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Contemporary outcomes from the use of regular imaging to detect relapse in high-risk cutaneous melanoma

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ABSTRACT

Background Agreement on the utility of imaging follow-up in patients with high-risk melanoma is lacking. A UK consensus statement recommends a surveillance schedule of CT or positron-emission tomography-CT and MRI brain (every 6 months for 3 years, then annually in years 4 and 5) as well as clinical examination for high-risk resected Stages II and III cutaneous melanoma. Our aim was to assess patterns of relapse and whether imaging surveillance could be of clinical benefit.

Patients and methods A retrospective study of patients enrolled between July 2013 and June 2015 from three UK tertiary cancer centres followed-up according to this protocol was undertaken. We evaluated time-to-recurrence (TTR), recurrence-free survival (RFS), method of detection and characteristics of recurrence, treatment received and overall survival (OS).

Results A total of 173 patients were included. Most (79%) had treated Stages IIIB and IIIC disease. With a median follow-up of 23.3 months, 82 patients (47%) had relapsed. Median TTR was 10.1 months and median RFS was 21.2 months. The majority of recurrences (66%) were asymptomatic and detected by scheduled surveillance scan. Fifty-six (68%) patients recurred with Stage IV disease, with a median OS of 25.3 months; 26 (31.7%) patients had a locoregional recurrence, median OS not reached (P=0.016). Patients who underwent surgery at recurrence for either Stage III (27%) or IV (18%) disease did not reach their median OS. The median OS for the 33 patients (40%) who received systemic therapy was 12.9 months.

Conclusion Imaging appears to reliably detect subclinical disease and identify patients suitable for surgery, conferring favourable outcomes. The short median TTR provides rationale to intensify imaging schedule in the first year of surveillance. The poor OS of patients treated with systemic therapy probably reflects the relatively inferior treatment options during this time and requires further evaluation in the current era.

Key messages

What is already known about this subject?
- There is no global consensus on the utility of imaging surveillance in high-risk melanoma.

What does this study add?
- The current UK imaging surveillance is well-accepted by patients, with high rate of compliance.
- We observed that high-risk, resected cutaneous melanoma has a tendency to relapse within the first 2 years of follow-up.
- CT imaging reliably detects subclinical disease, enabling some patients to have successful metastasectomy.

How might this impact on clinical practice?
- Metastasectomy confers favourable outcome and should be considered in appropriately selected cases.
- A more intensive CT surveillance schedule of every 3 months for the first year of follow-up may be considered.

INTRODUCTION

The role of imaging in the follow-up of patients with high-risk melanoma remains unclear. It is still questionable whether earlier detection of metastatic disease translates into improvement in overall survival (OS) outcomes. As such, there is no consensus between international guidelines on the frequency or duration of imaging in this setting.[1 2] This issue is increasingly relevant given the advent of targeted and immunotherapeutic agents that improve OS in the management of metastatic melanoma, especially as the prognosis is superior in patients treated with low-volume disease.[3 4] Surgical metastasectomy or stereotactic radiosurgery is also a standard of care in selected patients with oligometastatic disease and can achieve prolonged survival.[5–7] Imaging is required to detect low-volume or asymptomatic disease in these cases.

Contemporary series report that patients with Stages II and III melanoma have a 30%–46% risk of disease recurrence,[8–10] including asymptomatic distant metastases detected on imaging. Five-year recurrence-free survival (RFS) for Stages IIIB and IIIC melanoma is reported at 32% and 11%, respectively.[11] A UK consensus statement among melanoma oncologists, published in 2013, recommends a schedule of cross-sectional

imaging and clinical review for patients with resected Stages II and III high-risk cutaneous melanoma.[12] Here, we report the outcomes of the first group of patients followed-up according to this schedule across three institutions.

METHODS

Study design

We performed a multicentre retrospective analysis of patients from three cancer centres in the UK. Clinical and radiological data from consecutive patients, from July 2013 to June 2015, followed-up prospectively within the high-risk protocol as outlined in the Melanoma Focus Consensus Paper[12] were noted. The recommended surveillance schedule consisted of CT thorax, abdomen and pelvis or positron emission tomography (PET)-CT scans, as well as MRI of the brain, at baseline postoperatively, and then at 6-monthly intervals for 3 years, followed by annual scans to 5 years. The study censor date was 30 June 2016.

Patient cohort

The high-risk cohort was broadly defined as patients with a predicted OS of less than 50% at 5 years, encompassing those with Stages IIC, IIIB and IIIC disease as per the seventh edition of the American Joint Committee on Cancer TNM staging system.[12 13] Some patients with thick Stage IIB melanoma (>4 mm Breslow thickness) and Stage IIIA were also included at clinician discretion. Patients were identified by review of clinic lists and multidisciplinary tumour board meeting records. Characteristics of their primary melanoma, molecular profiling, stage at the time of diagnosis of high-risk disease, the number of scans performed until disease recurrence, time-to-recurrence (TTR), stage and location of recurrence, as well as the treatment(s) received for the recurrence episode were identified by medical record review.

We excluded patients with unresectable Stage III disease, mucosal or ocular melanoma and any patients who received adjuvant systemic treatment, including those recruited into clinical trials. Adjuvant radiotherapy was permitted.

Outcomes

The key outcomes evaluated were TTR, method of detection and characteristics of recurrence, treatment received and OS. If patients were symptomatic at the clinical review where scan results were discussed, they were deemed symptomatic of relapse. RFS for the whole cohort was also determined. We sought to explore characteristics of those patients experiencing recurrence within the first year of follow-up and to characterise the group who developed brain metastases. Adherence to the imaging schedule was also evaluated.

Statistical analysis

All statistical analyses were performed using SPSS V.23.0. Descriptive data were presented as median (interquartile range, IQR), mean±standard deviation (SD) and proportions were expressed as a percentage. χ^2 analysis was used to compare categorical variables, and Student's t-test was used to analyse continuous variables. P values were two tailed. Kaplan-Meier survival analyses estimated TTR (defined as the time from diagnosis of high-risk disease to confirmed recurrence on imaging or biopsy in those who relapsed), RFS (same definition as TTR but encompassing whole cohort, including those who remained disease free at censor date) and OS (defined as time from diagnosis of high-risk disease to death from any cause).

Compliance to the surveillance schedule was calculated as a proportion of the number of scans attended over the theoretical number of scans expected within the follow-up interval. For example, after 2 years of follow-up, a patient would have had had four surveillance CT scans to achieve 100% compliance (baseline postsurgical scan excluded from count).

RESULTS

Patient cohort

From July 2013 to June 2015, a total of 173 patients were managed according to the high-risk follow-up protocol. The median duration of follow-up was 23.3±8.4 months. The mean age was 62.5±14.9 years with 103 (59.5%) male patients. Table 1 outlines the baseline characteristics of this group. CT scan was used as the primary cross-sectional imaging modality in the majority (89.0%) and PET-CT in the remaining patients. At least one MRI-brain was performed in 43.9% (n=76/173).

TTR and RFS

Overall, 82 patients (47.4%) in this cohort relapsed with a median TTR of 10.1 months (95% CI 8.1 to 12.1) (figure 1A). The median TTR for Stages IIC, IIIB and IIIC were 5.9 months (95% CI 1.4 to 10.4), 11.7 months (95% CI 9.9 to 13.5) and 8.8 months (95% CI 5.6 to 12.0), respectively (figure 1C). There was no pairwise statistical significant differences between these groups (figure 1C,D). The sample size for Stages IIB and IIIA were inadequate for meaningful comparison here. The median RFS for the whole cohort was 21.2 months (figure 1B).

Patterns of recurrence and mode of detection

Of those who relapsed (n=82), 56 (68.2%) were distant and 26 (31.7%) were locoregional. Relapse was Stage M1c in 26 patients and lactate dehydrogenase (LDH) was elevated in 16.7% of the 66 patients in which it was measured (n=11/66). The most common sites of metastases were in lymph nodes (n=49/82, 59.8%) and the lung (n=30/82, 36.6%) (table 2).

Recurrence was detected on imaging in 65.9% (n=54/82) of patients, all of whom were asymptomatic. Physician-detected recurrence was 22.0% (n=18/82) and patient-detected recurrence was 12.2% (n=10/82). The median number of CT (or PET-CT) scans to the detection of relapse was 2.

Treatment on relapse

Following relapse, 87.8% (n=72/82) of patients went on to receive further therapy, with 51.3% (n=37/72)

Table 1 Baseline characteristics of the patient cohort (n=173)

Characteristics	
Gender	
Male	103 (59.5%)
Female	70 (40.5%)
Age (mean)	62.5 years±14.9
Site of primary melanoma	
Head/neck	12 (6.9%)
Torso	57 (32.9%)
Upper limbs	30 (17.3%)
Lower limbs	57 (32.9%)
Unknown	17 (9.8%)
Type of primary melanoma	
Superficial spreading	91 (68.4%)
Nodular	28 (21.1%)
Acral	10 (7.5%)
Lentigo maligna	2 (1.5%)
Others	2 (1.5%)
Unknown/missing data	40
Breslow thickness (median), n=146	3.5 mm (IQR 2.0–5.6)
Ulceration	
Present	92 (65.7%)
Absent	48 (34.3%)
Unknown/missing data	33
Mitoses	
Yes	92 (89.3%)
No	11 (10.7%)
Unknown/missing data	70
American Joint Committee on Cancer stage at diagnosis of high risk	
IIB	3 (1.7%)
IIC	32 (18.5%)
IIIA	1 (0.6%)
IIIB	88 (50.9%)
IIIC	49 (28.3%)
BRAF mutation status	
Mutant	54 (34.8%)
Wild type	101 (65.2%)
Unknown/missing data	18

Table 2 Patterns of recurrence (n=82)

Description of recurrence	
Disease recurrence	
Yes	82 (47.4%)
No	91 (52.6%)
Time-to-recurrence (median)	10.1 months (95% CI 8.1 to 12.1)
Number of scans to recurrence (median)	2 (1;3)
Detection of recurrence	
Patient detected/symptomatic	10 (12.2%)
Physician detected on examination	18 (22.0%)
Imaging/asymptomatic	54 (65.9%)
American Joint Committee on Cancer stage at diagnosis of high risk	
IIB	2 (2.4%)
IIC	11 (13.4%)
IIIA	1 (1.2%)
IIIB	34 (41.5%)
IIIC	34 (41.5%)
BRAF mutation status, n=88	
Mutant	30 (34.1%)
Wild type	58 (65.9%)
Substage breakdown of recurrence	
Locoregional	26 (31.7%)
M1a	13 (15.9%)
M1b	17 (20.7%)
M1c	26 (31.7%)
Site of recurrence	
Subcutaneous	22 (26.8%)
Lymph nodes	49 (59.8%)
Lung	30 (36.6%)
Liver	18 (22.0%)
Bone	6 (7.3%)
Brain	6 (10.9%)*
Others	9 (11.0%)
Lactate dehydrogenase at recurrence, n=66	
>Upper limit of normal (ULN)	11 (16.7%)
Normal or <ULN	55 (83.3%)

*Brain-only recurrence in N=2 (33.3%).

undergoing surgery, of which 40.5% (n=15/37) were metastasectomies for Stage IV disease (online Supplementary table S1). Of those 33 patients receiving systemic treatment, 48.5% (n=16/33) had BRAF mutant disease, 62.5% (n=10/16) of whom received BRAF inhibitor monotherapy with dabrafenib or vemurafenib first line. Among the rest, 51.5% (n=17/33) received upfront anti-CTLA-4 (ipilimumab), 15.2% (n=5/33) received anti-PD-1 (pembrolizumab) and one patient received chemotherapy. The majority of those treated with systemic therapies (n=24/29 recorded, 82.8%) had normal LDH at time of relapse.

Subgroup analyses

An exploratory subset analysis was undertaken looking at those who relapsed within 1 year (n=53/82, 64.6%) and those who relapsed after 1 year of surveillance (n=29/82,

35.4%). There was no significant difference observed in demographic profile, method of recurrence detection, stage at recurrence and type of treatment received (online Supplementary table S2 and S3).

Six patients (n=6/82, 7.3%) relapsed in the brain at time of diagnosis of their recurrence (online Supplementary table S4). Two patients relapsed with brain-only disease and were symptomatic at time of presentation. Both had a normal LDH.

Overall survival

The median OS for the whole cohort was not reached (figure 2A). Among those who had recurrent disease (n=82), median OS was not reached and 63.1% are alive at 2 years (figure 2B). Substage analysis showed that median OS was not reached for those relapsing with Stage III disease and was 25.3 months (95% CI 21.2 to 29.5, P=0.016) for those with a Stage IV disease at relapse (figure 2C). The median OS among those who received systemic therapies was 12.9 months (95% CI 2.6 to 23.2). For patients having surgery for relapsed disease, the median OS was not reached and 80.3% were alive at 2 years (figure 2D). There was no statistically significant difference (P=0.971) in median OS between those who had surgery for Stage III (n=22/37, 59.5%) versus Stage IV (n=15/37, 40.5%) relapse (figure 2E).

Adherence to the surveillance schedule

For surveillance CT and PET-CT scans, the majority of patients (n=156/173, 90.2%) attended all their scans on time as per protocol intervals (100% compliance), and no patients were lost to follow-up. The median number of scans missed for the remaining 9.8% (n=17/173) was one scan. The median number of CT (or PET-CT) scans to detection of recurrence was two (range 1–5 scans).

There was a much lower adherence to MRI brain surveillance where 97 patients (56.1%) did not have any brain imaging during their follow-up. Among the 76 patients (43.9%) in whom at least one brain scan was performed, 57.9% (n=44/76) were 100% compliant. The median number of scans missed for the remaining 42.1% (n=32/76) was one scan.

DISCUSSION

Our findings demonstrate that patients with high-risk cutaneous melanoma (79% Stages IIIB and IIIC) have a high rate of recurrence (47%), consistent with other reported series.[8 10] In our cohort, the majority of patients (65%) relapsed within 1 year of curative surgery for 'high-risk' disease. Our exploratory subanalysis did not find any significant predictors of relapse before 12 months. The median TTR of 10.1 months is shorter than the 17 months reported by Podlipnik *et al* in their series of 290 patients but they had a greater proportion of Stage II cases (37% vs 20%).[10] Although fewer in number (n=11), patients with Stage IIC disease who relapsed had a particularly short median TTR of 5.9 months, shorter than the median of 8.8 months for Stage IIIC (n=34; figure 1C). This supports application of the same imaging surveillance schedule in this group.

The RFS of our overall cohort (21.2 months) was longer than the RFS in the placebo arms of the adjuvant dabrafenib and trametinib trial (16.6 months) and RFS in the adjuvant ipilimumab trial (17.1 months), despite our population containing a greater proportion of Stages IIIB and IIIC patients.[14 15] Most likely this is due to three monthly scans performed in these large registration studies versus six monthly scans in our cohort. The median OS of the patients in these placebo arms was not reached; however, OS by first treatment received at relapse is not available. Interestingly, in these two adjuvant trials, 22%–50% of patients in the placebo arms who relapsed were not recorded as receiving further anticancer therapy, whereas in our study only 15% received best supportive care. Whether more regular surveillance imaging improves survival through earlier detection remains to be elucidated; therefore, outside of trials, three monthly scans with the additional radiation exposure increased financial costs and scan anxiety will need to be carefully considered.

Most relapses in our cohort (68%) were detected on surveillance scans, with 88% being asymptomatic of their disease. The main sites of relapse were lymph nodes, lung and skin and subcutaneous tissues, consistent with others.[10] Most patients who relapsed (68%) had metastatic disease, with the smaller proportion (32%) having locoregional disease. Although the detection of relapse depended on imaging for the majority of our group, clinical review and patient education regarding signs of potential relapse remain important. In the series by Romano *et al*,[11] only 32% of relapses were detected by imaging overall, but most systemic relapses were detected in this manner. In their series in which the frequency of scans was not defined, patients detected 47% and doctors 21% of relapses.[11]

The outcomes for patients who underwent surgery at relapse were very good. Surgery was the most commonly used treatment in those with locoregional disease (85%). The median OS of those who relapsed with Stage III disease was not reached, with 78% alive at 2 years. This is higher than previously reported[13] and may reflect changes in surgical management over time, such as more frequent ilioinguinal lymph node dissections. Of particular note, 27% of patients with a Stage IV relapse also underwent surgery as their initial treatment. The median OS of 25.3 months for all patients who relapsed with Stage IV disease was mostly attributable to the excellent survival of this surgically managed group whose median (not reached) and landmark (80% at 2 years) OS figures were no different to the surgically managed Stage III patients. This is superior to the median OS of 21 months (with 5 years of follow-up) reported in a series of 64 patients who were rendered disease free by metastasectomy.[5] A third of our surgically treated patients remained disease free at the time of censoring, including 53% (n=8/15) who underwent metastectomy. Superior

outcomes with surgically resectable recurrence have been reported in other imaging surveillance series[11 16] and most likely this is due to better prognostic factors such as lower volume, slower tempo disease. Our results reinforce the ongoing role of surgical management including metastasectomy and suggest these patients are being appropriately selected.

Patients who were treated with systemic therapy had a relatively poor outcome in our cohort, with a median OS of 12.9 months. This is likely most likely explained by the predominance of monotherapy (52% ipilimumab, 15% anti-PD-1, 30% BRAF inhibitor), reflecting access to treatment outside of clinical trials in the UK at that time. None of the patients received combination targeted or immunotherapy. Ipilimumab only became available in the first line setting in July 2014 and a subsequent audit reported a median OS of 6 months for these patients managed outside of clinical trials.[17] Vemurafenib became available in December 2012 and the vemurafenib access programmes reported a median OS of 10.5–12.1 months.[18 19] Anti-PD-1 therapy only became available in the second line in late 2016 and in untreated patients in mid-2017. However, given both the lead time afforded by imaging and the fact that the majority of patients were asymptomatic and had a normal LDH, these results are disappointing.

Although there was no formal prospective assessment of the acceptability of regular imaging, the high rate of compliance with CT/PET-CT imaging suggests that this is a feasible schedule for patients to undertake. The reason for such poor adherence to MRI imaging cannot be accurately determined from this retrospective data and we cannot comment on the value of screening for central nervous system metastases. The rate of brain metastases in the relapsed cohort (n=6/82, 7%) is within the range of 4%–13% reported in other series.[11] Analysis of subsequent patient cohorts surveilled by our schedule will be more informative if adherence has improved over time.

In contrast with others,[9–11] our contemporary cohort had targeted and immunotherapy treatments available on relapse, although treatment options have improved significantly since then. Unlike the Romano *et al*[11] and Lewin *et al*[9] series, we also included patients with Stage IIC whose prognosis is worse than those with Stage IIIA disease.[13] Meaningful subgroup analyses are limited, however, due to small numbers of Stage II patients. The approach with imaging was consistent and adherence to the schedule was analysed, unlike in the other cohorts. This is an analysis of a prospective policy that relied on retrospective medical record review and therefore is subject to quality of the data entry and collection. We acknowledge that our median follow-up period of 23 months is relatively short. Also, the landscape of management of resected Stage III patients has recently changed with the advent of systemic adjuvant treatments superior than interferon in efficacy and tolerability. Ipilimumab has been shown to improve overall survival compared with placebo[20]; however, nivolumab has recently demonstrated improved recurrence-free survival compared with ipilimumab.[21] The combination of dabrafenib and trametinib also improves recurrence-free survival over placebo.[15] Although there will remain a role for imaging surveillance after a course of adjuvant therapy, these treatments are likely to impact the natural history of subsequent relapse.

CONCLUSIONS

Patients with high-risk Stage II and III melanoma have a substantial relapse rate within the first 2 years of follow-up, with the majority of relapses detected by imaging surveillance. Imaging assists in the detection of subclinical disease, facilitating successful metastasectomy in some cases. Considering the short TTR in our study, we recommend a more intensive CT surveillance schedule of every 3 months for the first year. Effective adjuvant therapy will likely alter the natural history of relapse, but currently no adjuvant agents are funded in the UK. Biomarkers including circulating tumour DNA may also further refine clinical management in this high-risk population.

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