity and quality of oral pain in patients with C versus NC of the buccal mucosa harvest site. Secondary end points included oral morbidity as well as intensity of pain of the perineogenital region in the C versus NC group. A noninferiority design was used for the analysis of coprimary end points and the secondary end point intensity of pain of the perineogenital region. Other secondary end points were tested for differences between C and NC. Associations between categorical variables were assessed using the Fisher exact and χ^2 test. The dependent variables were analyzed using a generalized linear mixed model approach (SPSS routine GENLINMIXED), assuming a normal data distribution and a log-link function for oral pain intensity NRS score, NRS scores of pain intensity of the perineogenital region, oral sensory pain index, oral affective pain index and oral total pain index, a logit-link function and multinomial data distribution for oral morbidity, and a logit-link function with a binomial data distribution for oral complications. The patient was assumed a random effect and the time points as repeated measures within a patient. C and NC of the donor site and time from BMGU were considered as categorical independent fixed-effect variables in the models, as well as their interaction term. Model computations were adjusted for fixed effects of baseline values of the respective dependent variables, "length of buccal mucosa graft" and "age" that were considered continuous variables, as well as for the categorical baseline variables "analgesic medication" and "smoking versus nonsmoking." The p values of F tests of the fixed effects are presented, along with model-estimated coefficients. The GENLINMIXED-estimated marginal means and their 95% confidence intervals (CIs) are graphically presented. All tests are two sided and $p < 0.05$ was considered statistically significant. Noninferiority was considered established if the upper limit of the 95% CI for the NC versus C difference of the respective outcome variable did not include the predefined one point margin. All analyses were performed with SPSS 23 (SPSS Inc., IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patients' baseline characteristics and clinical features

In total, 28 patients (17%) were excluded from the trial due to intraoperative modifications from the initially planned surgical procedure (ie, three patients [11%] and 25 patients [89%] received bilateral buccal mucosa graft harvest and two-stage BMGU, respectively), resulting in 135 patients available for analyses (Supplementary Fig. 1). Overall, 63 (47%) and 72 (53%) patients received C and NC of the buccal mucosa harvest site, respectively. Table 1 presents data on age, length of the buccal mucosa graft, length of the urethral stricture, location and etiology of the urethral stricture, smoking status, perioperative analgesic medication, intensity of oral pain, and pain of the perineogenital region, as well as oral sensory, affective, and total pain index between the C and NC groups.

3.2. Postoperative intensity of pain

There was noninferiority for NC versus C in intensity of oral pain at every time point following BMGU. Figure 1 presents oral pain intensity NRS scores and NRS scores of pain intensity of the perineogenital region in the C versus NC group following BMGU, including the difference between C and NC as well as its 95% CI. With exception of postoperative day 1, there was noninferiority of NC versus C in intensity of pain of the perineogenital region. Supplementary Table 1 presents mean NRS scores and standard deviations following surgery in the C versus NC group.

Time from BMGU and length of the buccal mucosa graft had significant effects on the intensity of oral pain (Supplementary Table 2; $p \leq 0.001$). Owing to the log-link function used, an increase of 1 mm length of buccal mucosa graft corresponds to 1.014-fold increase of the NRS score. Time from BMGU, length of the buccal mucosa graft, and perioperative analgesic medication had significant effects on the intensity of pain of the perineogenital region (Supplementary Table 2; $p \leq 0.035$). Patients with NSAIDs and paracetamol plus weak opioid treatment had 39% higher NRS scores compared with patients without analgesics.

3.3. Postoperative quality of pain

Supplementary Table 3 presents postoperative sensory and affective dimension of pain in the C and NC groups. Overall, the most frequent sensory dimension of pain was "tender." The most common affective dimension of pain was "tiring–exhausting" on postoperative days 1 and 5, and 3 mo postoperatively. In contrast, on postoperative day 21 and at 6 mo postoperatively, the most frequent affective pain was "fearful." On postoperative day 5, 42 (69%) and 27 (52%) patients had "aching" sensory dimension of pain in the NC and C groups ($p = 0.029$), respectively. Three months postoperatively, no patient in the NC group and six patients (13%) in the C group had a "stabbing" sensory dimension of pain ($p = 0.038$). Six months postoperatively, eight (20%) and six (14%) patients in the NC and C groups, respectively, had a "cramping" sensory dimension of pain ($p = 0.042$).

Figure 2 presents oral sensory, affective, and total pain index following BMGU, including the difference between C and NC as well as its 95% CI. There was noninferiority for NC versus C in oral sensory pain index on postoperative day 21 and at 3 mo postoperatively. On postoperative days 1 and 5, and at 6 mo postoperatively, there was no noninferiority of NC versus C in oral sensory pain. There was noninferiority for NC versus C in oral affective pain index. There was noninferiority for NC versus C in oral total pain index at 21 d and 3 mo postoperatively. On postoperative days 1 and 5, and at 6 mo postoperatively, there was no noninferiority of NC versus C in oral total pain index. Supplementary Table 1 presents mean SF-MPQ scores and standard deviations at every time point following surgery in the C versus NC group.

Time from BMGU and length of the buccal mucosa graft had significant effects on oral sensory pain (Supplementary Table 4; $p \leq 0.020$). Time from BMGU, and interaction of C versus NC and time from BMGU had significant effects on oral affective pain (Supplementary Table 4; $p < 0.001$). Time from BMGU, and interaction of C versus NC and time from BMGU as well as the length of the buccal mucosa graft had

Table 1 – Clinical characteristics of 135 urethral stricture disease patients treated with buccal mucosa graft urethroplasty with closure versus nonclosure of the buccal mucosa harvest side [a]

	Nonclosure (n = 72)	Closure (n = 63)
Age (yr), median (1st quartile; 3rd quartile)	53 (34; 66)	55 (39; 68)
Length of buccal mucosa graft (mm), median (1st quartile; 3rd quartile)	45 (40; 60)	50 (50; 80)
Length of the urethral stricture (mm); median (1st quartile; 3rd quartile)	25 (20; 40)	30 (20; 40)
Location of the urethral stricture		
Bulbar urethra	53 (74)	47 (75)
Penile urethra	19 (26)	16 (25)
Etiology of the urethral stricture, n (%)		
Idiopathic	65 (90)	57 (91)
Iatrogenic	1 (1.4)	3 (4.8)
Traumatic	6 (8.3)	3 (4.8)
Smoking status, n (%)		
Negative	66 (92)	58 (92)
Positive	6 (8.3)	5 (7.9)
Perioperative analgesic medication, n (%)		
No medication	23 (32)	19 (30)
NSAIDs and paracetamol	26 (36)	23 (37)
NSAIDs and paracetamol plus weak opioid	23 (32)	21 (33)
Oral pain		
Pain intensity, numeric rating score, median (1st quartile; 3rd quartile)	0 (0; 0)	0 (0; 0)
Sensory pain index, McGill Pain Questionnaire short form, median (1st quartile; 3rd quartile)	0 (0; 0)	0 (0; 0)
Affective pain index, McGill Pain Questionnaire short form, median (1st quartile; 3rd quartile)	0 (0; 0)	0 (0; 0)
Total pain index, McGill Pain Questionnaire short form, median (1st quartile; 3rd quartile)	0 (0; 0)	0 (0; 0)
Pain of the perineogenital region		
Pain intensity, numeric rating score, median (1st quartile; 3rd quartile)	0 (0; 0)	0 (0; 1)

NSAID = nonsteroidal anti-inflammatory drug.
[a] Totals in percentages may not add up to exactly 100% due to rounding.

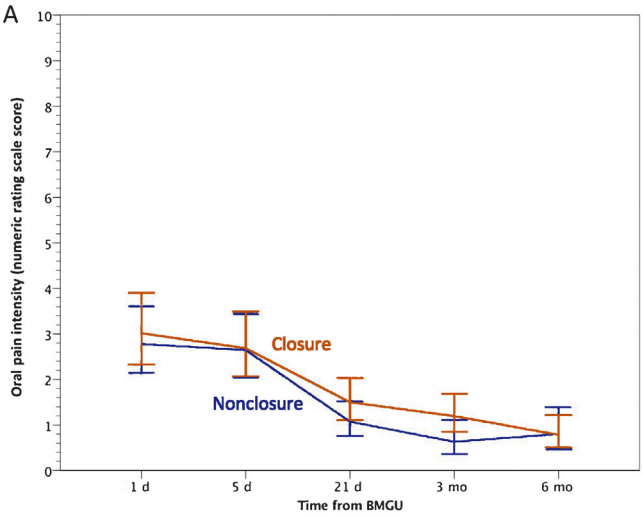
significant effects on oral total pain index (Supplementary Table 4; $p \leq 0.042$).

3.4. *Postoperative oral morbidity and complications*

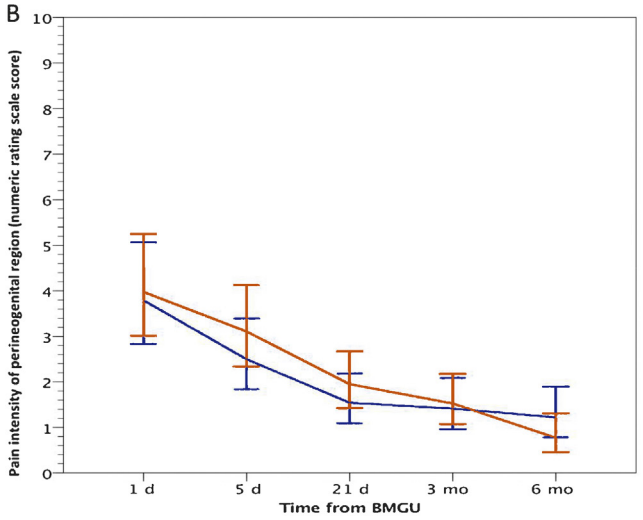
Table 2 presents oral morbidity and complications following BMGU. The most frequent oral morbidity included impairment of mouth opening, numbness, swelling, impairment of eating, and smiling. Oral complications consisted of Clavien grade 1 complications, including use of antipyretics and oral bleeding not requiring surgical intervention. C versus NC of the buccal mucosa harvest site had no significant effect on oral morbidity and complications (Supplementary Table 5). Time from BMGU had the strongest effect on oral morbidity and complications. With increasing time from BMGU, the proportion of patients reporting oral morbidity consistently declined (Supplementary Table 5).

4. Discussion

We found noninferiority for NC versus C in oral pain intensity at every time point following BMGU. Conversely, others have previously shown that C or NC may be associated with lower pain in the early postoperative period, specifically from postoperative day 1 to 5 [10–13]. Different findings among studies may be due to differences in cohort sizes, various factors that the studies adjusted for, and distinct statistical methods. In contrast to previous trials, we adopted a noninferiority approach and utilized generalized linear mixed models to evaluate the effect of various confounders on oral pain intensity, allowing a comprehensive analysis of repeated measurements including fixed and random effects [26]. We found that time from BMGU and length of the buccal mucosa graft had substantial impact on oral pain intensity. After reaching maximum NRS scores corresponding to moderate to mild pain on postoperative day 1, the intensity of pain steadily declined with increasing time from BMGU in patients with C and NC of the donor site. An increase of length of the buccal mucosa graft resulted in rising oral pain intensity. In comparison with prior randomized studies [10–13], the present trial included the highest patient number, contributing to adequately powered statistical analyses. For the first time, to the best of our knowledge, the present study incorporated several important factors, which may influence the intensity of oral pain, including perioperative analgesic medication. Analgesic medication may relief pain [25], thus representing a potential source of bias. Importantly, there was no difference in perioperative analgesic medication between the C and NC groups in the present study. In addition, we included data on pain intensity of the perineogenital region, permitting an analysis of the sensitivity and control of pain of both patient groups. Pain intensity NRS scores of the perineogenital region peaked on the 1st postoperative day, with subsequent decline until reaching a minimum of 6 mo after BMGU. Notably, satisfactory pain control was achieved in patients with C and NC, since the intensity of perineogenital pain was moderate and mild at any time following surgery, which



	Difference of NC vs C	95% Confidence interval	
		Lower	Upper
Postoperative day 1	−0.235	−0.987	0.517
Postoperative day 5	−0.040	−0.746	0.666
Postoperative day 21	−0.427	−0.915	0.060
3 mo postoperatively	−0.564	−1.060	−0.069
6 mo postoperatively	0.018	−0.502	0.537



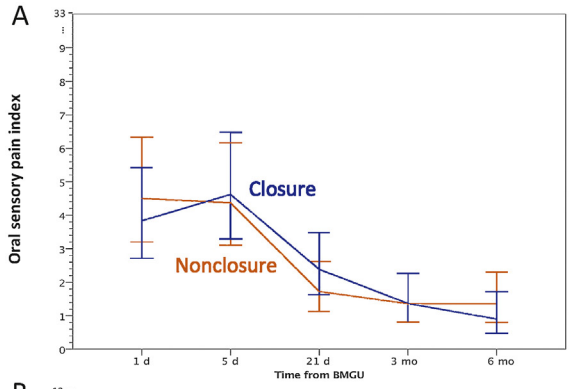
	Difference of NC vs C	95% Confidence interval	
		Lower	Upper
Postoperative day 1	−0.185	−1.052	1.044
Postoperative day 5	−0.609	−1.323	0.487
Postoperative day 21	−0.408	−0.984	0.168
3 mo postoperatively	−0.112	−0.710	0.105
6 mo postoperatively	0.451	−0.143	0.681

Fig. 1 – Estimated marginal means and 95% confidence intervals of numeric rating scale scores of (A) oral pain intensity and (B) pain intensity of the perineogenital region in 63 patients with closure versus 72 patients with nonclosure of the donor site during buccal mucosa graft urethroplasty. BMGU = buccal mucosa graft urethroplasty; C = closure; NC = nonclosure.

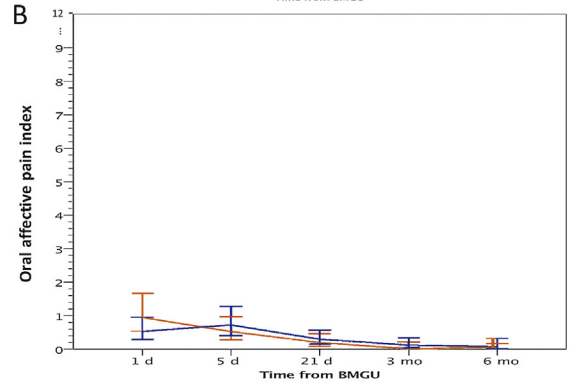
represents an acceptable range as recommended by the German S3 Guideline on acute perioperative pain [27].

For the first time, the present study evaluated quality of oral pain following BMGU. We found noninferiority for NC versus C in oral sensory pain on postoperative day 21 and at 3 mo postoperatively, but not on postoperative days 1 and 5, and at 6 mo postoperatively. The majority of patients reported "tender" sensory pain at any time after surgery, which corresponds to sensory pain following other surgical procedures, for example, inguinal hernia repair [28]. The most frequent sensory pain varied between the C and NC groups on postoperative day 5, as well as at 3 and 6 mo postoperatively. This may be due to differences in uncovered surface and variable tension of the wound following C versus NC of the donor site at the inner cheek. In addition, the absorbable suture may have an effect on sensory pain and thus contribute to differences in patients with C versus NC of the harvest site. We found noninferiority for NC versus C in oral affective pain at every time point following surgery. Overall, "tiring–exhausting" was the most common affective pain. On postoperative day 21 and 6 mo postoperatively, however, the most frequent affective pain was "fearful." Variable affective pain following BMGU may be due to unmet patients' preoperative expectation of pain. For example, in other surgical procedures, patients' age, and discrepancies between patients' preoperative anticipated pain and preoperative anxiety influenced postoperative pain [29,30]. Moreover, differences in sensory pain may also have an effect on affective pain. We found that noninferiority of NC versus C in oral total pain index could not be proved on postoperative days 1 and 5, and at 6 mo postoperatively. This may be due to observed differences in the quality of sensory and affective pain in the C versus NC group.

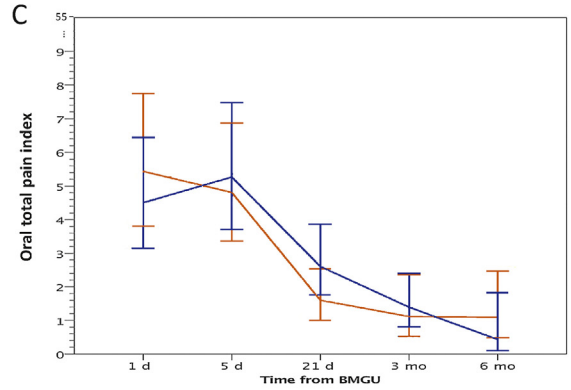
We found that C versus NC had no effect on oral morbidity. Time from BMGU had the strongest effect on oral morbidity. Oral morbidity was at the highest level on postoperative day 1 and decreased continuously with increasing time from surgery. Remarkably, 6 mo after BMGU, more than a quarter of patients still reported oral



	Difference of NC vs C	95% Confidence interval	
		Lower	Upper
Postoperative day 1	0.666	−0.729	2.060
Postoperative day 5	−0.247	−1.709	1.215
Postoperative day 21	−0.661	−1.561	0.239
3 mo postoperatively	−0.009	−0.870	0.851
6 mo postoperatively	0.458	−0.374	1.290



	Difference of NC vs C	95% Confidence interval	
		Lower	Upper
Postoperative day 1	0.416	−0.068	0.899
Postoperative day 5	−0.197	−0.601	0.206
Postoperative day 21	−0.102	−0.321	0.117
3 mo postoperatively	−0.180	−0.234	0.017
6 mo postoperatively	−0.014	−0.133	0.105



	Difference of NC vs C	95% Confidence interval	
		Lower	Upper
Postoperative day 1	0.923	−0.891	2.757
Postoperative day 5	−0.458	−2.253	1.337
Postoperative day 21	−1.004	−2.042	0.034
3 mo postoperatively	−0.279	−1.316	0.759
6 mo postoperatively	0.662	−0.398	1.722

Fig. 2 – Estimated marginal means and 95% confidence intervals of (A) oral sensory pain index, (B) oral affective pain index, and (C) oral total pain index in 63 patients with closure versus 72 patients with nonclosure of the donor site during buccal mucosa graft urethroplasty. BMGU = buccal mucosa graft urethroplasty; C = closure; NC = nonclosure.

swelling and numbness; impairment of mouth opening, whistling, and speech; as well as alteration of salivation, which is a considerably higher proportion compared with other studies [8,10–12]. Correspondingly, > 40% of patients had a burden in daily life due to oral morbidity. Previously, inconsistent findings from different randomized controlled studies have been reported on oral morbidity following C versus NC of the buccal mucosa harvest site. Rourke et al. [11] found that NC was favorable for mouth opening, return to a regular diet, and perioral numbness during the first 5 postoperative days. In contrast, Wong et al. [12] found that C was favorable for return to a regular diet in the early postoperative period. Conversely, Muruganandam et al. [10] did not find any differences between NC and C in mouth opening, perioral numbness, alteration of salivation, and return to regular diet. Differences in length of the buccal mucosa graft between the C and NC groups [10], bilateral buccal mucosa harvest [10,13] and harvest from the lower lip [10], and missing data on smoking status or perioperative analgesic medication [10–13] may contribute to conflicting results across studies. For example, smoking may have a detrimental impact on mucosal wound healing and facilitate scar formation [31], thus contributing to oral morbidity following surgery. We found that C versus NC had no effect on oral complications, including bleeding of the donor site. Similarly, others have previously reported no difference in complications of the buccal mucosa harvest site between C and NC [11]. At any time following BMGU, there were only Clavien grade 1 complications, corresponding to pain and swelling requiring treatment with analgesic medication and antipyretics, or bleeding requiring treatment with compression for hemostasis. Similar to oral morbidity, oral complications decreased with increasing time from surgery.

Table 2 – Oral morbidity and complications of 135 urethral stricture disease patients treated with buccal mucosa graft urethroplasty with closure versus nonclosure of the buccal mucosa harvest side [a]

	Nonclosure (*n* = 72)	Closure (*n* = 63)	*p* value [b]
Impairment of mouth opening, n (%)			0.3
Postoperative day 1 (20 patients [15%] missing)			
Not at all	6 (9.8)	1 (2)	
A bit	24 (39)	11 (20)	
Moderately	19 (31)	30 (56)	
Much	12 (20)	11 (20)	
Very much	0 (0)	1 (1.9)	
Postoperative day 5 (21 patients [16%] missing)			
Not at all	12 (20)	4 (7.5)	
A bit	19 (31)	24 (45)	
Moderately	19 (31)	19 (36)	
Much	11 (18)	6 (11)	
Very much	0 (0)	0 (0)	
Postoperative day 21 (21 patients [16%] missing)			
Not at all	21 (34)	12 (23)	
A bit	28 (45)	31 (60)	
Moderately	11 (18)	6 (12)	
Much	2 (3.2)	3 (5.8)	
Very much	0 (0)	0 (0)	
3 mo postoperatively (42 patients [31%] missing)			
Not at all	23 (49)	22 (48)	
A bit	16 (34)	12 (26)	
moderately	7 (15)	12 (26)	
Much	1 (2.1)	0 (0)	
Very much	0 (0)	0 (0)	
6 mo postoperatively (52 patients [39%] missing)			
Not at all	27 (66)	22 (52)	
A bit	10 (24)	16 (38)	
Moderately	2 (4.9)	4 (9.5)	
Much	2 (4.9)	0 (0)	
Very much	0 (0)	0 (0)	
Alteration of taste perception, n (%)			0.8
Postoperative day 1 (20 patients (15%) missing)			
Not at all	25 (40)	20 (38)	
A bit	23 (37)	23 (43)	
Moderately	9 (15)	6 (11)	
Much	4 (6.5)	4 (7.5)	
Very much	1 (1.6)	0 (0)	
Postoperative day 5 (20 patients [15%] missing)			
Not at all	31 (50)	30 (57)	
A bit	15 (24)	16 (30)	
Moderately	13 (21)	7 (13)	
Much	2 (3.2)	0 (0)	
Very much	1 (1.6)	0 (0)	
Postoperative day 21 (21 patients [16%] missing)			
Not at all	44 (71)	42 (81)	
A bit	12 (19)	10 (19)	
Moderately	4 (6.5)	0 (0)	
Much	2 (3.2)	0 (0)	
Very much	0 (0)	0 (0)	
3 mo postoperatively (41 patients [30%] missing)			
Not at all	36 (75)	35 (76)	
A bit	7 (15)	10 (22)	
Moderately	2 (4.2)	1 (2.2)	
Much	2 (4.2)	0 (0)	
Very much	1 (2.1)	0 (0)	
6 mo postoperatively (51 patients [38%] missing)			
Not at all	34 (83)	36 (84)	
A bit	3 (7.3)	7 (16)	
Moderately	1 (2.4)	0 (0)	
Much	2 (4.9)	0 (0)	
Very much	1 (2.4)	0 (0)	
Alteration of salivation, n (%)			0.8
Postoperative day 1 (19 patients [14%] missing)			
Not at all	27 (44)	26 (48)	
A bit	23 (37)	18 (33)	
Moderately	11 (18)	5 (9.3)	
Much	1 (1.6)	3 (5.6)	

Table 2 (*Continued*)

	Nonclosure (n = 72)	Closure (n = 63)	p value [b]
Very much	0 (0)	2 (3.7)	
Postoperative day 5 (20 patients [15%] missing)			
Not at all	31 (50)	31 (58)	
A bit	19 (31)	14 (26)	
Moderately	8 (13)	5 (9.4)	
Much	4 (6.5)	3 (5.7)	
Very much	0 (0)	0 (0)	
Postoperative day 21 (24 patients [18%] missing)			
Not at all	44 (73)	36 (71)	
A bit	11 (18)	13 (25)	
Moderately	5 (8.3)	1 (2.0)	
Much	0 (0)	1 (2.0)	
Very much	0 (0)	0 (0)	
3 mo postoperatively (42 patients [31%] missing)			
Not at all	33 (69)	32 (71)	
A bit	10 (21)	12 (27)	
Moderately	3 (6.3)	0 (0)	
Much	2 (4.2)	1 (2.2)	
Very much	0 (0)	0 (0)	
6 mo postoperatively (51 patients [38%] missing)			
Not at all	27 (66)	30 (70)	
A bit	10 (24)	11 (26)	
Moderately	3 (7.3)	2 (4.7)	
Much	1 (2.4)	0 (0)	
Very much	0 (0)	0 (0)	
Oral numbness, n (%)			0.9
Postoperative day 1 (19 patients [14%] missing)			
Not at all	13 (21)	9 (17)	
A bit	14 (23)	18 (33)	
Moderately	17 (27)	16 (30)	
Much	16 (26)	9 (17)	
Very much	2 (3.2)	2 (3.7)	
Postoperative day 5 (20 patients [15%] missing)			
Not at all	16 (26)	14 (26)	
A bit	21 (34)	20 (38)	
Moderately	16 (26)	10 (19)	
Much	6 (9.7)	7 (13)	
Very much	3 (4.8)	2 (3.8)	
Postoperative day 21 (22 patients [16%] missing)			
Not at all	12 (20)	16 (31)	
A bit	33 (54)	19 (37)	
Moderately	11 (18)	11 (21)	
Much	5 (8.2)	5 (9.6)	
Very much	0 (0)	1 (1.9)	
3 mo postoperatively (42 patients [31%] missing)			
Not at all	15 (32)	17 (37)	
A bit	16 (34)	14 (30)	
Moderately	8 (17)	8 (17)	
Much	5 (11)	5 (11)	
Very much	3 (6.4)	2 (4.3)	
6 mo postoperatively (51 patients [38%] missing)			
Not at all	12 (29)	18 (43)	
A bit	17 (40)	15 (36)	
Moderately	6 (14)	6 (14)	
Much	7 (17)	3 (7.1)	
Very much	0 (0)	0 (0)	
Impairment of eating, n (%)			0.4
Postoperative day 1 (23 patients [17%] missing)			
Not at all	7 (12)	8 (16)	
A bit	17 (28)	18 (35)	
Moderately	19 (31)	10 (20)	
Much	14 (23)	14 (27)	
Very much	4 (6.6)	1 (2.0)	
Postoperative day 5 (21 patients [16%] missing)			
Not at all	14 (23)	15 (29)	
A bit	18 (29)	23 (44)	
Moderately	14 (23)	8 (15)	
Much	12 (19)	5 (9.6)	
Very much	4 (6.5)	1 (1.9)	
Postoperative day 21 (21 patients [16%] missing)			

Table 2 (*Continued*)

	Nonclosure (*n* = 72)	Closure (*n* = 63)	*p* value [b]
Not at all	39 (63)	35 (67)	
A bit	19 (31)	11 (21)	
Moderately	2 (3.2)	5 (9.6)	
Much	2 (3.2)	1 (1.9)	
Very much	0 (0)	0 (0)	
3 mo postoperatively (41 patients [30%] missing)			
Not at all	45 (94)	42 (91)	
A bit	1 (2.1)	3 (6.5)	
Moderately	2 (4.2)	1 (2.2)	
Much	0 (0)	0 (0)	
Very much	0 (0)	0 (0)	
6 mo postoperatively (50 patients [37%] missing)			
Not at all	38 (90)	41 (95)	
A bit	3 (7.1)	2 (4.7)	
Moderately	1 (2.4)	0 (0)	
Much	0 (0)	0 (0)	
Very much	0 (0)	0 (0)	
Impairment of drinking, n (%)			>0.9
Postoperative day 1 (20 patients [15%] missing)			
Not at all	18 (30)	26 (48)	
A bit	21 (34)	17 (31)	
Moderately	13 (21)	3 (5.6)	
Much	7 (11)	7 (13)	
Very much	2 (3.3)	1 (1.9)	
Postoperative day 5 (24 patients [18%] missing)			
Not at all	22 (37)	30 (59)	
A bit	21 (35)	10 (20)	
Moderately	10 (17)	7 (14)	
Much	4 (6.7)	4 (7.8)	
Very much	3 (5.0)	0 (0)	
Postoperative day 21 (24 patients [18%] missing)			
Not at all	41 (66)	39 (80)	
A bit	16 (26)	6 (12)	
Moderately	4 (6.5)	3 (6.1)	
Much	1 (1.6)	1 (2.0)	
Very much	0 (0)	0 (0)	
3 mo postoperatively (42 patients [31%] missing)			
Not at all	42 (91)	44 (94)	
A bit	3 (6.5)	1 (2.1)	
Moderately	1 (2.2)	2 (4.3)	
Much	0 (0)	0 (0)	
Very much	0 (0)	0 (0)	
6 mo postoperatively (51 patients [38%] missing)			
Not at all	38 (90)	40 (95)	
A bit	2 (4.8)	1 (2.4)	
Moderately	2 (4.8)	1 (2.4)	
Much	0 (0)	0 (0)	
Very much	0 (0)	0 (0)	
Oral bleeding, n (%)			0.8
Postoperative day 1 (19 patients [14%] missing)			
Not at all	46 (74)	43 (80)	
A bit	13 (21)	9 (17)	
Moderately	2 (3.2)	2 (3.7)	
Much	0 (0)	0 (0)	
Very much	1 (1.6)	0 (0)	
Postoperative day 5 (21 patients [16%] missing)			
Not at all	47 (77)	45 (85)	
A bit	9 (15)	5 (9.4)	
Moderately	3 (4.9)	3 (5.7)	
Much	0 (0)	0 (0)	
Very much	2 (3.3)	0 (0)	
Postoperative day 21 (23 patients [17%] missing)			
Not at all	50 (81)	45 (90)	
A bit	10 (16)	2 (4.0)	
Moderately	0 (0)	0 (0)	
Much	0 (0)	1 (2.0)	
Very much	2 (3.2)	2 (4.0)	
3 mo postoperatively (41 patients [30%] missing)			
Not at all	45 (96)	43 (91)	
A bit	2 (4.3)	3 (6.4)	

Table 2 (*Continued*)

	Nonclosure (n = 72)	Closure (n = 63)	p value [b]
Moderately	0 (0)	0 (0)	
Much	0 (0)	0 (0)	
Very much	0 (0)	1 (2.1)	
6 mo postoperatively (51 patients [38%] missing)			
Not at all	42 (100)	40 (95)	
A bit	0 (0)	1 (2.4)	
Moderately	0 (0)	1 (2.4)	
Much	0 (0)	0 (0)	
Very much	0 (0)	0 (0)	
Impairment of smiling, n (%)			0.5
Postoperative day 1 (19 patients [14%] missing)			
Not at all	13 (21)	7 (13)	
A bit	24 (39)	27 (50)	
Moderately	15 (24)	14 (26)	
Much	9 (15)	3 (5.6)	
Very much	1 (1.6)	3 (5.6)	
Postoperative day 5 (20 patients [15%] missing)			
Not at all	16 (26)	20 (38)	
A bit	31 (50)	19 (36)	
Moderately	9 (15)	12 (23)	
Much	5 (8.1)	2 (3.8)	
Very much	1 (1.6)	0 (0)	
Postoperative day 21 (23 patients [17%] missing)			
Not at all	32 (52)	29 (58)	
A bit	25 (40)	15 (30)	
Moderately	5 (8.1)	4 (8.0)	
Much	0 (0)	1 (2.0)	
Very much	0 (0)	1 (2.0)	
3 mo postoperatively (39 patients [29%] missing)			
Not at all	30 (63)	34 (71)	
A bit	14 (30)	12 (25)	
Moderately	4 (8.3)	2 (4.2)	
Much	0 (0)	0 (0)	
Very much	0 (0)	0 (0)	
6 mo postoperatively (51 patients [38%] missing)			
Not at all	30 (71)	37 (88)	
A bit	9 (21)	3 (7.1)	
Moderately	3 (7.1)	2 (4.8)	
Much	0 (0)	0 (0)	
Very much	0 (0)	0 (0)	
Impairment of whistling, n (%)			0.4
Postoperative day 1 (20 patients [15%] missing)			
Not at all	14 (23)	7 (13)	
A bit	13 (21)	21 (40)	
Moderately	14 (23)	8 (15)	
Much	13 (21)	12 (23)	
Very much	8 (13)	5 (9.4)	
Postoperative day 5 (21 patients [16%] missing)			
Not at all	20 (33)	16 (30)	
A bit	13 (21)	19 (36)	
Moderately	13 (21)	9 (17)	
Much	9 (15)	7 (13)	
Very much	6 (9.8)	2 (3.8)	
Postoperative day 21 (22 patients [16%] missing)			
Not at all	25 (40)	25 (49)	
A bit	23 (38)	14 (27)	
Moderately	4 (6.5)	4 (7.8)	
Much	7 (11)	6 (12)	
Very much	3 (4.8)	2 (3.9)	
3 mo postoperatively (40 patients [30%] missing)			
Not at all	17 (36)	31 (65)	
A bit	17 (36)	11 (23)	
Moderately	9 (19)	3 (6.3)	
Much	1 (2.1)	3 (6.3)	
Very much	3 (6.4)	0 (0)	
6 mo postoperatively (51 patients [38%] missing)			
Not at all	22 (52)	26 (62)	
A bit	14 (33)	12 (29)	
Moderately	4 (9.5)	1 (2.4)	
Much	2 (4.8)	3 (7.1)	

Table 2 (*Continued*)

	Nonclosure (*n* = 72)	Closure (*n* = 63)	*p* value [b]
Very much	0 (0)	0 (0)	
Oral swelling, n (%)			>0.9
Postoperative day 1 (20 patients [15%] missing)			
Not at all	0 (0)	0 (0)	
A bit	13 (21)	6 (11)	
Moderately	21 (34)	20 (38)	
Much	20 (32)	21 (40)	
Very much	8 (13)	6 (11)	
Postoperative day 5 (19 patients [14%] missing)			
Not at all	3 (4.8)	1 (1.9)	
A bit	28 (45)	21 (39)	
Moderately	15 (24)	19 (35)	
Much	11 (18)	11 (20)	
Very much	5 (8.1)	2 (3.7)	
Postoperative day 21 (23 patients [17%] missing)			
Not at all	6 (9.7)	11 (22)	
A bit	42 (68)	24 (48)	
Moderately	11 (18)	12 (24)	
Much	3 (4.8)	2 (4.0)	
Very much	0 (0)	1 (2.0)	
3 mo postoperatively (40 patients [30%] missing)			
Not at all	18 (38)	24 (51)	
A bit	15 (31)	13 (28)	
Moderately	11 (23)	6 (13)	
Much	3 (6.3)	4 (8.5)	
Very much	1 (2.1)	0 (0)	
6 mo postoperatively (51 patients [38%] missing)			
Not at all	20 (48)	21 (50)	
A bit	14 (33)	14 (33)	
Moderately	5 (12)	6 (14)	
Much	2 (4.8)	1 (2.4)	
Very much	1 (2.4)	0 (0)	
Slurred speech, n (%)			0.4
Postoperative day 1 (20 patients [15%] missing)			
Not at all	16 (26)	12 (23)	
A bit	28 (45)	30 (57)	
Moderately	14 (23)	5 (9.4)	
Much	3 (4.8)	6 (11)	
Very much	1 (1.6)	0 (0)	
Postoperative day 5 (19 patients [14%] missing)			
Not at all	25 (40)	20 (37)	
A bit	23 (37)	28 (52)	
Moderately	10 (16)	4 (7.4)	
Much	4 (6.5)	2 (3.7)	
Very much	0 (0)	0 (0)	
Postoperative day 21 (22 patients [16%] missing)			
Not at all	48 (77)	34 (67)	
A bit	11 (18)	14 (27)	
Moderately	3 (4.8)	2 (3.9)	
Much	0 (0)	1 (2.0)	
Very much	0 (0)	0 (0)	
3 mo postoperatively (41 patients [30%] missing)			
Not at all	32 (68)	33 (70)	
A bit	13 (28)	13 (28)	
Moderately	2 (4.3)	1 (2.1)	
Much	0 (0)	0 (0)	
Very much	0 (0)	0 (0)	
6 mo postoperatively (51 patients [38%] missing)			
Not at all	30 (71)	32 (76)	
A bit	11 (26)	10 (24)	
Moderately	1 (2.4)	0 (0)	
Much	0 (0)	0 (0)	
Very much	0 (0)	0 (0)	
Burden in daily life due to oral morbidity, n (%)			0.3
Postoperative day 1 (19 patients [14%] missing)			
Not at all	6 (9.7)	4 (7.4)	
A bit	15 (24)	15 (28)	
Moderately	18 (29)	14 (26)	
Much	18 (29)	15 (28)	
Very much	5 (8.1)	6 (11)	

Table 2 (*Continued*)

	Nonclosure (n = 72)	Closure (n = 63)	p value [b]
Postoperative day 5 (19 patients [14%] missing)			
Not at all	10 (16)	5 (9.3)	
A bit	22 (35)	23 (43)	
Moderately	15 (24)	12 (22)	
Much	13 (21)	12 (22)	
Very much	2 (3.2)	2 (3.7)	
Postoperative day 21 (22 patients [16%] missing)			
Not at all	18 (30)	16 (31)	
A bit	34 (56)	22 (42)	
Moderately	6 (9.8)	11 (21)	
Much	2 (3.3)	2 (3.8)	
Very much	1 (1.6)	1 (1.9)	
3 mo postoperatively (42 patients [31%] missing)			
Not at all	21 (44)	18 (40)	
A bit	17 (35)	19 (42)	
Moderately	9 (19)	5 (11)	
Much	1 (2.1)	3 (6.7)	
Very much	0 (0)	0 (0)	
6 mo postoperatively (52 patients [39%] missing)			
Not at all	23 (58)	25 (58)	
A bit	11 (28)	13 (30)	
Moderately	4 (10)	4 (9.3)	
Much	2 (5.0)	1 (2.3)	
Very much	0 (0)	0 (0)	
Oral complications, n (%)			>0.9
21 d following BMGU (2 patients [1.5%] missing)			
Clavien grade 1	25 (35)	23 (37)	
3 mo following BMGU (3 patients [2.2%] missing)			
Clavien grade 1	2 (2.9)	4 (6.5)	
6 mo following BMGU (6 patients [4.4%] missing)			
Clavien grade 1	0 (0)	2 (3.2)	

BMGU = buccal mucosa graft urethroplasty.
[a] Totals in percentages may not add up to exactly 100% due to rounding.
[b] Interaction of C versus NC and time from buccal mucosa graft urethroplasty, results from ordinal mixed model regression analysis.

Although representing currently the largest randomized controlled trial evaluating in detail intensity and quality of pain, morbidity, and complications following BMGU with C versus NC of the donor site, it is not devoid of limitations. The dropout rate of up to 18% and up to 39% of patients on postoperative day 21 and at 6 mo, respectively, might appear relatively high. Owing to in-detail analysis, the standardized questionnaire included a quantity of items, which may affect patients' motivation to answer the complete questionnaire. Buccal mucosa grafts were consistently ovoid shaped with 15 mm width, presumably impeding an indiscriminate generalizability of our findings. Other centers dedicated to reconstructive urology frequently use a larger width or different shape of buccal mucosa grafts, and may therefore report divergent findings. Data on denture use were not assessed, although it might have an effect on postoperative pain and morbidity, particularly in older patients. Important confounders (eg, stricture length and stricture location), which might impact pain of the perineogenital region, were not included in the generalized linear mixed model. This might have biased the results, particularly regarding the effect of the length of the buccal mucosa graft on pain intensity of the perineogenital region. Oral morbidity was evaluated with nonvalidated questions, which may render objective measurement difficult. However, no validated questionnaire is currently available on oral morbidity following BMGU. According to our results, oral morbidity affects a relevant number of patients up to 6 mo postoperatively. Hence, future development of a validated questionnaire on oral morbidity after BMGU seems worthwhile.

5. Conclusions

In patients with urethral stricture disease treated with BMGU, NC is noninferior to C of the donor site in intensity and quality of oral pain and offers a treatment alternative. Time from BMGU and length of the buccal mucosa graft have effects on oral pain, morbidity, and complications.

Author contributions: Armin Soave 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.

Study concept and design: Soave, Dahlem, Pinnschmidt, Ahyai, Fisch.
Acquisition of data: Soave, Dahlem, Langetepe, Engel, Loechelt, Ahyai.
Analysis and interpretation of data: Soave, Pinnschmidt, Ahyai.
Drafting of the manuscript: Soave.
Critical revision of the manuscript for important intellectual content: Dahlem, Pinnschmidt, Rink, Langetepe, Engel, Kluth, Loechelt, Reiss, Ahyai, Fisch.
Statistical analysis: Soave, Pinnschmidt.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2017.11.014.

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