Effective and enduring surgical treatment for targeted therapy-related paronychia
A retrospective study

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Abstract
The development of targeted therapy has improved treatment outcomes for patients with non-small cell lung cancer (NSCLC). However, paronychia, a common adverse effect of targeted therapy, remains burdensome. Although conservative treatments for paronychia have been well reported in the literature, studies on the efficacy of surgical partial matricectomy for paronychia are scarce. This study aimed to evaluate the effect of surgical partial matricectomy in targeted therapy-induced paronychia in patients with NSCLC. This retrospective cohort study included 11 patients with a total of 18 lesions on the big toes. Data on lung cancer stages, types and duration of targeted therapy, onset of paronychia, pain scale scores, conservative treatments, course of matricectomy, paronychia-free interval after matricectomy, and wound condition were collected from medical records. The Wilcoxon signed-rank test was used for analysis. The mean pain scale score after matricectomy was significantly lower than that after conservative treatments (1.00 ± 0.00 vs 2.94 ± 0.87; P < .001) and before treatment (1.00 ± 0.00 vs 3.06 ± 0.80; P < .001). The mean duration of matricectomy was significantly shorter than that of conservative treatments (3.22 ± 1.00 vs 56.56 ± 52.29 weeks; P < .001). Surgical partial matricectomy is an effective and enduring intervention for targeted therapy-related paronychia. It provides a shorter course of treatment, reduced pain, and improved appearance of the healed wound. Furthermore, surgical partial matricectomy could result in a better quality of life during targeted therapy than that of conservative treatments.

Abbreviations: EGFR = epidermal growth factor receptor, EGFRI = effect of EGFR inhibitor, NSCLC = non-small cell lung cancer, PCM = phenol chemical matricectomy.

Keywords: epidermal growth factor receptor, non-small cell lung cancer, surgical partial matricectomy, targeted therapy, therapy-induced paronychia

1. Introduction
Lung cancer is the most common malignancy and is a leading cause of death worldwide.1 Non-small cell lung cancer (NSCLC) accounts for 75% to 80% of all lung cancers.2 Studies have reported that the incidence of epidermal growth factor receptor (EGFR) involvement in NSCLC range from 8.4% to 62.5%.3 Hence, EGFR has become one of the targets of NSCLC therapy. Paronychia is inflammation of the nail folds of fingers or toes4 and is a common adverse effect of EGFR inhibitor (EGFRI) therapy. The mechanism through which EGFRRIs exert their effect involves epithelial maturation, leading to instability and inflammation of periungual tissues.5 The incidence of paronychia in EGFRI therapy is reportedly to be 17%.6

In the past, the treatment for targeted therapy-related paronychia involved the use of topical corticosteroids, antibiotics, and cryotherapy.7 However, surgical partial matricectomy, which is a common and effective treatment method for recalcitrant chronic paronychia,8 is seldom considered for patients with NSCLC undergoing EGFRI therapy.4,9 Surgical partial matricectomy is a procedure involving lateral nail avulsion and electrocautery ablation of the germinal matrix under local anesthesia.10 Since refractory paronychia with pain was observed in patients despite receiving multiple conservative treatments in the out-patient department of dermatology or oncology, we designed this retrospective study to assess whether an invasive management approach with surgical partial matricectomy would result in improved patient outcomes relating to wound pain, duration of treatment, and disease-free interval. This single-centre retrospective study aimed to evaluate the effect of surgical partial matricectomy in targeted therapy-induced paronychia in patients with NSCLC.
2. Patients and Methods

2.1. Patient population

This retrospective cohort study was approved by the Institutional Review Board of our hospital (approval number: A202105066). The requirement for informed consent was waived by the review board owing to the retrospective nature of the study. Patients treated with EGFRIs for NSCLC between July 1, 2019, and January 31, 2021, were identified at the Tri-Service General Hospital, Taipei, Taiwan. Patients who underwent both surgical partial matricectomy for paronychia and conservative treatment were included. Patients who had paronychia before the administration of EGFRIs targeted therapy were excluded. The flowchart of inclusion and exclusion is presented in Figure 1.

2.2. Surgical procedure

The procedure was conducted under the one-injection method; local anesthesia (2% lidocaine) was administered on the affected side of the toe. A glove and mosquito clamp tourniquet was used to control the bleeding, keep the surgical field clear, and prevent the surgeons from forgetting to loosen the tourniquet. The partially split nail was gently separated from the nail fold and nail bed with a dissector and was subsequently cut off with a scissor. Electrical cauterisation was performed in the affected germinal and sterile matrix without causing injury to the dorsal roof of the proximal nail fold. Finally, the wound was covered with a layer of paraffin gauze using 1% framycetin, followed by a sterile gauze dressing with compression.

2.3. Outcomes

From medical records, we collected data on patient characteristics, including age, sex, cancer stage, and targeted therapy agents. We also collected information related to paronychia, including symptoms, types, and duration of treatments. We designed a pain scale to assess wound pain (Table 1). Our pain scale grades pain according to the number scale as well as the degree of pain relief achieved following the use of analgesic medications; such grading has more clinical utility than an abstract number. Further, we compared outcomes, including pain scale scores, treatment durations, and disease-free intervals, between surgical partial matricectomy and several common conservative treatments, including topical beta-blockers, topical povidone–iodine, topical antibiotic ointment, and steroid ointment.

2.4. Statistical analyses

In the descriptive analysis, we used the mean ± standard deviation to present the distribution of continuous variables. Categorical variables are presented as counts and percentages. The Wilcoxon signed-rank test was used to assess the difference in the pre- and post-operative pain scores. All data were analysed using Statistical Package for the Social Sciences 27.0 software (IBM Corp., Armonk, NY), and statistical significance was set at \( P < .05 \) (two-tailed) for all tests.

| Table 1 Pain scale. |
|---------------------|------------------|
| Score | Description |
| 1     | Painless       |
| 2     | Mild pain, no need for analgesic medication |
| 3     | Moderate pain, obvious relief after analgesic medication |
| 4     | Severe pain, slight relief after analgesic medication |
| 5     | Severe pain, no relief after analgesic medication |

Figure 1. Flow chart of inclusion and exclusion criteria and evaluation of treatment results.
3. Results

Conservative treatment was given to 11 patients for paronychia within 1 to 24 weeks after undergoing targeted therapy for NSCLC. They underwent surgical partial matricectomy for refractory paronychia of a total of 18 big toenails. The demographic data of these patients are shown in Tables 2 and 3. The mean age was 72 years (range, 57–94 years). The female to male ratio was 7:4, and seven patients had stage IV disease.

Overall, seven and four patients received single and multiple EGFR-targeted therapies, respectively, for NSCLC. The average onset time of targeted therapy-related paronychia was 12.55 ± 9.67 weeks. Patients rated their pain before treatment for a total of 18 lesions, with scores of 2, 3, and 5 for 3 (16.67%), 13 (72.22%), and 2 lesions (11.11%), respectively. After conservative treatment, the pain scores were 2, 3, and 5 for five (27.78%), 11 (61.11%), and two lesions (11.11%), respectively. Finally, after surgical partial matricectomy, the score was 1 for all 18 lesions (100%). To summarise, all patients showed reduction in wound pain after conservative treatment as well as after matricectomy. The serial images of two cases pre- and post-procedure, details of the surgical partial matricectomy, and wound condition more than 6 months after operation, are shown in Figures 2 and 3. Wound images for two more cases pre- and post-procedure are depicted in Figures 4 and 5.

The number of conservative treatments received separately or in combination before surgery was 3.7 ± 1.1. The durations of conservative treatments and matricectomy were 56.56 ± 52.29 and 3.22 ± 1.00 weeks, respectively. The paronychia-related wound pain score after matricectomy was significantly lower than that before the intervention (1.00 ± 0.00 vs 3.06 ± 0.80, P < .001) or after conservative treatments (1.00 ± 0.00 vs 2.94 ± 0.87, P < .001). The mean disease-free interval after surgical treatment was 35.44 ± 11.44 weeks (Table 4). No recurrence of lesions was observed.

4. Discussion

In our study, patients who underwent surgical partial matricectomy for treatment of targeted therapy-related paronychia had shorter treatment durations, significantly lower pain scores, and longer disease-free intervals than that of patients who underwent conservative treatments.

The use of oral EGFRIs is a standard treatment for NSCLC with EGFR mutations. EGFRIs block the adenosine triphosphate binding site of EGFRs, thereby preventing phosphorylation and subsequent cell growth and proliferation.[14] However, EGFRi therapy induces paronychia via interference of growth, migration, apoptosis, chemokine expression, abnormal matura-
tion, and differentiation of keratinocytes.[15]

Paronychia occurs in 7% to 8% of patients after 11 to 14 weeks of treatment with a first-generation EGFRi and in 46.9% of patients after 8 weeks of treatment with a second-generation EGFRi.[16] Paronychia also reportedly occurs in 22% to 31% of patients receiving a third-generation EGFRi.[17] In the current study, first-, second-, and third-generation EGFRIs were used to treat patients with NSCLC.[16,17] The mean onset of targeted therapy-related paronychia was 12.55 ± 9.67 weeks in our study.

Based on the mechanisms of EGFRIs, there are several potential strategies for the management of EGFRi-related paronychia; dividing the EGFRi dose minimises the peak and trough levels, whereas escalating the EGFRi dose allows for compensatory signaling.[18] Local irrigation and skin rupture were prevented or improved using emollients, cushioning the affected areas, trimming the nails, and using gloves, while superficial infection was prevented by antimicrobial soaks or by administration of antibiotics or antifungal agents.[19] Paronychial inflammation was treated with steroids, and in severe cases, EGFRi therapy was discontinued for 2 to 4 weeks.[16] However, the dose of EGFRi was not found to be related to the onset of paronychia. Avoidance of compression may be effective in the prevention or improvement of paronychia.[19]

According to the Common Terminology Criteria for Adverse Events Version 5.0, paronychia initially involves edematous or erythematous nail folds (grade I). Grade II paronychia is characterized by deterioration with pain, impacts on instrumental activities of daily livings, and controllable with local treatment or oral medication. Grade III paronychia affects self-care activities of daily livings and is an operative indication. Surgery is indicated after failure of local interventions or drugs or for wounds with abscesses or fluctuance.[19]

Several studies have also compared the outcomes of different conservative treatments for cancer therapy-induced paronychia. Goto et al found that among several treatments, corticosteroid ointment and phenol chemical matricectomy (PCM) resulted in significant improvement in paronychia.[17] 27% of 111 patients after topical corticosteroid ointment use and 10% of 30 patients after PCM required reduction of dose or discontinuation of the EGFRi.[17] The adverse event grade was decreased from 1.94 to 1.52 under topical corticosteroid ointment and from 2.17 to 1.30 after PCM.[17] However, all patients did not require adjustment or discontinuation of targeted therapy drugs and became pain free after surgery in our study.

Capriott et al compared different concentrations of topical povidone-iodine and revealed that 2% formulation was better for treating cancer treatment-related paronychia.[13] However, the percentage of pain free nails increased from 34.5% to 82.8% after 68 weeks of treatment.[13] In our study, all remissions were achieved at 3.22 ± 1.00 weeks after surgery on the affected big toes. Similarly, Olamiju et al showed that 0.5% topical timolol had limited efficacy as monotherapy for targeted therapy-related paronychia and suggested combined non-surgical or surgical treatment.[20]

However, in our study, the condition of none of the 11 patients improved after long-term conservative treatments, which included topical povidone-iodine, topical steroid, topical antibiotic agent, oral antibiotic, silver nitrate, and cryotherapy. Thereafter, these patients were referred to the out-patient department of plastic surgery for a second opinion. After surgical partial matricectomy, the pain scores of the patients decreased along with improved wound healing.

All patients in our study were common terminology criteria for adverse events grade II and were recommended for conservative treatment. In our study, the average number of conservative treatment types received per patient was 3.7 ± 1.7. This result suggests that patients have a strong need to pursue other

### Table 2

Demographic characteristics of patients.

|                          | N = 11 (%) | Mean ± SD |
|--------------------------|------------|-----------|
| Male                     | 4 (36.36)  |           |
| Female                   | 7 (63.64)  |           |
| Age (yrs)                |            | 72.00 ± 10.95 |
| Cancer stage             |            |           |
| Stage I–III              | 4 (36.36)  |           |
| Stage IV                 | 7 (63.64)  |           |
| Single targeted therapy  |            |           |
| Afatinib                 | 7 (63.64)  |           |
| Gefitinib                | 3 (27.27)  |           |
| Multiple targeted therapies |            |           |
| Afatinib + Osimertinib   | 4 (36.36)  |           |
| Erlotinib + Osimertinib  | 2 (18.18)  |           |
| Erlotinib + Gefitinib + Osimertinib | 1 (9.09) |          |

SD = standard deviation.
types of treatments to improve their quality of life if improvements are not achieved by the suggested treatment from the guide. No recurrence was observed in the follow-up period (27 and 29 weeks) after surgical treatment regardless of the conservative treatment duration (192 and 4 weeks), suggesting that surgery is a feasible option in the routine management of these patients.

Considering the treatment costs under Taiwan’s National Health Insurance System, surgical partial matricectomy is superior to conservative treatment due to fewer required out-patient visits and fewer prolonged local interventions or oral medication use.

Regarding unconventional paronychia treatment options other than surgery, topical injection therapy may be considered. However, only one study has demonstrated the effect of this treatment, wherein long-acting steroids with topical injections were administered once per month. Only two patients (7.1%) achieved complete remission. Four weeks after the second and third booster injections, 24 (85.7%) and 27 (96.4%) patients achieved complete remission, respectively. After 24 weeks of follow-up, one (3.6%) patient showed relapse. However, the pain of local injections is often unbearable, especially with repeated injections. In our study, patients received only one local injection of intraoperative anesthesia, and most patients achieved complete remission without recurrence.

Overall, conservative treatments and surgical partial matricectomy have the following pros and cons. Surgical treatment is superior to conservative treatment (including local injection) in terms of pain improvement, wound recovery, recurrence, time consumption, and medical expenditures. In addition, surgical treatment does not affect the progress of targeted drug therapy or require changing the drug or dose reduction.

The possible surgical indications for patients with cancer include no improvement after two or more conservative treatments, no improvement after 2 to 4 weeks of conservative treatment, or current targeted therapy with good control of the cancer combined with severe paronychia.

| Patient number/sex/age | Stage of NSCLC | EGFRi | Time from start of EGFRi to nail toxicity (wk) | Location of paronychia | Conservative treatment | Course of treatment (wk) |
|------------------------|---------------|-------|-----------------------------------------------|------------------------|------------------------|-------------------------|
| 1/M/73                 | Stage IA1     | Afatinib | 26                                           | Left big toe           | Topical beta-blockers, topical antibiotics, topical steroids, cryotherapy, oral antibiotics | 104                     |
|                        |               |        |                                               | Right big toe          |                        | 104                     |
| 2/M/64                 | Stage IA2     | Afatinib | 7                                            | Left big toe           | Topical beta-blockers, topical antibiotics, topical steroids | 24                      |
|                        |               |        |                                               | Right big toe          |                        | 24                      |
| 3/F/75                 | Stage IIIA    | Gefitinib | 8                                           | Left big toe           | Topical antibiotics, oral antibiotics | 9                       |
|                        |               |        |                                               | Right big toe          |                        | 9                       |
| 4/M/57                 | Stage IVA     | Afatinib; Osimertinib | 7                                           | Left big toe           | Topical antibiotics, topical steroids, oral antibiotics, phenol chemical matricectomy | 97                      |
|                        |               |        |                                               | Right big toe          |                        | 97                      |
| 5/F/78                 | Stage IVB     | Gefitinib | 18                                          | Left big toe           | Topical beta-blockers, topical antibiotics, topical steroids, oral antibiotics | 4                       |
| 6/F/80                 | Stage IB      | Gefitinib | 25                                          | Left big toe           | Topical antibiotics, topical steroids, oral antibiotics | 10                      |
| 7/M/94                 | Stage IVA     | Afatinib | 9                                            | Left big toe           | Topical beta-blockers, topical antibiotics, topical steroids, phenol chemical matricectomy, oral antibiotics | 192                     |
|                        |               |        |                                               | Right big toe          |                        | 192                     |
| 8/F/75                 | Stage IVA     | Gefitinib; Osimertinib | 27                                          | Left big toe           | Topical beta-blockers | 40                      |
|                        |               |        |                                               | Right big toe          |                        | 40                      |
| 9/F/76                 | Stage IVA     | Gefitinib | 2                                           | Right big toe          | Topical antibiotics, topical steroids, oral antibiotics | 60                      |
| 10/F/59                | Stage IVB     | Afatinib; Osimertinib | 8                                           | Left big toe           | Topical beta-blockers, topical antibiotics, topical steroids, oral antibiotics | 8                       |
|                        |               |        |                                               | Right big toe          |                        | 4                       |
| 11/F/61                | Stage IVA     | Gefitinib; Osimertinib | 1                                           | Left big toe           | Topical beta-blockers, topical antibiotics, topical steroids, cryotherapy, oral antibiotics, silver nitrate | 96                      |

**Figure 2.** A case of complicated paronychia of the left big toe in a 78-year-old female with lung adenocarcinoma and left iliac bone soft tumor metastasis; cT1b-N3M1c, stage IVB, under Iressa (gefitinib; AstraZeneca, Cambridge, UK) treatment. (A) Severe paronychia of the left big toe before surgery. (B) Partial removal of bilateral nails. (C) Matricectomy with electrocautery. (D) Suture closure after removal of granulation tissue. (E) Well-healing wound 29 weeks after surgery.
Our study is limited by the small number of cases and the retrospective design that does not effectively represent the general population. Nevertheless, this study demonstrates the benefits of a common surgical procedure, such as partial matricectomy, which is routinely performed although rarely in this patient group. This efficacy of surgical partial matricectomy in the treatment of paronychia can pave way for further research to reduce varied health complications after cancer therapy. Therefore, future studies are warranted to include large numbers of cases and to analyse the effect of this matricectomy approach in different age groups and different types of cancer at various stages to strengthen our findings.

To conclude, in this retrospective cohort study, surgical partial matricectomy was found to be an effective and enduring...
treatment option for targeted therapy-related paronychia. The common conservative treatments of targeted therapy-related paronychia have a longer treatment course and do not significantly reduce pain. Surgical partial matricectomy consists of a short-course treatment that provides a long paronychia-free interval after surgery, thus saving time and expenses for both patients and clinicians. No recurrence of lesions with great wound appearance was observed in any patient. Additionally, in terms of quality of life and maintenance of targeted therapy for cancer control, this study demonstrated that surgical partial matricectomy was largely superior to other common conservative treatments for targeted therapy-related paronychia. Thus, surgical partial matricectomy can be considered an effective and enduring treatment option for intractable paronychia.

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