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Radiological staging and surveillance imaging of high risk cutaneous malignant melanoma in the Mid-West of Ireland

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Abstract

Aim

To assess compliance with National Institute of Clinical Excellence (NICE) guidelines on staging and surveillance imaging of patients with stage IIC melanoma without sentinel lymph node biopsy (SLNB) and stage III melanoma and review ~~of~~ recent guidelines to inform clinical practice in the Midwest.

Methods

A retrospective analysis of melanoma cases from 2016 to 2020 was performed. Patients with stage IIC without SLNB and stage III melanoma were identified. Variables examined included demographics, SLNB status at diagnosis, AJCC staging at diagnosis, staging and surveillance imaging, and interval duration between surveillance imaging. Data were analysed using Microsoft Excel.

Results

310 patients with invasive malignant melanoma were identified. 12 patients were diagnosed with Stage IIC without SLNB, 12 with stage III. 100% of patients were offered radiological imaging for staging purposes. Ten (83.3%) patients with stage IIC had a staging CT TAP, four (33%) had CT brain and one (8%) had MRI brain. Ten (83%) patients with stage III had staging CT TAP, four (33%) had CT brain. Five (50%) patients with stage IIC had surveillance CT TAP, 2 (20%) within 6 months (mean 7.9, SD+-6.6 months). Eight (80%) patients with stage III had surveillance CT TAP, 3 (25%) within 6 months (mean 6.4, SD+-2.9 months).

Discussion

Current practice demonstrated overall compliance with NICE guidelines 2015 on staging imaging and moderate compliance for surveillance of stage IIC and III melanoma patients. Surveillance to identify early radiological relapse in high risk groups is warranted given the rapid advances in targeted and immunotherapy which deliver durable survival benefits not previously seen in melanoma. This is reflected in both European guidelines 2019 and NICE guidelines 2022 which further increase the intensity of radiological surveillance, polarising the

need for investment and resources to deliver a rapidly evolving standard of care for patients diagnosed with melanoma.

Introduction

Melanoma is the fourth most common cancer in Ireland with approximately 1100 new cases diagnosed each year.[1] There are approximately 160 deaths from melanoma every year in Ireland.[1] The incidence of melanoma continues to grow. Prompt diagnosis of metastases and the recent development of therapeutic targets may improve the overall survival in melanoma.[2]

An updated NICE guideline 14 on the assessment and management of melanoma was published in July 2022. The preceding NICE guideline on the assessment and management of melanoma (NG14), published in 2015, recommended that patients with stage IIC melanoma without sentinel lymph node biopsy (SLNB), stage III or suspected stage IV melanoma are offered CT staging, including brain imaging for people with suspected stage IV melanoma.[3] These guidelines also recommend that surveillance imaging is included in the follow-up of patients who have stage IIC melanoma with no SLNB or stage III melanoma who would become eligible for systemic therapy as a result of early detection of metastatic disease.[3] This should be performed every 6 months for 3 years from the primary diagnosis[3]. Brain imaging ~~is~~ was recommended if patients ~~are~~ were having imaging as part of their surveillance, or if metastatic disease outside of the central nervous system ~~is~~ was suspected (CT brain as standard, MRI brain if <24 years old).[3]

Treatment of metastatic disease in melanoma continues to develop rapidly, reflected in changes in guidance since our data collection. It has been demonstrated that intensive radiological surveillance has resulted in earlier detection of melanoma recurrence in patients.[2,4,5] One long-term follow-up study showed a gain in survival time for the detection of metastasis in an early phase of development beyond lead time bias.[6] Evidence suggests that patients treated with earlier stage and/or low volume disease are most likely to get prolonged benefit from immunotherapy and targeted treatments.[7,8] Adjuvant systemic therapy has clearly demonstrated efficacy in improving both relapse free survival and distant metastasis free survival for resected Stage III and IV melanoma.[9,10,11] Luke et al. (2021) have also recently demonstrated an improvement in relapse free survival for patients with resected Stage IIB and IIC melanoma.[12]

This evidence is reflected in the updated European consensus-based best practice guideline for melanoma published in 2019.[13] These guidelines recommend that staging imaging for patients with stage IIC and above includes ultrasound (US) of the regional lymph node basin,

CT of the thorax, abdomen and pelvis (CT-TAP) or PET-CT, and MRI brain.[13] These guidelines recommend that surveillance imaging be performed at 3-6 month intervals for the first 3 years after diagnosis.[13] Emphasis is placed on the importance of structured follow-up to detect relapses and new primary melanomas.[13] Notably more emphasis is placed on ultrasound of the nodal basins in surveillance and ultrasound is also included in surveillance of stages IB-IIB melanoma in these guidelines. Nodal ultrasound for cutaneous melanoma requires specific radiological expertise. Access to ultrasound can limit this potentially cost-effective non-invasive modality of surveillance.

The early 2022 Update to the Melanoma Focus 2013 Position Paper on Follow-up of Cutaneous Melanoma in the UK ~~has~~ recommended that stages of melanoma which are considered high risk enough to warrant imaging surveillance needed to be re-defined, given both the changes in treatment options and the differences in survival across different Stage II and III groups.[14] The subsequent updated NICE guideline 14 on the assessment and management of melanoma (July 2022) recommends that Stages IIB-IIC melanoma warrants two whole body and brain contrast-enhanced CT (CE-CT) scans and two ultrasound scans of the draining nodal basin (if SLNB not done) each year for the first 3 years after diagnosis, then one whole body and brain CE-CT each year for years 4 and 5 as part of their surveillance schedule.[15] Stages IIIA-IIIC not currently having adjuvant therapy should be offered two whole body and brain CE-CTs each year and two ultrasound scans of the draining nodal basin (if SLNB positive) for the first 3 years after diagnosis, then one whole body and brain CE-CT each year for years 4 and 5 as part of their surveillance schedule.

The aim of this study was to assess compliance with NICE 2015 guidelines on staging and surveillance imaging of patients with stage IIC without SLNB and stage III melanoma in the Mid-West from 2016 to 2020 and to compare our practice to the 2019 updated European guidelines.

Methods

A retrospective analysis of our clinical melanoma database from 2016 to 2020 was performed. Patients with stage IIC who had not had SLNB, and stage III melanoma, were identified. Radiology imaging systems in the Mid-West Region were searched for staging and surveillance imaging in these patients. Variables examined included demographics, SLNB status at diagnosis, AJCC staging at diagnosis, baseline and surveillance imaging and interval duration between surveillance imaging. Data were analysed using Microsoft Excel. NICE guidelines were reviewed and summarised. Staging and surveillance imaging of patients with stage IIC without SLNB and stage III melanoma was compared to the standard recommended

in the 2015 NICE guidelines. The updated European consensus-based guidelines were similarly reviewed and summarised. Staging and surveillance imaging of patients with stage IIC without SLNB and stage III melanoma were also compared to the standard recommended in these guidelines to highlight changes in practice.

Results

Demographics

A total of 310 patients were diagnosed with invasive malignant melanoma over the 5-year period 2016-2020 inclusive in our centre. Twelve patients were diagnosed with Stage IIC without SLNB. Twelve were diagnosed with stage III. The mean age at diagnosis of melanoma was 67.2 years (n = 24, range 27-94). There were 15 male and 9 female patients.

Staging: Compliance with NICE guideline 14: assessment and management of melanoma (2015) and European Consensus Guideline (2019) for melanoma staging

Table 1 summaries the imaging recommended by NICE guideline 14 (2015), ~~and~~ the European consensus guidelines (2019) and NICE guidelines 2022 for melanoma staging.

	NICE (2015)	European consensus guidelines (2019)	NICE (2022)
Stage IIC	*without SLNB only* CT imaging	*High risk IIC* US of regional lymph node basin, CT TAP/PET-CT and MRI brain	*Including stage IIB and IIC* Whole body and brain contrast enhanced CT (CE-CT); MRI brain instead of CT if locally available and after discussion with specialised MDT. Whole body and brain MRI instead of CE-CT if 0-24 years or pregnant

Stage III	CT imaging Suspected stage IV: brain MRI 0-24 years of age with stage III, suspected stage IV whole body MRI	US of regional lymph node basin, CT TAP/PET-CT and MRI brain	Whole body and brain contrast enhanced CT (CE-CT) MRI brain instead of CT if locally available and after discussion with specialised MDT, mitotic index of 5 or above, primary melanoma on the scalp

Table 1. Summary of expert melanoma guidelines for melanoma staging

Melanoma staging at diagnosis in our cohort of patients with stage IIC without SLNB and stage III melanoma in accordance with the 2015 NICE guidelines and the 2020 European consensus guidelines is presented in Figure 1. 10 (83%) patients with stage IIC melanoma without SLNB had CT-TAP as part of their staging imaging. Two (17%) patients declined staging imaging; one due to claustrophobia, another due to frailty. Overall four (33%) had a CT brain performed; one (8%) had an MRI brain. Ten (83%) patients with stage III melanoma had CT TAP performed as part of their staging imaging. 3 (24%) had brain imaging, 2 (16%) had a CT brain; 1 (8%) had an MRI brain. 2(16%) patients had ultrasounds of regional lymph node basin performed.

Ir Med J; November-December 2023; Vol 116; No. 10; P868
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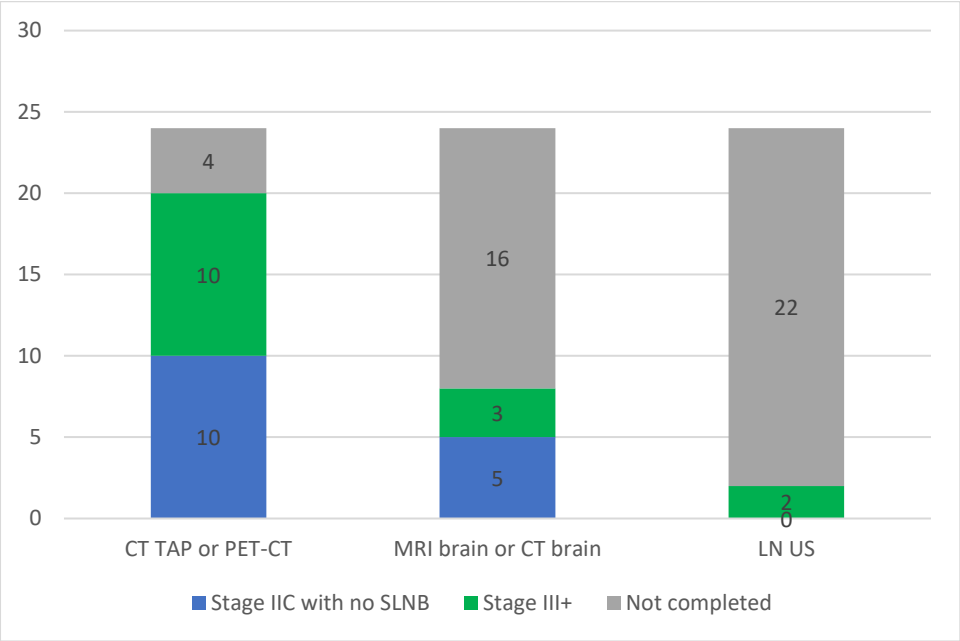

Figure 1. Staging imaging performed in accordance with NICE guidelines 2015 and European consensus-based guidelines 2020 (n=24)
Surveillance: Compliance with NICE guideline 14: assessment and management of melanoma (2015) and European Consensus Guideline (2019) for melanoma surveillance

Table 2 summarises the recommendations for melanoma surveillance in the European consensus guidelines (2019), ~~and~~ NICE guideline 14 on the assessment and management of melanoma (2015) and NICE guidelines 2022.

	NICE (2015)	European consensus guidelines (2019)	NICE (2022)
Stage IIC	*without SLNB only* Consider imaging in clinical trial or every 6 months for 3 years (with policy and funding)	US of regional lymph node basin every 3-6 months for 1-3 years CT TAP/PET-CT + MRI brain every 6 months for 1-3 years	Years 1-3: 2 whole body and brain CE-CT <u>AND</u> 2 ultrasound scans of draining nodal basin each year if SLNB not done Years 4-5: 1 whole body and brain CE-CT each year

Stage III	Consider imaging in clinical trial or every 6 months for 3 years (with policy and funding)	US of regional lymph node basin every 3-6 months for 1-3 years CT TAP/PET-CT + MRI brain every 3-6 months for 1-3 years	Year 1-3: 2 whole body and brain CE-CT AND 2 ultrasound scans of draining nodal basin each year if SLNB + Years 4-5: 1 whole body and brain CE-CT each year

Table 2. Summary of expert melanoma guidelines for melanoma surveillance

Melanoma surveillance imaging in our patients with stage IIC without SLNB and stage III melanoma was compared to both the NICE guidelines (2015) and the European consensus guidelines (2019). Surveillance imaging performed on 20 patients in our centre is presented in Figure 2.

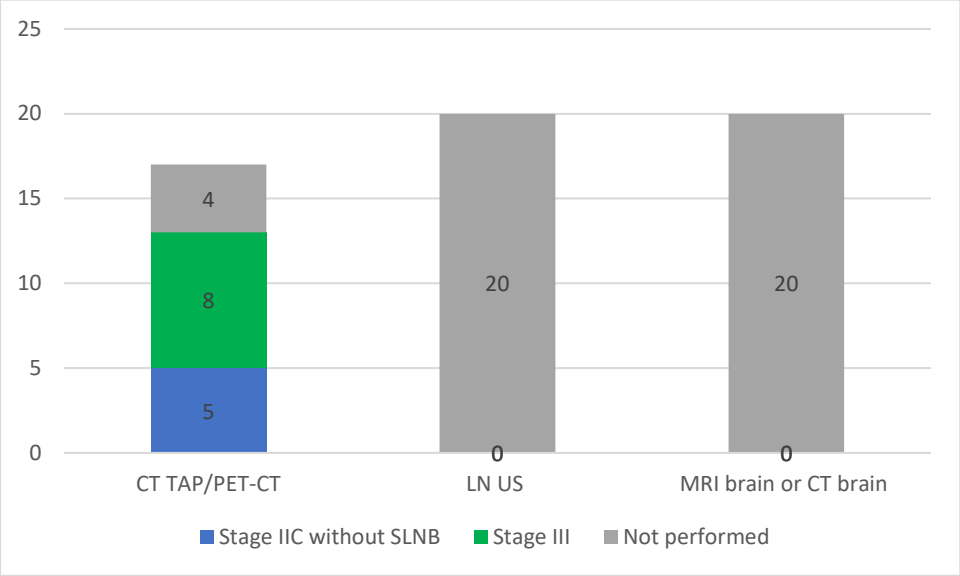

Figure 2. Surveillance imaging performed in accordance with NICE guidelines (2015) and European consensus guidelines (2019) (n=20)

Four patients were excluded from the analysis of surveillance imaging: two patients who declined imaging at time of initial diagnosis (previously outlined above) and two patients who were subsequently followed up outside our service. Five (50%) patients with stage IIC without

SLNB had CT TAP performed as part of their surveillance imaging, two (20%) within 6 months. Mean interval duration between imaging was 7.9 (SD ±6.6) months. Four of the five patients that did not have surveillance CT TAP performed had head and neck melanomas. Eight (80%) patients with stage III melanoma had CT TAP performed as part of their surveillance imaging, three (25%) within 6 months. Mean interval duration between imaging was 6.4 (SD±2.9) months. No patient had ultrasound of the lymph node basin or brain imaging performed as part of their surveillance for melanoma.

Frequency of surveillance imaging

Recommendations for surveillance range from every 3-6 months for a duration of three years. Initial surveillance imaging was performed on 5 patients (50%) with stage IIC melanoma with a mean duration between initial staging and surveillance imaging of 7.9 (SD ±6.6 months, range 3-23 months). Two (20%) patients had further surveillance CT TAP at an interval of 4.6 months and 4.5 months respectively. One (10%) patient had a third surveillance CT TAP performed after an interval of 10 months.

Eight patients (80%) with stage III melanoma had initial surveillance imaging performed, with a mean interval duration of 6.4 (SD±2.9) months between initial staging and surveillance imaging. Four patients had further surveillance CT TAP performed after the initial surveillance imaging at the time of data collection. One patient had 3 more interval CT TAP scans after initial surveillance imaging, two patients had 4 more interval scans and one patient had six more interval CT TAP scans performed (average 4.25 scans). Subsequent CT surveillance imaging was performed over a shorter interval in this cohort. Average intervals between surveillance scans for each of these patients were 5.5 months, 10.7 months, 4.5 months and 5.5 months respectively.

Patients with stage III melanoma had a higher average number of total CT scans than those in stage IIC cohort (4.4 scans *vs* 2.6 scans).

Discussion

Mounting evidence suggests that prompt diagnosis of melanoma recurrence and the development of therapeutic targets will improve overall survival in melanoma.[2,3,4,13] Current practice in our centre demonstrates good compliance with the 2015 NICE guidelines for staging imaging of our stage IIC and stage III melanoma patients. 83% of patients had staging imaging performed in accordance with the 2015 NICE guidelines for assessment and management of melanoma. While the majority of patients with stage III had surveillance imaging, this was the case for only half of those with stage IIC. Furthermore, this was often

outside the recommended 6-month interval (7.9 (SD ±6.6) months for stage IIC patients and 6.4 (SD±2.9) months for stage III patients), and there was low frequency of subsequent surveillance imaging despite guidelines recommendations.

The updated European consensus-based guidelines for melanoma recommend more intensive imaging with the addition of both ultrasound imaging of the lymph node basin and MRI brain as part of the staging and surveillance imaging schedules for melanoma.[13] Only two patients had ultrasound imaging of the regional lymph node basin as part of their staging imaging in our cohort. Similarly only two patients had MRI brain performed as part of their staging imaging. No patients had ultrasound of the lymph node basin or MRI brain as part of their surveillance imaging. The DeCOG-SLT and MSLT-2 clinical trials showed no survival benefit for Completion Lymph Node Dissection (CLND) in patients with a positive SLNB but no macroscopic (radiologically or clinically evident) lymph node disease.[16,17] These pivotal studies have resulted in a rapid alteration of clinical practice where CLND is now not standard of care for the majority of patients with clinical occult positive SLNB and negative radiological staging. Clinical practice has shifted to consideration of adjunctive therapy (targeted or immunotherapy) and clinical and radiological surveillance for this cohort of patient.

Access to radiological investigations has been challenging, particularly for “non-urgent” or “routine” surveillance imaging. This has been further exacerbated by the impact of covid-19 on hospital services. The delay in access to radiological investigations is a multifactorial and complex issue that warrants further exploration at a local and national level. Implementation of the 2019 European guideline recommendations or the 2022 NICE guidelines would require enhanced resourcing and staff training, for example in the setting of ultrasound imaging which requires specific skills and is user-dependent.

Mounting evidence for improved survival with early diagnosis of recurrent melanoma on radiological surveillance and ongoing rapid development of therapeutic options offering significant survival benefits emphasises the importance of offering staging and surveillance to appropriate patients in the setting of multidisciplinary melanoma services. Our data and summary of guidelines are useful to illustrate the increasing need to consider and offer surveillance in moderate to high risk melanoma patients.

In conclusion, melanoma management is a rapidly changing field and delivery of an up-to-date melanoma service which is guideline-led in Ireland requires resourcing to allow improved staging, surveillance and reduction in intervals of surveillance imaging. The addition of lymph node ultrasound imaging (which requires expertise), MRI brain as part of radiological staging and surveillance and trend towards staging and surveillance in earlier stages of

melanoma are important considerations for multidisciplinary teams to keep pace with recommended best practice for management of melanoma in Ireland.

Declarations of Conflicts of Interest:
None declared.

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