



Inadvertent excision of malignant soft tissue tumours

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- Inadvertent excision of lumps which turn out to be sarcomas is not uncommon.
- Imaging has a limited role in detecting microscopic residual disease but can show the extent of the previous surgical field.
- Standard treatment is wide re-excision, usually combined with radiotherapy.
- Residual tumour is found in an average of 50% of reported cases.
- The presence of residual disease is an adverse prognostic factor.
- All lumps bigger than a golf ball should have a diagnosis prior to excision.

Keywords: inadvertent excision; local recurrence; soft tissue sarcoma; unplanned excision; wide re-excision

Cite this article: *EFORT Open Rev* 2019;4
DOI: 10.1302/2058-5241.4.180060

Soft tissue sarcomas (STS) are rare, with a combined incidence of about 60/100,000 population a year. It is generally stated that there are 100 benign soft tissue tumours for every soft tissue sarcoma. As a result of this there is a low level of awareness of the possibility of a sarcoma entering the differential diagnosis in many situations. Delays in diagnosis of both bone and soft tissue sarcomas are common, and paralleling this is the high frequency of inadvertent excision (IE) of lesions which then turn out to be sarcomas. This was first described by Giuliano and Eilber in 1985¹ but has undoubtedly been commonplace for many years. It has acquired the eponym of a 'whoops' procedure as the surgeon (and the patient) are both surprised and maybe distressed when the pathologist reports that the lesion which they thought was benign, is in fact malignant!² Almost always the surgeon will have 'shelled out' the lump and will usually confidently say that they 'have got it all out'. In the past many of these patients then had no further treatment but there was a very high rate of

local recurrence (up to 70%) and it is now far more common for these patients to be referred to a sarcoma unit for definitive management.² In 1994, Gustafson et al showed that patients treated somewhere other than a tumour centre required significantly more operations than those treated primarily at a tumour centre, either to have a re-excision to get clear margins, or for management of local recurrence.³

The significance of an inadvertent excision has been assessed by numerous authors and this article aims to summate the body of knowledge there is on the subject, identify current best practice and suggest future possibilities for research and investigation.

Incidence

The actual incidence of inadvertent excisions (IE) is unknown but numerous reports on this topic have now been published. Whilst some papers report only on patients who have had an IE, others report on the incidence of this as a proportion of total referrals. These are summarized in Table 1 and show that the proportion of IEs ranges from 18% to 53% of all referrals with an average of 33%.

Cause

The reasons for which patients undergo IE are multiple but very often it is because the operating surgeon has not thought that the lump could be a sarcoma. If they had entertained this thought, then the patient would have been properly investigated first with imaging and usually biopsy. There are multiple guidelines now available defining the management pathway for a suspicious lump.⁴⁻⁶

Alamanda et al investigated whether IEs were more common the further the patient lived away from a sarcoma centre but found no evidence of this.⁷ They also found no difference based on insurance status. Kang et al noted that patients who had the primary IE at a tertiary centre tended to have a lower rate of residual tumour than those having the IE at a non-tertiary hospital and that they

Table 1. The main papers dealing with inadvertent excision of soft tissue sarcomas

Author (Ref)	Year	Total number	Number with IE	% IE	Number reexcised	% with residual tumour	LR at 5 yrs after reexcise
Giuliano ¹	1985	90	all	all	90	49%	
Peabody ³⁹	1994	172	74	43%	72	51%	
Zornig ⁴⁰	1995	189	67	35%	67	45%	7%
Goodlad ⁴¹	1996	236	95	40%	95	59%	
Noria ¹⁵	1996	292	65	22%	65	35%	8%
Davis ⁴²	1997	239	239	all	186		8%
Siebenrock ⁴³	2000		16	all	16	63%	19%
Lewis ³⁵	2000	1092	407	38%	407	39%	15%
Zagars ²⁷	2003	666	all	all	295	46%	15%
Peiper ⁴⁴	2004	110	all	all	110	31%	13%
Davies ¹⁰	2004		111	all	111	57%	
Wong ²⁰	2004	76	18	24%	16	56%	
Rougraff ⁴⁵	2005	106	75	all	75	65%	11%
Fiore ⁴⁶	2006	598	318	53%			
Chandrasekar ¹⁹	2008	2201	402	18%	316	59%	21%
Potter ²¹	2008	203	64	32%	64	72%	34%
Morii ⁴⁷	2008		77	all	45	45%	12%
Rehders ⁴⁸	2009		143	all	139	31%	12%
Arai ²²	2010	191	63	33%	63		8%
Funovics ¹⁸	2010	752	310	41%			
Han ¹⁷	2011		104	all	104	51%	26%
Zacherl ⁴⁹	2012	266	131	49%			
Umer ³⁰	2013	135	51	38%	4		14%
Alamanda ⁷	2013	400	147	37%			
Arai ³²	2014		113	all	113	51%	7%
Morii ³¹	2015	92	24	26%	24	71%	
Koulaxouzidis ⁵⁰	2015	204	110	39%	110	53%	11%
Saeed ²⁴	2016	245	34	14%	25	72%	45%
Charoenlap ³⁶	2016	451	161	36%	161	55%	13%
Jones ²⁵	2016		44	all	44	39%	5%
Smolle ³⁴	2017	728	281	39%			
Gingrich ¹¹	2017		76	all	64	70%	
Nakamura ⁵¹	2017		197	all	197	58%	9%

Note: The first author and year of publication are followed by columns listing: The total number of STS in the series; the number of these with IE and then the % of the whole series with IE. The next column is the number who underwent re-excision and the following column details the % found to have residual tumour. The final column gives the rate of LR reported at 5 years. IE, inadvertent excision; LR, Local Recurrence

also ended up with a lower rate of local recurrence, but that there was no difference in survival.⁸

Size and depth

Current guidelines suggest that any lump which is either deep or bigger than 5 cm should be investigated prior to excision and thus it would be expected that most lumps submitted to IE would be small and subcutaneous.^{4-6,9} This is supported by several papers that have documented the size of the tumour that has been excised and the depth of the tumours. The average size of IE tumours varies from 3.2 to 8.9 cm with a mean of 5.7 cm, with most authors commenting that superficial tumours undergoing IE were smaller than deep tumours. In our own practice we have investigated the proportion of patients undergoing IE related to the actual size of the tumour. Fig. 1 shows the data for superficial (to the fascia) tumours showing a decreasing proportion of IEs as the tumours became bigger. However, it was still the case that 56% of all superficial STS presented to our unit following an IE. Those

papers which have reported depth conclude that 55% of all patients with inadvertent excision had superficial tumours, this contrasts with the generally accepted incidence of superficial soft tissue sarcomas being about 25%.

Changes with time

It is generally accepted that the better the education of the surgical fraternity, the lower the proportion of IEs that will be carried out. In the UK, national guidelines were produced in 2000 (and re-issued five-yearly thereafter) and sent to all GPs stating that any patient with a lump that was

- bigger than 5 cm
- increasing in size
- deep to the fascia
- painful

should be considered to be a sarcoma until proved otherwise and referred for investigation to a sarcoma unit.⁹ It

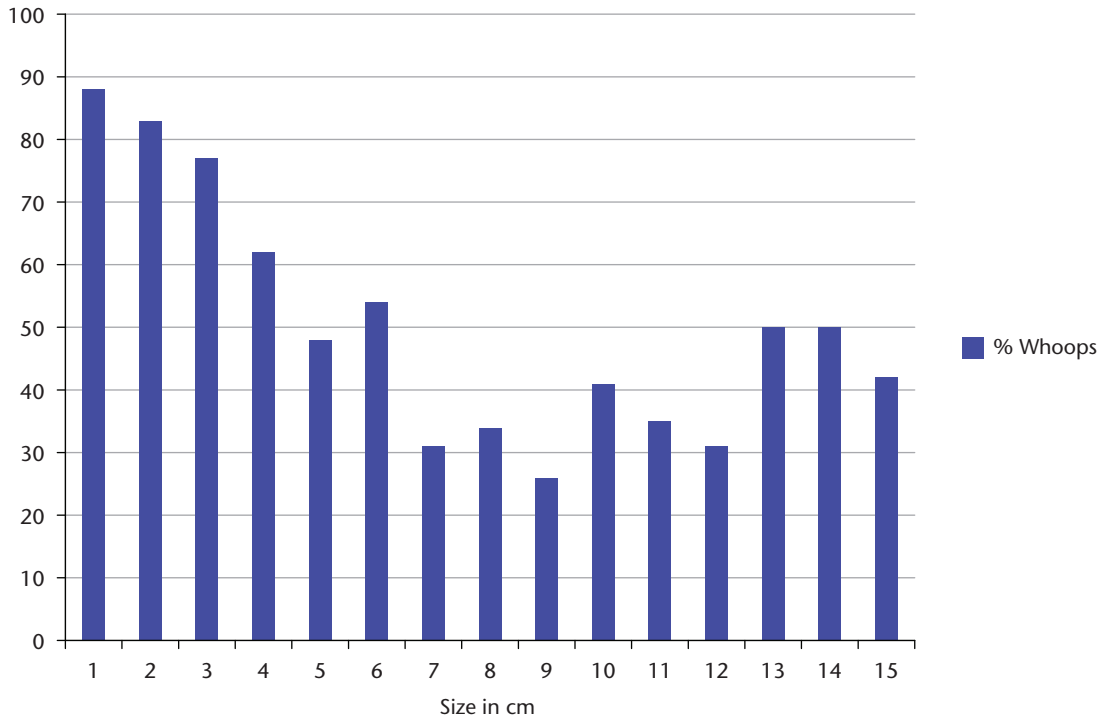


Fig. 1 The proportion of patients referred to our unit with an inadvertent excision based on the size of the original tumour (subcutaneous tumours only).

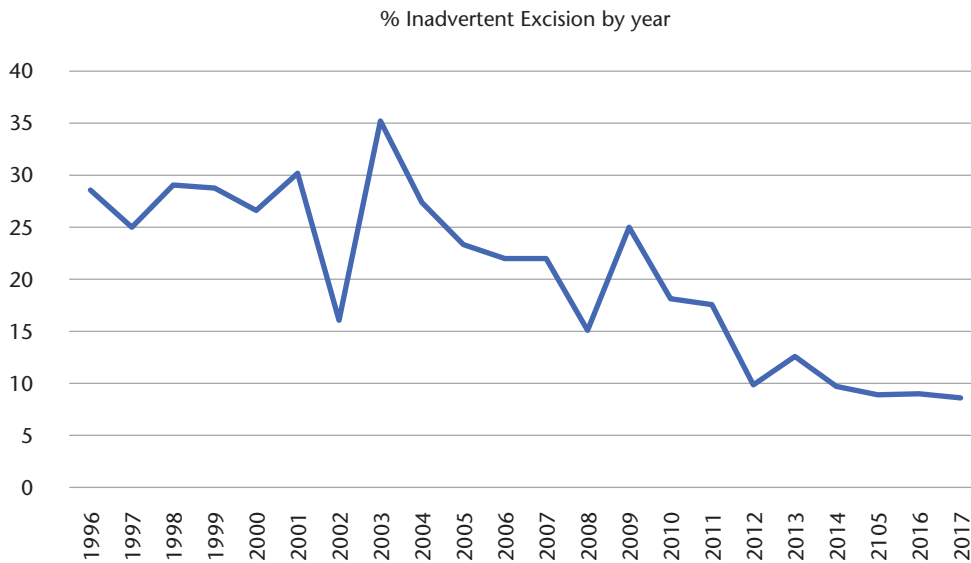


Fig. 2 Graph showing how the percentage of inadvertent excisions as a proportion of all new referrals has decreased over a 20-year period.

was hoped that this would result in both earlier diagnosis of sarcomas and less IEs.

Data from our own unit show that the proportion of patients with an IE referred over the past 20 years has slowly decreased but is still around 10% of all referrals (Fig. 2).

Imaging

When a patient has undergone an IE for sarcoma it is mandatory for them to be referred to a sarcoma centre for ongoing management. If pre-operative imaging has been performed, this should be reviewed as it will help greatly

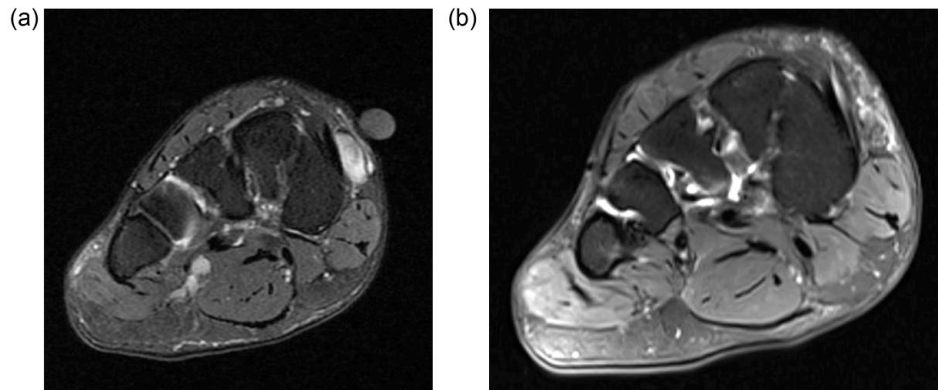


Fig. 3 (a) Coronal fat suppressed image shows a 1 cm lesion in the medial mid foot. Inadvertent excision of this lesion was performed with a subsequent histological diagnosis of synovial sarcoma. (b) Coronal fat suppressed image at restaging shows some oedema in the superficial fat at the site of the previous synovial sarcoma and no definite macroscopic residual disease. Wide re-excision showed no residual tumour.

in establishing the extent of the primary tumour. Furthermore, an appreciation of the imaging appearances of the tumour at presentation is of value in the assessment of any potential residual tumour. Following IE, standard practice is to perform a new MRI to assess whether there is any residual tumour apparent. In the presence of post-surgical change after IE, visualizing areas within the surgical bed that show similar imaging appearances on MRI to the original tumour is highly suggestive of residual disease. Several papers have reported on the utility of this, comparing the radiologists' reports with the eventual findings at re-excision. Davies et al's paper in 2004 found that MRI had a poor negative predictive value (0.67) but a positive predictive value of 0.93 with sensitivity of 0.64 and specificity of 0.93, although these were all non-contrast enhanced scans.¹⁰ Gingrich et al in 2017 found that the overall accuracy of MRI was only 78% in predicting residual disease, which they described as 'modest' and Wang et al in 2018 also found that MRI was not that accurate but commented that extensive soft tissue oedema increased the likelihood of finding residual tumour.^{11,12}

Whilst there are no studies showing the optimum imaging modality, MRI is widely considered the most useful (Fig. 3). Whilst ultrasound can certainly be used to detect residual disease, the surgical planning of re-excision is typically performed on MRI. The timing of the MRI is also important; carried out too early following the IE it will show post-operative oedema/haemorrhage, and carried out too late it may delay re-excision. The optimum timing is thus probably between 4 and 8 weeks following the IE. In general, this is the typical timeframe in which patients will be seen at a sarcoma centre following IE. This apparent delay in management is needed to allow review of the histology of the IE to confirm sarcoma and clinical review to explain the management plan.

The aim of the MRI is not only to show the extent of any residual tumour but also to show the extent of the previous surgical excision. Clearly the patient should also have appropriate staging studies, usually a CT chest as a minimum, according to local or national guidelines. PET-CT is not used to try and detect residual disease as there will be high uptake from the wound in the post-operative period.

Pathology

It is essential that the previously excised lesion should be reviewed by an experienced pathologist. Studies have shown up to a 30% error in non-specialist reporting of soft tissue lesions thought to be sarcomas. The pathologist should also be able to get an idea of the margins of excision and the size of the lesion, which are often not reported in the initial pathology report from a non-specialist centre.

Numerous papers have commented on the types of tumour most likely to have residual disease left behind after IE. The most common tumours are DFSP (Dermato Fibro Sarcoma Protuberans), MPNST (Malignant Peripheral Nerve Sheath Tumour) and myxofibrosarcomas, followed by synovial sarcoma and undifferentiated pleomorphic sarcoma. The ones with the lowest risk of residual tumour are liposarcoma and leiomyosarcoma.

Margins

Most lumps that are inadvertently removed will be 'shelled out' resulting in either an intralesional or marginal margin (through the 'reactive zone') as described by Enneking.¹³ Although the operating surgeon will almost always say 'I got it out completely' this is usually false optimism with sarcomas. One of the problems with

an inadvertent excision is that they are often carried out through inappropriate approaches (e.g. transverse incisions) and there may have been a drain placed which further extends the field of contamination.

It is essential that a true 'wide' excision should be achieved, but the actual extent of this is difficult to decide. Very often the post-excision MRI will show haemorrhage or oedema and the surgeon must make an experience-based decision as to how extensive any further surgical excision should be. It is also helpful to obtain comment from the pathologist on the appearance of the margins of the excised lesion and whether they show a diffuse infiltrating pattern as this may influence the width of re-excision. Lewis et al aimed to get 2 cm around the 'residual' tumour, whilst Sugiura and Arai suggested that 3 cm should be the target.^{35,14} Noria et al in 1996 highlighted the difficulty of achieving adequate margins when there is no residual tumour left to feel and give the surgeon the tactile sensation of how close he/she may be to the tumour.¹⁵ They also pointed out the surprisingly high rate of positive margins when residual disease was present, in 9 of 23 of their patients (39%), compared with their expected rate of 10% in primary excisions.

The principles therefore of managing a patient following an inadvertent excision are to firstly establish the diagnosis, grade, size, stage and location of the excised tumour and then to identify the likelihood of there being any residual tumour. Next the surgeon should evaluate whether those margins could be improved with further surgery and also, with the Multi Disciplinary Team, decide whether adjuvant or neoadjuvant therapy may have a role in managing the tumour.

In many situations, especially with superficial tumours, the mainstay of further treatment will be a wide re-excision, taking generous margins around the previous excision cavity and often removing the deep fascia as a relatively impermeable deep barrier. This may require plastic surgical reconstruction. For inadvertently excised deep tumours, obtaining wide margins at the time of re-excision may be more challenging and may involve sacrifice of deep structures. If, however, the re-excision might involve critical structures such as nerves or blood vessels then there may be a role for more aggressive adjuvant or neoadjuvant therapy. In this setting of a previous IE, obtaining a planned positive margin as described by Gerand et al may be difficult.¹⁶ Amputation is sometimes needed either due to the nature of the excised tumour or due to its location.

Timing of re-excision

The optimum timing of re-excision has not been established. Han et al reported no difference in outcomes between patients undergoing early re-excision (before 32

Table 2. Showing rates of residual tumour depending on depth and grade (ROH data)

	Total	High	Inter	Low
Total	60%	72%	55%	49%
Deep	68%	78%	59%	63%
SC	55%	67%	53%	47%

Note: SC, subcutaneous

days, the median in his series) and after 32 days.¹⁷ Funovics et al found that undergoing re-excision within 12 weeks of initial IE led to a better prognosis.¹⁸

Re-excision findings

There have been over 45 publications dealing with inadvertent excision of soft tissue sarcomas, with 2693 patients having a re-excision. Of those, 1350 (50%) were found to have residual tumour. The rates in different series varied, however, from 31% to 74% (Table 1). The risk of residual tumour was greatest with high-grade deep tumours and lowest with low-grade superficial tumours (Table 2).

Following re-excision there are likely to be four categories of situations:

- No residual tumour found
- Macro or microscopic residual tumour excised with clear margins
- Macro or microscopic tumour excised with a marginal margin
- Macro or microscopic residual disease excised but with an involved margin

In the first two situations, re-excision has been successful and the only decision is whether further adjuvant therapy is needed. In most cases of a high-grade tumour, radiotherapy should be considered, especially for larger or deep tumours, according to national guidelines.⁴⁻⁶ If residual disease is encountered and there are involved margins, then further excision should be considered as it should with a marginal margin.

Few publications have reported the rate and quality of the re-excision margins, but those which have (Table 1) have reported clear margins in 74–91% of cases.^{15,19}

Reconstruction

Several authors have commented on the high rates of limb reconstruction needed after wide re-excision. The highest numbers of patients requiring plastic surgery, not surprisingly, come from units with very active plastic surgery support. Wong et al in 2004 reported that 89% of patients undergoing re-excision required plastic surgery reconstruction.²⁰ These rates have not been matched by others

but there is no doubt that patients undergoing re-excision have a greater number of operations and are more likely to need plastic surgery than those having primary resections.^{21,22}

Radiotherapy

The use of radiotherapy varies from country to country although more recent guidelines have emphasized the importance of radiotherapy (RT) in decreasing the risk of Local Recurrence (LR) after sarcoma resection. In general, most guidelines will now stipulate that all high-grade sarcomas and all larger low-grade tumours should include radiotherapy as part of their treatment. There is thus no difference between patients with IEs and those treated primarily. There has, however, been an increasing trend for the use of neoadjuvant RT, especially in primary STS, following the results of the Canadian trial.²³ This has been explored for patients who have had an IE and Jones et al reported that following pre-operative RT followed by excision they only had a 5% LR rate at 5 years, although they did report a peri-operative morbidity of 25%. This was supported in a small series by Saeed et al who found a 9% LR after pre-op RT and 33% with post-op RT combined with re-excision after IE.^{24,25}

In 1998 Pollack et al reported on their experience of radiotherapy alone in treating patients who had undergone IE, finding a 25% rate of LR at 10 years which they found unacceptable.²⁶ They also found that a dose of 50 Gy after IE was insufficient. Zagars et al in 2003 reported a similar outcome with 22% LR at 5 years in those just receiving radiotherapy after IE compared with 15% in those undergoing re-excision and RT ($p = 0.03$).²⁷ This, however, contrasts with the experience of Kepka et al who identified 78 patients treated with RT alone after IE.²⁸ They used a 66 Gy dose and reported a 12% LR rate at 5 years but with 10 major radiotherapy complications. Most of their patients were treated in the 1970s or 1980s since when they have also carried out re-excision.

Several papers have commented on how difficult it is to identify what benefit RT has after re-excision for IE as it is so heavily case selected with those cases at highest risk receiving RT whilst low-risk cases may not have it.^{19,21}

Cost analysis

Alamanda et al carried out a detailed analysis of the financial burden of an IE, finding that the charges for re-excision surgery were approximately 1/3 greater than for a primary tumour and thus the total cost of an IE was almost double that of primary treatment at a specialist centre.²⁹ Umer et al commented that from the patient's point of view one operation was better than two as it meant less time in hospital and away from work.³⁰

Function

It might be expected that with wide re-excision, patients with IE may end up with worse functional outcomes than those undergoing primary excision. Morii et al investigated this and found no difference in functional outcomes, probably because many of their patients had small superficial tumours.³¹ Interestingly they found that patients who underwent a re-excision had better emotional acceptance than those undergoing primary surgery.

Local recurrence

Clearly the aim of wide re-excision is to eventually obtain wide margins of excision to minimize the risk of local recurrence. Numerous authors have reported the rate of local recurrence after wide re-excision with results ranging from 5% to 45% at 5 years. The average, however, of the 2693 patients reported is 14% at 5 years. This figure is similar to figures from large series of primary excisions. Nearly all series, however, found that patients with residual tumour had a higher rate of local recurrence. Potter et al reported a 17% LR rate if the re-excision showed no residual tumour, rising to 38% if residual tumour was found and 64% if there was gross residual disease.²¹ Results from our own series demonstrate the effect of grade and residual tumour on LR.

- High-grade / residual tumour / +ve margin = 63%
- High-grade / residual tumour / -ve margin = 25%
- High-grade / no residual tumour = 23%
- Low-grade / residual tumour / +ve margin = 16%
- Low-grade / residual tumour / -ve margin = 11%
- Low-grade / no residual tumour = 2%

Arai et al found the converse, with an 8% LR rate in patients with IE compared to 15% LR in their patients treated with a planned excision.³² They attributed this to their aggressive policy of wide excision and use of flaps in 71% of their patients, which resulted in a very low use of RT (19% after planned excision and 13% after IE).

O'Donnell et al have taken the work of Gerrand further by looking at the Toronto Unit's experience of local recurrence and confirming that with a planned positive margin their LR rate was 14.6% but for a tumour bed re-excision with a +ve margin it was 21.1%.³³ They have commented on how the biology of the tumour (and its invasiveness) is reflected by the ability to obtain clear margins and in the eventual rate of LR as well as the cause-specific survival.

Disease-free survival

It is generally accepted that the main risk factors for survival in soft tissue sarcomas are grade, size and depth of

the tumour as well as age of the patient. Numerous published papers have compared outcomes in patients having an inadvertent excision with those treated primarily, and the general consensus is that, compared to age and matched case controls, there is little difference overall as patients with IEs tend to have smaller and more superficial tumours which themselves have a better prognosis. Smolle et al confirmed this in a large recent study using propensity scores to show that IE did not seem to adversely affect prognosis.³⁴

As long ago as 2000, however, Lewis et al reported that in their patients who had an IE and then had a wide re-excision, there were better rates of disease-free survival at 5 years in those undergoing re-resection even when factors such as age, grade, depth, histology and margins were taken into account.³⁵ This was particularly marked for those with AJCC (American Joint Committee on Cancer) Stage 3 tumours (high-grade, deep, > 5 cm). This led to the conclusion that ‘two excisions are better than one’. This unexpected finding was not matched by improved local control rates in the re-excised group. It was postulated that this could be due to the removal of histologically undetectable microfoci of disease. Charoenlap et al also compared outcomes for patients with IE by stage versus those treated primarily and found that residual disease indicated a worse prognosis both in terms of LR, survival and also a higher eventual amputation rate (18% vs. 1.8%).³⁶ There was very little difference in outcomes when patients were matched by stage. Most authors, however, have found no such improvement in survival, particularly when account is taken of the fact that most tumours undergoing IE are small and many are superficial. The general consensus is that the finding of residual disease is likely a hallmark of tumour aggressiveness which is also then linked to worse rates of both LR and disease-free survival.³²

Outstanding issues

It seems clear from these papers that wide re-excision remains the standard therapy in most units around the world following IE. If the original excision can be proved (pathologically) to have obtained wide margins, or if further surgery is impossible without amputation then there may be a case for giving the appropriate adjuvant (radiotherapy) and careful follow up. In the majority of cases, however, where excision has been with a ‘shell out’, then repeat imaging, re-excision and radiotherapy are likely to provide the best outcome. The width of the re-excision remains debatable. The greater the margin attempted the more likely a flap will be needed and the morbidity of this needs taking into account, as do the effects of radiotherapy. Wider margins are, however, likely to improve local control. Impressive results of local control are now being

reported from units routinely giving radiotherapy prior to re-excision and it may be that a randomized trial could be considered to compare this with standard post-operative radiotherapy. Undoubtedly, however, virtually all authors agree that avoiding IEs remains the ideal aim and this will involve continuing education of not only GPs but also surgeons. A good mantra is that ‘any lump bigger than a golf ball should have a diagnosis prior to excision’.³⁷

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ICMJE CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING STATEMENT

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

LICENCE

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