



Review

Lingual mucosal graft urethroplasty 12 years later: Systematic review and meta-analysis



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Abstract *Objective:* To evaluate the functional results and complications of the lingual mucosal graft (LMG) urethroplasty and to sum up the current state of the art of this surgical technique.

Methods: A systematic search of PubMed and Scopus electronic databases was performed, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies involving male patients treated with LMG urethroplasty for urethral stricture were included. Complete protocol is available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017080121. A meta-analysis comparing functional and long-term oral complication outcomes of LMG and buccal mucosal graft (BMG) was performed, calculating the odds ratio (OR) and 95% confidence interval (CI).

Results: Twenty original articles were included in the qualitative analysis. Strictures of 1.5–16.5 cm have been treated with LMG urethroplasty, due to the improvement of harvesting technique and very low rate of long-term oral complications. Very good functional results have been reported by different authors for LMG urethroplasty, with lower rate of oral complications than BMG. The meta-analysis included six comparative studies involving 187 and 178 patients treated with LMG and BMG urethroplasty, respectively. An OR of 1.65 (95% CI [0.95–2.87], $I^2 = 0\%$) and 0.18 (95% CI [0.03–1.26], $I^2 = 68\%$) were found for LMG vs. BMG urethroplasty, in terms of success and oral complication rate, respectively.

Conclusion: LMG urethroplasty can be reasonably considered a first choice technique for urethral stricture with very good results. Oral complications are temporary and minimally disabling, basically less than those for BMG, and depend mainly on the graft extent.

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1. Introduction

The management of long anterior urethral strictures is based on augmentation urethroplasty, which may either be a one- or two-stage procedure. Over the last decades, efforts were made to find the appropriate tissue for repairing urethral stenosis, in order to ensure good aesthetic and functional results and no complications at the harvesting site. Thus several tissues, including genital and extragenital skin [1], oral mucosa, bladder mucosa [2], colonic mucosa [3] and postauricular skin [4], have been proposed over the years.

Nowadays, the term oral mucosal graft is considered as including three graft donor sites: The inner lower lip, the inner cheek and the tongue [5].

Currently, the cheek remains the primary donor site for oral mucosa (buccal mucosal graft, BMG) for substitution urethroplasty [6]. However, its harvesting has been widely shown to be associated with several donor site morbidities, including perioral numbness, difficulty in opening the mouth, but also scarring and dry mouth [7].

The lingual mucosal graft (LMG) urethroplasty was first proposed in 2006 [8]. Since then the technique of LMG harvesting and implanting has improved according to the cases published in literature.

This systematic review and meta-analysis aims to evaluate the functional results and complications of the LMG urethroplasty, also in comparison with BMG (considered the standard of care), and to sum up the current state of the art of the technical aspects of the surgical technique after 12 years of experience worldwide.

2. Materials and methods

A systematic search of PubMed and Scopus electronic databases was performed by two reviewers (Abrate A and Simonato A) in January 2018, according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [9]. All field lists were searched, from January 2006 to December 2017, for the following search terms: "Lingual urethroplasty", "lingual mucosal graft urethroplasty" and "tongue urethroplasty".

Only original articles in the English language were considered eligible for this review. We reviewed titles and abstracts of each record found, focusing on the functional results, complications and surgical technique of the LMG urethroplasty.

As recommended by the PRISMA guidelines, we used the population (P), intervention (I), comparator (C), and outcome (O) approach (PICO) to define study eligibility [9]. Studies were considered relevant to this systematic review if they included male patients diagnosed with urethral stricture (P) and treated with LMG urethroplasty (I), also in comparison with other types of substitution (e.g. BMG) urethroplasty (C), to determine functional and complication outcomes (O) of this approach. The complete protocol has been registered in PROSPERO 2017 CRD42017080121, available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017080121. Studies clearly stating inclusion criteria, results, complications and surgical technique of the urethroplasty with LMG were included in the qualitative analysis. Studies with an

unclear protocol, and not investigating LMG urethroplasty were excluded. Other exclusion criteria were: More than one type of graft analyzed all together as oral mucosal graft urethroplasty in the same population; LMG urethroplasty performed to repair hypospadias; experimental animal settings; women. A narrative synthesis of included studies was performed. Descriptive data of patients, stricture length, graft type and length, follow-up period and methods, success rate, rate of urethral and oral complications were summarized.

The quality of each study was evaluated by two reviewers (Abrate A and Gregori A), based on the Oxford 2011 Levels of Evidence (LE) [10].

A meta-analysis comparing LMG to BMG urethroplasty in terms of functional and long-term oral complication outcomes was performed. Random effect model was applied considering the variability between the studies in terms of sample size, inclusion criteria and surgical techniques. The odds ratio (OR) and the corresponding 95% confidence interval (CI) were calculated through Mantel-Haenszel method. Heterogeneity was assessed through DerSimonian-Laird estimator for τ^2 . A p -Value <0.05 was accepted as statistically significant. A funnel plot was produced to estimate the likelihood of publication bias using the pooled OR and standard error (SE). All statistical analyses were performed using Rcmdr v2.3-0 for R software (R Foundation, Vienna, Austria).

3. Results

Out of 244 items found through online database search, after removal of duplicates, 20 original articles, published between January 2006 and December 2017, were included in the current review (Fig. 1). The majority (75%) of the included studies were retrospective (LE 4): Out of the five (25%) prospective studies, only two randomized controlled trials (LE 2) have been published so far. Overall, the data of 857 patients treated with LMG urethroplasty for bulbar,

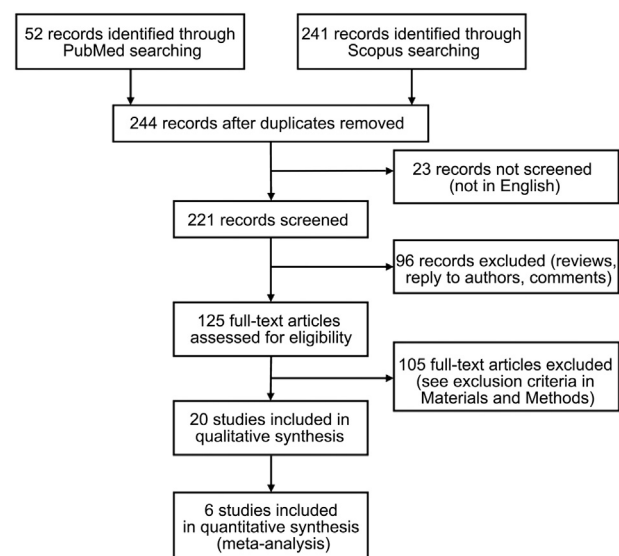


Figure 1 Flow of information through the different phases of the systematic review.

penile or panurethral (also with meatus involvement) strictures were reported (Table 1).

3.1. Preoperative considerations

Since its introduction, it has been widely accepted that the preoperative evaluation of the patient candidate for LMG urethroplasty should include clinical history, physical examination, urine culture, residual urine measurement, uroflowmetry, retrograde and voiding cystourethrography, and urethroscopy [11]. Thus it is clear that the surgeon recommending an LMG urethroplasty does not need any further investigation compared to other kinds of surgery for urethral stricture.

On the contrary, the indications to perform an LMG urethroplasty have evolved during these 12 years. In particular, while the first experiences involved relatively short strictures, literature now includes case series of long urethral strictures treated with good outcomes. Simonato et al. [8] treated the first eight patients with a 1.5–4.5 cm long urethral stricture. They made this choice considering that the lateral aspect of the tongue offers short mucosal tracts that are up to 7–8 cm long and up to 1.5 cm wide. However, as the graft harvesting technique improved, longer strictures began to be

considered for LMG as well. Singh et al. [12] reported in 2008 their experience in a population of 55 men with an anterior urethral stricture of 3.5–12.9 cm. The same group [13] showed the results of the LMG urethroplasty in the treatment of patients with strictures up to 16.5 cm, concluding that the LMG can be a suitable substitute for BMG for the reconstruction of anterior urethral strictures.

3.2. Functional results

There is no particular correspondence of postoperative evaluation and follow-up of the patients. However the functional results are generally evaluated through the following tests, combined in different protocols: Pericatheter urethrography, uroflowmetry, flexible cystourethroscopy, retrograde urethrography and micturating cystourethrography (Table 2).

Simonato et al. [11] proposed postoperative follow-up of all patients with pericatheter urethrography and voiding cystography after 2 weeks and uroflowmetry, cystourethrography, and flexible urethroscopy after 3 and 12 months. Similarly, other authors suggested performing uroflowmetry, retrograde urethrography, and micturating cystourethrography after 3 and 6 months [13] and 12, 24 and 36 months [14]. Kumar et al. [15] reported a strict

Table 1 Quality assessment of the studies included in the systematic review, ordered by LE.

Author [Ref.]	Type of study	Patients, n (LMG)	Type of graft	Follow-up, month (range)	LE
Sharma et al., 2013 [17]	Prospective randomized controlled study	30 (15)	LMG vs. BMG	15.2 (NA)	2
Chauhan et al., 2016 [20]	Prospective randomized controlled study	102 (50)	LMG vs. BMG	25 (12–52)	2
Lumen et al., 2016 [18]	Prospective non-randomised controlled cohort study	58 (29)	LMG vs. BMG	30 (NA)	3
Pal et al., 2016 [21]	Prospective non-randomised controlled cohort study	60 (30)	LMG vs. BMG	14.1 (7–19)	3
Sharma et al., 2016 [26]	Prospective non-randomised study	12 (12)	LMG	11.6 (6–14)	3
Simonato et al., 2006 [8]	Retrospective case series	8 (8)	LMG	18 (NA)	4
Kumar et al., 2007 [22]	Retrospective case series	30 (30)	LMG	3.8 (NA)	4
Simonato et al., 2008 [11]	Retrospective case series	29 (27)	LMG or LMG + BMG	17.7 (6–71)	4
Singh et al., 2008 [12]	Retrospective comparative study	55 (55)	LMG	13–22 (NA)	4
Barbagli et al., 2008 [16]	Retrospective case series	10 (10)	LMG	5 (3–12)	4
Kumar et al., 2008 [29]	Retrospective case series	25 (25)	LMG	4.2 (2.5–7.4)	4
Das et al., 2009 [13]	Retrospective case series	30 (30)	LMG	9 (4–12)	4
Xu et al., 2010 [25]	Retrospective case series	92 (76)	LMG or LMG + foreskin flap or LMG + BMG	17.2 (3–33)	4
Kumar et al., 2010 [15]	Retrospective comparative study	79 (41)	LMG vs. BMG	17.5 (12–26)	4
Xu et al., 2011 [24]	Retrospective case series	110 (110)	LMG	22 (6–41)	4
Xu et al., 2014 [14]	Retrospective case series	36 (22)	LMG vs. BMG vs. LMG + BMG	38.7 (12–110)	4
Abdelhameed et al., 2015 [27]	Retrospective case series	23 (23)	LMG	66 (60–72)	4
Zhang et al., 2016 [28]	Retrospective case series	101 (101)	LMG	23 (13–37)	4
Xu et al., 2017 [23]	Retrospective case series	81 (69)	LMG or LMG + BMG	41 (15–86)	4
Fu et al., 2017 [19]	Retrospective comparative study	293 (94)	LMG vs. skin flap	12 (NA)	4

LE, level of evidence; BMG, buccal mucosal graft; LMG, lingual mucosal graft; NA, not available.

Table 2 Functional results and urethral complications of LMG urethroplasty.

Author [Ref.]	Stricture length, mean (range), cm	Follow-up method	Definition of failure	Success rate, %	Urethral complications, n (%)
Simonato et al., 2006 [8]	3.1 (1.5–4.5)	Uroflowmetry 3 and 12 mo Urethrography 2 weeks, 3 and 12 mo Urethroscopy 3 and 12 mo	$Q_{\max} < 15$ mL/s Need for any instrumentation	87.5	Stricture recurrence 6 (20.7) Contrast extravasation, 2 (6.9)
Simonato et al., 2008 [11]	3.6 (1.5–9.8)	Uroflowmetry 3 and 12 mo Urethrography 2 weeks, 3 and 12 mo Urethroscopy 3 and 12 mo	Inability to void Post void residual Need for any instrumentation	81.5	NA
Singh et al., 2008 [12]	10.2 (3.7–16.5) 9.8 (3.5–12.9)	Uroflowmetry 3, 6 and 12 mo Urethrography 3, 6 and 12 mo	Need for any instrumentation	76.6–80	Meatal narrowing, 8 (14.5) Stricture recurrence, 7 (12.7) Contrast extravasation, 3 (5.5) Wound infection, 3 (5.5) Penis curvature, 1 (1.8) Contrast extravasation, 1 (10) Stricture recurrence, 1 (10)
Barbagli et al., 2008 [16]	NA	Uroflowmetry 4, 8 and 12 mo Urethrography if needed Urethroscopy if needed Urethral ultrasound if needed	Need for any instrumentation	90	Contrast extravasation, 5 (16.7) Wound infection, 2 (6.7) Haematoma, 2 (6.7) Stricture recurrence, 1 (3.3) Meatal stenosis, 4 (13.3) Penis curvature 1 (3.3) Contrast extravasation, 4 (4.3) Stricture recurrence, 4 (4.3)
Das et al., 2009 [13]	10.2 (3.7–16.5)	Uroflowmetry 3 and 6 mo Urethrography 3 weeks, 3 and 6 mo	$Q_{\max} < 15$ mL/s Need for any instrumentation	83.3	Contrast extravasation, 5 (16.7) Wound infection, 2 (6.7) Haematoma, 2 (6.7) Stricture recurrence, 1 (3.3) Meatal stenosis, 4 (13.3) Penis curvature 1 (3.3) Contrast extravasation, 4 (4.3) Stricture recurrence, 4 (4.3)
Xu et al., 2010 [25]	6.5 (2.5–18.0)	Uroflowmetry 3, 6, 12, 18, 24 and 36 mo Urethrography if needed Urethroscopy if needed	Need for any instrumentation	91.3	Contrast extravasation, 6 (14.6) Stricture recurrence, 5 (12.2) Meatal stenosis, 5 (12.2) Wound infection, 3 (7.3)
Kumar et al., 2010 [15]	8.8 (4.0–16.5)	Uroflowmetry 3, 6 and 12 mo Urethrography 3, 6 and 12 mo	$Q_{\max} < 15$ mL/s Need for any instrumentation	87.8	NA
Sharma et al., 2013 [17]	7.7 (3.2–9.6)	Uroflowmetry 3 weeks, 3, 6, 12 mo Urethrography 3 mo Urethroscopy 6 mo	$Q_{\max} < 10$ mL/s Residual stricture Need for any instrumentation	93.3	Meatal stenosis, 2/22 (9.1) LMG Fistula, 1/9 (11.1) LMG + BMG
Xu et al., 2014 [14]	12.5 (6.0–18.0)	Urethrography 4 weeks Uroflowmetry 3, 6, 12, 24, and 36 mo	$Q_{\max} < 12$ mL/s Obstructive symptoms Need for any instrumentation	90.9	Contrast extravasation, 1 (4.3) Wound infection, 4 (17.4) Postvoid dribbling, 3 (13.0)
Abdelhameed et al., 2015 [27]	4.6 (3.0–11.5)	Uroflowmetry 3, 6, 12, 24, 36, 48 and 60 mo Urethrography 3 and 6 mo	Obstructive symptoms Residual stricture Need for any instrumentation	86.9	(continued on next page)

Table 2 (continued)

Author [Ref.]	Stricture length, mean (range), cm	Follow-up method	Definition of failure	Success rate, %	Urethral complications, <i>n</i> (%)
Pal et al., 2016 [21]	9.6 (3.5–15.5)	Uroflowmetry 3 and 6 mo Urethrography if needed	$Q_{\max} < 15$ mL/s Significant postvoid residual volume Need for major instrumentation	83.3	Contrast extravasation, 5/30 (16.7) Stricture recurrence, 2/30 (6.7) Meatal stenosis, 4/30 (13.3) Haematoma, 1/30 (3.3) Stricture recurrence, 1 (8.3)
Sharma et al., 2016 [26]	4.7 (3.0–8.5)	Urine analysis 1, 3, 6 and 12 mo Uroflowmetry 1, 3, 6 and 12 mo Postvoid residual assessment 1, 3, 6 and 12 mo Urethrocystoscopy 3 mo	Need for any instrumentation	91.6	Stricture recurrence, 1 (8.3)
Lumen et al., 2016 [18]	5.0 (1.0–16.0)	Uroflowmetry Urethrography if needed Urethrosocopy if needed	Stricture recurrence or fistula Need for any instrumentation	89.7	Stricture recurrence, 2/29 (6.9) Fistula, 1/29 (3.4)
Chauhan et al., 2016 [20]	6.7 (3.8–12.2)	Uroflowmetry 1, 3 and 6 mo Urethrography if needed Urethrosocopy if needed	Obstructive symptoms Need for any instrumentation	80	NA
Zhang et al., 2016 [28]	7.0 (2.0–16.0)	Uroflowmetry 4 weeks, 3, 6, 12, 24 and 36 mo Urethrography 4 weeks, 3, 6, 12, 24 and 36 mo	Stricture recurrence Fistula	81.2	Stricture recurrence, 17 (16.8) Fistula, 2 (2.0)
Xu et al., 2017 [23]	12.1 (8.0–20.0)	Urethrography 4 weeks Uroflowmetry 3, 6, 12, 18 and 24 mo Urethrography if needed Urethrosocopy if needed	$Q_{\max} < 12$ mL/s Obstructive symptoms Need for any instrumentation	82.7	Stricture recurrence, 10 (12.3) Fistula, 4 (4.9)
Fu et al., 2017 [19]	4.9 (1.5–12.0)	Uroflowmetry 3 weeks, 3 and 12 mo	$Q_{\max} < 12$ mL/s Fistula or diverticulum Obstructive symptoms Need for any instrumentation	85.1	NA

BMG, buccal mucosal graft; LMG, lingual mucosal graft; $Q_{\max}$, peak urinary flow rate; mo, months; NA, not available.

follow-up at 3, 6 and 12 months with uroflowmetry, retrograde urethrography, and micturating cystourethrography, and then only uroflowmetry and symptoms questionnaire every 6 months. On the other hand, some authors proposed a simpler follow-up protocol. Barbagli et al. [16] suggested repeating uroflowmetry associated with urine culture every 4 months in the first year and annually thereafter. Thus, urethrography, urethral ultrasound, and urethrosocopy were recommended only when obstructive symptoms were present and peak urinary flow rate ($Q_{\max}$) was < 14 mL/s.

Moreover, right from its introduction, LMG urethroplasty was shown to be feasible and easy to perform. Good short- and long-term results were described by several authors. For this purpose, the most commonly accepted criteria for successful repair were $Q_{\max} > 15$ mL/s with spontaneous voiding and insignificant post-void residual urine, and no need for further intervention (Table 2).

Again Simonato et al. [8] in 2006 first reported a good functional outcome ($Q_{\max} > 15$ mL/s) in seven (87.5%) patients after a median follow-up of 18 months, in comparison to a preoperative mean $Q_{\max}$ of 6 mL/s. After this first pilot study, the same authors published in 2008 their experience after a follow-up of up to 71 months (median: 17.7 months) in a wider population [11]. The one-stage bulbar, penile and bulbopenile urethroplasties without meatal involvement had an 81.8%, 100% and 60% success rate, respectively.

Singh et al. [12] showed a similar success rate of 83.4% vs. 90.0% at 6 months and of 76.6% vs. 80.0% at 12 months, comparing Barbagli's technique with a ventral sagittal approach.

Kumar et al. [15] in 2010 first directly compared in the same work 38 patients treated with BMG to 41 men treated with LMG in a follow-up period of at least 12 months and they found that the two techniques were comparable in terms of functional results with similar postoperative $Q_{\max}$.

Similar results were obtained in other populations over the short term [17] and long term [14]. In particular Lumen et al. [18] estimated a mean 2-year failure-free survival rate of 85.4% and 89.3% in BMG and LMG urethroplasty, respectively ($p = 0.434$), in a prospective study including also complicated urethral strictures requiring a two-stage intervention.

More recently, LMG was also compared to pedicled skin flaps urethroplasty showing to have similar overall success rate (85.1% vs. 83.4%, $p = 0.713$) but to be a better choice for proximal penile and bulbar urethral strictures (83.3% vs. 69.0%, $p = 0.345$; 92.3% vs. 66.7%, $p = 0.036$, respectively) [19].

Interestingly no significant association between success rate and etiology was reported, but the success rate was shown to be higher when a wider graft was used ($p = 0.001$) [20].

3.3. Urethral complications

LMG graft did not show significant contractures or sacculations at cystourethrography and it was reported as almost indistinguishable from native urethra at urethroscopy [8]. Moreover LMG was found to be indistinguishable from BMG, revealing equivalent imbibition, inosculation, and revascularization properties [11].

However the most commonly expected complications should be similar to those described for the other urethroplasty techniques: Fistula, chordee, blood loss, infection, stricture recurrence and meatal stenosis. Some of these urethral complications have been reported by several studies even with limited incidence (Table 2).

In particular the wider variety of complications was described in a population of 30 patients by Das et al. [13] reporting a rate of 16.7% of mild extravasation of contrast on pericatheter urethrography requiring a prolonged catheterization, 6.7% of wound infection after a postoperative hematoma, one case of stricture recurrence managed with an optical internal urethrotomy, 13.3% of meatal stenosis and one case of penile curvature.

A comparison between an LMG dorsal onlay through a ventral sagittal approach and the conventional Barbagli technique in 55 patients showed that the first had certain advantages in terms of a lesser chance of anastomotic stricture at 12 months and postoperative chordee, operative time and blood loss; on the contrary, the rates of infection and meatal narrowing needing a meatotomy at 12 months were the same in the two groups [12].

Again according to the technique, Barbagli et al. [16] showed that one of two patients treated with ventral LMG urethroplasty for bulbar stricture had a fistula at the first postoperative urethrography, requiring prolonged catheterization time.

Recently two prospective studies in quite ample populations showed similar results in terms of stricture recurrence (6.7%–6.9%) [18,21], substantially confirming data previously reported. The incidence of meatal stenosis has been also confirmed (13.3%) [21].

Importantly, no other major perioperative complications occurred and were described in the articles included in this analysis.

3.4. Donor site complications

The incidence of donor site complications described for other mucosal grafts was surely one of the principal reasons that led to the tongue being considered as an alternative donor site for oral mucosa in urethroplasty. The LMG has readily emerged for its low incidence of complications of the donor site: A complete review of the literature is summarized in Table 3.

Immediate complications have been widely defined as mild although quite frequent in different settings. Over the years the oral complications have been investigated more precisely through specific questionnaire and scores. Commonly, almost 100% patients who have undergone an LMG reported oral discomfort or pain and difficulty in moving the tongue, affecting speech as well, in the days immediately after the operation.

Postoperative pain was clearly investigated by Kumar et al. [22] submitting to their patients a standard long-form McGill pain questionnaire. In their population of 30 patients, the authors reported pain at the donor site in 90% of patients on the 1st postoperative day: Mild pain in seven (23%) patients, discomfort in 17 (56.6%) patients and distressing and horrible pain in two (6.6%) patients, respectively, with no significant difference in terms of graft length. By the 3rd postoperative day 20 (66.6%) patients were pain free, eight (26%) patients had mild pain and only two (6.6%) had discomforting pain. By the 6th postoperative day no patient reported pain at the donor site.

Longer term results regarding pain were recently achieved by Lumen et al. [18]. They assessed oral pain by numerical rating scale (NRS) at day 3, week 2 and month 6. They confirmed previous results by finding a progressive reduction of pain from a median NRS of 6 to 0 after 6 months.

The other most frequent immediate complications described were bleeding (16%), difficulty in chewing (48%), swelling of the tongue (26%), difficulty in articulation (44%), difficulty in opening the mouth (38%), dry mouth (14%) and sensitivity disorders (46%), interestingly less common compared to BMG (all but bleeding) [20].

While LMG showed a wide variety of immediate/short-term complications, it was often shown to have no or infrequent long-term complications. Again, Lumen et al. [18] reported a wider and more precise series of long-term complications in a recent prospective study. Interestingly they showed a comparison between LMG and BMG with a clear (although not significant) advantage for LMG in terms of lower rates of each oral complication considered. However donor site complications have been shown to be primarily limited to the first postoperative year [23].

As longer LMG reach to the base of the tongue and could therefore cause increased edema and consequent pain and difficulty in speech compared to BMG, some authors considered it a second choice for strictures >7 cm [17]. However, Xu et al. [24] found that bilateral or longer LMGs were significantly associated with a higher incidence of complications ($p < 0.001$), but most of these oral complications subsided gradually within 1 year. In particular delayed feeding and difficulty in moving the tongue were reported only by patients with bilateral graft, while

Table 3 Donor site complications after lingual mucosa harvesting: Post-operative and 1 year after surgery (or at the end of the follow-up period).

Author [Ref.]	Graft length, mean (range), cm	Immediate complications, <i>n</i> (%)	Long-term complications, <i>n</i> (%)
Simonato et al., 2006 [8]	3.3 (3.0–7.0)	Oral discomfort, all (100)	None
Kumar et al., 2007 [22]	8.5 (4.2–16.2)	Pain, 28 (93.3) Slurring speech, 6 (20)	None
Kumar et al., 2008 [29]	6.5 (3.5–16.4)	Pain, 23 (92) Slurring speech, 6 (24)	None
Simonato et al., 2008 [11]	NA	Oral discomfort, all (100) Slurring speech, all (100) Difficulty in mouth opening, 2 (100) LMG + BMG Reduced salivatory flow, 1 (50) LMG + BMG Neurosensory deficit, 2 (100) LMG + BMG	None
Das et al., 2009 [13]	10.7 (3.9–17.0)	Pain, all (100) Slurring speech, all (100)	None
Xu et al., 2010 [25]	NA (4.0–14.0)	Oral discomfort, all (100) Difficulty in moving the tongue, all (100)	Numbness, 10 (13.2)
Kumar et al., 2010 [15]	9.2 (4.5–17.0)	Pain, 38 (92.7) Slurring speech, 9 (21.9) Numbness, 2 (4.9) Salivatory disturbance, 1 (2.4) Delayed feeding, 1 (2.4)	None
Xu et al., 2011 [24]	5.2 (3.0–7.0) 11.5 (7.5–14.5)	Pain, 105 (95.4) Delayed feeding, 8 (17.6) bilateral graft Difficulty in moving the tongue, 14 (48.3) bilateral graft Numbness, 35 (31.8) Parageusia, 12 (10.9) Slurring speech, 38 (34.5)	Numbness, 7 (6.4) Parageusia, 3 (2.7) Slurring speech, 3 (2.7)
Sharma et al., 2013 [17]	NA	Bleeding, 1 (6.7) Pain, all (100) Swelling of the tongue, 2 (13.3) Difficulty in opening the mouth, 2 (13.3) Difficulty in tongue protrusion, all (100) Swallowing, all (100) Difficulty in chewing, all (100) Speech difficulty, all (100) Numbness, 6 (40)	Difficulty in tongue protrusion, 2 (13.3) Speech difficulty, 3 (20)
Xu et al., 2014 [14]	NA (7.0–15.0)	Pain, all (100) Difficulty in moving the tongue, all (100)	None
Abdelhameed et al., 2015 [27]	5.6 (4.0–12.0)	Oral discomfort, all (100) Difficulty in moving the tongue, all (100) Speech difficulty, all (100) Numbness, 9 (39.1)	None
Pal et al., 2016 [21]	10.1 (4.8–16.2)	Pain, 27 (90) Difficulty in moving the tongue, 11 (36.7) Slurring speech, 11 (36.7)	None
Chauhan et al., 2016 [20]	NA	Pain, 20 (40) Bleeding, 8 (16) Difficulty in chewing, 24 (48) Swelling of the tongue, 13 (26) Difficulty in articulation, 22 (44) Difficulty in opening the mouth, 19 (38) Dry mouth, 7 (14) Sensitivity disorders, 23 (46)	Difficulty in articulation, 1 (2)
Lumen et al., 2016 [18]	5.0 (1.0–20.0)	Pain, 17 (58.6) Difficulty in eating, 18 (62.1) Sensitivity disorders, 21 (72.4) Speech difficulty, 27 (93.1) Dysgeusia, 14 (48.3)	Difficulty in eating solids, 1 (3.4) Oral tightness, 1 (3.4) Sensitivity disorders, 9 (31)

Table 3 (continued)

Author [Ref.]	Graft length, mean (range), cm	Immediate complications, <i>n</i> (%)	Long-term complications, <i>n</i> (%)
Zhang et al., 2016 [28]	7.2 (2.5–16.0)	Pain, all (100) Numbness, 25 (24.7)	Salivary changes, 2 (6.9) Speech difficulty, 4 (13.8) Dysgeusia, 1 (3.4) Numbness, 5 (5.5) Slurring speech, 5 (5.5) Swallowing dysfunction, 5 (5.5) Parageusia, 3 (3.3)
Xu et al., 2017 [23]	NA (9.0–17.0)	Pain, all (100) Difficulty in moving the tongue, all (100)	Numbness, 4 (4.9) Slurring speech, 2 (2.5) Difficulty in moving the tongue, 5 (6.2)

BMG, buccal mucosal graft; LMG, lingual mucosal graft; NA, not available.

numbness, parageusia and slurring speech were more frequent in the same patients.

3.5. Surgical technique

The surgical technique has been improved over the last 12 years, as several cases were published. Different urethral approaches have been used [25]. Fig. 2 shows the key steps of what should be the standard surgical technique, based on worldwide experience.

Recently a novel technique of circumferential tubularised LMG has been proposed in which scarred urothelium was completely removed from the corpora spongiosum, in obliterative and near obliterative bulbar urethral strictures longer than 2 cm [26]: In their experience with 12 patients, the authors asserted that placing the graft horizontally could provide a wider lumen and need less suturing. Although initial results were encouraging, after a mean follow-up of 11.6 months the results were comparable to those reached by standard onlay techniques (success rate: 91.6%).

It has been reported that LMG harvesting could start during the latter part of the urethral mobilization [13], or that it could be performed by a second team operating at the same time [27]. However it was immediately clear that the help of an otolaryngologist was not necessary, at least after a short training period [8], with the same results [16].

An interesting debate took place as to the site of the graft harvesting. Although it was initially defined as the lateral mucosal lining of the tongue between the papillae situated on the dorsum and the sublingual mucosa [8], it was rapidly corrected to the ventrolateral mucosal surface of the tongue [16]. However, it has been stated recently that harvesting the graft from the lateral lining of the tongue is a valid option in patients requiring long oral grafts >7 cm to repair anterior strictures [28].

The graft can be easily harvested with a scalpel and sharp scissors without infiltrating with any solution [8].

However, some authors preferred to infiltrate with a solution of adrenaline 0.01‰ and normal saline 0.9‰ [24], or xylocaine 1% and adrenaline 0.01‰ in order to facilitate dissection and hemostasis [18].

Chauhan et al. [20] suggested to leave 4–5 mm mucosal edge from dorsal edge to prevent injury to taste buds, at least 1 cm of the mucosa from the tip of the tongue to prevent slurring of speech, and to carefully avoid taking underlying genioglossus muscle and lingual nerve in the graft, which could cause contractures, numbness, and increased bleeding.

The donor site is closed with absorbable sutures [11,15], but Lumen et al. [18] suggested closing it only if the mucosal edges could be approximated without excessive tension: In their experience the majority of donor areas were left open (65.5% of the LMG).

The standard length of a graft harvested from the tongue is between 4 and 8 cm [16,29]. If a long graft is required, the same procedure can be repeated on the contralateral side [16,25] or extended to the opposite side across the midline in continuity [12]. Moreover, Chauhan et al. [20] proposed a width of 15–25 mm to guarantee a lumen of at least 24 Fr after tubularization.

Finally, overall operative time was reported to be comparable to other urethroplasties: In particular Lumen et al. [18] showed 105 (60–240) min for LMG compared to 120 (45–230) min for BMG ($p = 0.549$). The same results were obtained by Chauhan et al. [20] with 146 (114–184) min for LMG and 148 (120–185) min for BMG. Similarly for graft harvesting, the mean time required was 13.2 min for one-side LMG, 22 min for bilateral LMG and 16 min for BMG ($p < 0.01$) [17].

3.6. Meta-analysis

We performed a meta-analysis including six comparative studies analyzing the success rate, and five comparative studies analyzing the long-term oral complication rates of

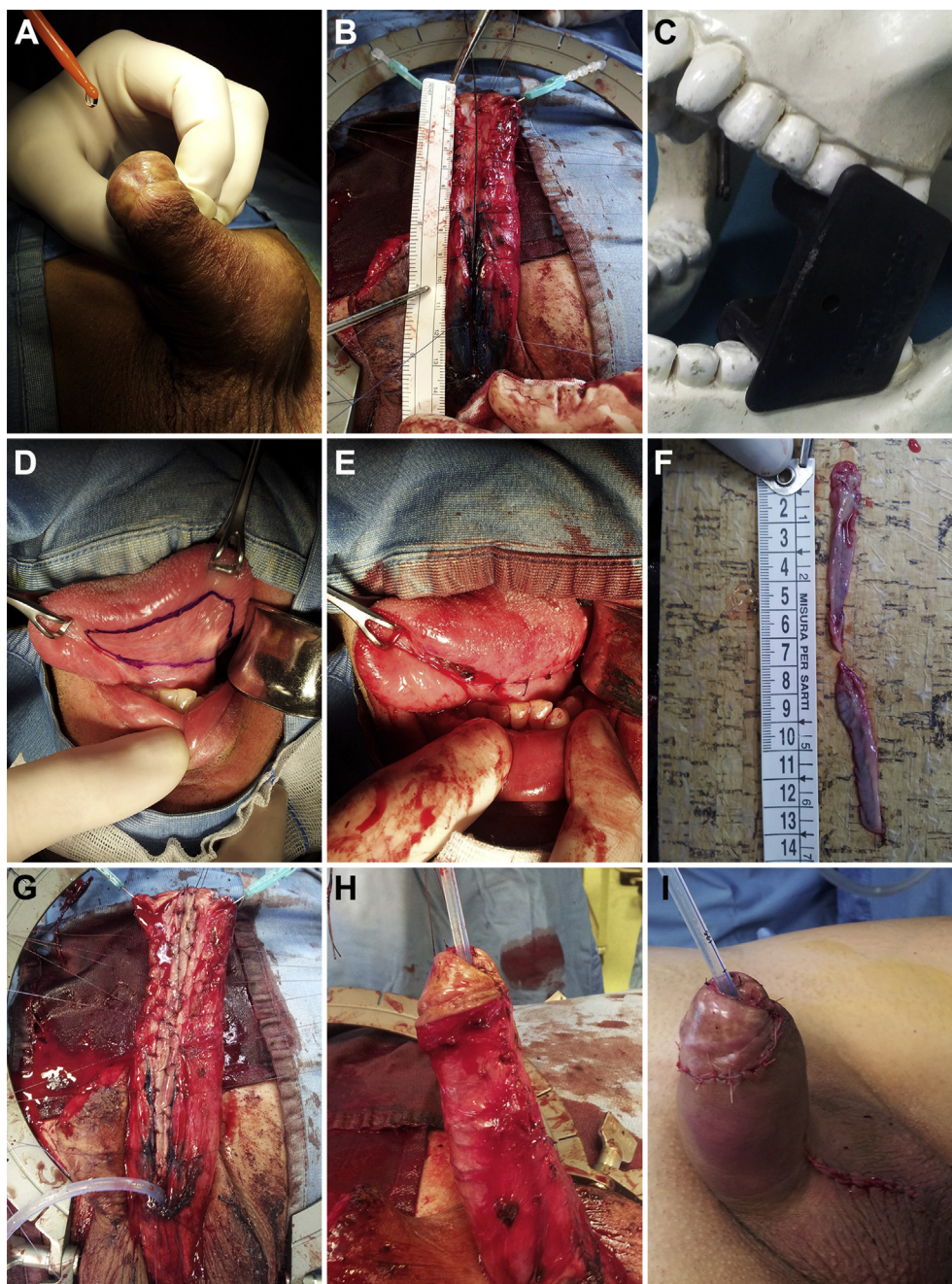


Figure 2 Fundamental steps of the surgical technique for LMG urethroplasty. (A) Patient is placed in lithotomy position under general anesthesia with naso-tracheal intubation. Urethra is probed with a catheter to detect the stricture. (B) The stenotic urethra is completely mobilized from the corpora cavernosa after a complete degloving of the penis (in case of long penile urethroplasty) or a perineoscrotal incision (in case of bulbar urethroplasty). The strictured tract is fully opened by a ventral midline incision and carefully measured. The urethral plate is longitudinally incised on the dorsal midline down to the corpora and the wings of the urethral plate are laterally mobilized. (C) LMG harvesting can be started during the latter part of the urethral mobilization or at the same time by two teams. A silicone bite block prop—mouth opener—is placed. (D) Direct traction is applied with two Babcock clamps to expose the ventrolateral surface of the tongue. A surgical pen is used to mark the required graft after identification of the opening of the Warton duct. (E) The graft edges are incised with a scalpel and a full-thickness mucosal graft is harvested using sharp scissors. Although a graft of 7–8 cm can be easily harvested from one half of the tongue, it should be at least 2 cm longer than the measured stricture length and 15–25 mm wide. Thus for long strictures the procedure can be repeated on the contralateral side. After the lingual mucosa is harvested, the wound is closed with interrupted polyglactin 4-0 sutures, without excessive tension. (F) Lingual mucosa is then prepared completely removing the underlying fibrovascular tissue. (G) The LMG is sutured and quilted on the bed of the dorsal urethral incision with tension free, interrupted, absorbable and at least 4-0 sutures, and an augmentation of the urethral plate is obtained. (H) The urethra is closed and tubularized over an indwelling 14Ch silicone catheter. A dartos fascial flap is obtained to cover the urethral suture. (I) The glans and penile skin are closed with interrupted 3-0 absorbable sutures. A Foley 14Ch silicone catheter should be left in place for at least 3 weeks. LMG, lingual mucosal graft.

LMG and BMG. Overall 365 patients were included in studies analyzing the success rate: 187 (51.2%) and 178 (48.8%) patients treated with LMG and BMG urethroplasty, respectively. An OR of 1.65 (95% CI [0.95–2.87], $I^2 = 0\%$) was found for LMG in terms of success rate. On the other hand, 329 patients were included in studies analyzing the long-term oral complication rate: 165 (50.2%) and 164 (49.8%) patients treated with LMG and BMG urethroplasty, respectively. An OR of 0.18 (95% CI [0.03–1.26], $I^2 = 68\%$) was found for LMG in terms of long-term oral complication rate (Fig. 3). The funnel plots for publication bias are reported in Fig. 4.

4. Discussion

In this systematic review and meta-analysis, we showed that LMG urethroplasty has good functional results with a very low incidence of complications. Furthermore we summarized the current state of the art of the surgical technique, collecting data from 12 years of experience worldwide.

Generally treatment of urethral strictures is complex and depends on several factors: Stricture length, site, number, presence of infection, or history of prior procedures. Thus clinical decisions should be carefully tailored to each patient. Although substitution urethroplasty is usually considered a second line therapy after one or two internal urethrotomy failures [30], patients with multiple recurrence risk factors should proceed to urethroplasty if suitable, thus limiting the indication to dilatation or internal urethrotomy to those patients with no or only one risk factor [31].

Several tissues, including genital and extragenital skin, have been proposed over the years. Oral mucosa has been selected as the tissue of choice for substitution urethroplasty as it is constantly wet, it is resistant to skin disease, and it has a privileged immunology [32].

Buccal mucosa from the inner cheeks has been the preferred tissue due to its constant availability and readiness to harvest, handle and engraft. However, BMG harvesting is associated with several morbidities, including not only perioral numbness and difficulty in opening the mouth, but also scarring and dry mouth [7].

In 2006, Simonato et al. [8] first reported a preliminary experience with LMG urethroplasty supported by the fact that lingual mucosa had constant availability, easy harvesting, and favorable immunological properties (resistance to infection) and tissue characteristics (a thick epithelium, high content of elastic fibers, thin lamina propria and rich vascularization) similar to those described for the buccal mucosa. Their pathological examination of LMG biopsy revealed survival of the grafts with no pathological alterations, confirming that it was as good as BMG. Subsequently, several groups reported the feasibility, the technical steps and the outcomes of patients undergoing this type of surgery.

Unfortunately, even with long follow-up and relatively ample populations, most of the published studies are retrospective. Only four recent studies [17,18,20,21] prospectively compared LMG to BMG urethroplasty and substantially confirmed previous reported data. However, LMG seems to show a mild (but not significant) superiority to BMG in terms of long-term outcomes and donor site complications.

The majority of the studies include strictures with varying etiology and different previous interventions, but these concerns seem not to affect the results [20]. On the other hand, there is enough consensus on the definition of failure (weak urinary peak flow and/or the need of any kind of intervention to treat a stricture recurrence), making it possible to say with some degree of certainty that the LMG urethroplasty has good results in different settings.

Interestingly only one study compared two different techniques for LMG urethroplasty (dorsal onlay by

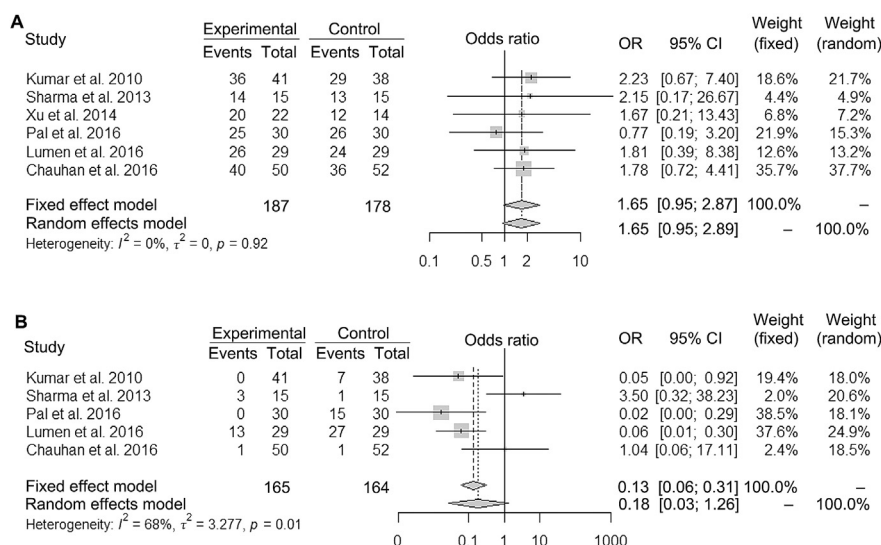


Figure 3 Forest plot of OR (95% CI) for success rate (A) and long-term oral complications (B) of LMG (Experimental) vs. BMG (Control) urethroplasty. The center of each square represents the OR, the area of the square is the number of samples and thus the weight used in the meta-analysis and the horizontal line indicates the 95% CI. LMG, lingual mucosal graft; BMG, buccal mucosal graft; OR, odds ratio; CI, confidence interval.

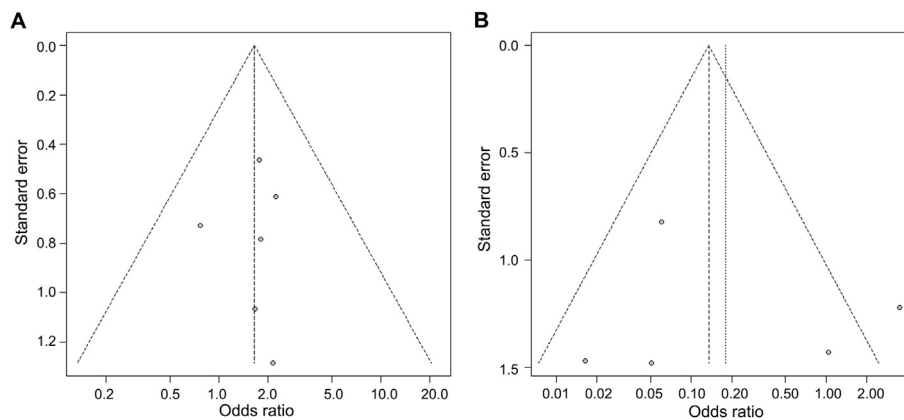


Figure 4 Funnel plots for publication bias. (A) Six studies analyzing success rate of LMG vs. BMG urethroplasty; (B) Five studies analyzing long-term oral complication rate of LMG vs. BMG urethroplasty. LMG, lingual mucosal graft; BMG, buccal mucosal graft.

Barbagli's technique vs. through a ventral sagittal urethrotomy approach) and no significant differences were shown [12].

In this review we analyzed the LMG urethroplasty for urethral stricture in male patients, as it is still the first indication for this surgery. However, the same graft has been successfully adopted in case of hypospadias (success rate 76%–87%, comparable with previous data and BMG), with low rate of urethral complications [33–35]. The possibility of using LMG in women should also be mentioned, although only one study, involving 15 women with urethral stricture, has been published so far, reporting only one failure [36].

In terms of length of the graft, as evidenced by the data collected, a graft of 3–7 cm in length and 1.5 cm in width was initially reported [8]; then larger and bilateral grafts were described to meet the need for even wider tissue for longer and more complicated urethral strictures. This usually ensures a proper urethral substitution, but it is also possible to associate two different types of donor tissue in order to cover the entire length of the stricture [23].

It should also be considered that surgical harvesting technique and operator experience can play an important role both at the donor and on the receiving sites. All the works agree on the ease of the harvesting: Even Barbagli et al. [16] reported that there was no difference in morbidity at the harvest site when LMGs were harvested by an oral surgeon or urologist.

The introduction of LMG has awakened interest in donor site complications. In fact, postoperative questionnaires were used together with instrumental evaluations. It is worth noting that some authors have found some minimal complications of the donor site: These complications are related to the size of the graft itself, thus confirming that the bigger the graft, the greater the chances of detecting complications, as it is for the lip and cheek. Nevertheless long-term speech difficulties are recorded in a small percentage of patients and only by three studies [17,18,24]. Interestingly, LMG has attracted more interest from the Asian rather than the western countries. This may be due to a greater need for an alternative donor site due to environmental conditions or eating and recreational habits (like chewing tobacco) that may damage the cheek mucosa [37], or to treat longer urethral stricture.

Finally, the meta-analysis aimed at obtaining an objective conclusion over the comparison between LMG and BMG urethroplasty. However, only a few studies could be included. Thus the results should be only interpreted as a trend toward improved success rates and long-term oral complication rates for LMG urethroplasty, as already mentioned in the descriptive analysis of the actual literature.

5. Conclusion

Although LMG is generally thought to be fragile and difficult to be managed by inexperienced surgeons, our review of the current literature shows that LMG harvesting is feasible and easy to perform. LMG urethroplasty is comparable to BMG urethroplasty, which has been the technique of reference, in terms of functional results. Urethral complications rates are low. Oral complications are temporary and minimally disabling, basically less than those for BMG, and depend mainly on the extent of the graft. Thus today LMG can be considered both as a first choice and a valid alternative for tissue supplement in substitution urethroplasty.

Author contributions

Conception and design of study: Alchiede Simonato.

Data collection: Alberto Abrate, Alchiede Simonato.

Analysis and interpretation of data: Alberto Abrate, Andrea Gregori.

Drafting the manuscript: Alberto Abrate.

Revising the manuscript critically: Alchiede Simonato.

Conflicts of interest

The authors declare no conflict of interest.

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