

**Impact of the National Sarcoma Guidelines on the Prevalence and Outcome of Inadvertent
Excisions of Soft Tissue Sarcomas: An Observational Study from a UK Tertiary Referral
Centre**

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Running title: Impact of NICE Policies for Inadvertent Excision of STSs

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Abstract

Objectives: This study aims to investigate the impact of the national guideline on the prevalence and outcome in patients with soft-tissue sarcoma (STS) who had undergone inadvertent excisions.

Methods: A total of 2,336 patients were referred to a tertiary sarcoma centre from six regions (North East, North West, East Midlands, West Midlands, Wales, and South West) in the United Kingdom with a diagnosis of STS between 1996 and 2016, of whom 561 patients (24.0%) had undergone inadvertent excisions. Patients were categorised into two groups of 10-year periods pre and post the National Institute for Health and Clinical Excellence (NICE) guideline implementation in 2006.

Results: The proportion of inadvertent excisions decreased after the NICE guideline implementation: 27.2% (pre-NICE) versus 19.8% (post-NICE). A substantial regional variation (18.0%–34.5%) in the proportion of inadvertent excisions in the pre-NICE era was reduced in the post-NICE era (14.3%–22.4%). The 5-year disease-specific survival was 77.7% (pre-NICE) versus 75.6% (post-NICE) ($p=0.961$) and there was a trend toward lower incidence of local recurrence in the post-NICE era; 13.5% (pre-NICE) versus 10.5% (post-NICE) ($p=0.522$). Multivariate analyses revealed that residual tumours in re-resection specimens were independently associated with an increased risk of disease-specific mortality (HR, 3.35; $p<0.001$) and local recurrence (HR, 1.99; $p=0.017$), which was significantly reduced after the NICE guideline implementation (53.2% versus 42.0%; $p=0.022$).

Conclusions: The NICE guideline implementation reduced the proportion of patients with STS who had undergone inadvertent excisions and residual tumour in re-resection specimens, indicating an improved pre-referral management of STSs.

Introduction

Soft tissue sarcomas (STSs) account for less than 1% of all malignant tumours [1-3]. Owing to the lack of awareness and rarity of tumours, some patients undergo inappropriate inadvertent surgical excision of STS presumed to be benign [4, 5]. Inadvertent excisions frequently result in inadequate surgical margins and, thus, further contamination of surrounding tissues. This increases surgical complexity during any re-excision surgeries; patients require more extensive surgery and face an increased risk of local recurrence (LR) [3].

In England and Wales, the National Institute for Health and Clinical Excellence (NICE), an organisation that provides national guidance on the promotion of good health and disease prevention and treatment, published early diagnosis guidelines in 2005, 2010 and 2015. It also reported the improved outcomes of patients with sarcoma in March 2006 [6-8]. These guidelines were disseminated to general practitioners (GPs) to raise awareness about the clinical features of common cancer types, including sarcomas. The features of lumps that are suggestive of malignancy were diameters > 5 cm, increasing size, situated deep to the fascia, and tenderness [9]. The key recommendations of the guidelines include the ideal care of patients with STS based on a multidisciplinary team (MDT) that manages the care of at least 100 new patients with STS per year [9] and ‘two week wait’ referral pathway to a specialist centre for patients with suspected malignancy [9-11]. In addition, the guidelines recommended that biopsy and surgical treatment of tumours should be performed by sarcoma MDTs to prevent patients undergoing inappropriate or unplanned excisions.

Currently, there are 12 specialist centres for approximately 2,900 patients with STS diagnosed annually in England and Wales [12]. The current system was created by the evolution of regional STS management in the early 2000s, relevant to the issue of the NICE guidelines. Our institution has

historically treated patients with STS from many regions in England and Wales using standardised strategies before the evolution of regional management. Our institution also reported the most activity, reflecting our expertise among the specialist centres. Recently, we reported the impact of the NICE guidelines and the evolution of regional managements on the survival of newly diagnosed patients with STS. An improvement in survival improvement was observed [13], and regional variations in survival disappeared [14] after the introduction of the guidelines in newly diagnosed patients with high-grade STS. However, it remains unclear whether these recommendations changed the prevalence and outcome of patients who underwent inadvertent surgeries before a referral to specialist sarcoma centres and the referral pattern in different regions of the United Kingdom.

This study aims to investigate the impact of the national guideline on the prevalence and outcome in patients with STS who had undergone inadvertent excisions before referral to a specialist sarcoma centre in the United Kingdom.

Patients and methods

Data sources

A retrospective study was done on patients who were referred to a single tertiary supraregional sarcoma centre. The inclusion criteria were patients with a primary STS located in the limbs or trunk wall who were referred from April 1996 to March 2016 after an inadvertent excision of STSs and received treatments in our centre. These patients were searched prospectively from a collated oncology database in our centre. Amongst 2,412 patients registered in the database with a primary STS that was treated in our centre, 561 patients who underwent unplanned STS excision were identified.

We collected and reviewed the following data: age at diagnosis, sex, histological diagnosis

and grade, tumour size, tumour site, tumour depth, TNM (UICC Cancer Staging Manual, 6th edition), type of treatment (surgical and nonsurgical) and surgical margins. All patients were categorised into one of two groups based on the referral date; a pre-NICE group (referred from April 1996 to March 2006) and a post-NICE group (referred from April 2006 to March 2016). For geographic variation, we determined region based on the residence of patients. Ethical approval for a retrospective, observational study using a large oncological database was granted by our institutional review board.

Statistical analysis

We used the Kaplan–Meier method for the analysis of disease-specific survival (DSS) and assessed comparisons with the log-rank test. In addition, factors associated with survival were analysed using the Cox proportional hazards models. We defined the DSS as the period between the date of diagnosis and tumour-related death. Patients who died of causes other than STSs were considered as censored at the time of death. The cumulative incidence was estimated for LR using a competing risk analysis. Death was regarded as a competing event to LR. Multivariate analysis was performed using Fine and Gray model and calculated subdistribution hazard ratios (HRs) for the final predictor variables. The variables of each group were compared using the chi-square test or the Fisher’s exact test. All statistical analyses were conducted using SPSS (version 23; IBM SPSS, Armonk, NY) and the R version 3.5.5. Differences were considered to be statistically significant at less than 0.05.

Results

Regional variation before and after the introduction of NICE guideline. Amongst ten geographical regions with fewer than 50 patients (approximately 2%) from Scotland (n = 3), Northern Ireland (n = 5), South East (n = 30), and Greater London (n = 8), and other regions (other countries; n = 45) were

excluded from the study because of an insufficient statistical power for the analysis of regional variations in the prevalence of inadvertent excision of STS. Thus, the changes in the percentage of inadvertent excisions among all referrals were calculated from 2,336 patients (representing approximately 11% of the overall STS population over the study period) who were referred from the six regions of North East, North West, East Midlands, West Midlands, South West and Wales.

The total number of referrals received after inadvertent excisions was 561 of 2,336 patients (24.0%). The number of inadvertent excisions markedly decreased after the introduction of the NICE guidelines; 361 of 1325 (27.2%) patients in the pre-NICE era and 200 of 1011 (19.8%) patients in the post-NICE era ($p = 0.001$; **Table 1**). The geographic distributions of patients with inadvertent excisions in the pre- and post-NICE era are shown in **Table 1**. In the pre-NICE period, the rate of referral after inadvertent excisions was highest in the West Midlands (34.5%), followed by North West (25.5%), Wales (22.7%), East Midlands (19.3%), North East (18.0%), and South West (17.4%). In the post-NICE period, the rate declined to 14.3–22.4%, which was highest in Wales (22.4%), followed by West Midlands (20.7%), South West (19.2%), East Midlands (18.9%), North East (16.7%), and North West (14.3%). In the North West ($p = 0.029$) and West Midlands ($p < 0.001$), where the investigating institute is located, 1,198 patients representing majority (approximately 63%) of patients with limb and trunk wall STS in the region were referred; the reduction in referral after inadvertent excisions was statistically significant (**Table 1**).

Characteristics of patients who were referred after inadvertent treatment. Patient characteristics for all 561 patients who were referred after inadvertent excisions from the six regions are shown in **Table 2**. There were 309 males and 252 females, with a mean age of 54 (range, 2 to 95) years. The

tumour grade was high-grade in 78.3% (n = 439) and low-grade in 21.7% (n = 122), and the tumour depth was superficial in 51.9% (n = 291) and deep in 48.1% (n = 270). The site of involvement was the extremity in 73.8% (n = 414) and trunk in 26.2% (n = 147). The tumour size was ≤ 5 cm in 44.4% (n = 249), > 5 cm in 44.9% (n = 252), and unknown in 10.7% (n = 60). The most common histological diagnosis was leiomyosarcoma (13.4%; n = 75), followed by synovial sarcoma (12.1%; n = 50), undifferentiated pleomorphic sarcoma (11.2%; n = 63), undifferentiated spindle cell sarcoma (10.0%; n = 56), myxofibrosarcoma (7.7%; n = 43), and myxoid liposarcoma (6.4%; n = 36). In a comparison of the pre- and post-NICE era, patients in the post-NICE era were older, had higher grade, and had smaller tumours excised inadvertently than in the pre-NICE era.

The management for these inadvertent ‘whoops’ procedures was consistent during the study period. The principal treatment form was re-excision with clear margins unless further surgery would cause considerable disability or if the patient declined. Surgical re-excision was performed in 86.5% of patients in the pre- (n = 312) and post-NICE era (n = 173). In the whole study period, surgical margins were negative in 88.6% (n = 430) of patients who underwent surgical re-excision. Residual tumours were seen in 56.9% (n = 276) of resected specimens. Soft tissue coverage using a skin graft or soft tissue flap was performed in 14.8% of patients in the entire study period, which was more frequently performed in the post-NICE era (20.2%) than in the pre-NICE (11.9%; $p = 0.016$). Adjuvant radiotherapy was offered to patients with tumours > 5 cm in diameter, intermediate or high-grade tumours, those whose final excision was marginal, and those who did not undergo tumour re-excision. The decision for radiotherapy and/or chemotherapy was taken at the sarcoma MDT meeting after considering the histological subtype, imaging and final pathology reports. Radiotherapy and chemotherapy were administered in 41.4% (n = 232) and 8.6% (n = 8.6%) of patients, respectively.

Post-operative surveillance involved the clinical examination for LR with MRI and chest radiography with CT, if indicated. A follow-up consult was done every three months for the first two years, every six months until five years, and annually until 10 years after the surgery. The LR rate was 13.9% (n = 78) in the entire study period.

Survival outcomes in the pre- and post-NICE era. The 5-year DSS in this entire cohort was 77.7%, with a mean follow-up of 73 months (range, 1 to 218 months). Univariate analysis revealed that the age equal to or older than 55 years ($p < 0.001$), high-grade tumours ($p < 0.001$), tumours deep to fascia ($p < 0.001$), metastases at diagnosis ($p < 0.001$), no surgical re-excision ($p < 0.001$), radiotherapy ($p < 0.001$), and/or chemotherapy ($p = 0.001$), negative margins ($p < 0.001$), residual tumours in the excised specimens ($p < 0.001$; **Figure 1**), and LR ($p < 0.001$) were significantly associated with worse DSS (**Table 3**). There was no significant difference in DSS between the pre- and post-NICE era (5-year, 77.7% versus 75.6%; $p = 0.961$) or among the regions of residence ($p = 589$). Multivariate analysis revealed that age equal to or older than 55 years (HR, 1.58; $p = 0.021$), high-grade tumour (HR, 4.11; $p < 0.001$), tumour larger than 5 cm (HR, 2.29; $p < 0.001$), metastasis at diagnosis (HR, 4.74; $p < 0.001$), no receipt of surgical treatment (HR, 7.19; $p < 0.001$), residual tumour in the re-excision specimens (HR, 3.35; $p < 0.001$), and LR (HR, 1.85; $p = 0.002$) were independent prognostic factors associated with worse prognosis (**Table 3**). Among these, the percentage of patients who are equal to or older than 55 years and had high-grade tumours increased in the post-NICE era, whereas those who had tumour size larger than 5 cm, residual tumour, and LR significantly decreased after the introduction of the NICE guidance (**Table 1**).

Local control in the pre- and post-NICE era. The 5-year cumulative incidence of LR was 12.9%. We observed a trend toward lower incidence of LR after the introduction of NICE guidance despite no statistical significance: the 5-year LR incidence was 13.5% and 10.5%, respectively ($p = 0.522$). Multivariate analysis revealed that high-grade tumour (HR, 2.83; $p = 0.009$), re-excision with positive margins (HR, 1.87; $p = 0.040$) and residual tumour in the re-resection specimens (HR, 1.99; $p = 0.017$) were independent predictors of LR (**Table 4**). Thus, higher tumour grade and residual tumour in the re-resection specimens (**Figure 2**) commonly predicted worse outcome of both local control and survival. As previously described, not only the number of ‘whoops’ treatments but also the detection of residual tumours after inadvertent excisions decreased after the introduction of NICE guidance: the proportion of residual tumours in the re-resected specimens decreased from 53.2% to 42.0% ($p = 0.022$; **Table 2**).

Discussion

Accumulating evidence established that inadvertent excisions should be avoided to reduce the risk of local recurrence and the potential need for additional and more extensive surgery [3, 15-17]. Although sarcoma specialists have mostly recognised this finding, it is not well recognised by non-specialists including other surgical specialties and general practitioners (GPs) who often perform minor surgeries. Constant vigilance and awareness of the potential for malignancy is crucial to decreasing the incidence of inadvertent surgeries on soft-tissue sarcomas, which could be improved by nationwide guidelines. To date, clinical guidelines have been published in various countries; for instance, the National Comprehensive Cancer Network (NCCN) STS guideline in the United States [18], the European Society of Medical Oncology (ESMO) guideline in European countries [19] and the NICE guideline

in the United Kingdom [6]. However, their impact on inadvertent treatment before referral to a specialist centre, and their interregional variation, has not been reported previously. This study identified a significant decline in referrals after inadvertent excisions and the presence of residual tumours after implantation of the NICE guideline. Interestingly, the regional variation in the proportion of referrals after ‘whoops’ treatments also declined from 17.4%–34.5% to 14.3%–22.4%. Treatment-related factors such as surgical strategy and resection margins did not change between the pre- and post-NICE era, suggesting that pre-referral management, rather than post-referral, improved after the introduction of the NICE guidance. Our results support the positive impact of the nationwide guideline on the improved awareness of STS management in non-specialist physicians.

The reported 5-year DSS in patients with an inadvertent excision is 77%–94% [4, 20-25]. Size larger than 5 cm, higher grade, and the residual tumour in the re-resection specimens are common independent prognostic factors [4, 20, 26-28]. In this study, the 5-year DSS was 77.7% and the prognostic factors included older age, high-grade tumours, larger tumour size, metastasis at diagnosis, no receipt of surgical treatment, residual tumour in the re-resection specimens, and LR, which were consistent with previously published papers [4, 16, 20, 26-29]. Of note, we observed no statistical difference in the DSS between the pre- and post-NICE era. The prognostic effect of a decreased rate of patients who had tumour size larger than 5 cm at referral, residual tumour after re-resection, and LR, may have been cancelled due to an increased rate of patients who are equal to or older than 55 years and had high-grade tumours. In general, there is little difference in prognosis as patients with inadvertent excisions tend to have smaller and more superficial tumours, which tend to have a better prognosis [29]. The NICE guidance seems to have had little effect on the survival outcomes in patients with inadvertent excisions, however we have demonstrated that the guidance has reduced the need for

additional, often more extensive, surgery.

The cumulative incidence of LR in this study (12.9% at five years) was comparable to previous reports (5%–45%) [4, 16, 20-31]. Tumour grade, surgical margin, and residual tumour in the re-resection specimens were independent prognostic factors for local control, which was also consistent with the reported studies [4, 16, 20, 26, 30]. The rate of positive resection margins, as high as 9.8%, was comparable to the previous reports [28, 32, 33]. The ability to resect the residual tumour with negative margins could be compromised by the previous surgery. There was a trend toward decreased LR (5-year, 10.5%) in the post-NICE era compared to the pre-NICE era (5-year, 13.5%), although the difference did not reach statistical significance in a competing analysis. This could be attributed to the effect of decreased rate of the residual tumours in re-resection specimens in the post-NICE era (57% versus 42%; $p = 0.001$), which may be cancelled by the increased rate of high-grade tumours (76% versus 83%; $p = 0.043$). Since LR is an independently negative prognostic factor for survival, more attempts to raise awareness of the clinical features (bigger than a golf ball [34]) of possible high-grade malignancy, with subsequent appropriate referral to a tertiary sarcoma centre before undergoing inappropriate or unplanned excisions, would minimise the risk of local failure and disease-specific mortality.

Despite these national guidelines, we still experience approximately 20 referrals per year. This suggests that the dissemination of these guidelines to GPs may not be sufficient to avoid inadvertent excisions completely, and this underlines the need to continuously alert non-specialists. In our previous study, an improvement in survival was observed after the issuance of the NICE guidelines in 2006, which was mainly attributed to decreased tumour sizes and incidence of detectable metastases [13]. A decrease in tumour size could be attributed to these guidelines and to the introduction of social

projects, such as the National Sarcoma Awareness Project [35] or Sarcoma Awareness Week [36]. Including the information about the increased risk of local control and functional loss by re-excision surgeries to these projects may further contribute in avoiding inadvertent STS excisions.

The prevalence of inadvertent excisions in the North West and East Midlands, where the investigating institution is located, significantly decreased after the issuance of the national guidelines, while that in other regions (North East, East Midlands, Wales, and South West) did not change significantly. The regional difference may be due to the awareness of the potential for malignancy and management of STS by GPs and patients and due to geographic barrier. There are more rural areas in the North East, Wales, and South West, and these districts are further away from the investigating institute, indicating a lower accessibility to tertiary centre. There is a great need in reducing the inequalities in sarcoma management related to geographic barriers. In France, the national organisation in the reference network for sarcoma, which is called NETSARC+, was established in 2010. It provides remote access to specialised diagnosis and MDT-based sarcoma care [37, 38]. More than 30 reference centres throughout the nation were included and structured the “hub-and-spoke” model: the organisation structures collaborations between a relatively high number of centres (spokes) to ensure a geographical coverage and a limited number of reference centres (hubs) that concentrate the best expertise available [38]. This system virtually centralises some services, such as pathological diagnosis, referring some patients for selected procedures, such as surgical treatment, and directly carrying out other treatments within a clinical strategy shared with the MDT [38]. Fayet et al. reported that, in the context of the French organisation in the reference network, a quintile of patients furthest away from reference centres has lower chances of early access to specialised diagnosis and MDT discussion; however, this influence of distance is less in comparison with clinical factors [38]. However, the impact

of the French reference network in the prevalence of inadvertent STS excision before and after the establishment of this system has not yet been reported. This discussion would contribute to the understanding about what the effective system is to reduce the geographic and social barriers for patients to pursue appropriate sarcoma care.

This study has several limitations. First, this is a retrospective study based on the patient data from a single tertiary referral centre, although this would introduce less bias on treatment-related variables compared to a multi-centre study. Thus, the data based on the patient cohort of this study do not represent the nationwide impact of the NICE guidelines. Further analysis using the national database could elucidate the impact of the NICE guidelines for ‘whoops’ excisions in England and Wales. Second, the number of patients with inadvertent treatments in the post-NICE period was smaller than that of the pre-NICE period with fewer follow-up periods; however, we believe that this was the aim of the guideline. Third, since the information about the post-operative morbidity and extension of resections was not fully available in the database, a comparison of these outcomes between the pre- and post-NICE era could not be included. Finally, this study lacks the details of physicians who performed inadvertent excisions. Hence, further investigation of referral details may identify a medical speciality where further education is needed.

In summary, this study identified a significant reduction in the referral number and regional variation of patients who had undergone inadvertent excisions after the introduction of the NICE guidance. Whilst the DSS remained unchanged, there was a trend toward lower incidence of LR in the post-NICE era. Furthermore, residual tumour in re-resection specimens, which is a negative prognostic factor for LR, significantly decreased. Overall, the national guidelines have helped reduce the prevalence and improve the outcome of patients with STS who underwent inadvertent excisions.

Continuous alerts to non-specialists may further contribute in avoiding inadvertent STS excisions.

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Author contribution

All authors designed the study, searched the published work, accrued patients, collected, and interpreted data. AA was responsible for study design, search of the published work, data interpretation, and preparation of the report. TF performed data collection, data analysis, and writing of the draft of the manuscript. SE, JS and YT performed data analysis. SE, JS, YT, JG, RG and AA reviewed the manuscript and provided helpful discussion. The manuscript was finalized by AA with the assistance of all authors.

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