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Surgery for lower extremity symptomatic neuroma: Long-term outcomes

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Summary *Introduction:* Traumatic neuroma caused by injuries or surgery can result in neuropathic pain, functional impairment, and psychological distress, which has an impact on quality of life. The aim of this study was to identify the factors related to successful treatment of symptomatic lower extremity symptomatic neuromas using patient-reported outcome measures (PROMs).
Methods: Thirty-two patients with 48 symptomatic neuromas completed the PROMIS mobility, PROMIS pain interference (PI), Numeric Rating Scale (NRS) for pain (0–10) for both pre- and post-operative pain, and the PROMIS depression at a mean of 8.9±4.5 years following neuroma surgery. Neuromas were located around the foot and ankle (n=18, 38%), leg (n=14, 29%), around the knee (n=13, 27%), and in the thigh (n=3, 6.3%). Surgical treatment included neuroma excision and implantation (n=29, 60%) followed by neuroma excision alone or excision with placement in the subcutaneous tissue (n=12, 25%). We performed multivariable analysis to identify the factors influencing the PROMs.
Results: Patients reported significant reduction in mean NRS pain after surgery (7.3 vs 4.9, p=0.0013). Higher PROMIS depression scores were independently associated with inferior PROMIS mobility scores (β=-0.38, p=0.001), higher PROMIS PI scores (β=0.68, p<0.001), and higher NRS pain scores (β=0.1, p=0.001). Additionally, smoking was independently associated with higher NRS pain scores (β=1.59, p=0.049)
Conclusion: Surgical treatment of symptomatic neuromas of the lower extremity provides a long-term improvement in 59% of patients, but 19% of patients still reported severe persistent

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pain despite surgical treatment. Smoking and negative mood have negative effects on patient-reported outcomes after neuroma surgery.

Introduction

A neuroma is a disorganized growth of nerve tissue caused by injury or surgery and can result in neuropathic pain, functional impairment, and psychological distress, leading to reduction in quality of life.[1] Neuromas can be caused by multiple mechanisms, including transection, contusion, or stretch injuries. After nerve injury, patients are at risk of developing a symptomatic neuroma if axonal regeneration is disorganized or if no distal target is available.[2-4] Although the exact pathophysiology of the development of a painful neuroma is unclear, mechanism of injury has been suggested as a contributing factor.[5,6] Patients diagnosed with symptomatic neuroma have neuropathic-type pain in a defined neural anatomical distribution along with a history of nerve injury. Furthermore, at least one of following three objective criteria should be met: 1) positive non-advancing Tinel sign; 2) positive response to local anesthetic injection; or 3) confirmation by ultrasound or magnetic resonance imaging.[7] The treatment of symptomatic neuroma varies depending on the nerve involved as well as physiologic and psychosocial factors of the individual patient. The options include occupational therapy with desensitization, pharmacotherapy, and surgical treatment directed at the specific nerve.[1,5]

Historically, neuroma excision followed by implantation in bone or muscle has been the most common treatment modality, especially in the lower extremity.[8] However, in the past decade, newer techniques actively addressing the terminal nerve end have emerged. These include nerve allograft/autograft reconstruction, centro-central neurorrhaphy, end-to-side neurorrhaphy, relocation nerve grafting, targeted muscle reinnervation (TMR), and regenerative peripheral nerve interface (RPNI).[9-14] Recent studies have shown that nerve repair or reconstruction leads to fewer reoperations and improved patient-reported outcomes than nerve excision alone.[15-17]

The **s**urgical treatment of symptomatic neuroma can decrease pain and improve quality-of-life metrics.[18-20] However, studies have shown variable outcomes and most studies are based on a small numbers of patients.[21-25] Therefore, the aim of this study was to identify the factors influencing patient-reported outcome measures (PROMs) after surgical treatment of symptomatic neuroma in the lower extremity.

Materials & methods

This retrospective cohort study was performed after Institutional Review Board approval. We identified patients who underwent surgery for symptomatic neuroma of the lower extremity at one of five academic hospitals between January 2002 and April 2016 using Current Procedural Terminology (CPT) codes .[16] This initial query yielded 278 patients; 115 patients were excluded because they underwent an additional operation at the time of neuroma surgery. We also excluded 58 patients with diagnosis of Morton's neuroma and two patients with diagnosis of cluneal neuroma. A total of 103 patients were contacted by letter and phone to complete the patient-reported outcome questionnaires, of which 32 (31%) participated. **There were no demographic differences amongst participants and non-participants.** Eight of the 32 patients have previously been reported on **in a retrospective case series using only epidemiological data, without long-term outcomes.**[8] There were no demographic differences amongst the patients who did and did not complete questionnaires (Appendix 1).

A medical chart review was performed to collect patient-, neuroma-, and treatment-specific factors. A terminal neuroma was defined as a neuroma without a distal target (e.g. amputation-stump neuroma or end neuroma). A neuroma in-continuity was defined as any neuroma with a distal nerve target available for reconstruction.[15] Some patients underwent neuroma surgery exclusively proximal to the site of the symptomatic neuroma; these were placed into a third group. Pain relief following diagnostic injection, if performed, was based on the medical charts and defined as 1) significant relief (recorded as complete relief or greater than or equal to 70% relief); 2) partial relief (less than 70% relief); and 3) no relief (reported no change in pain). Numeric Rating Scale (NRS) for pain was considered to be clinically improved if there was a decrease of two points between pre- and post-operative pain scores, based on a previously reported minimal clinically important difference (MCID) amongst chronic musculoskeletal pain patients.[26] Because of sample-size considerations, we grouped surgical intervention as muscle/bone implantation versus other surgical techniques for the purposes of our analysis. The age reported is the age at time of completion of the questionnaire. Follow-up was defined as the date of last neuroma surgery until the date of completion of the questionnaires.

Study population

A total of 48 neuromas of the lower extremity in 32 patients were analyzed; nine patients underwent surgery for multiple neuromas. The mean patient age was 59.7 years (SD: 10.8) and the median follow-up time was 8.4 years (interquartile range (IQR): 5.3–12.8). There were 17 males (53%) and 15 females (47%), and half (n=16, 50%) were smokers (Table 1). The cause of symptomatic neuroma included prior surgery (n= 27, 84%) and trauma (n=4, 13%). In one patient, the cause of neuroma could not be identified from the medical chart. In this study, total knee arthroplasty (n=5) and soft tissue excision or biopsy (n=5) were the most common surgical procedures that resulted in a symptomatic neuroma (Table 2).

Table 1 Patient characteristics.

Patient characteristics (n=32)	
Age: years	
Mean (SD)	59.7 (10.8)
Gender, n (%)	
Male	17 (53.1)
Female	15 (46.9)
Diabetes, n (%)	
Yes	3 (9.4)
No	29 (90.6)
Smoking, n (%)	
Yes	16 (50)
No	16 (50)
Cause of neuroma, n (%)	
Surgery	27 (84.4)
Trauma	4 (12.5)
Unknown	1 (3.1)
Amputation, n (%)	
Yes	2 (6.3)
No	30 (93.8)
Number of neuroma surgeries, n (%)	
>1	11 (34.4)
1	21 (65.6)
Pre-operative diagnostic injection, n (%)	
Yes	22 (68.8)
No	10 (31.3)
Result of pre-operative diagnostic injection*, n (%)	
Significant relief	16 (72.7)
Partial relief	5 (22.7)
No relief	1 (4.6)

* n=22.

Table 2 Surgical cause of neuroma (n=27).

Knee arthroplasty	5
Excision mass or biopsy	5
Wound debridement	3
Ankle arthroscopy	3
Ankle fracture fixation	2
Achilles tendon repair	2
Flap reconstruction	2
Below knee amputation	2
Knee arthroscopy	1
Ankle ligament reconstruction	1
Ankle arthrodesis	1

The sural (n=12, 25%) and saphenous nerves (n=12, 25%) were most commonly involved and a terminal neuroma was found in two-thirds (67%) of the patients (Table 3). Five patients had surgery proximal to the neuroma without distal nerve exploration, all of whom were diagnosed pre-operatively using a diagnostic injection resulting in significant or complete pain relief. Eighteen neuromas (38%) were located at the level of the foot and ankle, 14 neuromas (29%) at the level of the leg, 13 neuromas (27%) at the level of the knee, and three neuromas (6.3%) in the thigh (Figure 1).

Table 3 Neuroma characteristics.

Neuroma characteristics (n=48)	
Nerve, n (%)	
Sural nerve	12 (25.0)
Saphenous nerve	12 (25.0)
Superficial peroneal nerve	7 (14.6)
Deep peroneal nerve	4 (8.3)
Femoral nerve	4 (8.3)
Common peroneal nerve	2 (4.2)
Lateral femoral cutaneous nerve	2 (4.2)
Sciatic nerve	2 (4.2)
Tibial nerve	2 (4.2)
Unspecific cutaneous nerve	1 (2.1)
Type of neuroma, n (%)	
Terminal neuroma	32 (66.7)
Neuroma in-continuity	11 (22.9)
Unknown*	5 (10.4)
Type of surgery, n (%)	
Implantation	29 (60.4)
Muscle	19 (65.5)
Bone	10 (34.5)
Excision alone/left in subcutaneous tissue	12 (25)
Neurolysis	3 (6.3)
Excision repair/reconstruction	2 (4.2)
Excision with alloderm wrapping	2 (4.2)

* Surgery proximal to site of neuroma.

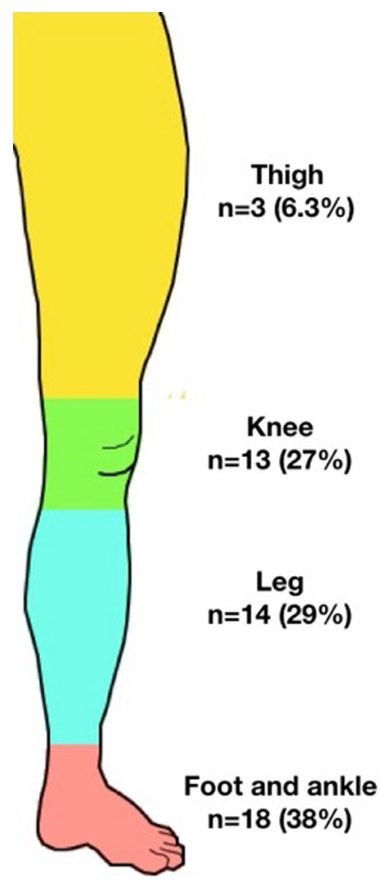

Figure 1 The location of symptomatic lower extremity neuromas.

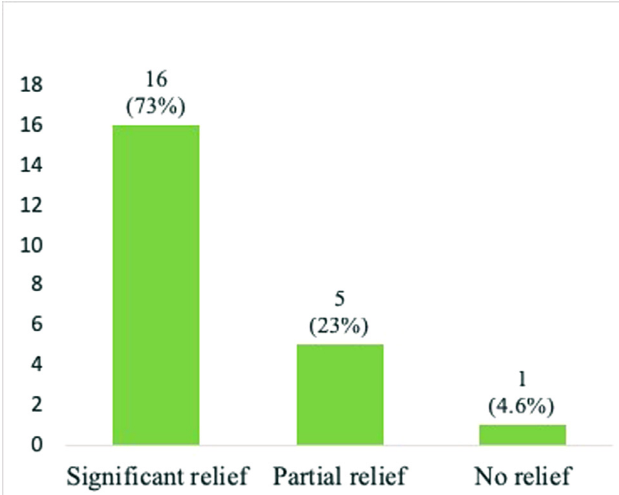

Figure 2 The result of diagnostic injection.

A diagnostic injection prior to surgery was performed in 22/32 patients (69%). Sixteen patients (73%) reported significant relief after injection, five patients (23%) reported partial relief, and one patient had no improvement in pain prior to undergoing surgery for symptomatic neuroma (Figure 2). The most frequent surgical treatment was neuroma excision and muscle/bone implantation (n=29, 60%). Of these, 19 nerve ends (66%) were implanted in muscle and 10 nerve ends (34%) were implanted into bone. Other treatments included neuroma excision alone or excision with placement in the subcutaneous tissue (n=12, 25%), neurolysis alone (n=3, 6.3%), excision with nerve repair/reconstruction (n=2, 4.2%), and excision with AlloDerm wrapping of nerve end (n=2, 4.2%; Table 3). Neuromas were treated by orthopaedic surgeons (n=17, 53%), plastic surgeons (n=12, 38%), neurosurgeons (n=2, 6.3%), and by a general surgeon in one patient (3.1%).

Patient-reported outcomes

The PROMs used were the PROMIS mobility v.2.0 computer adaptive testing (CAT), PROMIS depression v.1.0 CAT, PROMIS pain interference (PI) v.1.1 CAT, and the NRS for pain (0-10) for both pre- and post-operative pain. The PROMIS mobility assesses the self-reported function of the lower extremities and the PROMIS PI assesses patient's ability to cope with pain and the self-reported effect of pain on daily activities. The PROMIS depression was collected to assess whether depression confounded other patient-reported outcomes, as has been shown in the past.[15] The PROMIS depression assesses the self-reported negative mood, view of self, social cognition, affect, and engagement, where a higher score correlates with more depressive symptoms. A previous study reported that a PROMIS depression score of 58.6-64.7 indicates moderate depression, a score of 64.7-70.3 indicate moderate/severe depression and a score of more than 70.3 indicate severe depression.[27] For the PROMIS mobility, PROMIS PI, and PROMIS depression, a score of 50 is the average for the United States general population with standard deviation of 10. Pain severity using the NRS pain score was grouped as severe pain (NRS≥8), moderate pain (NRS=6-7), mild pain (NRS≤5), and no pain at all (NRS=0).[28]

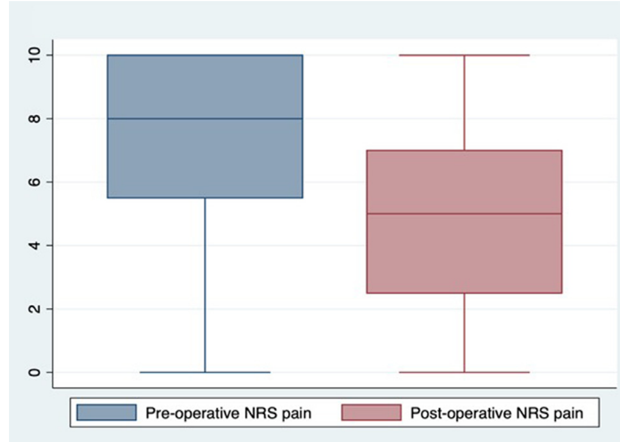

Figure 3 The diagram for comparison of pre- and post-operative NRS pain scores.

Study data were collected using REDCap (Research Electronic Data Capture) electronic data capture tool hosted at our institution.[29] REDCap is a secure, web-based application which designed for data collection in research study. The system provides 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for accurate data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Statistical analysis

Categorical variables were reported as frequencies and percentages, normally distributed continuous variables were reported as mean and standard variation, and non-normally distributed continuous variables were reported as median with IQR. To compare pre- with post-operative NRS pain scores, we used a Wilcoxon signed-rank test. To evaluate the influence of explanatory variables on PROMIS mobility scores, PROMIS PI scores and NRS post-operative pain scores, we used linear regression for continuous variables, dichotomous variables, and categorical explanatory variables. To adjust for confounding, we selected all explanatory variables with a p-value < 0.1 in bivariate analysis and included them in a multivariable linear regression model using generalized estimating equations. All analyses were performed using STATA 13.0 (STATA Corp, College Station, USA).

Results

At the time of last follow-up, patients overall reported significant reduction in mean NRS pain after surgery (7.3±3.0 vs 4.9±3.2), p=0.0013; Figure 3). Nineteen patients (59%) had post-operative pain improvement exceeding the MCID. Six (19%) patients continued to report severe pain (NRS≥8), nine patients (28%) reported moderate pain (NRS=6-7), 10 patients (31%) reported mild pain (NRS≤5), and 7 patients (22%) reported no pain at all (NRS=0).

Table 4 Patient-reported outcomes.

		PROMIS mobility mean (SD)	PROMIS PI median (IQR)	NRS pain mean (SD)
Overall		40.0 (9.8)	61.9 (50.5, 67.2)	4.9 (3.2)
Patient factors				
Age (coefficient)		-0.075	0.18	0.09
	P-value	0.65*	0.57*	0.08*
Gender				
Male		38.6 (8.7)	60.4 (12.9)	5.5 (2.8)
Female		41.4 (10.9)	56.1 (12.6)	4.2 (3.4)
	P-value	0.43*	0.36*	0.26*
Smoking				
Yes		38.2 (8.9)	59.9 (11.7)	6.1 (2.6)
No		41.6 (10.5)	56.8 (13.8)	3.7 (3.3)
	P-value	0.33*	0.51*	**0.03***
Diabetes				
Yes		27 (8.3)	68.5 (6.3)	4.3 (4.0)
No		41.4 (9.0)	57.1 (12.8)	4.9 (3.1)
	P-value	**0.013***	0.15*	0.76*
Number of neuroma surgeries, n (%)				
> 1		35 (9.3)	64.4 (8.5)	5.9 (2.5)
1		42.3 (9.3)	55.2 (13.5)	4.3 (3.4)
	P-value	**0.048***	0.06*	0.18*
PROMIS depression (coefficient)		-0.43	0.67	0.092
	P-value	**0.002***	**<0.001***	0.076*
Neuroma factors				
Surgical treatment				
Excision and implantation		39.3 (7.2)	61 (12.9)	5.3 (2.8)
Other		36.7 (13.0)	60.4 (10.8)	6.2 (3.3)
	P-value	0.38*	0.86*	0.31*
Neuroma location				
Foot and ankle		40.2 (7.8)	58.6 (14.2)	4.7 (2.6)
Leg		31.3 (8.9)	65.2 (5.2)	6.7 (4.1)
Knee		44.1 (10.1)	58.0 (13.5)	5.7 (2.0)
Thigh		35.9 (9.3)	65.5 (10.6)	6.3 (1.5)
	P-value	**0.005***	0.32*	0.25*
Type of neuroma				
End neuroma		37.8 (10.7)	62.2 (10.6)	6.3 (2.2)
Neuroma in-continuity		39.2 (9.8)	55.5 (13.9)	4.5 (4.4)
Other (operate proximal to lesion)		39.5 (5.4)	63.7 (14.8)	3.8 (2.4)
	P-value	0.89*	0.24*	0.08*
Result of pre-operative injection				
Incomplete relief		37.4 (13.1)	61.3 (11.5)	6.6 (1.2)
Complete relief		39.6 (9.1)	60.8 (13.2)	5.3 (3.3)
	P-value	0.55*	0.91*	0.14*

* Using linear regression.

The mean PROMIS mobility score was 40.0±9.8, the mean NRS post-operative pain score was 4.9±3.2, and the median PROMIS PI score was 61.9 (IQR: 50.5-67.2; Table 4). In multivariable analysis, higher PROMIS depression scores were independently associated with inferior PROMIS mobility scores (β=-0.38, 95% CI: [-0.6, -0.16], p=0.001), higher PROMIS PI scores (β=0.68, 95% CI: [0.38, 0.97], p<0.001), and higher NRS pain scores (β=0.1, 95% CI: [0.04-0.16], p=0.001). Additionally, smoking was independently associated with higher NRS pain scores (β=1.59, 95% CI: [0.01, 3.2], p=0.049; Table 5).

Discussion

There are several limitations in this study which should be considered when interpreting the results. First, there were 32 patients who participated in our study: only 31% of all initially identified patients. We did not identify demographic differences amongst patients that participated and those who did not. The low response rate is likely due to the long time that elapsed after the neuroma surgery, which has been shown to negatively influence the response rate.[30] Second, this study reports the result of older

Table 5 Multivariable linear regression.

PROMIS mobility score				
Variable	Coefficient	SE	95% CI	P-value
PROMIS depression score	-0.38	0.11	[-0.60, -0.16]	0.001
More than 1 surgery	0.55	2.7	[-4.7, 5.8]	0.21
Diabetes	-1.4	5.4	[-12.1, 9.3]	0.8
Location (ref: foot and ankle)				
Leg	-1.39	2.72	[-6.72, 3.95]	0.61
Knee	4.17	2.47	[-0.68, 9.0]	0.09
Thigh	-1.85	4.61	[10.9, 7.2]	0.69
PROMIS PI Score				
Variable	Coefficient	SE	95% CI	P-value
PROMIS depression score	0.68	0.15	[0.38, 0.97]	<0.001
More than 1 surgery	-1.95	3.75	[-9.3, 5.4]	0.6
NRS post-operative pain score				
Variable	Coefficient	SE	95% CI	P-value
PROMIS depression score	0.1	0.03	[0.04, 0.16]	0.001
Age	0.02	0.04	[-0.05, 0.09]	0.58
Smoking	1.59	0.8	[0.01, 3.2]	0.049
Type of neuroma (ref: terminal neuroma)				
Neuroma in-continuity	-1.1	0.9	[-2.8, 0.72]	0.24
Other (operated proximal to lesion)	-1.6	1.3	[-3.9, 0.96]	0.24

surgical techniques for neuroma management, as 60% were treated with excision and implantation and most others were treated with excision of the neuroma alone (25%). As a result, these data may represent outcomes for traditional surgical techniques, and do not give insight into current movement to treat nerve ends actively such as with nerve graft reconstruction, TMR, RPNI, or relocation nerve grafting.[31-33] Third, there may be recall bias in our study, especially when assessing the pre-operative NRS pain score as the follow-up time is long. Lastly, there is a high percentage (50%) of smokers in our study, which may reflect selection bias or may reflect the relationship between smoking and symptomatic neuroma.

This long-term study evaluated 32 patients with 48 symptomatic lower extremity neuromas at a median follow-up of 8.4 years and showed post-operative pain reduction, of which 59% were clinically significant according to the **MCID amongst chronic musculoskeletal pain patients.**[26] Most symptomatic neuromas were treated with excision followed by implantation into muscle or bone, and we were not able to differentiate the effect of specific surgical technique on outcomes. We found that patients with negative mood, based on the PROMIS depression, had significantly worse pain, along with inferior PROMIS PI and PROMIS mobility scores. In addition, we also observed that smoking was associated with higher post-operative pain scores.

Generally, patients with symptomatic neuromas should initially be treated with desensitization, physical/occupational therapy, and non-opioid medications, however, the results of non-operative treatment vary; for patients with recalcitrant neuropathic pain, surgery should be considered.[1] Our study demonstrated an overall improvement in pain following neuroma surgery; there were 19 patients (59%) who had improvement in pain exceeding the MCID. There were an additional two patients that had a pain reduction of 1-point on the NRS pain score, and six experienced no change in pain. Six patients (19%) reported severe pain (NRS $\geq$8) at final follow-up. It is important to be aware that the MCID was based on patients with chronic pain due to osteoarthritis of the knee, hip, or hand, rheumatoid arthritis or ankylosing spondylitis, with median baseline NRS pain scores of 5–6.5 depending on the diagnosis, whereas patients with a symptomatic neuroma in our study had a median baseline NRS pain score of 8. A specific MCID for neuroma patients is yet to be calculated.

Overall, our data emphasize that the outcomes for neuroma excision and implantation alone are modest. Contemporary treatments for neuroma such as allograft reconstruction, TMR, or RPNI have demonstrated improved pain compared with conventional techniques, especially in amputees.[13,31,33] Surgical techniques that "actively" address the nerve end may further improve the treatment outcomes of surgery for lower extremity neuroma.[32,34] A recent study on upper extremity amputees reported that none of the 26 patients who underwent TMR developed new neuroma pain and that 14 of 15 patients treated for a neuroma had complete pain relief.[13] Another study reported the outcomes after RPNI treatment in 16 upper or lower extremity amputees with 71% reduction in neuroma pain and 53% reduction in phantom limb pain.[33] These newer techniques typically do not require exploration of the distal neuroma, as long as the nerve is transected proximally and addressed effectively. This approach may be appropriate in patients with a clear diagnosis of symptomatic neuroma, if the nerve does not have a distal function.[7] Further prospective study is required to determine the effectiveness of newer, active techniques for lower extremity neuroma management, such as allograft reconstruction, TMR, and RPNI.

It is suggested that diagnostic injection may help predict outcomes after surgery.[35] We did not find this was correlated with outcome in the 22 patients who underwent pre-operative diagnostic injection in this study; however, our study was not powered to study this specific question. We observed that in the seven patients without NRS pain improvement post-operatively, three had significant relief, three had partial relief, and one had no relief following diagnostic injection. In comparison, amongst the patients experiencing NRS pain improvement after surgery, two had partial relief and 12 had significant relief following diagnostic injection.

The NRS pain scores were higher amongst smokers and patients with higher PROMIS depression scores in this study. These results are consistent with previous reports which have shown that patients with a negative mood and poor coping strategies tend to have inferior results after surgery.[36-40] This also occurs in patients with chronic pain, where smokers experience more pain and worse functional and psychological outcomes compared with non-smokers.[41] The fact that smokers had increased pain may be related to the higher anxiety levels and inferior coping skills.[42-44] Another explanation for increased pain in these patients is that nicotine may lead to hypersensitivity.[42]

In this study, the mean PROMIS mobility score was lower than the average of the United States normal population. The patients in this cohort were relatively old, with a mean age of 59.7 years, which may in part explain diminished mobility. We found that the main factor negatively influencing PROMIS mobility was higher PROMIS depression scores. Many previous studies demonstrate the relationship between depression and functional scores.[37-40] Amongst patients undergoing total knee or total hip arthroplasty, those with lower pre-operative scores on psychological measures (e.g. depression, anxiety) had lower post-operative pain and better functional outcomes.[45] This highlights the relationship between function and psychosocial well-being, and based on our results, patients with persistent high PROMIS depression scores following neuroma surgery may benefit from addressing this to optimize surgical outcomes.

In current study, the only factor found to have a significant correlation with the PROMIS PI was PROMIS depression score. The older age of the patients in this cohort may explain this, as their ability to cope with pain may be inferior as PROMIS PI scores are positively correlated with age.[38] Decreased resilience in older patients may be a reason for the inferior coping skills.[46,47] Additionally, this is similar to our previous findings in patients with an upper extremity condition showing that higher PROMIS PI scores were independently associated with the diagnosis of major depression.[37,48]

Our findings have shown an important role of mood, measured in the form of PROMIS depression, on the outcomes of lower extremity neuroma surgery. However, it is difficult to determine the directionality of its impact. It may be that patients with (persistent) symptomatic neuroma develop depressive mood as a result of the pain and impairment, and it could also be that depressed patients experience higher levels of the aforementioned. This bi-directional impact of chronic illness has been previously described in patients with fibromyalgia syndrome.[49] The interaction between depression and pain has been labeled as the depression–pain syndrome, as these conditions often coexist, respond to similar treatment, exacerbate one another, and share biological pathways and neurotransmitters.[50-52] Therefore, it is important to recognize patients with depressive symptoms because treatment of pain and mood should be mutually addressed.

In conclusion, surgical treatment of symptomatic neuromas of the lower extremity provides a long-term improvement in 59% of patients, but 19% of patients still reported severe persistent pain despite surgical treatment. Smoking and negative mood have negative effects on patient-reported outcomes after neuroma surgery. Further investigation focusing on the use of novel surgical techniques for lower extremity symptomatic neuroma should be evaluated along with addressing psychological well-being.

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Author contributions

Study design: NA, JL, NC, KRE; Data assembly: NA, JL, AM; Data analysis: NA, JL, AM, RFS, KRE; Initial draft: NA, JL, AM, RFS, NC, KRE; Final approval of manuscript: NA, JL, AM, RFS, NC, KRE.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2020.01.034.

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