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Observational study to estimate the proportion of surgical site infection following excision of ulcerated skin tumours (OASIS study)

Running head: Observational study of surgical site infection in ulcerated skin cancers

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What's already known about this topic?

- The risk of surgical site infection (SSI) may be higher in ulcerated skin lesions following excision. There is currently no validated tool for assessing SSI following skin surgery and there is inter-rater variability in diagnosing SSI by dermatologists.

What does this study add?

- This is the first study to explore the use of a postal/ online questionnaire to assess SSI following skin surgery. Data are provided on patient characteristics, SSI rates and feasibility of a future trial. These data will inform the design of a multicentre, randomised controlled trial to determine the benefits and harms of perioperative oral antibiotics following excision of ulcerated tumours.

Summary

Background

Ulceration is a recognised risk factor for SSI, however the proportion of patients developing SSI after excision of an ulcerated skin cancer is unknown.

Objectives

To determine the proportion of participants with SSI after surgical excision of an ulcerated skin cancer. Secondary aims included feasibility outcomes to inform the design of a randomised controlled trial to investigate the benefits and harms of peri-operative antibiotics following excision of in ulcerated tumours.

Methods

We undertook a multi-centre prospective, observational study of patients undergoing excision of an ulcerated skin cancer between March 2019-March 2020. Prior to surgical excision, surface swabs of the ulcerated tumours of participants recruited from one centre were undertaken to determine organism growth. Four weeks after surgery, all participants were e-mailed or posted the Wound Healing Questionnaire (WHQ) to determine whether they had developed SSI.

Results

148 participants were recruited (105 (70.9%) males; mean (standard deviation) age 77.1 years (12.3). Primary outcome data were available for 116 (78.4%) participants of whom 35 (30.2%) were identified to have SSI using the WHQ with a cut-off score of 8 and 47 (40.5%) with a cut-off score of 6. Using the modified WHQ in participants with wounds left to heal by secondary intention, 33 (28.4%) and 43 (37.1%) were identified to have SSI respectively.

Conclusions

This prospective evaluation of SSI identified with the WHQ following excision of ulcerated skin cancers demonstrated a high proportion with SSI. The WHQ was acceptable to patients, however further evaluation is required to ensure validity in assessing skin wounds.

Introduction

Surgical excision is the gold-standard treatment for skin cancer; but can be complicated by surgical site infection (SSI). SSI confers significant morbidity for patients, requiring antibiotic treatment and potentially multiple healthcare consultations to assess resolution, delayed wound healing and poor cosmetic outcome.¹ Moreover, SSI is associated with increased healthcare costs.²

Ulcerated tumours occur commonly in dermatological surgical lists.^{3,4} Several studies suggest that ulceration is a risk factor for SSI; including a single-centre cohort which reported the proportion of participants developing SSI as 33%³, a randomised, controlled trial (RCT) in Brazil which reported SSI in 30% of participants with ulcerated keratinocyte cancers undergoing excision⁵ and an Australian study which reported a three-fold increase in SSI risk for excision of ulcerated tumours but did not report frequency of SSI.⁶

This study aimed to ascertain the proportion of patients developing SSI following surgery for ulcerated skin cancers, and determine feasibility work to inform the design of a future RCT to investigate the benefits and harms of oral antibiotics following surgery for ulcerated skin tumours.

Methods

Study design and setting

This prospective, observational study opened in three dermatology departments: University Hospital of Wales (UHW), Cardiff; Churchill Hospital, Oxford and Queen Elizabeth Hospital, Birmingham.

Participants

Consecutive adult patients aged ≥ 18 -years-old presenting with an ulcerated skin cancer listed for excision of any type affecting any body site were invited to participate between March 2019-March 2020. Ulceration was defined as loss of the epidermis +/- dermis. Exclusion criteria included clinical evidence of wound infection, skin cancer excision undertaken by curettage or Mohs micrographic surgery, lack of capacity to consent, concurrent systemic immunosuppressive treatment or oral antibiotic use.

Outcome measures

The primary outcome was the proportion of participants with SSI within four weeks of surgery. There is no validated tool to assess SSI in skin surgery. The Centers for Disease Control and Prevention criteria are widely used but open to subjective interpretation and broad inter-rater variability has been reported in dermatologists.^{7,8} Given the potential costs associated with clinical assessment to determine SSI and the limited resources for this feasibility study, we made the pragmatic decision to use a patient-reported Wound Healing Questionnaire (WHQ). The WHQ was designed and validated by Macefield *et al.*⁹ following abdominal surgery with primary closure and used with permission (Supplementary file 1). The WHQ consists of 19 questions and the Bluebelle Study group have demonstrated that a cut off score of 6-8 reliably identifies SSI.¹⁰ The WHQ has been modified for use in second intention wounds following vascular surgery with removal of questions 6, 12 and 15.¹¹

Secondary outcomes included the proportion of participants, over 12 months from those screened, who were eligible and willing to be randomised in a future trial to: (a) no treatment, (b) topical treatment, (c) a short course of oral antibiotics, (d) a long course of oral antibiotics. We also analysed the proportion of eligible participants who were recruited over 12 months and the proportion of participants completing the study.

For patients who developed a SSI, we assessed the feasibility of 'wound selfies' or wound photographs as an exploratory outcome measure. Furthermore, we calculated the proportion of participants with SSI who were prescribed oral antibiotics at the time of surgery.

To identify the most common microorganisms on ulcerated skin cancers, swab analyses were performed. All participants at UHW had a surface swab taken from their ulcerated skin tumour. These were analysed in the Specialist Antimicrobial Chemotherapy Unit (SACU), Public Health Wales laboratory at UHW.

Data collection

Investigators collected data using study specific case report forms (CRFs) at three time-points: immediately before surgery, immediately after, and four-weeks post-surgery. Completed CRFs were received by Cardiff University Centre for Trials Research (CTR) in a secure database.

Participants were invited to e-mail 'wound selfies' to the CTR if they developed SSI as detailed in the study information leaflet. The number of participants attending medical photography to have wound photographs was recorded.

WHQs were posted or e-mailed to participants to complete and return (by stamped addressed envelope, included) four weeks after surgery. If no completed WHQ was received, then three reminder attempts were made via telephone / text. A letter was sent to uncontactable participants asking them to contact the study centre directly.

Sample size

Given the wide range in reported SSI from published case series between 0.5-33%⁴, we anticipated an SSI of approximately 10% in our participants. Our aim was to recruit 311 participants with an intended sample size of 283 participants (allowing for a dropout rate of 10%).

Statistical analysis

Baseline demographic, pre-operative and clinical data for patients were summarised using means and standard deviation for continuous data, and frequencies and percentages for categorical data. Patients who were re-recruited were included in the analysis and treated as independent observations.¹² Primary and secondary outcomes were reported similarly with a 95% confidence interval (CI). The reporting of findings are in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline.¹³ Statistical analysis was performed in IBM SPSS Statistics V.26.

Ethics approval and trial registration

The study conformed to the Declaration of Helsinki and followed Good Clinical Practice (GCP) guidelines and was conducted with accordance to UK Policy Framework for Health and Social Care Research (2017). The study received ethical approval from Health and Care Research Wales (HRCW) and South Central-Hampshire B Ethics Research Committee. Data were registered in accordance with the General Data Protection Regulation and Data Protection Act 2018. The trial was registered on the National Institute for Health Research website prior to its start (<https://clinicaltrials.gov/ct2/show/NCT03782727>).

Results

Recruitment

Over 12 months, 171 patients were screened for eligibility of whom 17 were ineligible. 154 were eligible; two couldn't be recruited as research staff were unavailable and 4 declined. Overall, 148 (96.1%) participants (105 males; mean age 77.1 years, SD 12.3) were recruited over 12 months from Cardiff (70.9%) and Oxford (29.1%). 116/148 (78.4%) participants completed the study (responded at least one item of the WHQ) (Figure 1). Overall, 89/116 (79.0%) fully completed the WHQ, with the remainder missing between one and eight items (of the 19-item score). One individual was re-recruited.

Study population

Baseline demographic, pre-operative and clinical data for participants are summarised in Table 1.

Willingness to participate

The proportion of participants who were willing to be randomised in a future trial was high for both topical treatment (135, 91.2%) and oral antibiotics (131, 88.5%) with no preference for course length. Clinicians also showed support for randomisation to oral antibiotics (144, 98.0%), with no preference for course length of, or topical treatment (142, 96.6%).

Antibiotic prescribing in participants are described in Table 2.

Primary outcome - surgical site infection

Most participants (127, 86%) requested to receive the WHQ via post. Completed WHQs were returned by 116 (78.4%) with 35/116 (30.2%, 22.7 to 30.2%) identified to have SSI using a cut-off score of ≥ 8 within four weeks of surgery. When this cut-off score was reduced to ≥ 6 , 47/116 (40.5%, 95% CI: 32.0 to 49.6%) were identified to have SSI. When using the modified WHQ in participants with secondary intention healed wounds, 33/116 (28.4%, 21.0 to 37.2%) and 43/116 (37.1%, 28.8 to 46.1%) respectively were identified to have SSI.

Dropout rate at four weeks post-surgery was 21.6% (32/148). 14/116 (12.1%) participants were prescribed peri-operative antibiotics of whom 5/14 (35.7%) developed SSI whilst 102/116 (87.9%) participants were not prescribed peri-operative antibiotics of whom 42/102 (41.2%) developed SSI.

Characteristics associated with a higher proportion of SSI included recruitment in Oxford (10/23, 43.5% vs 33/93, 35.5% in Cardiff), site of tumour on leg (7/16, 43.8%) and trunk (6/13, 46.2%), repair with skin flap (3/5, 60%) and secondary intention (10/32, 31.3%). The proportion of SSI by age, gender and topical treatment were comparable.

Wound selfies

No 'wound selfies' were e-mailed to the CTR and three wound photographs were taken by medical photography (Cardiff 2/3, Oxford 1/3).

Ulcerated tumor swab analysis results

101 surface swabs were analysed: 71% (72/101) contained Gram-positive species, with 40 containing *Staphylococcus aureus* and 26 coagulase-negative *Staphylococcus*; 38% (38/101) contained Gram-negative species, either alone (18) or in combination with *S.aureus* (16/34) or another Gram-positive species (4). Eleven swabs showed no growth. The most prevalent organisms were *Staphylococcus aureus* and coagulase-negative streptococci, the latter being common skin contaminants (Table 3). A large number of Enterobacterales (Gram-negative bacteria) were identified, such as *Escherichia coli*, which can cause wound infections and can be linked to faecal contamination. Of the Staphylococci (*S. aureus* and Coagulase-negative staphylococci) isolated 6.4% were flucloxacillin resistant (MRSA) whilst 3.3% of Enterobacterales showed resistance to 3rd generation cephalosporins.

Discussion

Key results

This is the first study to explore utility of a postal/online questionnaire to assess SSI following skin surgery. This prospective evaluation of SSI following excision of ulcerated skin cancers demonstrated a high proportion (40.5%) with SSI as determined by a WHQ score ≥ 6 . However, if using a WHQ score of ≥ 8 , then 30.2% SSI is comparable to those reported previously; 30%⁵ and 33%³ (n=68 & 33).

The proportion of eligible participants completing the study over 12 months was 78.4%, lower than our anticipated 90% (with 10% loss to follow-up). The advent of Covid-19 led to 8.8% (13/148) WHQs not being sent to participants plus there were reduced opportunities to chase-up non-returned forms by CTR staff. The high proportion of completed WHQs and low levels of

missing data suggest that the WHQ is an acceptable tool to assess SSI.

Only 3/148 participants had wound photographs taken and none submitted 'wound selfies'. The low response rate may be due to participants lack of access to the internet/ smartphones and may be attributed to the mean age of our cohort being 77-years-old. Evaluation of digital literacy and detailed instructions could improve this response rate.

The organisms identified on tumour swabs varied considerably. This is in contrast to an Australian study of ulcerated skin cancer excisions which reported: *Staphylococcus aureus* isolated from 93 lesions before surgery, three lesions also contaminated by Gram-negative bacteria, and Gram-negative organisms alone isolated from three lesions.¹⁴ Swab culture methods may explain this difference, with our study employing a range of non-selective and selective media whilst standard practice is to culture swabs onto selective media only.

Features associated with increased SSI risk in this study are similar to reported findings with lower leg excisions and skin flap repairs being recognised to increase SSI risk.^{1,15,16}

Limitations

The WHQ has not been validated in patients undergoing skin surgery. The WHQ was designed and validated to assess SSI in closed primary wounds after abdominal surgery, whilst our study included wounds repaired with flaps and grafts as well as those left to heal by secondary intention (36/148, 24.3%). To address this, we reported the overall SSI rate using the modified WHQ in participants with secondary intention healed wounds.

Recruitment of 148 participants was less than half of our initial target of 311. We extended the study recruitment period from the initial planned eight months, however due to Covid-19, we closed the study at 12 months. Reasons for low recruitment include delays to open recruiting sites, lack of research support staff and competing pressures in busy skin cancer clinics.

Generalisability

This study collected data from two recruiting UK centres. Patients' demographics and clinical characteristics were comparable with previous audit data from three UK centres (mean age 77.5 years, skin cancer size 15.8mm) therefore we believe these findings would be generalisable.⁴

Conclusion

This study aimed to inform the design of a future RCT to investigate whether the use of peri-operative oral antibiotics following excision of ulcerated skin tumours reduces the proportion of wounds developing SSI. This aim has been met by providing data on SSI rates, characterising the eligible participant population and exploring the use of the WHQ to assess SSI. Further research is required to validate the use of the WHQ in assessing SSI in skin surgery.

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Figure Legend

Figure 1: Flowchart of recruitment and completion of data collection

Supporting Information

Supplementary file 1: Bluebelle Wound Healing Questionnaire

Table 1. Demographic, clinical and pre-operative characteristics of recruited patients

	Total N=148
N individual patients	148
N (%) re-recruited	1
Demographics	
Site, n(%)	
Cardiff	105 (70.9)
Oxford	43 (29.1)
Age (years), mean(SD)	77.1 (12.3)
18-59	13 (8.8)
60-64	9 (6.1)
65-69	11 (7.4)
70-74	17 (11.5)
75-84	32 (21.6)
85+	66 (44.6)
Gender, n(%)	
Male	105 (71.9)
Female	41 (29.1)
<i>Missing</i>	2
Clinical data: pre-operative	

Suspected type of skin cancer (clinical diagnosis), n(%)	
Basal cell carcinoma	78 (52.7)
Squamous cell carcinoma	64 (43.3)
Melanoma	6 (4.1)

Table 2. Post-operative characteristics of recruited patients, n=148

	Total N=148
Treatment given	
Post-operative antibiotics prescribed, n(%)	
No	126 (85.1)
Yes	22 (14.9)
Topical treatment eg. Inadine™ dressings, n(%)	
No	69 (46.6)
Yes	79 (53.4)
Type of procedure, n(%)	
Direct closure	101 (68.2)
Skin graft	1 (0.7)
Skin flap	10 (6.8)
Secondary intention	36 (24.3)
Final histological diagnosis	
BCC	81 (55.5)
SCC	47 (32.2)
Melanoma	3 (2.1)
Other (see below)	15 (10.3)
<i>Missing</i>	2

Other: actinic keratosis (6), keratoacanthoma (4), poorly differentiated carcinoma of uncertain type, hidradenoma, benign melanocytic naevus, pyogenic granuloma, superficial perivascular dermatitis.

Table 3. Organisms isolated from ulcerated skin tumour swabs

Bacterial species isolated	Count (% of total)
No growth	11 (9.1)
Acinetobacter species*	9 (7.4)
Enterobacterales*	24 (19.8)
Pseudomonas species*	9 (7.4)
<i>Staphylococcus aureus</i> *	41 (33.9)
Coagulase-negative staphylococci (CNS)‡	27 (22.3)
Weight of growth	
No growth	11 (10.9)
+/- (scant)	33 (32.7)
+ (mild)	32 (31.7)
++ (moderate)	18 (17.8)
+++ (heavy)	7 (6.9)
Number of species isolated	
0	11 (10.9)
1	61 (60.4)
2	18 (17.8)
3	9 (8.9)
4	1 (1)
5	1 (1)

*potential infectious agents, ‡ skin contaminants

