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***The Current Role of Sentinel Lymph Node  
Biopsy in the Management of Cutaneous  
Melanoma – a UK Consensus Statement***

*based on a multi-disciplinary meeting held in Cambridge, UK  
on 17 May 2018*

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## Introduction

Sentinel node biopsy (SNB) has been at the forefront of the surgical staging of melanoma patients for the past 15 years. The high accuracy of this prognostic staging procedure is now recognised in all international guidelines for melanoma. However during this period there have been a number of important changes in the management of melanoma, many occurring within the past five years. The outcomes of five recent randomised Phase 3 trials have established the role of adjuvant targeted therapy and immunotherapy in resected Stage 3 and Stage 4 disease and have potentially changed the role of SNB. Two landmark international prospective studies[1, 2] have examined the benefit of performing a completion lymph node dissection (CLND) following the detection of microscopically-involved sentinel nodes. Finally, the marked increase in the incidence of melanoma and the role of SNB in potentially guiding therapy has resulted in a significant increase in the pathological workload of the dermatopathology services.

To address these issues a multi-disciplinary consensus meeting involving many melanoma experts from the UK was convened in May 2018. Three main areas were considered: oncology, surgery and pathology. This report is a summary of the conclusions reached during that meeting. The conclusions have been agreed by the clinicians and nurses attending the meeting (listed, together with patient representatives, in Appendix 1), summarised in a Consensus Statement (page 10).

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## Discussion

### *Oncology*

Five adjuvant therapy trials have now reported: EORTC 18071, CheckMate 238, EORTC1325/Keynote 054, Combi-AD and Brim-8. The inclusion criteria, based around AJCC v7 rather than v8.0, varied between the trials, ranging from Stage 2C to Stage 4 resected. All five trials showed a significant improvement in relapse-free survival; however three of the trials are too immature to report on overall survival.

- EORTC 18071[3] showed a significant survival benefit at 5 years for adjuvant ipilimumab 10mg/kg in patients with Stage 3A (tumour deposit >1.0mm) – 3C disease (65% vs 54%, HR 0.72,  $p < 0.001$ ). However this was at the expense of significant toxicity including 1.2% treatment-related deaths. Adjuvant ipilimumab 10mg/kg was approved by the FDA but not submitted for approval in Europe.
- The subsequent Checkmate 238[4] study compared adjuvant nivolumab 3mg/kg versus ipilimumab 10mg/kg in resected Stage 3B – 4 disease. This showed a significant advantage for nivolumab for RFS (HR 0.66,  $p < 0.001$ ), with a median follow-up of 24 months. Adjuvant nivolumab is approved by the EMA and by NICE for patients with resected Stage 3A – 4.
- The Combi-AD study[5] examined the role of adjuvant dabrafenib + trametinib in BRAF positive resected 3A (tumour deposit >1mm) – 3C disease. The survival analysis for this trial was a pre-planned interim analysis so did not meet significance criteria for the survival advantage, despite the small P value. The 4-year RFS benefit for adjuvant dabrafenib + trametinib versus the placebo group was 54% and 38% respectively (HR 0.49). This translated into a 47% reduction in the risk of developing distant metastases, or death, in the group treated with dabrafenib + trametinib and has led to the approval of this combination by the EMA and by NICE.
- The EORTC1325/Keynote 054 study[6] examined the role of adjuvant pembrolizumab 2mg/kg every 3 weeks in resected Stage 3A (>1mm tumour deposit) – 3C disease and showed a significant impact on RFS (HR 0.57,  $p < 0.001$ ). This has led to the approval of adjuvant pembrolizumab by the EMA and by NICE.
- The BRIM8 study[7] examined the role of adjuvant vemurafenib in Stage 2C - 3C disease. This showed a modest impact on RFS and is not being taken forward.

OS was a secondary endpoint in most of these studies. However RFS is a surrogate for OS in metastatic disease. In the adjuvant setting, RFS is a surrogate for OS for both adjuvant interferon and adjuvant ipilimumab[8]. Extrapolating from this, it is assumed that RFS is a surrogate for OS with adjuvant PD-1 inhibitor therapy; and so it is expected that –

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provided the HR is large – RFS is a surrogate for OS with adjuvant PD-1 inhibitor therapy. Based on this, it is expected that those studies which have shown a significant improvement in RFS will translate into improvements in OS. However this remains unproven and modern post-relapse treatment in the metastatic setting may negate any survival benefit of adjuvant therapy.

The potential to improve relapse-free survival (53% improvement with COMBI-AD), which may then translate into an improvement in overall survival, highlights the importance of identifying patients who are Stage 3A and above. Patients with AJCC Stage 3A disease are, *a priori*, diagnosed by sentinel node biopsy. Current NICE Guidelines recommend the use of sentinel node biopsy for patients with primary tumour >1mm[9]. However, given the implications of effective adjuvant therapy for patients with sentinel node positive disease and the broad approval by the EMA of dabrafenib + trametinib, pembrolizumab and nivolumab in all Stage 3 patients, there is clearly an argument for extending the indication for sentinel node biopsy, so that more patients can benefit from adjuvant therapy.

Many patients with 3A disease have an excellent prognosis and the role of adjuvant therapy in these patients remains unclear. An emerging international consensus, based on a large published dataset from the EORTC[10] is that microscopic tumour burden of >1mm identifies the group of patients at highest risk of recurrence, though emerging tissue-based molecular markers may also play a key role[11]. However the current AJCC Version 8 does not consider tumour burden when staging patients; rather, patients are staged based on whether the lymph nodes are clinically occult or clinically detected. There is a recommendation that the maximum diameter of any metastatic nodal deposit should be recorded, but it does not quantify either the number of deposits or assess the microscopic tumour burden when staging patients with microscopic nodal disease.

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## *Surgery*

### **Sentinel Node Biopsy**

The recent adjustments introduced with AJCC v8 state that pT1b (0.8-1mm) patients with no sentinel node biopsy (cN0) are deemed clinical Stage 1B, with 5-year and 10-year OS of 97% and 93% respectively. Patients with pT1b tumours who have a negative SNB (pN0) are deemed pathological Stage 1A with 5-year and 10-year OS of 99% and 96% respectively[12]. Lee et al. highlighted that in patients with a thin melanoma ( $\leq 1\text{mm}$ ), their 10-year OS, following a +ve SNB and CLND, is 84% [13]. These data support SNB as being prognostic even in patients with thin melanomas.

Current UK national guidelines recommend sentinel node biopsy only for patients with a Breslow thickness of  $>1\text{mm}$ . However several studies and meta-analyses have shown that subgroups of patients with thin melanomas ( $\leq 1\text{mm}$ ) are at risk of a positive sentinel node. Older reports, pre AJCC v8, highlighted that pT1a patients with an ulcerated primary  $\leq 1.0\text{mm}$ , microsattellites, Clark's level IV/V or mitoses  $\geq 1/\text{mm}^2$  had a  $\leq 10\%$  chance of having a positive sentinel node[14-16]. AJCC v8 removed mitotic rate as part of the staging for pT1 melanomas; however it acknowledges that increasing mitotic rate is significantly associated with decreasing melanoma-specific survival (MSS) in univariate analysis[17], where there is a clear cut-off at  $\geq 2\text{mitoses}/\text{mm}^2$ . Regardless of this change, the new staging notes that pT1b melanomas continue to have a 5%-12% risk of a positive SLN, before other adverse prognostic indicators are considered.

Currently pT1b patients who do not undergo a SNB (cN0) will remain as clinical Stage 1B with follow-up for 5 years. The benefits of SNB in patients with a thin melanoma include being either downstaged (90% will be SNB -ve) to AJCC pathological Stage IA, meaning a better prognosis; or upstaged to Stage 3, meaning early identification for adjuvant therapy. In either case the post-treatment clinical surveillance will be significantly altered.

SNB provides significant prognostic data in patients with a melanoma of Breslow thickness  $>4\text{mm}$ , where 30% of patients with a tumour  $>4\text{mm}$  will have a positive sentinel node[18, 19]. Previously SNB was not recommended because the prognosis was driven by the risk of metastatic disease, determined by the thickness of the primary tumour. In the era of modern adjuvant therapy, patients with a positive sentinel node will be upstaged to Stage 3 and will be eligible for adjuvant treatment. Patients with T4b tumours are considered at high risk of metastatic disease, have previously been involved in adjuvant therapy trials and are recommended to undergo high risk follow-up. [7] [9]. Stratification of this high risk group, either by SNB or by future developments in blood or tissue biomarkers, will impact on their individual treatment pathway and advice on adjuvant systemic therapy.

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## Completion Lymphadenectomy (CLND)

Two trials have recently reported on the outcome of patients with a positive sentinel node. The MSLT-2[2] and DeCOG[1] trials both randomised patients with a positive sentinel node either to observation with close radiological imaging or to a completion lymph node dissection (CLND). The radiological imaging varied between trials. The DeCOG trial specified 3-monthly clinical and ultrasound imaging of the primary scar and draining nodal basin, with (6-monthly) either CT scan, MRI scan, PET scan, or chest x-ray and abdominal ultrasound as a minimum. The MSLT-2 trial specified ultrasound examination of the nodal basin during the 5-year follow-up period.

Neither trial demonstrated a survival advantage for having a completion lymph node dissection compared with observation and imaging of the positive nodal basin. Both trials demonstrated an increased risk of nodal recurrence in those patients who were in the observation arm and an increase in morbidity, which was generally related to lymphoedema, in those who underwent a CLND. There is significant morbidity associated with CLND[20], particularly when undertaken within the groin/pelvic region, and there should be clear indications for recommending such surgery.

### Risk Factors

The trials had similar exclusion criteria, which included: extracapsular spread; in-transit metastases; micro satellites;  $\geq 3$  involved local fields; age  $<18$  or  $>75$  years; immunosuppression; and previous melanoma primary disease. In both trials, nearly 70% of the metastatic deposits found within the involved sentinel node were  $<1.0$  mm; and in MSLT-2, 40% of primary lesions were ulcerated. Subgroup analysis from the MSLT-2 trial showed a non-significant trend towards improved survival, for patients with a primary within the head and neck who underwent CLND rather than observation. This trial also reported that the presence of an involved non-sentinel node (false negative sentinel node biopsy or an involved node on CLND) was a significantly poor prognostic factor for melanoma-specific survival, when compared to those patients with a positive sentinel node.

The exclusion criteria for both of the aforementioned trials – and the relatively low volume disease identified within the sentinel nodes – means it is difficult to extrapolate the findings of the trials, when other factors suggest individuals are at high risk for regional relapse, namely: extracapsular spread; immunocompromised;  $\geq 3$  involved sentinel lymph nodes; micro-satellites on the primary and extensive nodal involvement. AJCC v8 discussed nodal tumour burden, highlighting that microscopic deposits  $>2-4$ mm,  $>4-15$ mm and  $>15$ mm were associated with 5-year survival of 86%, 72% and 66% respectively[12], but this was not included in the staging system due to concerns over reproducibility.

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SLN tumour burden is also associated with Non Sentinel Node (NSN) status[21-23]. Dewar et al. considered the anatomical site of the melanoma deposit within the SLN and demonstrated that parenchymal or multifocal or extensive deposits were associated with NSN involvement in 19%, 37% and 42% respectively of the CLND specimens[24]. The nomogram produced by Rossi[25], which predicted the risk of non-sentinel node involvement following a positive sentinel node, identified high risk pathological features similar to those identified from the MSLT-2 and DeCOG studies. It should be noted however that the forest plot analysis of MSLT-2 demonstrated that a nodal deposit of >1mm favoured observation rather than CLND; and so these patients may be best managed with adjuvant systemic therapy rather than adjuvant surgery.

The consensus meeting attendees discussed management of those patients who subsequently relapsed with macroscopic nodal disease, either due to a false negative sentinel node biopsy or those who were in the observation arm and subsequently relapsed. Data are limited, but there is no evidence to suggest this relapse would be unresectable: local recurrence does not equate with loss of local control. However in the head and neck region, the complexity of resecting macroscopic nodal disease and achieving complete clearance can be surgically challenging, requiring complex reconstruction. The trend to a survival advantage, seen in this subgroup analysis of MSLT-2, may be partly explained by this difficulty in managing recurrent nodal disease in the neck.

## **Imaging**

The evidence for the most efficient modality for routine follow-up imaging of melanoma patients is limited and recognised in the 2015 NICE guidance, which suggested a clinical trial to investigate this area further[9]. Both the MSLT-2 and DeCOG trials employed different radiological follow-up protocols, with regular nodal basin high resolution ultrasound as a minimum imaging requirement. This does have an operator-dependent sensitivity (15%-50%) for identifying micro-metastatic nodal disease, when compared to sentinel node biopsy. Despite protocol trial imaging for both MSLT-2 and DeCOG, neither trial commented on how recurrent nodal disease was detected – whether by the patient, imaging or clinical examination. Lee et al. looked at routine surveillance in 738 Stage 2 patients, where increasing risk of recurrence was found with increasing stage of disease. 155 developed a relapse within 5 years, with 42 recurrences detected by imaging in asymptomatic patients CT (11%), CXR (6%), PET CT (1%) and Ultrasound (0.5%)[13].

NICE recommends routine imaging follow-up of high risk patients (Stage 2C and higher)[9], but does not specify the modality or frequency, instead suggesting that local policies should be developed. Most centres currently arrange cross-sectional imaging using either CT, MRI or PET on a 6-monthly basis for the first 3 years for Stage 2C patients who did not undergo a SNB, or for all Stage 3 patients as these are deemed to be at high risk of distant disease. It should be noted that there is no evidence to suggest any survival benefit for routine imaging; and whilst some centres recommend USS surveillance of at-risk nodal



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basins, there is a low rate of detection of recurrent disease using USS[26] when compared with other modalities. However USS was included in the trial protocol for both the MSLT-2 and DeCOG trials.

## *Pathology*

With its key role in identifying patients for treatment, histopathology has made an important contribution to the recent improvements in managing cutaneous melanoma. Pathology using sentinel node biopsy is now a standard of care that informs management decisions.

Several different protocols exist for assessing the sentinel node pathologically; however the standard procedure for the UK is that advocated by the EORTC[27]: bivalving the node through the longest meridian, where the afferent lymphatics enter the node and continue into the subcapsular sinus – targets where melanoma cells are most likely to be seen. Multiple sections are taken through each half of the SLN, stained and examined. The number of sections, and the gap between them, vary with different protocols. The EORTC protocol aims to achieve a micro-metastasis detection rate of around 25%. Increasing the number of sections increases the workload but since smaller metastatic deposits could potentially be detected it also improves the sensitivity of detection.

Surgical staging follows a protocol known as the 10% rule[28]. Following the removal of the SLN, further nodes are removed until the background count of the nodal basin, registered on the gamma probe, falls to <10% of the highest SLN reading. Nodes removed that are deemed to be non-sentinel nodes should be clearly labelled as such, as they will be processed using a standardised protocol rather than one specific for a sentinel node. The consensus meeting attendees agreed to adhere to the 10% surgical staging rule. Although increasing this threshold above 10% would mean a reduction in the number of nodes removed for examination, this has been shown to compromise accuracy[29].

AJCC v8 identified that in the T1 tumour group, Breslow thickness and ulceration were stronger predictors of melanoma-specific survival (MSS) than mitotic rate (0 mitoses vs  $\geq 1$  mitoses). Consequently Stage 1 criteria were revised, removing mitotic rate. However the AJCC analysis also stated that, in the T1 group, mitotic activity is associated with increased risk of SLN metastasis. In Stage 1 – 2 patients, AJCC v8 quoted 10-year survival for mitotic rates of 0, 1, 2-3, 4-10 and  $\geq 11$  as 97%, 96%, 91%, 86% and 77% respectively. The numbers of patients in the T1 group with a mitotic rate greater than  $1/\text{mm}^2$  is relatively small. However, given its predictive value for both SLN status and NSN status[25], consideration should be given to offering T1 patients with a mitotic rate of greater than  $1\text{mm}^2$  the option of SNB.

There is no definition as to the size of microscopic metastatic deposit within the node that should be considered significant; however the adjuvant systemic therapy trials have



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had a cut-off of  $\geq 1$ mm. AJCC v8 for melanoma categorises patients with microscopically-identified regional node metastasis detected by SLN biopsy – and without clinical or radiographic evidence of regional node metastasis (termed ‘microscopic’ nodal metastasis in AJCC v7) – as clinically occult. In contrast, ‘clinically detected’ nodal metastasis describes patients with regional node metastasis identified by clinical, radiographic or ultrasound examination (termed ‘macroscopic’ nodal metastasis in AJCC v7) as clinically involved. The use of RT-PCR to detect molecular involvement of the SLN was not recommended as it was not found to be discriminatory in the MSLT-2 trial[2].

Previously, when sentinel node biopsy was purely prognostic, the impact of a false negative result on patient outcome was less important than it is now, when a false negative result may impact on a patient’s treatment pathway – especially access to adjuvant therapy. The emphasis should therefore be on reducing the false negative rate. For the same reason, protocols for lymphoscintigraphy, surgical extraction and histological analysis of the sentinel node need to be standardised to minimise the potential for false negative results. However demands to increase the processing of SLN so as to improve sensitivity – against a background of the rising incidence of melanoma – must inevitably increase the workload of histopathology departments.

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## CONSENSUS STATEMENT

1. Emphasis should be placed on identifying all patients at risk of metastatic disease since the primary role of sentinel node biopsy is changing from that of a prognostic indicator to one that now influences access to adjuvant therapy.
2. SNB is indicated for patients with primary cutaneous melanoma pT2a and above.
3. Patients with a pT1b primary melanoma should be considered for SNB, particularly where the primary tumour displays either of the following features:
  - a. Lymphovascular invasion
  - b. Mitotic rate  $\geq 2/\text{mm}^2$
4. CLND should not be recommended routinely for patients who have a positive sentinel node biopsy. Patients deemed at high risk should be considered for adjuvant therapy. A lymph node dissection should be considered for those patients who subsequently present with node ONLY recurrence having failed first line systemic treatment.
5. CLND could be considered for those patients with features identified in their SNB that indicate a high risk of regional relapse, namely:

AND

<ol style="list-style-type: none"><li>a. extracapsular spread</li><li>b. <math>\geq 3</math> involved sentinel nodes</li><li>c. Dewar criteria (multifocal or extensive)</li></ol>	}	who are unsuitable for adjuvant therapy, either due to medical co-morbidities or where geographical constraints may limit access to routine follow-up at a regional cancer centre
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6. Following a positive SNB, patients who undergo observation rather than a CLND should have a routine clinical examination and – notwithstanding the lack of evidence for benefit – access to routine USS imaging of their nodal basin. This imaging surveillance will differ for those patients on adjuvant systemic therapy.

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7. CLND is not recommended for primary head and neck melanomas with a positive sentinel node where appropriate adjuvant therapy could be recommended. However there is concern that, compared to other nodal basins, surgical rescue for macroscopic cervical node-only disease, following either observation or failed first line systemic therapy, is significantly more complex. The potentially greater surgical morbidity and expectation of post-operative radiotherapy means that these patients require careful monitoring. The advantages and disadvantages of all treatment options should be discussed with the patient and an individualised management plan agreed.
  8. A microscopic deposit is considered to be to be  $\geq 0.1\text{mm}$ . Any histological processing protocol should be able to detect a deposit of this size.
  9. The sentinel lymph node histological processing protocol requires formal review in order to manage workload. The 10% surgical staging rule should be maintained for the present.
  10. It is accepted that a prospective randomised trial may be unrealistic, but valuable retrospective information is available from numerous prospectively-completed databases.
  11. The 2015 NICE guideline *Melanoma: assessment and management* refers to the 2013 MSLT-1 data, which are now outdated. Given extensive surgical and non-surgical changes in melanoma management, it is recommended that the NICE guidance should be reviewed and revised urgently.

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## *Appendix 1 – Attendees*

Mr Shahid Aslam, Consultant Surgeon  
Dr Thiagarajah Balamurugan, Consultant Histopathologist  
Dr Ruth Board, Consultant Medical Oncologist  
Dr Andrew Boon, Consultant Pathologist  
Mr Michael Brotherston, Consultant Plastic Surgeon  
Mr Peter Budny, Consultant Plastic & Reconstructive Surgeon  
Mr Oliver Cassell, Consultant Plastic Surgeon  
Professor Martin Cook, Consultant Histopathologist  
Dr Pippa Corrie, Consultant Medical Oncologist  
Mrs Carol Cuthbert, Macmillan Clinical Nurse Specialist  
Miss Maharukh Daruwalla, Consultant Plastic Surgeon  
Mr Amer Durrani, Consultant Plastic Surgeon  
Dr Sarah Ellis, Consultant Medical Oncologist  
Dr Somaia Elsheikh, Histopathology Consultant  
Dr Paul Gatt, Consultant Dermatologist  
Mrs Jenny Geh, Consultant Plastic Surgeon & Skin Oncologist  
Mr Stephen Hamilton, Consultant Plastic Surgeon  
Dr Shaheen Haque-Hussain, Consultant Dermatologist  
Ms Lesley Hawkes, CNS  
Mr Andrew Hayes, Consultant General Surgeon & Surgical Oncologist  
Mr Martin Heaton, Consultant Plastic Surgeon  
Mrs Jane Henderson, Patient Representative  
Ms Gemma Hewitt, Skin Cancer Nurse Specialist  
Mrs Caroline Hough, Plastic Surgery Skin CNS  
Dr Laszlo Igali, Consultant Histopathologist  
Mr Nick James, Consultant Plastic Surgeon  
Miss Polly King, Consultant Oncoplastic Breast & Skin Cancer Surgeon  
Mr Gerard Laitung, Consultant Plastic Surgeon  
Dr James Larkin, Consultant Medical Oncologist  
Ms Michelle Lo, Specialty Registrar in Plastic Surgery  
Professor Paul Lorigan, Professor of Medical Oncology  
Mr Alastair MacKenzie Ross, Consultant Plastic Surgeon  
Mr Dan Marsh, Consultant Plastic Surgeon  
Mr Stuart McKirdy, Consultant Plastic, Reconstructive & Aesthetic Surgeon  
Dr George Meligonis, Consultant Histopathologist  
Professor Marc Moncrieff, Consultant Plastic & Reconstructive Surgeon  
Dr Paul Mulholland, Consultant in Medical Oncology  
Dr Paul Nathan, Consultant Medical Oncologist  
Dr Steve Nicholson, Consultant Medical Oncologist  
Dr Jenny Nobes, Consultant Clinical Oncologist  
Dr Bode Oladipo, Consultant Medical Oncologist

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Ms Fionnuala O'Leary, Consultant Plastic Surgeon  
Dr Farrokh Pakzad, Consultant Surgeon  
Dr Deepa Pandit, Consultant Histopathologist  
Dr Christine Parkinson, Consultant in Medical Oncology  
Mr Animesh Patel, Consultant Plastic & Reconstructive Surgeon  
Mr Andy Pay, Consultant Plastic Surgeon  
Dr Miranda Payne, Consultant in Medical Oncology  
Mr Howard Peach, Consultant Plastic & Reconstructive Surgeon  
Mr Jonathan Pollock, Consultant Plastic & Reconstructive Surgeon  
Mr Matthew Potter, Consultant Plastic Surgeon  
Professor Barry Powell, Consultant Plastic & Reconstructive Surgeon  
Mr Rowan Pritchard Jones, Consultant Burns & Plastic Surgeon  
Dr Marzena Ratynska, Consultant Histopathologist  
Mrs Saskia Reeken, CNS  
Mr Simon Rodwell, CEO Melanoma Focus  
Mr Amit Roshan, Plastic Surgery Registrar  
Mr John Rouse, PPI Representative  
Dr Patrick Shenjere, Consultant Histopathologist  
Mr Andrew Snelling, Consultant Plastic Surgeon  
Dr Neil Steven, Honorary Consultant in Medical Oncology  
Mr Chris Stone, Consultant Plastic Surgeon  
Ms Sheena Stothers, Complex Skin Cancer CNS  
Ms Beverly Underwood, CNS/Research Nurse - Skin Cancer  
Mr Siva Veeramani, Consultant Plastic Surgeon  
Dr Sarah Westwell, Consultant Clinical Oncologist  
Mr Martin Wiener, Consultant Plastic Surgeon  
Dr Hugh Wright, ST7 in Plastic Surgery  
Miss Helen Wyke, Skin Cancer CNS

### *External Reviewers*

Professor Daniela Massi, Professor of Pathology, University of Florence  
Dr Alexander van Akkooi, Surgical Oncologist, Netherlands Cancer Institute

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