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Neuropathic pain at the donor-site following free fibula flap harvest: A multicenter study

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Summary *Background:* The free fibula flap (FFF) is widely used and considered the workhorse flap for osteocutaneous head and neck reconstruction. Donor-site morbidity is considered to be low and mild, and has therefore received little attention. Although sensory deficits and chronic pain have been reported in the donor-site, the incidence of neuropathic pain remains unclear. This study aimed to identify the incidence and prognostic factors associated with neuropathic pain at the donor-site following FFF harvest and investigate its impact on leg function and quality of life.
Methods: In this multicenter, cross-sectional study, 150 patients who underwent FFF surgery between 2010–2020 were included. Baseline characteristics were collected. All patients received questionnaires to measure self-reported pain (Doleur Neuropathique 4 and visual analog scale Pain), leg function (Lower Extremity Functional Scale), and quality of life (EuroQol-5D). Multivariable regression analysis was used to identify prognostic factors associated with the outcomes.
Results: A total of 82 patients completed the questionnaires. Neuropathic pain was present in 21% of the patients. Multivariable analysis revealed that donor-site complications (p=0.025) and younger age (p=0.003) were independently associated with neuropathic pain. No difference in neuropathic pain incidence was found between primary and skin graft closure (p=0.54). Patients with neuropathic pain showed a significantly poorer quality of life (p=0.01).
Conclusion: One-fifth of all patients experienced neuropathic pain at the donor-site following FFF harvest. Younger patients and patients with donor-site complications are more prone to developing neuropathic pain. Future research should focus on analyses of surgical factors and optimalization of wound care to reduce the incidence of neuropathic pain.

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The free fibula flap (FFF) is widely used in reconstructive microsurgery. Since it was first described in 1975 by Taylor,[1] it has functioned as the workhorse for osteocutaneous reconstruction in the head and neck area. Donor-site morbidities associated with FFF are generally considered to be low and mild, and therefore it has received relatively little attention. The most commonly reported donor-site morbidities of the FFF include wound dehiscence or delayed wound healing, sensory deficits, and gait disturbance. Depending on the defect size, the donor-site is closed primarily or using a skin graft. A prospective trial by Momoh et al. that included 157 patients showed no difference in complication rates between both the closure methods.[2]

Various studies have investigated sensory problems at the FFF donor-site. A systematic review by Ling et al. reported that 21% of all patients experience sensory deficits following FFF harvest, mostly due to damage to the peroneal nerve.[3] In addition, they reported that 10% experience cold intolerance and 6.5% experience chronic pain. However, owing to the retrospective nature of most included studies and the absence of validated pain questionnaires, the latter percentage is most likely to be an underestimation. So far, no studies have elaborated on the origin or extent of these sensory deficits, or how often neuropathic pain may have been present.

Neuropathic pain occurs spontaneously pain without evident stimuli, which may be accompanied by sensory deficit, allodynia, or dysesthesia, such as a burning or electrical sensation. Neuropathic pain develops as a direct consequence of a lesion or disease affecting the somatosensory system; however, its exact pathology and mechanism are yet to be determined.[4] Neuropathic pain has been associated with a poorer quality of life compared to other chronic diseases including heart failure or type 2 diabetes.[5]

Although earlier studies have reported on the occurrence of chronic pain,[2-4] no studies have focused on the exact incidence of neuropathic pain following FFF harvest. Therefore, the aim of this study was to identify the incidence of and prognostic factors for neuropathic pain at the FFF donor-site. In addition, this study aimed to investigate the impact of neuropathic donor-site pain on the patients' leg function and quality of life.

Methods

After medical ethical committee approval (MEC-2021-0066), we retrospectively identified all consecutive adult patients who underwent FFF harvest between January 2010 and December 2020 at 2 academic medical centers (n=273). A total of 120 patients had deceased and 3 patients were excluded because of poor understanding of Dutch or English, and the remaining 150 patients were invited to participate in this study. We followed the STROBE guideline for cross-sectional studies.

Questionnaires

A set of 4 questionnaires were sent to the patients to investigate the incidence of neuropathic donor-site pain, general lower leg and/or foot pain, lower extremity function, and quality of life. The Doleur Neuropathic 4 (DN4) is an internationally validated questionnaire specifically designed to identify neuropathic pain and includes 7 questions about the presence of indicators for neuropathic pain.[6] A score of 4 or more is considered as neuropathic pain.[7] The visual analog scale (VAS, Pain) is a widely used and validated psychometric measure instrument used to determine the subjective level of pain, which was used to score pain levels in the lower leg and foot. A score of 3 or more was considered clinically significant pain.[8] The lower extremity functional scale (LEFS) is a validated questionnaire for pain and function solely for the affected lower extremity. The questionnaire includes 20 questions each with a maximum score of 4 points, where a total score of 80 represents perfect function. Finally, the EuroQol 5D (EQ-5D-5L) is a widely used and validated generic and preference-based health-related quality of life (HR-QoL) measure. It is a multi-attribute instrument, which considers 5 dimensions including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with a total health-state score ranging from 0 (death) to 1 (perfect health).[9]

Data extraction

Prior to the administration of the questionnaires, medical records were reviewed to collect data regarding patient demographics, surgery characteristics, and post-operative complications. Follow-up time was defined as the time from surgery to the last clinical visit recorded in the medical charts. Patient demographics included age, gender, comorbidities (diabetes and smoking), and body mass index. Surgery characteristics included indication for FFF, flap size, inclusion of a skin island, harvesting a part of the flexor hallucis longus (FHL) muscle, and type of closure at the donor-site. Post-operative characteristics included complications, reoperations, and wound problems. Complications were classified into minor (Clavien Dindo score 1–2) or major (Clavien Dindo score ≥3) complications.[10]

Statistical analysis

Categorical variables are presented as absolute values and percentages. Continuous variables are presented as median and interquartile range (IQR). To evaluate the prognostic factors associated with neuropathic pain, univariate analyses were performed using the Fisher's exact test for

categorical variables and Mann-Whitney U-test for non-parametric outcomes. A multivariable regression analysis was performed to correct for any potential confounding factors. A two-sided p-value of < 0.05 was considered statistically significant for all tests. All analyses were performed using STATA 14.0 (StataCorp, Texas, USA).

Results

Study population

The cohort comprised 150 patients including 64 men (43%) and 86 women (57%), with a median age of 61 years (IQR: 49-69 years). The median length of follow-up was 5.0 years (IQR: 3.2-7.5 years) after surgery. Most patients received an FFF for oncological reconstructions (76%). Other indications included reconstruction after trauma (13%), mandibular osteo(radio)necrosis (8.7%), or benign tumor excision (2.7%). Preoperative angiographic computed tomography (CTA) scans were performed in 99 (66%) patients. In 18% of the patients who underwent CTA, mild atherosclerosis or stenosis was found in the femoral or popliteal artery tract (Table 1). A total of 82 patients (55%) completed the questionnaires. No significant differences were found between the respondents and non-respondents, thus we assume that the respondents represent the total cohort (Appendix 1).

Neuropathic pain and impact

In general, 27% of all patients experienced long-term postoperative lower leg pain with a median VAS-score of 5.0 (Table 2). In 21% of all patients, a score of 4 or higher for the DN4 questionnaire was recorded, indicating neuropathic pain (Figure 1). Among the neuropathic pain indicators, hypoesthesia was most commonly present (49%), followed by paresthesia (28%), itching (23%), stinging (23%), burning sensation (18%), cold intolerance (17%), and electrical shocks (12%; Figure 2). Neuropathic pain was significantly associated with lower scores on the LEFS (p=0.01) and EQ-5D-5 L (p=0.01) questionnaires, both suggesting poorer leg function and HR-QoL (Table 3).

Surgical details of the donor-site

Most donor-sites were closed with a skin graft (55%), either with a split-skin graft (42%) or a full-thickness skin graft (13%). Primary closure was performed in the other patients (45%). The flexor hallucis longus muscle was partly included in the flap for 67 patients (45%). Most (92%) flaps were osteocutaneous, and 8% were osseous flaps. No statistically significant associations were found between neuropathic pain and closure type (p=0.53), FHL inclusion (p=0.55), or skin island inclusion (p=0.19; Table 4).

Table 1 Patient characteristics.

Characteristic	All patients (n=150)
Age, median (IQR)	61 (49 - 69)
Male gender, n (%)	64 (43)
Smoking, n (%)	40 (27)
Diabetes, n (%)	18 (12)
BMI, mean (SD)	25 (4.9)
Artherosclerosis in operated leg*	18 (18)

FFF: free fibula flap; IQR: interquartile range; BMI: body mass index; SD: standard deviation;
* total n= 99

Table 2 Outcomes following FFF harvest.

Characteristic	All patients (n=82)
Neuropathic pain in donor-site, n (%)	17 (21)
Leg pain, n (%)	22 (27)
VAS score, median (IQR)	5 (4 - 6)
LEFS score, median (IQR)	71 (62 - 79)
EQ5D index, median (IQR)	0.9 (0.8 - 1.0)

FFF: free fibula flap; VAS: visual analog scale; IQR: interquartile range; LEFS: lower extremity functional scale; EQ5D: EuroQol of life

Complications

Donor-site complications occurred in 33% of all 150 patients. Univariate analysis showed a statistically significant association between donor-site complication and neuropathic pain (p=0.02; Table 4). Among all donor-site complications, 69% were classified as minor and 31% as major complications. Minor donor-site complications included delayed wound healing, superficial wound infection, and partial skin graft necrosis. Major complications included complete skin graft necrosis, abscess formation requiring incision and drainage, and compartment syndrome in 1 patient. Most major complications (53%) required reoperation, which was in 5% among all patients. Undergoing reoperation owing to a major complication at the donor-site was significantly associated with neuropathic pain in univariable analysis (p=0.03; Table 4).

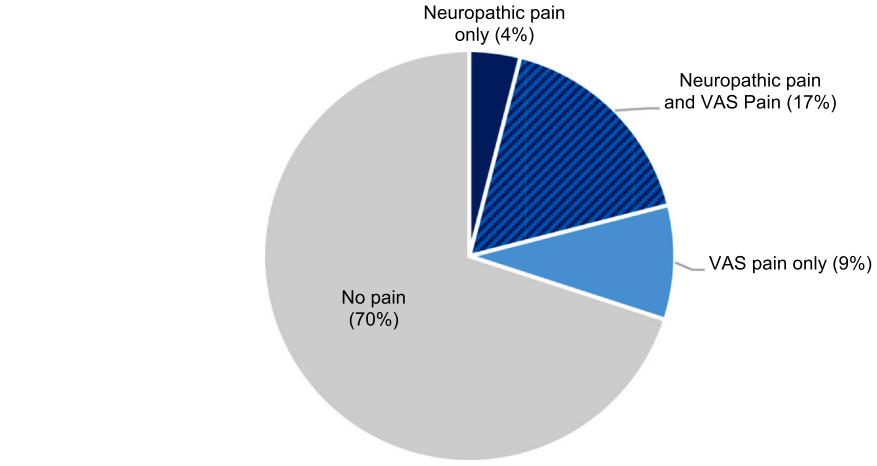
Multivariable analysis

Patients with neuropathic pain were significantly younger (p=0.02; Table 3) and younger age was independently associated with a higher likelihood of developing neuropathic pain (OR 0.94, 95% CI 0.91-0.98, p=0.003; Table 5). In addition, having a complication at the donor-site was also independently associated with neuropathic pain (OR 7.6, 95% CI 2.0-30, p=0.003; Table 5).

Discussion

In this multicenter study, 21% of all patients experienced neuropathic pain at the donor-site following FFF harvest. In total, 150 patients with a median follow-up of 5 years were included. Prognostic factors including a younger age and donor-site wound complications were associated with neuropathic pain. Patients with neuropathic pain at the donor-site reported a significantly poorer quality of life.

The FFF is an important flap in osseous reconstruction (Figures 3 and 4).[11] It is considered the gold standard for all significant osseous defects, mostly including mandibular



FFF: free fibula flap; VAS: visual analog scale

Figure 1 Incidence of pain following FFF harvest.

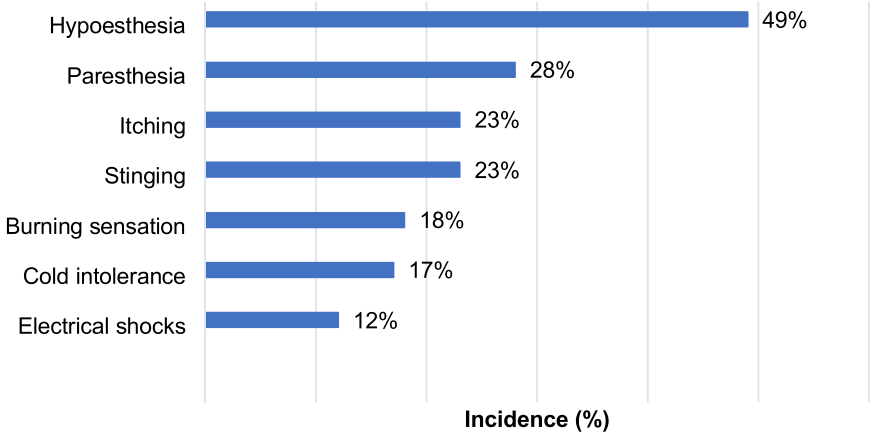


Figure 2 Indicators for neuropathic pain following FFF harvest.

and maxillary bone reconstruction following oncological tumor resection,[11,12] but also of the lower[13,14] and upper extremities.[15,16] Although the FFF provides excellent functional outcomes,[17] with satisfactory functioning of the operated leg,[18,19] neuropathic pain at the donor-site occurs in one-fifth of all patients. Chronic pain with neuropathic characteristics after various lower limb surgeries have been reported in numerous studies, with a prevalence varying

Table 3 Patient characteristics and reported outcomes associated with neuropathic pain in the donor-site following FFF harvest.

Characteristic	Neuropathic pain (n=17)		Non-neuropathic pain (n=65)		
Patient characteristics	*median*	*IQR*	*median*	*IQR*	***P*-value**
Age in years	53	37 - 62	62	56 - 69	0.02
	mean	*SD*	*mean*	*SD*	
BMI	23	2.7	25	5.4	0.06
	n	*%*	*n*	*%*	
Male gender	11	65	26	40	>0.99
Smoking	7	30	16	70	0.23
Diabetes	0	0	10	100	0.11
Atherosclerosis in operated leg	1	9	10	91	0.43
Patient reported outcomes	*median*	*IQR*	*median*	*IQR*	***P*-value**
LEFS	62	46 - 73	73	65 - 80	<0.01
EQ5D	0.8	0.6 - 0.9	0.9	0.8 - 1.0	<0.01

FFF: free fibula flap; IQR: interquartile range; SD: standard deviation; BMI: body mass index; LEFS: lower extremity functional scale; EQ5D: EuroQol-5D

Table 4 Surgery and postoperative characteristics associated with neuropathic pain in the donor-site following FFF harvest.

Characteristic	Neuropathic pain (n=17)		Non-neuropathic pain (n=65)		
Surgery characteristics	*n*	*%*	*n*	*%*	***P*-value**
Indication FFF					0.09
Oncologic	11	17	55	83	
Non-oncologic	6	38	10	62	
FHL included in flap	6	17	29	83	0.55
Closure type					0.53
Primary	7	23	23	77	
Skin graft	5	16	27	84	
Skin island					0.19
Included	14	19	58	81	
Not included	2	50	2	50	
	median	*IQR*	*median*	*IQR*	
Flap size in cm^2	100	50-100	100	60-140	0.78
Postoperative characteristics	*n*	*%*	*n*	*%*	***P*-value**
Donor-site complication					0.02
Yes	11	35	20	65	
No	6	12	45	88	
Complication classification					> 0.99
Minor	8	38	13	62	
Major	3	30	7	70	
Donor-site reoperation					0.03
Yes	3	75	1	25	
No	14	18	64	82	

FFF: free fibula flap; FHL: flexor hallucis longus; IQR: interquartile range

Table 5 Multivariable logistic regression analysis including factors associated with neuropathic pain following FFF harvest.

Characteristic	Odds Ratio	95% Confidence Interval	P-value
Age in years	0.94	[0.91 - 0.98]	0.003
Complication in donor-site	7.6	[2.0 - 30]	0.025

FFF = free fibula flap.

between 10% and 25%.[20,21] However, these studies reported lower limb surgery following minor or major trauma and, so far, no studies have yet examined the prevalence of neuropathic pain after FFF surgery.

The impact of neuropathic pain on the quality of life in this study was in line with a large multicenter retrospective study in the United Kingdom, which found that neuropathic pain of the lower limb after trauma surgery severely affected the quality of life.[20] Moreover, after the quality of life, function of the operated lower leg was also found to be affected by neuropathic pain in our cohort. Although FFF surgery is known to provide good leg function with minimal gait disturbance,[19,22] the presence of neuropathic pain in the lower limb was found to affect leg function.[20]

In our study, the relevant prognostic factors for neuropathic pain after FFF harvest included younger age and having a minor or major wound complications at the donor-site. Our results indicated that younger patients are more prone to developing neuropathic pain. The odds ratio suggests that with every 10-year increase in age, the chance of developing neuropathic pain increases by 1%. Although this percentage may appear relatively small, the finding is in accordance with results of numerous other studies that reported younger age as a significant prognostic factor for developing neuropathic pain following numerous different surgery types.[20,21,23] Furthermore, having a donor-site complication was also independently associated with neuropathic pain. In fact, this odds ratio was over 7 times higher than age, indicating that this is a more relevant predictor of neuropathic pain. No statistical difference was found between minor and major complications. However, our results showed that undergoing reoperation at the donor-site, which in all 4 cases was due to major wound complications including complete necrosis or abscess, was associated with neuropathic pain. Age and donor-site wound complications are important clinical factors in determining patients at higher risk of developing neuropathic pain.

Elaborating on the origin of neuropathic pain complaints following FFF harvest is a highly interesting, yet, difficult matter. It is important to distinguish neuropathic pain from sensory complaints of the skin graft. This study found no statistical differences in the association between neuropathic pain and primary and skin graft closure. Moreover, no differences were found between the groups in the prevalence of the individual neuropathic pain indicators, including hypoesthesia, paresthesia, itching, stinging, burning sensation, cold intolerance, or electrical shocks. These findings align with the results of a large prospective cohort study by Momoh et al., who found no difference in sensory complication rates between primary and skin graft closure at the FFF donor-site.[2] Moreover, FHL muscle inclusion does not influence the flexion strength of the fibula,[24] and our results showed that it does not influence donor-site pain complaints either.

Considering the potential origins for neuropathic pain following FFF harvest, nerve branches are potentially injured

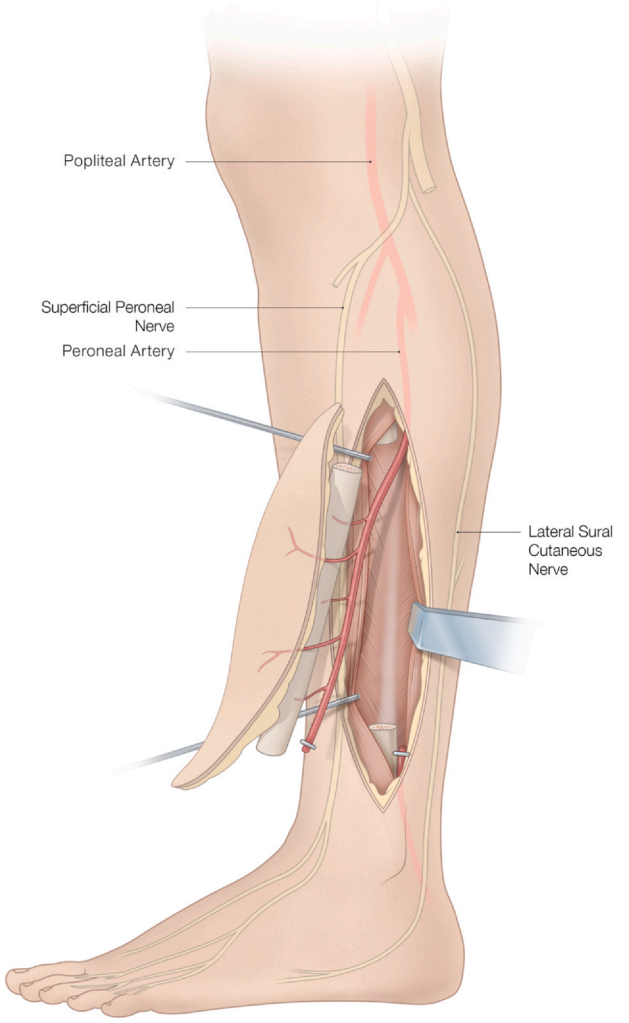


Figure 3 Anatomy of the donor-site of FFF.

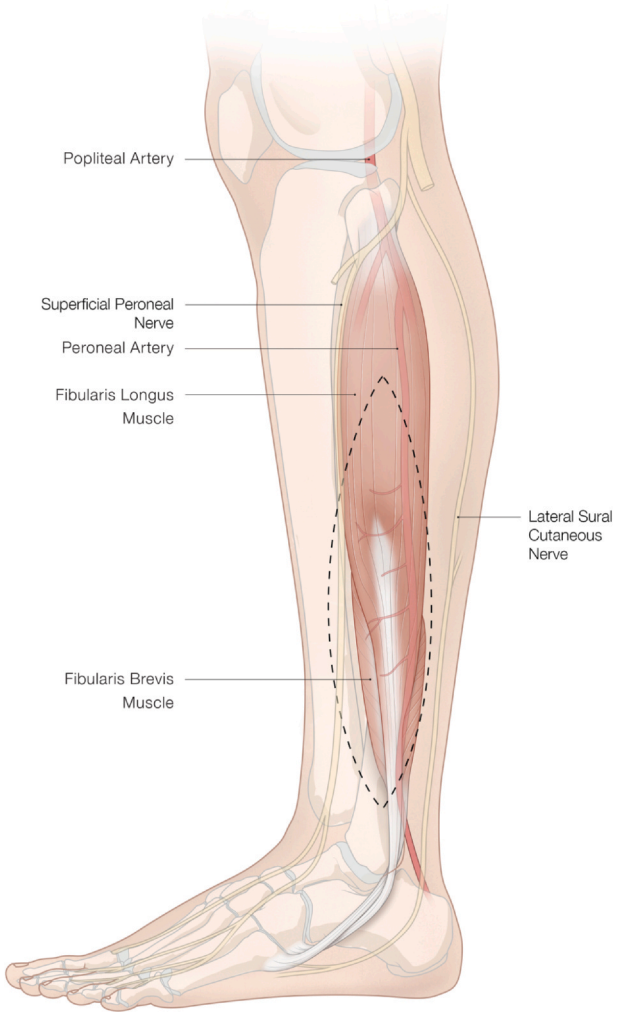


Figure 4 Anatomy of the FFF.

during flap harvesting. The lateral sural cutaneous nerve (LSCN), a branch originating from the common peroneal nerve (CPN) that joins the medial sural cutaneous nerve distally to form the combined sural nerve, is generally responsible for sensation in the lower leg.[25,26] The superficial peroneal nerve, which also originates from the CPN, and LSCN nerve branches are often encountered during fibula dissection and can be easily damaged, potentially leading to the development of neuropathic pain.

Moreover, the well-known challenges documented in wound healing may create an inflammatory environment that may lead to irritation or inflammation of the local nerve branches and subsequently to neuropathic pain.[27] Future research elaborating on the origin of neuropathic pain at the FFF donor-site is important to identify possible solutions. Surgical mapping to prevent iatrogenic nerve damage, denervation of the nerve branches to avoid neuropathic pain development, or a more optimized wound care management can be employed to minimize irritation or inflammation of the nerves.

The results of this study should be interpreted in the context to its strengths and limitations. First, the questionnaire design made this study dependent on sufficient patient participation, although the response rate in our cohort was reasonably high (55%). No significant differences in baseline characteristics were found between the respondents and non-respondents, as depicted in Appendix 1. However, it is plausible that patients without complaints were less likely to respond to the questionnaires resulting in a potential patient selection bias. Second, confirming of the suspected neuropathic pain location without physical examination of the nerve distributions is challenging. Patients who reported sensibility problems could have referred to the skin graft, rather than to a specific nerve distribution, even though this was specifically explained in the questionnaire. Nevertheless, a comparative analysis showed no differences in the prevalence of neuropathic pain indicators between donor-sites with primary versus skin graft closure. Moreover, we used a cut-off value of 4 for the 7-item DN4. A prior validation study by Van Seventer et al. reported that when using the 7-item DN4, a cut-off value of 4 provides the highest sensitivity and specificity for diagnosing neuropathic pain among a Dutch population.[7] Therefore, it is unlikely that patients who experienced 4 or more indicators for neuropathic pain were mistakenly referring to their skin graft.

Conclusion

In conclusion, one-fifth of all patients undergoing a free fibula flap harvest experience neuropathic pain at the donor-

site. Younger age and donor-site complications appear to be prognostic risk factors, whereas the type of closure does not appear to influence neuropathic pain occurrence. Patients with neuropathic pain following FFF harvest experience poor leg function and quality of life. Future research should focus on identifying clinical and surgical factors that can help reduce or prevent neuropathic pain development, ultimately improving leg function and quality of life.

Ethical approval

Medical ethical committee approval was obtained from the medical ethical board at the Erasmus Medical Center in Rotterdam, The Netherlands. Number: MEC-2021-0066.

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Disclosure

The authors have no financial interest to declare concerning the content of this article.

Conflicts of interest

None.

Appendix 1. Non-respondent analysis

Characteristic	Respondents (n=82)	Non-respondents (n=68)	*P*-value
Age in years, median (IQR)	61 (48 - 68)	62 (48 - 69)	0.62
Male gender, n (%)	37 (45)	27 (39)	0.87
Smoking, n (%)	23 (28)	17 (25)	0.85
Diabetes, n (%)	10 (12)	8 (12)	0.60
BMI, mean (SD)	26 (5.1)	25 (4.7)	> 0.99
Oncologic indication, n (%)	66 (80)	48 (71)	0.17

IQR: interquartile range; BMI: body mass index; SD: standard deviation.

Appendix 2. Indicators for neuropathic pain following FFF harvest with and without skin graft

Indicator	Primary closure (n=30) %	Skin graft (n=32) %	*P*-value
Hypoesthesia	43	56	0.45
Paresthesias	27	22	0.78
Itching	17	38	0.09
Stinging	23	22	> 0.99
Burning sensation	13	19	0.73
Cold intolerance	23	13	0.33
Electrical shocks	7	19	0.26

FFF: free fibula flap.

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