ACTA OTORHINOLARYNGOLOGICA ITALICA 2023;43(SUPPL.1):S84-S94; doi: 10.14639/0392-100X-suppl.1-43-2023-11

Head and Neck section

Treatment of relapsing functional and organic dysphonia: a narrative literature review

Trattamento delle disfonie funzionali e organiche recidivanti: una review narrativa

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SUMMARY

Information about failure and relapses is critical in deciding whether and how to treat a given condition, as well as during patient counselling before therapy. This paper aims to perform a non-systematic review of relapses and failure of dysphonia treatment in the adult population. Studies on failure and relapses after treatment of benign vocal fold lesions, functional dysphonia and neurogenic dysphonia were analysed. The frequency and the duration of follow-up were heterogeneous, and the management of relapses was reported in only a portion of the studies. Relapses after surgical treatment of benign vocal fold lesions ranged between 1% and 58% of cases, and their management was mainly surgical. Rates of relapse after voice therapy for functional dysphonia and spasmodic dysphonia were 12%-88% and 8%-63%, respectively. Rates of relapse after surgical treatment for unilateral and bilateral vocal fold paralysis were 10%-39% and 6%-25%, respectively; treatment was mainly represented by surgical revision. In conclusion, failure and relapses of functional and organic dysphonias after therapy are not rare, but treatment modalities are seldomly reported. The data from this non-systematic review stresses the need for further research in this area.

KEY WORDS: relapse, failure, organic dysphonia, functional dysphonia

RIASSUNTO

La conoscenza del possibile fallimento terapeutico e delle recidive è cruciale per decidere se e come trattare una patologia, così come nel counseling del paziente. Questo lavoro si propone di affrontare una revisione non sistematica dei fallimenti e delle recidive dopo trattamento della disfonia nell'adulto. Sono stati analizzati diversi lavori in tema di lesioni cordali benigne, disfonia funzionale e disfonia neurogena. La frequenza e la durata del follow-up sono eterogenee, e la gestione delle recidive è descritta solo in alcuni lavori. Le recidive dopo chirurgia per lesioni benigne variano tra l'1% e il 58% dei casi, e sono gestite primariamente mediante revisione chirurgica. I tassi di recidiva dopo logopedia per disfonia funzionale e disfonia spasmodica sono pari a 12%-88% e 8%-63%, rispettivamente. Le recidive dopo chirurgia per paralisi cordale unilaterale e bilaterale sono pari a 10%-39% e 6%-25%, rispettivamente; la loro gestione è eminentemente chirurgica. In conclusione, i fallimenti e le recidive delle disfonie funzionali e organiche dopo terapia non sono infrequenti, ma le relative modalità di trattamento non sono spesso descritte. Le analisi della presente revisione non sistematica sottolineano la necessità di ulteriori ricerche in questo ambito.

PAROLE CHIAVE: *recidiva, fallimento, disfonia organica, disfonia funzionale*

Received: January 15, 2023
Accepted: January 21, 2023

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How to cite this article: Robotti C, Mozzanica F, Barillari MR, et al. Treatment of relapsing functional and organic dysphonia: a narrative literature review. Acta Otorhinolaryngol Ital 2023;43(SUPPL.1):S84-S94. https://doi.org/10.14639/0392-100X-suppl.1-43-2023-11

Introduction

Dysphonia is a symptom due to an impairment of voice production and charac-

terised by the alteration of voice quality or by vocal effort that impairs communication and affects quality of life. It has a lifetime prevalence of 29.9% and a point-prevalence of 6.6%. It impacts working activities as 7.2% of employed adults were absent from work 1 or more days in the past year because of their voice, and 2% had more than 4 days of voice-related absence [1]. In clinical practice, dysphonia accounts for up to 0.26% and 3.2% of visits for general practitioners and otorhinolaryngologists, respectively [2]. Several conditions may lead to dysphonia, and they can be grouped in three major categories of voice disorders based on pathophysiology, auditory-perceptual and visual-perceptual observations: organic, functional and neurogenic dysphonias. Organic dysphonias are due to pathologies of laryngeal structures (vocal folds and laryngeal cartilages) and are usually subdivided into diseases of the vocal fold epithelium (papillomatosis, dysplasia, carcinoma), diseases of Reinke's space (polyps, nodules, cysts, Reinke's oedema), and impairments of the laryngeal cartilages (as after partial laryngectomy). Functional dysphonias include impairments in voice production without a laryngeal pathology due to a dysfunction of voice behaviour and include muscle tension dysphonia and psychogenic dysphonia. Neurogenic dysphonias are due to impairment of laryngeal movements because of diseases affecting either the peripheric (vagal or recurrent laryngeal nerve impairment) or central nervous system (such as spasmodic dysphonia or tremor). Organic, functional and neurogenic dysphonia represent 18.8%, 43.7% and 37.3% of the Italian population seeking treatment for dysphonia, respectively; multidimensional voice analysis showed that neurogenic dysphonia generally presents more severe voice impairment compared to organic and functional dysphonia [3]. An additional condition often encountered in otorhinolaryngological clinical practice with potential effects on voice is Laryngo-pharyngeal Reflux Disease (LPRD).

Different treatments are now available for dysphonia including pharmacological (steroids, anti-reflux medicaments, botulinum toxin injection), surgical (microsurgical removal of laryngeal lesions, laryngeal framework surgery, filler injection) and behavioural therapy (voice therapy) [4,5]. While several studies aimed to analyse the safety and efficacy of the available treatments, little is known about failure and relapses. Relapses consist in the return of a disease or its signs and symptoms after a period of improvement, while failure is defined as the lack of success or the inability to meet an expectation. Information about failures and relapses is critical in deciding whether and how to treat a given condition, and it is crucial during patient counselling before therapy. In particular, clear patient information about failure and relapses will avoid inappropriate discussions and requests, including legal issues, after treatment. The aim of this paper is to perform a non-systematic review of the frequency of relapses and failure of dysphonia treatment in the adult population.

Failure and relapses of benign organic dysphonia

Benign organic dysphonias are generally treated with surgery, with the only exception of vocal fold nodules. Although there is general consensus that benign vocal fold lesions should be treated surgically, voice therapy may play a role as an alternative treatment [4,5], or as an adjunctive therapy before or after therapy. However, the role of voice therapy is controversial and poorly investigated [6-8]. Nonetheless, when analysing failures and relapses of surgical treatment, the potential impact of voice therapy as a complementary treatment should also be considered. In Table I studies on relapses and their treatment after surgery for vocal fold polyps, cysts, Reinke's oedema and nodules are reported [9-29]. The 9 studies considered in this review on surgical treatment for vocal fold polyps included more than 1000 patients, with a follow-up raging from 0 to 24 months and relapses ranging from 1% to 5%; post-surgical voice-therapy was reported in the majority of studies (7/9), while treatment of relapses was reported in only three studies, being surgical in all cases. The 6 studies considered in this review on surgical treatment for vocal fold cysts included less than 1000 patients, with a follow-up of 0-54 months and relapses ranging from 2% to 5%; post-surgical voice-therapy was reported in more than half of studies (7/9), while only one study reported the treatment of relapses, being surgical. The 5 studies considered in this review on surgical treatment for Reinke's oedema included over 600 patients, with a follow-up raging from 0 months to 8 years and relapses ranging from 2% to 58%; post-surgical voice-therapy was reported in 3 of 5 studies, while treatment of relapses (surgical) was reported only in one study.

With regards to the management of vocal fold nodules, several areas of uncertainty remain, including poorly defined nomenclature, the natural history of paediatric vocal nodules, the establishment of criteria to measure successful treatment, optimal configuration of speech therapy regimens and the rationale for surgical intervention; nonetheless, there is general consensus that vocal fold nodules should be treated primarily through voice therapy. A recent systematic search on the effectiveness of voice therapy in adult patients with vocal fold nodules retrieved 9 papers [30]. Although the study design and the evidence levels were low, all studies reported positive effects of voice therapy on different vocal parameters (perceptual, acoustic and self-assessment scores), but no data regarding the number of failures was reported. Data on the time interval between end of treatment and vocal fold nodules reduction or resolution was not available. Only in the study by Chernobelsky [28], conducted on 28 patients who

Table I. Rates of failure and relapses after surgery for vocal fold polyps, cysts, Reinke's edema, and nodules.

Disease	Author, year	Patients	Follow-up length	Relapses (%)	Post-surgical voice therapy	Relapses treatment
Polyp	Bouchayer et al., 1992 [9]	267	n/a	3/267 (1.12%)	267 (100%)	n/a
	Hochman et al., 2000 [10]	40	2-24 months	1/40(1.25%)	35 (87.5%)	Surgery
	Ju et al., 2013 [11]	118	3 months	7/118 (5.9%)	55 (46.6%)	n/a
	Byeon et al., 2013 [12]	280	6-12 months	11/280 (3.9%)	18 (0.36%)	n/a
	Zhang et al., 2015 [13]	60	n/a	2 /60 (3.33%)	n/a	Surgery
	Barillari et al., 2017 [14]	70	12 months	4/70 (5.7%)	70 (100%)	n/a
	Agarwal et al., 2019 [15]	120	5.5 months	4/120 (3.3%)	68/91 (74,7%)	n/a
	Lee et al., 2020 [16]	235	13.7 ± 22.3, (0.1- 119.8) months	14/235 (5,53%)	69%	7 Voice therapy 7 Surgery 10 Voice therapy and surgery
	Patrial et al., 2020 [17]	396	0-210 months	20/396 (5.5%)	n/a	n/a
Cyst	Bouchayer et al., 1992 [9]	494	n/a	12/494 (2.4%)	494/494 (100%)	n/a
	Chang et al., 2003 [18]	21	3 months	1/21 (4.8%)	n/a	n/a
	Hsu et al., 2009 [19]	25	12 months	1/25 (4%)	n/a	n/a
	Tibbetts et al., 2018 [20]	21	5.5 (0.1-54) months	1/21 (4.8%)	14/21 (66.7%)	Surgery
	Lee et al., 2019 [16]	92	13.7 (0.1-119.8) months	2/92 (2.2%)	69%	n/a
	Patrial et al., 2020 [17]	349	0-210 months	6/349 (1.7%)	n/a	n/a
Reinke's edema	Nielsen et al., 1986 [21]	111	6 months - 8 years	64/111 (58%)	55/111 (49.5%)	Surgery
	Bouchayer et al.,1992 [9]	138	n/a	3/138 (2.29%)	138/138 (100%)	n/a
	Goswami et al., 2003 [22]	92	12 months	4/92 (4.35%)	92/92 (100%)	n/a
	Tasar, 2013 [23]	21	6 months	1/21 (4.7%)	n/a	n/a
	Patrial et al., 2020 [17]	261	0-210 months	8/261 (3.1%)	n/a	n/a
Nodules	Nagata et al., 1983 [24]	372: 72 surgery 300 conservative	Over 5 months	4/36 (11%) surgery 34/101 (33%)	0/372	n/a
	Lancer et al., 1988 [25]	34	5 years	9/34 (26%)	20/34 (59%)	n/a
	Murry et al., 1992 [26]	39 voice therapy 20 surgery & voice therapy	11/39 voice therapy 20/20 (3 months)	9/39 (23%) 4/20 (20%)	n/a	n/a
	Zeitels et al., 2002 [27]	119	Individualised	4/119 (3.2%)	119/119 (100%)	Microsurgery
	Chernobelsky et al., 2007 [28]	28 voice therapy	Over 10 years	22 relapses 6 failures	n/a	n/a
	Bequignon et al., 2013 [29]	62	9.5 (5-15) years	20/62 (32%)	46 (51%)	n/a

underwent voice therapy, some information on relapses and failures was available; over a 10-year period, relapses were 22/28 (78%) and failures were 6/28 (21%). The 5 studies considered in this review on surgical treatment for vocal fold nodules included overall over 300 patients, with a follow-up ranging from 5 months to 15 years and relapses ranging from 3% to 33%; post-surgical voice-therapy was reported in 4 of 5 studies, while only one study reported the treatment of relapses, being surgical.

Failure and relapses of functional dysphonia

Functional dysphonias are generally treated through voice therapy. Although there is now evidence on the efficacy of voice therapy in this group of patients, little is known on relapses and failures. In Table II the studies on relapses and their treatment after voice therapy for muscle tension dysphonia and psychogenic dysphonia are reported [31-37]. The 4 studies considered in this review on muscle tension dysphonia included less than 100 patients with failures ranging from 12% to 68%; data on failure and/or relapses management was not available [31-34]. The 3 studies on psychogenic dysphonia included 81 patients with failures or relapses ranging from 50% to 88%; data on failure and/or relapses management were available in 2 of the 3 studies and always included the involvement of a psychologist [35-37].

Failure and relapses of neurogenic dysphonia

Unilateral vocal fold paralysis

Different treatments are now available for unilateral vocal fold paralysis (UVFP) including voice therapy, laryngeal injection with a variety of fillers, laryngeal framework surgery and laryngeal re-innervation; however, no consensus exists on which is the most effective treatment, or on the selection and timing for surgical or behavioural therapy. A recent systematic review analysed several studies on the efficacy of voice therapy for UVFP, showing a general improvement in voice, which is maintained for up to 1-year [38]. However, no data on failure or relapses was reported. Only one study analysed the need for surgery after voice therapy: over 60% of the patients who underwent voice therapy for UVFP were satisfied with the results and did not require any additional treatment [39]. In Table III the studies on failures and relapses and their treatment after surgery for UVFP are reported [40-51]. Two studies conducted on almost 140 patients, investigating the efficacy of injection laryngoplasty with a follow-up up to 36 months, reported relapses in 10%-35% of cases; voice therapy was prescribed for all patients with relapses who underwent additional surgery, being reinjections in most cases. Eight studies on a total of over 1000 patients who underwent laryngeal framework surgery, with a follow-up range of 1-132 months, reported relapses in 10%-18% of cases; data on voice therapy after surgery was not available, but all patients with relapses underwent revision laryngeal framework surgery with a variety of surgical techniques. Finally, two studies analysed failure and relapses after laryngeal re-innervation; patients undergoing this surgery are still limited, and failures could be managed with either laryngeal framework surgery or laryngeal injection.

Bilateral vocal fold paralysis

Laryngeal dyspnoea due to bilateral vocal fold paralysis

Table II. Rates of failure and relapses after voice therapy for muscle tension dysphonia and psychogenic dysphonia.

Disease	Author, year	Patients	Treatment duration/follow-up	Treatment failure/relapses (%)	Relapses management
Muscle tension dysphonia	Roy et al., 1997 [31]	25	1 session	13/19	
	Carding et al., 1999 [32]	45	8 weeks	7/45 (15%)	
	Lee et al., 2005 [33]	8	1-2.5 months	1/8 (12.5)	
	Ogawa et al., 2013 [34]	23	1 session	5/23 (21.7%)	
Psychogenic dysphonia	Butcher et al., 1987 [35]	19	n/a	6/12	Joint therapy with a speech therapist and a psychologist with a cognitive-behavioural approach
	Reiter et al., 2013 [36]	8	16 (± 8) months	7/8 (88.5%)	n/a
	Tezcaner et al., 2019 [37]	54	21.4 (± 3.7) months follow-up	10/20 (50%)	Psychological follow-up

Table III. Rates of failure and relapses after surgery for UVFP.

Author, year	Patients	Follow-up lenght	Relapses (%)	Post-surgical voice therapy	Relapses treatment
Havas et al., 1999 [40]	51 (12 laryngeal reinnervation)	24 months	18/51 (35.3%)	n/a	Not specified. 4 had TP following reinnervation, 4 had TP following injection aumentation
Maragos, 2001 [41]	331, LFS	n/a	48/331 (14.5%),	n/a	TP1 45/406 (11.1%); TP2 1/10 (10%), TP3 3/8 (37.5%); TP4 5/45 (11.1%), AA 5/142 (3.5%); AF 2/17 (11.8)
Woo et al., 2001 [42]	n/a, LFS	0.5 – 132 months	20	n/a	Revision ML + AA 9/20 (45%), implant removal 4/20 (20%), revision ML 2/20 (10%), lipoinjection 2/20 (10%), AA 3/20 (15%)
Cohen et al., 2004 [43]	156, LFS	1-15 months	16/156 (10.2%)	n/a	Revision Gore-Tex ML 9/22 (40,9%), injection augmentation 9/22 (40,9%), implant removal 2/22 (9,09%), AA 2/22 (9,09%).
Parker et al., 2015 [44]	208, LFS	14.6 months	39/208 (18.7%)	n/a	Injection ML prior to revision ML in 14/48 (29%) surgeries. 28 AUG; 1 arytenopexy; 3 AUG + arytenopexy; 1 AUG + cricothyroid subluxation; 2 arytenopexy + cricothyroid subluxation; 11 AUG + arytenopexy + cricothyroid subluxation.
Kwak et al., 2016 [45]	40 TP	46.5 months	6/40 (15%)	n/a	6 revision TP
Silva Merea et al., 2018 [46]	135 ML (56 with prior injection augmentation)	unclear	14 (10,4%): 5/56 (8.9%) of those with prior IA + 9/79 (11.4%) of those with no prior IA	n/a	6 removal of old implant + new implant + AA; 3 removal of old implant + new implant; 1 addition of new implant; 1 removal of old implant + new implant + contralateral medialisation; 1 removal of old implant + new implant + AA + pharyngoplasty; 1 partial removal of implant + AA
Marie et al., 2020 [47]	n/a. Previous TP or VF augmentation	36 months	8	n/a	8 unilateral laryngeal reinnervation (ansa to RLN)
Prstačić et al., 2020 [49]	78, IA	12 months (unclear)	8/78 (10.3%)	Before fat augmentation	Second surgery not specified
Kishimoto et al., 2020 [48]	149	1-109 months	19 pz (12,75%)	n/n	Revision framework surgery (TP1 13; AA 5; TP1+TP4 1; TP1+AA 2)
Mes et al., 2021 [50]	61, LFS	>12 months	6 (9.8%)	n/a	3 additional AA, 3 injection augmentation
Miaśkiewicz et al.,2021 [51]	51, IA	36 months	18/51(35%)	yes	18 reinjections

TP: Thyroplasty; AA: Arytenoid adduction; AF: arytenoid fixation; AUG: anterior augmentation; LFS: laryngeal framework surgery, ML: medialisation laryngoplasty, IA: injection augmentation; n/a: not available; RLN; recurrent laryngeal nerve.

can be managed through a variety of surgical techniques, aiming to maintain oral respiration and limiting the impact on voice production. In Table IV the studies regarding failures and relapses and their treatment after surgery for bilateral vocal fold paralysis are reported [52-74]. In the 23 studies on almost 580 patients who underwent surgery, with a follow-up up of 3-60 months, relapses were reported in 6%-25% of cases; voice therapy was not prescribed in any of the studies; treatment of relapses was reported in 8 of 23 studies, and in 7 of them it was revision surgery.

Spasmodic dysphonia

There is general agreement that voice therapy can not significantly improve any voice parameter in patients with spasmodic dysphonia. Several other effective treatments are currently available, including botulinum toxin injection and a range of surgical approaches, such as thyroarytenoid myoneurectomy, thyroplasty type II (without or with a titanium bridge), selective laryngeal adductor denervation-reinnervation and laryngeal nerve resection. Botulinum injection is the most widely applied treatment by both otorhinolaryngologists and neurologists, but should be repeated approximately every 3-4 months. Surgical approaches are more invasive, but have the potential to achieve stabilisation of the disease. In Table V several studies are reported, describing failures and relapses after treatment

Table IV. Rates of failure and relapses after surgery for bilateral vocal fold paralysis.

Author, year	Primary treatment	Patients	Follow-up duration	Relapses (%)	Post-surgical voice therapy	Relapses treatment
Dennis et al., 1989 [52]	Posterior cordectomy	6	1-5 years	n/a	no	n/a
Laccourreye et al., 1999 [53]	Posterior partial transverse cordotomy	25	10 months	n/a	no	n/a
Pia et al., 1999 [54]	Posterior ventriculocordectomy	41	43 months	n/a	no	n/a
Manolopoulos et al., 1999 [55]	Partial posterior cordectomy	18	0.6-6 years	2 (11%)	no	Revision surgery
Maurizi et al., 1999 [56]	Subtotal arytenoidectomy and medial-posterior cordotomy	39	30 months	5(12,8%)	no	Revision surgery
Hans et al., 2000 [57]	Posterior transverse cordotomy	4	24 months	0	no	n/a
Segas et al., 2001 [58]	Unilateral posterior ventricular cordectomy	20	n/a	n/a	no	n/a
Dursun et al., 2006 [59]	Posterior transverse laser cordotomy	22	14-48 months	4 (18%)	no	Revision surgery
Misiolek et al., 2007 [60]	Total arytenoidectomy with posterior cordectomy	30	5 years	0	no	n/a
Harnisch et al., 2008 [61]	Posterior cordectomy (n = 2), laterofixation (n = 1), posterior transverse cordotomy(n = 7)	10	6-57 months	1 (10%)	yes	Revision surgery
Bajaj et al., 2009 [62]	Bilateral posterior vocal fold release	9	0.3-4 years	1(11%)	no	Conservative treatment
Hyodo et al., 2009 [63]	Laterofixation	11	3-80 months	1 (9%)	no	n/a
Ezzat et al., 2010 [64]	Laterofixation	21	6 months	n/a	no	n/a
Riffat et al., 2012 [65]	Unilateral laser posterior cordotomy (n = 12), bilateral posterior cordotomy (n = 8), combined cordotomy and arytenoi- dectomy (n = 9), excision of a posterior glottic scar (n = 5)	34	24 months	n/a	no	n/a
Yilmaz, 2012 [66]	Total arytenoidectomy, vocal fold lateralization	50	1-3 years	3(6%)	no	Revision surgery
Nawka et al., 2015 [67]	Posterior chordotomy, partial or total arytenoidectomy, permanent laterofixation	32	6 month	0	no	n/a
Asik et al., 2016 [68]	Monolateral posterior transverse cordotomy	11	2 months	0	no	n/a
Fabre et al., 2019 [69]	Vocal fold lateralization	18	n/a	n/a	no	n/a
Rashid et al., 2019 [70]	Posterior cordotomy	34	2 months	6 (17,6%)	no	n/a
Qazi et al., 2021 [71]	Transverse posterior cordotomy	20	442 days	5 (25%)	no	Revision surgery
Filauro et al., 2021 [72]	Posterior cordotomy (± medial partial arytenoidectomy)	33	n/a	6 (18,1%)	no	Revision surgery
Ghodke et al., 2021 [73]	Transverse cordotomy with anteromedial arytenoidectomy	10	n/a	n/a	no	n/a
Benninger et al., 2022 [74]	Unilateral coblator cordotomy	94	16 months	n/a	no	n/a

Table V. Rates of failure and relapses of spasmodic dysphonia after surgery and botulinum toxin injection.

Author, Year	Treatment	Patients	Follow-up lenght	Relapses (%)	Post-surgical voice therapy	Relapses treatment
Aronson et al., 1983 [75]	LNR	33	36 months	21 (63.64%)	n/a	Not reported
Berke et al., 1999 [76]	SLAD-R	21	36 months	4 (19.05%)	n/a	1/4 (25%) BTX, 1/4 (25%) collagen injection, 1/4 (25%) TMN, 1/4 voice therapy
Smith et al., 2000 [77]	BTX-ona	2	3-7 years	2 (100%)	n/a	No further treatment
Galardi et al., 2001 [78]	BTX-ona, BTX-abo	15	3.53 years (1-8)	12 (80%) pt had ³ 1 non effective injection	n/a	n/a
Park et al., 2003 [79]	BTX-ona	71	5 years	6 (8.45%)	n/a	n/a
Isshiki et al., 2004 [80]	TPII	25	3-6 months	1 (4.0%)	n/a	Revision TPII with TB (1/1, 100%)
Chhetri et al., 2006 [81]	SLAD-R	83	49 months	12 (14.46%)	n/a	5/12 (41.67%) BTX; 7/12 (58.33%) not reported
Cannito et al., 2008 [82]	BTX-ona	42	3-6 weeks	7 (16.67%) all over 70 years of age	n/a	n/a
Sanuki et al., 2009 [83]	TPII	90	12-36 months	7 (7.78%)	1	2/7 (28.57%) removal of goretex or TB, no revision surgery; 5/7 (71.43%) new TB
Su et al., 2010 [84]	TMN	29	31 (12-63) months	11 (37.93): 3 (10.34%) unsuccessful surgery	n/a	Revision TMN (7/8, 87.5%)
Sanuki et al., 2010 [85]	TPII	10	17.6 (7-25) months	0 (0.0%)	n/a	-
Tsuji et al., 2012 [86]	TMN	15	31 (4-96) months	2 (13.33%)	n/a	n/a
Nomoto et al., 2015 [87]	TMN vs TPII	65 (30 TMN, 35 TPII)	6 months	1 TMN (3.33%)	n/a	Revision TMN 1/1 (100%)
Schuering et al., 2020 [88]	TMN	22	30 months	10 (45.45%)	n/a	TMN 10/10 (100%)
Zhao et al., 2020 [89]	BTX-ona	131	n/a	67 (12%) injections	n/a	n/a
Kohli et al., 2022 [90]	BTX-inc	9	2.56 months	4 non responders	n/a	n/a

TMN: thyroarytenoid myoneurectomy; TPII: thyroplasty type II; TB: titanium bridge; SLAD-R: selective laryngeal adductor denervation-reinnervation; LNR: laryngeal nerve resection; BTX-ona: onabotulinumtoxinA (Botox®); BTX-inc: incobotulinumtoxinA (Xeomin®, "naked" toxin with no surrounding proteins); BTX-abo: abobotulinumtoxinA (Dysport®).

for spasmodic dysphonia and their management [75-90]. In the 6 studies on 270 patients who underwent botulinum toxin injection, with a follow-up up ranging from 3 months to 7 years, failures were reported in 8%-35% of cases, reaching a 80% failure rate in at least a single treatment; data on voice therapy in addition to surgery or for non-responding patients was not reported. No data on management of failures after botulinum toxin injection was reported. In the 10 studies on 393 patients who underwent surgical treatment, with a follow-up up ranging from 6 to 49 months, failures were reported in 3%-63% of cases; voice-therapy was prescribed in only one case. The management of failure was reported in 6 of 10 papers and included several options: surgical revision (in most cases), botulinum toxin injection and collagen injection.

Failure and relapses of laryngopharyngeal reflux

LPRD is an inflammatory clinical condition affecting the upper aero-digestive tract, causing several symptoms, including dysphonia. Treatment options mainly include diet and lifestyle

modifications, associated with proton pump inhibitors (PPIs) and/or alginate or magaldrate. Less frequently prescribed medications include prokinetic agents, H2 receptor antagonists, or γ-aminobutyric acid derivatives. Surgery (e.g. fundoplication) represents a treatment option only in selected patients. Similar to Gastro-oesophageal Reflux Disease (GERD) patients, individuals suffering from LPRD may experience recurrences throughout life. Based on the clinical course of the disease, three main LPRD subtypes have been recently described: (a) acute LPRD (29.3%), in case of complete resolution of symptoms with no relapses during a 3-year follow-up; (b) recurrent LPRD (40.7%), in case of one or more recurrences followed by a full response to medical treatment or dietary modifications, even if temporary; (c) chronic LPRD (30.0%), in case of chronic clinical course with absent or partial response to medical therapy, or when patients rapidly relapse if therapy is discontinued, thus requiring long-term treatment regimens [91]. With regards to recurrent LPRD, similar data were also found by Koufman and coworkers when analysing data from 225 GERD patients with extra-oesophageal symptoms [92]. The authors highlighted a chronic-recurrent clinical course in 25% of patients, even if high doses of PPIs were prescribed. A more recent study conducted by Verhasselt et al. on 100 LPR patients during a 3-year follow-up demonstrated a chronic-recurrent clinical course in one-third of cases [93]. Nevertheless, treatment regimens for recurrences were not described in detail.

The actual success of therapies remains hard to predict. However, many risk factors have been identified to date as potential markers of treatment failure, in terms of both absent or incomplete response and increased risk of recurrence. The most important ones include: hiatal hernia; prolonged contact between the mucosa and the acid refluxate demonstrated through Hypopharyngeal-Oesophageal Multichannel Intraluminal Impedance-pH Monitoring (HEMII-pH) [94]; celiac disease; proximal oesophageal dysmotility; achalasia; oesophageal spasms; gastroparesis; food intolerances; eosinophilic oesophagitis [95,96]. Several authors provided interesting insights into differential diagnoses, with particular reference to conditions affecting the head and neck district which may mimic or overlap with LPRD: chronic rhinosinusitis; autoimmune inflammatory laryngeal disorders (e.g. rheumatoid arthritis, Sjögren syndrome, sarcoidosis, fibromyalgia, musculoskeletal laryngeal disorders); aging voice. Similarly, Carroll et al. identified additional cofactors which may be associated with an "apparently" chronic-recurrent clinical course of LPRD: allergic rhinitis; asthma; chronic laryngitis; glottic insufficiency; post-viral vagal neuropathies [97]. Furthermore, active allergies can interfere with the therapeutic management of LPRD, since they may induce laryngeal signs and symptoms which are indistinguishable from those of LPRD.

In addition to pathological gastro-oesophageal or pharyngo-laryngeal conditions which may be associated or non-recognised, several other risk factors related to GERD and LPRD may play a key role in favouring chronic-recurrent clinical courses, even in case of thorough diagnostic approaches and adequate treatment regimens. These risk factors include: inadequate dietary regimens (lack of adherence to the Mediterranean diet); high consumption of specific foods (acid or with high protein or fat content); poor eating habits; tobacco smoke; alcohol abuse; obesity and overweight; sleep disorders; psychosocial distress [98].

Defining the exact recurrence rate with reference to treatment duration represents an additional issue. Success rates of therapy vary between 18% and 87%, but the heterogeneity of published research and the absence of long follow-up periods (often not longer than 6-12 months) make data unhelpful when investigating LPRD recurrences.

Lastly, even if accurate diagnoses and appropriate therapies are ensured, an additional confounding factor could be represented by the scarce compliance of patients towards treatment (poor adherence to dietary restrictions, inappropriate lifestyle, inaccurate timing of medications). According to Barrison et al., poor compliance may represent the first reason for therapeutic failure and a chronic-recurrent clinical course [99].

Conclusions

Although surgical, pharmacological and behavioural therapies for non-oncological voice disorders are widely provided in everyday clinical practice, data on failures and relapse has been little explored. The frequency and the duration of follow-up after treatment for non-oncological voice disorders are heterogeneous, highlighting the need to develop consensus in this area. The available data suggests that failures and relapses are not rare; this information should be regularly transferred to patients before any therapeutic planning. Treatment of failure and relapses is rarely reported; therefore, at the current state of knowledge, it should be decided on the basis of the experience and the skills of each team, which should include at the very least a phonosurgeon, a phoniatrician and a speech and language pathologist. The data from this non-systematic review underlines the urgent need for further research in this area.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Author contributions

CR: literature review, paper writing, paper corrections; FM: literature review, supervision; MRB: literature review, paper editing; MB: literature review, paper editing; GC: literature review, paper editing; FD: literature review, paper editing; MG: literature review, paper editing; SR: literature review, paper editing; AS: supervision, paper writing, paper corrections.

Ethical consideration

Not applicable.

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