Ann Surg Oncol (2019) 26:1860–1868
https://doi.org/10.1245/s10434-019-07311-0

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – MELANOMA

False-Positive Results and Incidental Findings with Annual CT or PET/CT Surveillance in Asymptomatic Patients with Resected Stage III Melanoma

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ABSTRACT

Objective. The aim of this study was to quantify false-positive and incidental findings from annual surveillance imaging in asymptomatic, American Joint Committee on Cancer stage III melanoma patients.

Methods. This was a cohort study of patients treated at Melanoma Institute Australia (2000–2015) with baseline computed tomography (CT) or positron emission tomography (PET)/CT imaging and at least two annual surveillance scans. False-positives were defined as findings suspicious for melanoma recurrence that were not melanoma, confirmed by histopathology, subsequent imaging, or clinical follow-up, while incidental findings were defined as non-melanoma-related findings requiring further action. Outcomes of incidental findings were classified as 'benign' if they resolved spontaneously or were not seriously harmful; 'malignant' if a second malignancy was identified; or 'other' if potentially harmful.

Results. Among 154 patients, 1022 scans were performed (154 baseline staging, 868 surveillance) during a median follow-up of 85 months (interquartile range 56–112); 57 patients (37%) developed a recurrence. For baseline and surveillance imaging, 124 false-positive results and incidental findings were identified in 81 patients (53%). The frequency of these findings was 5–14% per year, and an additional 181 tests, procedures, and referrals were initiated to investigate these findings. The diagnosis was benign in 109 findings of 124 findings (88%). Fifteen patients with a benign finding underwent an unnecessary invasive procedure. Surveillance imaging identified distant metastases in 20 patients (13%).

Conclusion. False-positive results and incidental findings occur in at least half of all patients undergoing annual surveillance imaging, and the additional healthcare use is substantial. These findings persist over time. Clinicians need to be aware of these risks and discuss them with patients, alongside the expected benefits of surveillance imaging.

Patients treated for stage III melanoma are at high risk of developing distant metastases. The 10-year melanoma-specific survival rates for American Joint Committee on Cancer (AJCC) 8th edition stage IIIA, B, C and D disease are 88%, 77%, 60%, and 24%, respectively.[1] In approximately half of the stage III patients, the first relapse is systemic.[2,3] Early detection enables earlier treatment and

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-07311-0) contains supplementary material, which is available to authorized users.

First Received: 18 October 2018;
Published Online: 25 March 2019

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increases treatment options. Thus, surveillance imaging has been proposed to improve overall survival, however this has not been demonstrated in randomized trials in other cancers.[4–6]

Clinical trial protocols frequently mandate regular follow-up with computed tomography (CT) or positron emission tomography (PET)/CT.[7–9] For patients who are not in trials, no general consensus exists and various follow-up schedules with different imaging modalities are used.[10] Recommendations for surveillance are based on evidence of moderately high sensitivity for detection of recurrence.[11] However, most studies are retrospective and report over half of the recurrences in asymptomatic stage III melanoma patients are detected by the patient or physician, rather than through imaging.[2,3,12–16] Therefore, recommendations in international melanoma guidelines vary markedly, from using frequent surveillance imaging in all patients with melanoma staged IIC or higher, to only considering imaging in a specific subset of high-risk patients.[17–22] Clinically, the prevalence of surveillance CT or PET/CT imaging has increased dramatically over the last two decades.[23,24]

While there may be benefits of surveillance CT or PET/CT imaging, frequent scans also have disadvantages. Surveillance imaging may create anxiety for patients and increases the risk of second cancers due to radiation exposure.[25,26] Furthermore, annual imaging may reveal other radiologic abnormalities, which is of concern if they are of little or no clinical significance yet result in further diagnostic tests, additional treatments, increased healthcare costs, possible adverse events, and further patient anxiety.[27,28] The aim of this study was to quantify the false-positive results, incidental findings, and subsequent healthcare activity related to findings from annual surveillance imaging in asymptomatic stage III melanoma patients. The true-positive findings are reported, to enable the clinical relevance of the data to be put into context.

METHODS

Study Design, Setting, and Participants

Consecutive melanoma patients with AJCC/Union for International Cancer Control (UICC) 8th edition stage III disease, treated at Melanoma Institute Australia (MIA) between 2000 and 2015, who underwent a baseline CT or PET/CT scan and who had at least two annual follow-up scans, were identified from the prospectively established MIA database. Our aim was to assess patients undergoing frequent surveillance imaging, and this criterion was used to identify a group who underwent a series of scans rather than just one scan. Patients participating in a trial (e.g. MSLT-II, C-VAX, DERMA) who had annual imaging follow-up were included. Most of these trials included sentinel node-positive patients only. CT imaging consisted of CT brain, CT chest, and CT abdomen/pelvis. Whole body PET/CT imaging was performed using 18-fluorodeoxyglucose (FDG). Baseline imaging was defined as any scan performed within 3 months after diagnosis, and annual surveillance imaging was defined as a follow-up scan performed 12 months (± 3 months) after the prior scan, in a patient without symptoms or clinical suspicion of distant recurrence. Patients were followed until a confirmed diagnosis of stage IV melanoma, death, or last follow up (as of 30 September 2017). Approval from the Royal Prince Alfred Hospital Ethics Committee was obtained (MIA2016/182).

Classification of Findings

Suspicious findings on CT or PET/CT imaging were categorized as those that did not require action versus those that did require additional action, i.e. further investigations (Fig. 1). Distant metastases identified on surveillance imaging before they were clinically apparent were considered true-positive findings, and were confirmed histologically or radiologically. False-positive results were defined as findings that were equivocal for metastasis on imaging, required further action to confirm or exclude this, and were ultimately found to be unrelated to melanoma using a reference standard of histopathology, subsequent imaging, or clinical follow-up. Incidental findings were defined as abnormalities that were not suspected to be melanoma-related.

The outcomes of incidental findings were classified into one of three categories: ‘benign’, if they disappeared spontaneously, did not change, or were not seriously harmful (e.g. calcified lung nodule); ‘malignant’ if a second malignancy was found; or ‘other’ if they were non-malignant but potentially seriously harmful (e.g. sarcoidosis). Where there was uncertainty in classification, agreement was reached through discussion with four of the authors (RM, ON, RS, JT). Findings reported on multiple follow-up scans were counted only once, at the first time of detection.

Data Extraction

All CT and PET/CT reports were reviewed by AN. The findings were compared with a blinded examination by MD on a subset of randomly selected patients, including 30 scan reports, to check inter-rater agreement. The MIA research database, clinical trial files, and patient charts were reviewed to extract information on patient and tumor characteristics, scans, clinical decisions, and follow-up.

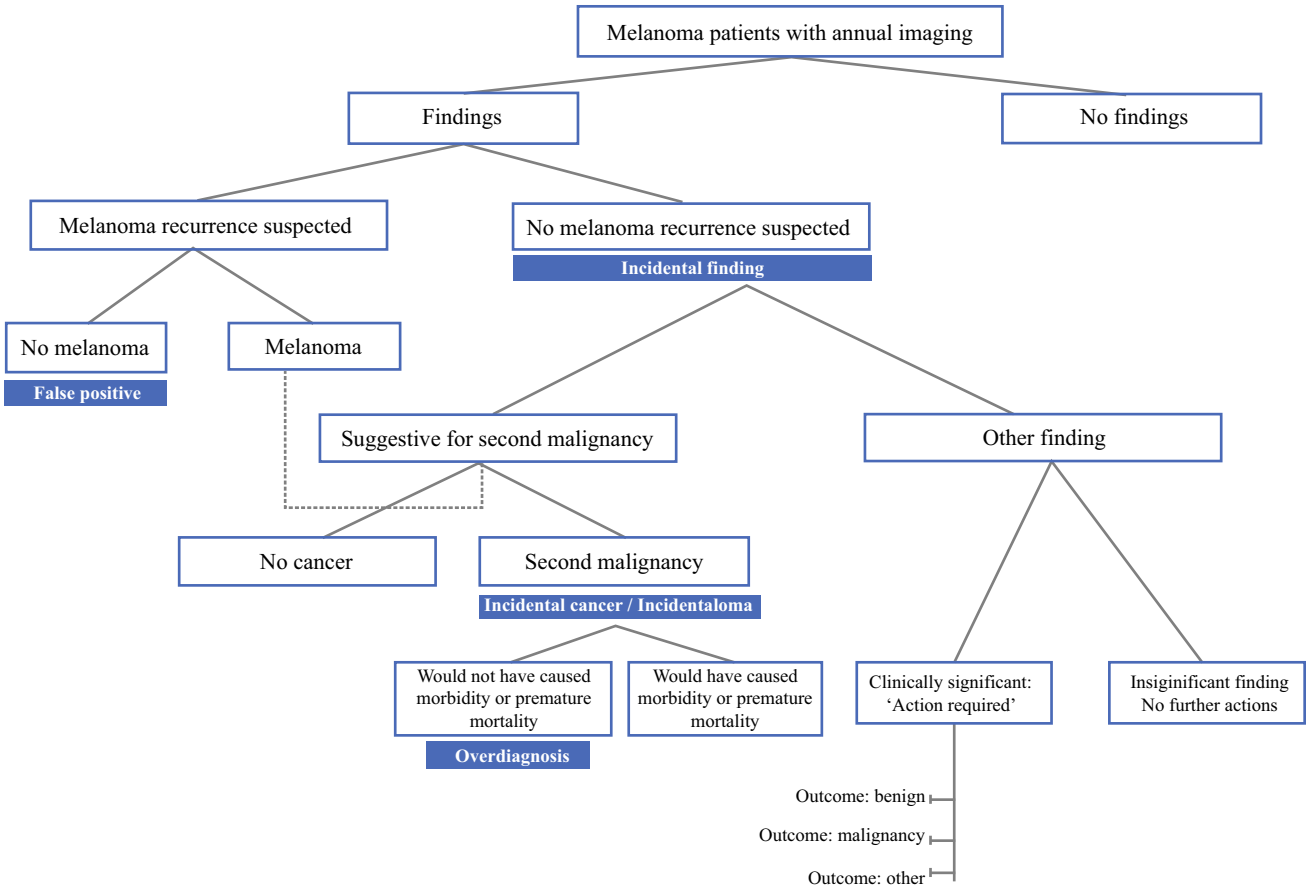


FIG. 1 Categorization for false-positive results and incidental findings

When a finding required further action, information on all additional scans, blood tests, biopsies, surgery, referrals, clinic visits, and other activities was sought through clinical notes, referral letters, and subsequent investigation request forms. Adverse events, defined as any untoward events documented as a consequence of further investigations, were recorded. Referrals to other specialists or primary care doctors were followed-up by contacting them.

Statistical Methods

Outcomes were reported as counts and proportions of incidental findings or false-positive findings, per patient over the study period, per single scan, and per follow-up year, and additional actions quantified. Results from baseline and follow-up scans were reported and analyzed separately, reflecting differences in clinical practice guidelines and enabling assessment of risk from one-time scanning versus serial scanning. Descriptive statistics were used to summarize the findings. Cumulative incidence was calculated by dividing the total number of patients with findings up to each year, by the number of patients included in the study. Data were analyzed using SPSS software version 24 (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient Characteristics

Overall, 351 patients with resected stage III melanoma and baseline CT or PET/CT imaging were identified. Of these patients, 154 (44%; mean age 49 years, 68% males) met the inclusion criteria of at least two annual surveillance scans (Table 1). Median follow-up was 85 months (interquartile range [IQR] 56–112). Most patients (147, 96%) had a sentinel node biopsy, which was positive in 143 patients (97%). Of these, 79 patients (51%) had a completion lymph node dissection, with non-sentinel node metastases found in 14 patients (18%). The AJCC 8th edition stage for the entire cohort was IIIA in 58 patients (38%), IIIB in 39 patients (25%), IIIC in 55 patients (36%), and IIID in 2 patients (1.3%).

In total, 1022 scans were performed and evaluated—154 baseline scans and 868 surveillance scans. The inter-rater

TABLE 1 Patient characteristics and outcomes

Characteristics	Number
Number of patients included	154
Mean age, years (SD)	49 (14)
Females/males [*n* (%)]	49 (32)/105 (68)
Primary tumor[a]	
Median Breslow thickness, mm (IQR)	2.2 (1.4–3.2)
Ulceration [*n* (%)]	44 (29)
Median mitotic rate, per mm^2 (IQR)	4 (2–7)
Microsatellite or in-transit lesions [*n* (%)]	9 (6)
Location of the primary melanoma [*n* (%)]	
Head and neck	19 (12)
Trunk	63 (41)
Upper extremity	22 (14)
Lower extremity	45 (29)
Occult	5 (3)
AJCC stage, 8th edition [*n* (%)]	
IIIA	58 (38)
IIIB	39 (25)
IIIC	55 (36)
IIID	2 (1.3)
Sentinel node biopsy performed [*n* (%)]	147 (96)
Sentinel node positive [*n* (%)]	143 (97)
Completion lymph node dissection performed [*n* (%)]	79 (51)
Additional non-sentinel nodes positive	14 (18)
Number of patients who developed recurrence [*n* (%)]	57 (37)[b]
Local	13
In-transit	17
Regional lymph node(s)	32
Distant	36
Median recurrence free survival, months (IQR)	30 (20–40)
Median distant metastasis-free survival, months (IQR)	38 (30–60)
Median follow-up time, months[c] (IQR)	85 (56–112)
Status at last follow-up (until September 2017) [*n* (%)]	
Alive, no sign of recurrence	119 (77)
Alive with recurrence	7 (5)
Alive, status unknown	4 (3)
Dead, melanoma	24 (16)

SD standard deviation, *IQR* interquartile range, *AJCC* American Joint Committee on Cancer

[a]Data missing for Breslow thickness in 5 patients, mitotic rate in 6 patients, and microsatellite or in-transit lesions in 14 patients

[b]Some patients had more than one recurrence

[c]Time until last follow-up or time until distant metastases (stage IV)

reliability between the two assessors was > 90%. There were 985 CT scans and 37 whole-body PET/CT scans. All patients had at least three scans, after which a yearly decline in patient numbers having annual scans was noted (electronic supplementary Fig. 1).

Overall, 57 patients (37%) developed a recurrence during the study period: 62 locoregional recurrences and 36 distant recurrences (in 36 patients). In 20 patients, distant metastases were identified on surveillance imaging (56% of patients with distant metastases, 13% of the cohort). These metastases were identified between scan number three and scan number ten. A median of four scans (IQR 3–5) were performed before a distant metastasis was identified. In 16 of 36 patients, the distant metastases were detected outside

surveillance imaging. Two of these recurrences were identified on an additional scan ordered to further assess incidental/true-positive findings.

False-Positives and Incidental Findings

On baseline and surveillance scans, 912 non-melanoma findings were identified in total, of which 124 initiated further evaluation or treatment (Table 2). Of these 124, 47 were identified on baseline imaging and 77 on surveillance scans. In 38 of 154 patients (25%), baseline CT or PET/CT imaging revealed false-positive ($n = 37$) or incidental findings ($n = 10$) requiring action (for the differences between CT and PET/CT, see electronic supplementary Table 1). In each subsequent year of follow-up (scans 2–9), 5–14% of patients had false-positive or incidental findings on surveillance imaging (Fig. 2, Table 3).

The cumulative incidence of findings on surveillance scans was 14% and 20% for the first and second annual scans, respectively (Table 3). Surveillance imaging identified 49 false-positive results and 28 incidental findings (77 findings in total) in 61 of 154 patients (40%) (Table 2).

Sixty-four (83%) suspicious lesions identified on surveillance imaging were found to be benign (electronic supplementary Table 2). Eleven findings in 11 patients (14% of the findings on surveillance imaging, 7% of the cohort) were potentially serious. These included two second malignancies (breast cancer and renal cell carcinoma) and nine other findings (4 patients with pneumonia, three with severe coronary artery calcification, one with sarcoidosis, and one with severe aortic calcification). In two patients, the outcome remained unknown as they were lost to follow-up.

Additional Procedures and Healthcare Utilization

On baseline imaging, 7 of 154 (5%) patients had findings that necessitated invasive procedures. In five of these patients (3%), the findings were benign, after undergoing six invasive procedures. Two of these procedures were surgical—an adrenal gland nodule resection (no abnormality was discovered pathologically), and a benign pelvic cyst removal.

For surveillance imaging, a total of 181 additional investigations, procedures, doctor's visits, and referrals were undertaken as a result of false-positive or incidental findings (electronic supplementary Table 2). Subsequent imaging with CT, ultrasound assessment, and referral to other physicians were most frequently undertaken. In 15 of 154 patients (10%), one or more invasive procedures (biopsy, colonoscopy ± polypectomy, bronchoscopy, and/or other surgery) were used to evaluate findings on surveillance imaging (electronic supplementary Table 2). Ten of these patients (6% of the cohort) were found to have a benign lesion, and underwent 13 invasive procedures, including two that were surgical. The surgical procedures consisted of a hemithyroidectomy in one patient (pathologically atypical follicular adenoma) and a hysterectomy with bilateral salpingo-oophorectomy in another patient for a broad ligament fibromyoma (pathological metaplasia, no malignancy). Additionally, one patient was found to have pneumonia rather than metastases, following a lung wedge resection. Incidental findings are listed in electronic supplementary Table 3. No adverse events were documented as a result of the evaluation of false-positives or incidental findings.

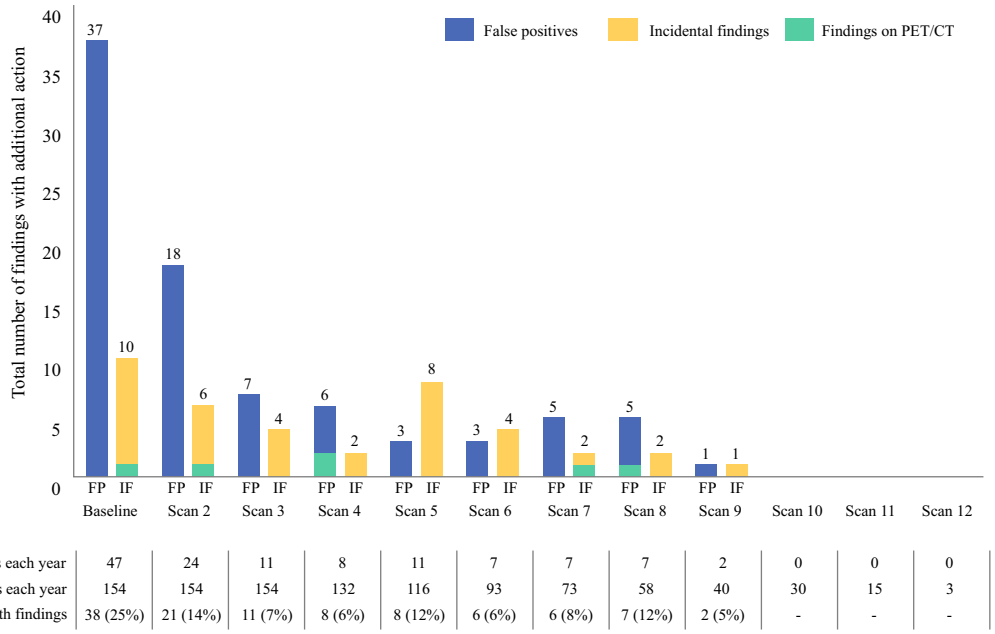
TABLE 2 Non-melanoma findings per patient and per scan for baseline and surveillance imaging

	Findings	Number of scans [$n = 1022$] (%)	Patients [$n = 154$] (%)
Incidental findings not requiring action	788	461	142
Findings requiring action on baseline imaging	47	38[a]	38[a] (25)
False-positives on baseline	37	32	32 (21)
Incidental findings on baseline	10	10	10 (6)
Findings requiring action on surveillance imaging	77	69 (7)	61[b] (40)
False-positives	49	45 (4)	42 (27)
Incidental findings	28	24 (2)	21 (14)
Total number of findings	912	510[c]	149[c]

[a]Four baseline scans in four patients had a false-positive finding as well as an incidental finding

[b]Two patients had an incidental finding as well as a false-positive finding on follow-up scans

[c]Scans and patients could have more than one finding



	Baseline	Scan 2	Scan 3	Scan 4	Scan 5	Scan 6	Scan 7	Scan 8	Scan 9	Scan 10	Scan 11	Scan 12
Total findings each year	47	24	11	8	11	7	7	7	2	0	0	0
Total of patients each year	154	154	154	132	116	93	73	58	40	30	15	3
Number of patients with findings	38 (25%)	21 (14%)	11 (7%)	8 (6%)	8 (12%)	6 (6%)	6 (8%)	7 (12%)	2 (5%)	-	-	-

FIG. 2 False-positives and incidental findings requiring additional action, per scan type, at baseline, and per surveillance year. *FP* false positive, *IF* incidental finding, *PET* positron emission tomography, *CT* computed tomography

TABLE 3 Cumulative incidence of false-positives and incidental findings

	Total patients each year	Findings	Patients with findings per year (%)	Unique patients with cumulative findings, including baseline scan (%)	Unique patients with cumulative findings, surveillance scans only (%)
Scan baseline	154	47	38 (25)	38 (25)	–
Scan 2	154	24	21 (14)	54 (35)	21 (14)
Scan 3	154	11	11 (7)	60 (39)	31 (20)
Scan 4	132	8	8 (6)	66 (43)	39 (25)
Scan 5	116	11	8 (7)	72 (47)	46 (30)
Scan 6	93	7	6 (6)	75 (49)	50 (32)
Scan 7	73	7	6 (8)	78 (50)	55 (36)
Scan 8	58	7	7 (12)	80 (52)	60 (39)
Scan 9	40	2	2 (5)	81 (53)	61 (40)
Scan 10	30	0	0	–	–
Scan 11	15	0	0	–	–
Scan 12	3	0	0	–	–

DISCUSSION

In this cohort study, non-melanoma findings requiring further action were identified in 53% of asymptomatic stage III patients as a direct result of CT or PET/CT imaging. The frequency of these false-positive and incidental findings persisted over time. Invasive procedures were undertaken in 14% of patients, with 10% undergoing invasive procedures for benign findings. Potentially serious incidental findings were discovered in 8% of imaged patients.

Surveillance imaging studies have focused on true-positive findings and identification of distant melanoma metastases. Our finding of 13% of asymptomatic stage III melanoma patients having distant metastases detected on annual follow-up imaging (after a median of 85 months follow-up) is in the range of the 5–29% reported in other

studies.[12,29–34] However, in these studies, various surveillance schedules were used, including 3-monthly scans, annual scans, and a single scan 3 years postoperatively, and follow-up was substantially shorter, between 2 and 5 years.

False-positives and incidental findings are rarely primary or secondary endpoints in melanoma research and are frequently not documented. In our well-documented cohort, 42% of patients had false-positive findings, which is higher than the 7–14% described in other studies.[32–34] Our study reported incidental findings in 21% of patients, similar to the upper range reported in previous studies (15% and 23%).[32,35] Given the limited methods of previous studies, false-positive and incidental findings rates were likely to be underestimated.

Annual surveillance imaging is expensive from the perspective of both the healthcare system and patients. A previous study reports a single surveillance scan after 3 years of clinical follow-up in stage IIB–III melanoma patients costs US$312,990 per recurrence diagnosed, which was not cost-effective compared with clinical follow-up without imaging.[2]

In the present study, approximately 8% of the cohort may have benefited from early detection and management of clinically significant non-melanoma findings. Others have included such findings as true-positives because the discovery was considered beneficial for the patient.[36] However, the identification of these findings was not the purpose of the imaging and we suggest that they should therefore be counted as incidental findings. Importantly, it is not certain that the early discovery conferred a survival benefit or whether these findings would lead to patient morbidity. This phenomenon is referred to as overdiagnosis and is described as an important problem in cancer screening.[37]

The strengths of this study include the use of a very well-documented longitudinal cohort of patients who had annual CT or PET/CT surveillance imaging over a median follow-up period of 85 months. The reason for imaging was known, and management details were easily retrieved due to detailed descriptions in high-quality clinical trial files and MIA records.

One limitation of our study is that only patients with at least two annual follow-up scans were included, thereby creating a selected study cohort and possibly decreasing the applicability of the findings to all stage III melanoma patients. This was necessary to ensure the test performance of a series of surveillance scans rather than just one follow-up scan. Our study cohort represents a relatively low-risk stage III population with 37% chance of recurrence and 23% chance of distant metastases after a median follow-up of 85 months.[3,38] A second limitation is that this study was not intended to quantify the true-positive rate and might therefore have underestimated the true-positive findings of distant metastases on annual imaging. Another further limitation is that most follow-up scans were CTs; only 37 were PET/CTs, reflecting historical practice. At MIA, PET/CT is replacing CT imaging for melanoma surveillance; however, in many other countries, CT surveillance is still predominantly used and recommended in clinical practice guidelines.[17,21] Furthermore, there is no evidence to suggest that imaging with PET/CT scans would yield less false-positive and incidental findings than imaging with CT.

The advent of more effective systemic therapies for stage III/IV melanoma has led to a more pronounced role for surveillance imaging. In many countries, stage III patients are offered adjuvant immunotherapy and/or targeted therapy. To prevent overtreatment of these patients, follow-up by medical oncologists is likely to be frequent and largely based on imaging. The frequency of scans is therefore likely to increase, perhaps even to 3-monthly, consistent with adjuvant therapy trial protocols.[7–9] Prospective cohort studies that record the benefits and harms of imaging are needed, as are cost-effectiveness analyses of long-term imaging schedules, because frequent imaging is likely to impose a huge financial burden on health systems and patients who pay out-of-pocket expenses. Several studies have been conducted investigating patient and clinicians' views of follow-up in early-stage melanoma, however further research is needed to assess the patients' perspective of surveillance imaging in long-term cancer survivorship programs following treatment for stage III or IV disease.[39–45]

CONCLUSIONS

False-positive results and incidental findings are reported in at least half of all asymptomatic stage III melanoma patients undergoing long-term annual surveillance imaging, incurring considerable additional healthcare costs and unnecessary invasive procedures. The risk of false-positives and incidental findings persist over time, and clinicians need to be aware of these risks and discuss them with their patients at the same time as the expected benefits of surveillance imaging are outlined.

ACKNOWLEDGMENT The authors sincerely thank Hazel Burke and Maria Gonzales at MIA for their help with data acquisition.

FUNDING This work was supported by Cancer Australia's Priority-driven Collaborative Cancer Research Scheme (Project Number 1129568).

DISCLOSURE Alexander M. Menzies has been on an advisory board for Bristol Meyers Squibb, Merck Sharp Dome, Novartis, and Pierre-Fabre, and has received speaking honoraria from Roche. Robyn P.M. Saw has been on an advisory board for Bristol Meyers Squibb, Merck Sharp Dome, Novartis, and Amgen, and has received a speaking honorarium from Bristol Meyers Squibb. John F. Thompson has been on an advisory board for and received honoraria and travel support from Bristol Meyers Squibb, Merck Sharp Dome, Provectus Inc., and GlaxoSmithKline. Amanda A.G. Nijhuis, Mbathio Dieng, Nikita Khanna, Sally J. Lord, Jo Dalton, Robin M. Turner, Jay Allen, Omgo E. Nieweg, and Rachael L. Morton have no conflicts of interest to declare.

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