The incidence and cost implications of surgical site infection following lymph node surgery for skin malignancy

Angus T McMillan[1], Ning Xuan Ho[1], Charlie Izard[1], Paolo L Matteucci[1], Joshua P Totty[1,2]

1 = Department of Plastic and Reconstructive Surgery, Hull University Teaching Hospitals NHS Trust, Hull, HU16 5JQ, United Kingdom

2 = Centre for Clinical Sciences, Hull York Medical School, Hull, HU6 7RX, United Kingdom

Corresponding author: Mr Angus McMillan Email: angusmcmillan@doctors.net.uk (AM)

Telephone: 01482 604444 Fax: N/A

Address: Department of Plastic and Reconstructive Surgery, Hull University Teaching Hospitals NHS Trust, Hull, HU16 5JQ, United Kingdom

Abstract

Background

Lymph node surgery, is commonly performed in staging of, and treatment of metastatic skin cancer. Previous studies have demonstrated sentinel lymph node biopsy (SLNB) and particularly lymph node dissection (LND) to be plagued by high rates of wound complications including surgical site infection (SSI) and seroma formation. This study evaluated the incidence of wound complications following lymph node surgery and provides the first published cost estimate of SSI associated with lymph node surgery in the UK.

Patients and methods

A retrospective cohort study was undertaken of 169 patients with a histological diagnosis of primary skin malignancy who underwent SLNB or LND of the axilla and/or inguinal region at a single tertiary centre during a 2 year period. Demographic, patient risk factor and operation characteristic data was collected and effect on SSI and seroma formation was analysed. Cost-per-infection was estimated using National Health Service (NHS) reference costs, and antibiotic costs.

Results

146 patients underwent SLNB, the SSI rate in this group was 4.1% and the seroma incidence was 12.3%. 23 patients underwent LND, the SSI rate was 39.1% and the seroma incidence was 39.1%. Seroma formation was strongly associated with development of SSI in both the SLNB (Odds ratio (*OR)* =18.0, p <0.001) and LND (*OR* = 21.0, p = 0.007) group. The median additional cost of care events and treatment for SSI in the SLNB and LND groups was £199.46 and £5187.04 respectively.

Conclusion

SSI remains a troublesome and costly event following both SLNB and LND. Further research into perioperative care protocols and methods of reducing lymph node surgery morbidity is required and could in turn produce significant cost savings to the NHS.

Keywords: *Sentinel lymph node biopsy; Lymph node dissection; Surgical site infection; Skin malignancy; Seroma; Healthcare costs*

Introduction

Lymph node surgery is an integral part of routine care in the staging and treatment of skin malignancies. Sentinel lymph node biopsy (SLNB) is used to diagnose and stage many skin cancers. A lymph node dissection (LND) may be undertaken in the presence of macroscopic disease or occasionally following a positive sentinel node biopsy to improve local disease control, though the efficacy of this procedure is debated and in recent years has become less popular in the treatment of malignant melanoma (1).

A number of studies have shown that both SLNB and LND are plagued by a high rate of wound complications with short term complications such as surgical site infection (SSI) and seroma/lymphocele formation amongst the most common (2-11). In a recent meta-analysis by Totty *et al.* which included over 45,000 patients, the overall risk of SSI after LND was estimated to be 10.39%, while it was 2.67% after SLNB; the risk of seroma formation was reported as 24.32% after SLNB and 8.08% after LND (12). However, despite advances in other surgical fields leading to a reduction in the incidence of SSI (13, 14), Totty et al. (12) found no significant change in the incidence of SSI over time across all studies they reviewed. Several studies have investigated methods of reducing the high rates of SSI and seroma following surgery to the lymph nodes for various malignancies. Courses of prophylactic antibiotics (15, 16), use of drains (17, 18), sealing agents (9, 19, 20), negative pressure wound therapy (21-23), and post-operative mobilisation (24) have been studied, though evidence remains limited and there is no consensus on a standard protocol for perioperative care.

SSI is a significantly costly complication of surgery. The cost attributable to SSI has been estimated to be between £2000 and £21,000 depending on the type of surgery (25). Chang *et al.* examined a series of 53 patients undergoing inguinal LND for melanoma and estimated the median additional cost of wound complications to be $2586, with costs associated with hospital admission being the largest contributor (6). Given the high rate of wound complications following lymph node surgery, SSI following SLNB or LND may represent a significant financial burden to the National Health Service (NHS), and to individuals who experience SSI.

The aim of this study was to evaluate the incidence of complications in all patients undergoing SLNB or LND at a single institution. This study also explored the management and care events associated with developing SSI following SLNB and LND and estimated the additional healthcare-associated costs due to SSI.

Patients and methods

This project was approved and registered by the institutional audit department (project number 2021.143, Hull University Teaching Hospitals NHS Trust). A retrospective cohort study was conducted to analyse all patients with a histological diagnosis of primary skin malignancy undergoing SLNB or LND of the axilla and/or inguinal region at a single tertiary university hospital in the UK, carried out by Plastic Surgeons. Patients were identified by searching operating theatre database records to identify all SLNB and LND procedures in the time period from 1st of October 2019 to 30th of September 2021. Patients were excluded if they underwent lymph node biopsy or dissection to an area other than the axilla or inguinal region.

Electronic patient records, physical patient case notes, and electronic primary care summary records were reviewed to collect data on patient demographics, risk factors, operation characteristics, incidence of SSI, and seroma formation. Cases identified with SSI were reviewed and data on antibiotic treatment, hospital re-admission, return to theatre for further operative intervention, and subsequent outpatient appointments related to SSI were gathered.

Estimates for additional healthcare-associated costs due to SSI were generated using NHS reference costs (26), antibiotic costs from the British National Formulary (BNF) (27), and Personal Social Services Research Unit (PSSRU) estimates for GP appointments (28).

Cases of SSI were defined in accordance with the latest guidance from the Centers for Disease Control and Prevention (CDC) (29). A seroma was defined as a palpable collection of fluid at the surgical site recognised by a clinician within 60 days of surgery. Extended wound support sutures were defined as any sutures not absorbed within 120 days as per manufacturer guidance.

Statistical analysis was undertaken using IBM SPSS Statistics Version 28.0. Pearson chi-squared and Fisher's exact tests were used for univariate analyses of categorical variables and binary logistic regression was used for univariate analyses of continuous variables and multivariate analysis. Variables were only included in the multivariate analysis if they had an alpha value of < 0.20 on univariate analysis. An alpha value of 0.05 was used to determine statistical significance. This manuscript was prepared and reported in line with the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines for reporting observational studies (30); the STROBE checklist is provided in the supplementary material.

Results

The study identified 169 patients who underwent either SLNB or LND in the study period. Among these patients, 146 underwent SLNB and 23 underwent LND. Table 1 outlines the differences in patient demographics and risk factors in the SLNB and LND groups. Table 2 outlines the differences in operative characteristics and outcomes in the SLNB and LND groups. Patients in the LND group were significantly older (73 vs 61.5 years, $P = 0.012$) and had a significantly different variation in primary histology ($P < 0.001$) but the two groups had otherwise similar characteristics for sex, BMI, diabetes, immunosuppression, smoking, and operative site. In the LND group, surgeons were significantly more likely to give prophylactic antibiotics ($P < 0.001$) and insert a drain ($P < 0.001$).

The incidence of SSI was significantly higher in the LND group compared with SLNB (39.1% vs 4.1%, $P < 0.001$). The incidence of seroma was also significantly higher in the LND group (39.1% vs 12.4%, $P = 0.001$). When adjusted for the differences in age and primary histology, the differences between the SLNB and LND group in SSI (adjusted $P < 0.001$) and seroma (adjusted $P < 0.001$) remained statistically significant.

Seroma formation was strongly associated with the development of SSI on univariate and mulitvariate analysis both in the SLNB group (OR = 18.0 (3.0 – 107.3 95% CI), $P < 0.001$; adjusted OR 13.7 (1.9 – 101.0 95% CI), adjusted $P = 0.01$) and the LND group (OR = 21.0, (2.40 – 184.0 95% CI), $P = 0.007$); adjusted

OR 14.0 (0.9 – 207.6 95% CI), adjusted *P* = 0.06). In the SLNB group 33.3% (n = 6) of seromas underwent at least one aspiration and in the LND group 88.9% (n = 8) of seromas were aspirated. Aspiration of the seroma did not have a significant effect on SSI in the SLNB (*P* = 0.25) or the LND (*P* = 1.0) group.

The effect of operative site (inguinal *vs* axilla) on SSI incidence was not statistically significant in the SLNB (9.1% vs 1.1%; *P* = 0.05; adjusted *P* = 0.21) or LND (41.7% vs 36.4%; *P* = 1.0) group. The operative site did, however, have a statistically significant effect on the incidence of seroma formation. In the SLNB group, a seroma was significantly more likely to occur if the inguinal nodes had been biopsied rather than the axillary nodes in both univariate and multivariate analyses (23.6% vs 5.6%; OR 5.2 (1.7 – 15.6 95% CI), *P* = 0.003; adjusted OR 6.2 (1.8 – 21.4 95% CI), adjusted *P* = 0.004). Similarly, in the LND group, dissections of the inguinal nodes were more likely to result in seroma formation compared with dissections of the axilla, however this was not statistically significant in the univariate or multivariate analyses (58.3% vs 18.2%; OR 6.3 (0.9 – 42.7 95% CI), *P* = 0.09; adjusted OR 3.5 (0.47 – 25.9 95%CI) adjusted *P* = 0.22). Patient demographics (sex, age, BMI, diabetes, immunosuppression, smoking, and primary histology) and operation characteristics (use of prophylactic antibiotics, use of extended wound support sutures, insertion of drain) had no statistically significant effect on the incidence of SSI or seroma in either the SLNB or LND groups on univariate or multivariate analyses. Figure 1 gives the odds ratios for the univariate analysis of risk factors for SSI. Variables which had an alpha value < 0.20 on the univariate analysis for each group were included in a multivariate analysis. Figure 2 gives the odds ratios for the multivariate analysis of risk factors for SSI.

Impact of SSI

There were 6 cases of SSI in the SLNB group and 9 cases in the LND group. Patients who had undergone LND were more likely than those who had undergone SLNB to be readmitted to hospital for treatment with intravenous antibiotics (55.6% vs 33.3%, *P* = 0.61). One case in each of the groups returned to theatre for a washout of the operative site. Readmission to hospital resulted in 3 additional days of hospitalisation for one patient in the SLNB group, the other patient was admitted to a hospital external the study centre so data associated with that admission could not be obtained. In the LND group, readmission to hospital resulted in 49 additional days of hospitalisation (median = 9, IQR 5 – 15).

Excluding any appointments that were planned as part of routine post-operative case, cases of SSI resulted in significantly more additional appointments in patients who had undergone SLNB compared with those who had undergone LND (*P* = 0.013). Cases of SSI resulted in 10 additional appointments in the SLNB group (median = 2, IQR 1 – 3) and 58 additional appointments in the LND group (median = 7, IQR 4 – 8). The majority of these additional appointments were at a nurse-led outpatient plastic surgery dressings clinic (40% SLNB appointments; 79.3% LND appointments) for wound review and dressings changes. Other appointments included review at an acute plastic surgery trauma clinic (10% SLNB appointments; 15.5% LND appointments), GP appointments (50% SLNB appointments; 3.4% LND appointments) and consultant outpatient clinic appointments (0% SLNB appointments; 1.7% LND appointments). There were 3 cases of SSI which were diagnosed and treated by a general practitioner and did not result in any additional secondary care appointments. Two cases of SSI in the SLNB group and one case of SSI in the LND group were diagnosed and managed by a general practitioner and did not result in any additional secondary care appointments.

Table 3 provides an estimate of additional healthcare-associated costs in the cases of SSI in the SLNB and LND groups. One case of SSI was excluded from cost analysis as the patient was admitted to a different hospital whilst on holiday and data associated with that admission could not be obtained. The total additional healthcare-associated cost of SSI cases in the SLNB group was £7,372.39 and £34,532.47 in the LND group. The median additional healthcare-associated cost of SSI was higher in the LND group (£5187.04, IQR £1,039.12 – 6025.55) than in the SLNB group (£199.46, IQR £50.90 – 3535.57).

Discussion

It is well established that SLNB and particularly LND, are associated with significant rates of post-operative morbidity (4, 9). This study further provides further evidence for the rates of complications following these procedures. LND was associated with significantly higher rates of SSI and seroma than SLNB, likely due to LND being a more complex procedure which results in more damage to the lymphatics of the operative site. A broad range of estimates for the incidence of SSI and seroma formation are given in the literature, though the rates reported in this study for SLNB and LND are generally in keeping with other studies (2, 8, 11, 31).

Several studies of wound complications following lymph node surgery have highlighted the heterogeneity in which data regarding SSI is collected and how this may cause underestimation of the true incidence of complications (2, 6, 7). In this study we utilised the CDC definition for SSI (29) and only counted cases which fell within this definition. However, our search of patient records was thorough and included searching electronic primary care records which allowed identification of three cases of SSI (20.0% of total cases of SSI) which were diagnosed and treated without presentation to secondary care. This study defined seroma as a palpable collection of fluid identified by a clinician as a seroma within a 60 days post-operative time period. Other studies have stricter definitions of seroma and only include those which have been aspirated by a clinician (2, 7, 11). The incidence of seroma when only aspirated seromas were included was 4.1% for the SLNB group and 34.7% for the LND group. The incidence of palpable seroma following LND in this cohort was generally similar to other studies in the literature (3, 5, 6, 9), as was the incidence of seroma requiring intervention (5, 7, 11). However, the incidence of seroma following SLNB in this cohort was generally higher compared to other studies, regardless of whether this included all palpable seromas or only seromas which were aspirated (4, 5, 9, 12).

Notably, this study identified that seroma formation was a significant risk factor for SSI and increased the odds of SSI by around 20 in both SLNB ($P < 0.001$) and LND ($P = 0.007$). Following multivariate analysis, the association between seroma and SSI was still significant in the SLNB (adjusted $P = 0.01$) and was strong in the LND group (adjusted $P = 0.06$), therefore seroma formation is an independent risk factor for development of SSI. The association between seroma formation and SSI has previously been identified (9, 31, 32) and is likely due to the protein-rich fluid within a seroma creating favourable conditions for bacterial growth. This highlights that further research into methods to reduce seroma formation may also improve rates of SSI following lymph node surgery.

Greuter *et al.* reported similar rates of seroma formation to this study for both SLNB (11.6% compared with 12.3% in this study) and LND (46.3% compared with 39.1% in this study) (9). They also reported that the odds of seroma formation were 2.7 times higher when the operative site was the inguinal region compared with the axilla. This study also reported a significant association between the operative site and formation of seroma, though the increase in odds of seroma formation as around three to six times higher (OR 5.2;

adjusted OR 6.2 in SLNB and OR 6.3; adjusted OR 3.5 in LND) if the operative site was the inguinal region compared with the axilla. Both SLNB and LND to the inguinal nodes has also previously been shown to be associated with high rates of SSI compared with surgery to the axilla (3, 11, 31). This study did not find a significant association between operative site and SSI. This is likely due to the low incidence of SSI within the SLNB group and similar rates of SSI for axillary and inguinal operations in the LND group. Other risk factors such as male sex, increasing age, high BMI, smoking, and diabetes have all been identified as increasing risk of wound complications (2, 3, 7-9, 11, 24). This study had limited conclusions regarding patient risk factors for SSI and seroma formation and was likely underpowered to detect any significant patient risk factors.

This study did not find any significant association between the use of prophylactic antibiotics, extended wound support sutures, or drains and the incidence of SSI or seroma formation. There was however significantly higher utilisation of prophylactic antibiotics ($P < 0.001$) and drains ($P < 0.001$) in the LND group compared with the SLNB group which suggests that surgeons are aware of higher rates of SSI and seroma formation in the LND group and try to mitigate this risk. Prophylactic antibiotics were used in 87.0% of LNDs in this study and have been widely adopted to reduce the risk of SSI following LND (15, 16), however some observational studies have found no difference in SSI despite use of antibiotics prophylaxis (2, 8). Likewise, drains were inserted in all LNDs in this study, and though the rationale for reducing seroma formation and subsequent SSI by removal of lymphatic exudate is seemingly plausible, drains are associated with colonisation and biofilm formation (33) and their use is widely debated, particularly in the field of breast surgery (34). This study did originally aim to explore the use of negative pressure wound therapy but there were no recorded uses of negative pressure wound therapy within this cohort. Recent studies of negative pressure wound therapy have shown early promising results for reducing rates of seroma formation and SSI in inguinal LND (22, 23) and further research is needed in this area to establish its clinical effectiveness and financial impact.

The key finding of this study was the substantial financial and healthcare opportunity cost associated with SSI following LND. The cost estimates relied on assumptions for antibiotic course lengths, and admission costs were derived as an average of a number of different Healthcare Resource Group codes covering comorbidities. The NHS reference costs (26) which were used are a fundamental average of national data so admission length was not accounted for in the cost analysis. This study only examined short term wound complications following SLNB or LND and did not investigate lymphoedema. Lymphoedema is associated with substantial direct healthcare costs (35) and SSI has been shown to increase risk of developing lymphoedema after SLNB or LND (19, 31). Inclusion of lymphoedema and its associated direct healthcare costs in a cost analysis of SSI would therefore greatly increase the estimated financial impact.

A systematic review by Badia *et al.* included 16 studies from the UK across a number of surgical specialties which reported significant additional cost associated with SSI, particularly in orthopaedic surgery (36). Readmission to hospital, increased length of stay, and need for further operations were all identified as major drivers of cost associated with SSI. The median additional healthcare-associated cost of SSI following SLNB and LND was £199.46 and £5187.04 respectively. The substantial difference in median additional cost between these two groups was likely related to the higher rates of readmission to hospital (55.5% vs 33.3%) and additional appointments (58 additional appointments vs 10 additional appointments) in the LND group compared with the SLNB group. There are no studies in the literature reporting SSI associated costs following lymph node surgery in UK hospitals, however Chang *et al.* estimated the median additional cost of wound complications to be $2586 following inguinal LND in a single centre in the United States (6). They also highlighted that the majority of this cost was associated with admission to hospital. It is difficult to compare cost estimates with Chang *et al.* given these are from a different healthcare system over 10 years ago. A recently published estimate of SSI-associated cost following vascular surgery in UK hospitals was £3776 per SSI (37). Despite the limitations of the assumptions used in this study to derive cost estimates, the estimates given are in keeping with costs of SSI reported in recent literature and this is the only study to estimate cost associated with SSI following lymph node surgery in UK hospitals. In the year 2021-22 there was 39,701 SLNBs and 2,915 inguinal and axillary LNDs in English hospitals alone (38). Using the incidence for SSI and median additional healthcare-associated cost estimates in this study the estimated additional financial burden of SSI associated with lymph node surgery in NHS hospitals in England is potentially £324,720.88 per year for SLNBs and £5,913,225.60 for LNDs.

Conclusion

This study reiterates the high incidence of wound complications following both SLNB and LND. It provides further evidence that seroma formation is an independent risk factor for the development of SSI, and therefore research into methods of reducing seroma formation is key to reducing the incidence of SSI. This study demonstrated and the significant financial and healthcare opportunity cost associated with SSI following lymph node surgery. In the SLNB group, cases of SSI resulted in an at least 3 additional days of hospitalisation, 10 additional appointments and an estimated total additional healthcare-associated cost of £7,327.39. In the LND group, cases of SSI results in 49 additional days of hospitalisation, 58 additional appointments and an estimated total additional healthcare-associated cost of £34,532.47. There is a clear economic case for further research into perioperative care protocols and methods of reducing morbidity associated with lymph node surgery, as a reduction in SSI could lead to significant cost savings for the NHS.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Ethical Approval

Ethical approval: Not required. Local audit/governance approval obtained.

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Figure Legends

Figure 1 - Results of the univariate analysis showing odds ratios and 95% confidence intervals for risk factors for surgical site infection (SLNB, sentinel lymph node biopsy; LND, lymph node dissection; IDDM, insulin dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus)

Figure 2 - Results of the multivariate analysis showing odds ratios and 95% confidence intervals for risk factors for surgical site infection. Variables were only included in the multivariate analysis if they had an alpha value of < 0.20 on univariate analysis (SLNB, sentinel lymph node biopsy; LND, lymph node dissection)

Tables

Table 1 – Comparison of patient demographics and risk factors in the SLNB and LND groups

Variable		**SLNB** **N = 146 (%)**	**LND** **N = 23 (%)**	**Significance**
Sex	Female	88 (60.3)	10 (43.5)	n.s.
	Male	58 (39.7)	13 (56.5)	
Age	Median	61.5	73	*P* = 0.12
	IQR	52 – 71.8	63 – 80	
BMI	Median	27	28.6	n.s.
	IQR	23.4 – 31.3	25.3 –32.9	
Diabetes	No diabetes	126 (86.3)	18 (78.3)	n.s.
	IDDM	3 (2.1)	0	
	NIDDM	17 (146)	5 (21.7)	
Immunosuppressed	No	136 (93.2)	22 (95.7)	n.s.
	Yes	10 (6.8)	1 (4.3)	
Smoker	No	117 (80.1)	20 (87)	n.s.
	Yes	16 (11)	3 (13)	
	Missing	13 (8.9)	0	
Primary Histology	Melanoma	140 (95.9)	19 (82.6)	*P* < 0.001
	Squamous cell carcinoma	0	4 (17.4)	
	Merkel cell carcinoma	5 (3.4)	0	
	Porocarcinoma	1 (0.7)	0	

SLNB, sentinel lymph node biopsy. LND, lymph node dissection; IDDM, insulin dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus; n.s. nonsignificant

Table 2 – Comparison of operation characteristics and outcomes in the SLNB and LND groups

Variable		SLNB N = 146 (%)	LND N = 23 (%)	Significance
Operative Site	Axilla	55 (37.7)	12 (52.2)	n.s.
	Inguinal	89 (61)	11 (47.8)	
	Both	2 (1.4)	0	
Prophylactic Antibiotics	No	84 (57.5)	3 (13)	$P < 0.001$
	Yes	58 (39.7)	20 (87)	
	Missing	4 (2.7)	0	
Extended Wound Support Sutures	No	129 (88.4)	20 (87)	n.s.
	Yes	12 (8.2)	3 (13)	
	Missing	5 (3.4)	0	
Drain Insertion	No	140 (95.9)	0	$P < 0.001$
	Yes	2 (1.4)	23 (100)	
	Missing	4 (2.7)	0	
Outcome				
Surgical Site Infection	No	140 (95.9)	14 (60.9)	$P < 0.001$
	Yes	6 (4.1)	9 (39.1)	
Seroma Formation	No	128 (87.7)	14 (60.9)	$P = 0.001$
	Yes	18 (12.3)	9 (39.1)	

SLNB, sentinel lymph node biopsy. LND, lymph node dissection; n.s. nonsignificant;

Table 3 – Estimates of additional healthcare-associated costs for cases of surgical site infection

	Sentinel Lymph Node Biopsy Group		Lymph Node Dissection Group	
	Number	**Total cost (£)**	**Number**	**Total cost (£)**
Care Events				
Emergency admission with one procedure	1	£6,253.34	1	£6,253.34
Emergency admission with no procedure	0	-	4	£17,843.40
Secondary care outpatient appointment	4	£607.60	47	£7,148.22
Acute trauma clinic appointment	1	£192.93	9	£1,736.37
Primary care appointment	5	£210.00	2	£84.00
Total care events cost		*£7,263.87*		*£33,065.33*
Antibiotic Courses				
Flucloxacillin (oral)	5	£27.80	5	£27.80
Clarithromycin (oral)	1	£6.68	0	-
Clindamycin (oral)	0	-	1	£33.81
Co-amoxiclav (oral)	1	£2.04	3	£6.12
Linezolid (oral)	0	-	1	£890.79
Flucloxacillin (intravenous)	1	£72.00	5	£360.00
Clindamycin (intravenous)	0	-	1	£120.00
Co-amoxiclav (intravenous)	0	-	3	£28.62
Total antibiotic cost		*£108.52*		*£1,467.14*
Total cost		***£7,327.39***		***£34,532.47***