Radiological imaging of melanoma: a review to guide clinical practice in New Zealand

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ABSTRACT

The aim of this review is to propose guidelines for initial radiological staging and the follow-up imaging regime for melanoma. This will provide consistency in the access and delivery of quality melanoma care. Radiological imaging plays an important role in assessing the extent of disease, guiding individual treatment and evaluating treatment response. However, there exists limited literature addressing the optimal radiological staging and surveillance imaging regimes for melanoma. The lack of consensus on imaging for melanoma can generate inconsistency in the standard of skin cancer care provided. This review considers the appropriate imaging techniques for both initial melanoma staging and follow-up specifically in the New Zealand clinical environment. The recommendations in this article are based on evaluation of the currently available literature and consensus of feedback from consultation with a working group of New Zealand clinicians involved in providing care to patients with melanoma. The proposed guidelines are considered the standard of care, but regional practice may differ based on access to imaging technology, cost limitations and the clinical experience of healthcare professionals.

In recent decades, there has been a substantial worldwide rise in reported rates of skin cancers, including melanoma.[1] New Zealand has one of the highest rates of melanoma in the world.[2] In 2016, 2,571 patients with melanoma (including melanoma *in situ* (MIS)) were recorded by the New Zealand Cancer Registry (age standardised rate 36.4 per 100,000).[3] Although melanoma is less common than other forms of skin cancer (accounting for less than 5% of skin cancers), the mortality rate is significantly greater, causing the majority of skin cancer related deaths.[3] New Zealand has the highest rate of melanoma mortality (age standardised rate 4.5 per 100,000) with 362 deaths in 2016.[3] The high mortality rate is related to the aggressive nature of the disease, which results in metastasis and various barriers in the effective early detection of melanoma.[4]

The most widely used histopathological staging system of melanoma is the American Joint Committee on Cancer (AJCC) TNM system. The most recent AJCC staging update is the eighth edition,[5] which is used in this review. Radiological imaging plays an important role in the evaluation of disease, guiding treatment and assessing response. However, the optimal imaging technique for staging and the appropriate regime for surveillance imaging for melanoma remains controversial, as the literature assessing this is limited. The application of positron emission tomography-computed tomography (PET-CT) in the management of patients with melanoma is rapidly evolving. PET-CT has superior diagnostic accuracy over computed tomography (CT) and is more accurate for staging of distant metastasis.[6] Surveillance imaging is used to detect local recurrence/metastasis of melanoma and

assess treatment response. Previously, the role of surveillance imaging was considered unjustified due to the limited treatment options available. However, with the emergence of new and improved therapies, surveillance imaging may have a benefit on overall survival.

This review evaluates the current literature and proposes guidelines for radiological staging and surveillance imaging for melanoma based on the AJCC TNM stage of disease. The guidelines proposed in this review are considered to be the standard of care. However, it is acknowledged that regional practice may vary according to the availability of imaging technology, cost limitations and clinical experience.

Initial staging imaging

Cross-sectional body imaging

All staging imaging investigations should ideally be completed within two weeks of referral to radiology. Indication for radiological staging is dependent on TMN status and intended treatment. The available literature assessing various imaging techniques for radiological staging of melanoma is limited. Most studies are of retrospective design and are difficult to compare due to variability in both methodology and the patient groups assessed.[7] PET-CT has improved diagnostic accuracy over CT, particularly for detection of extracerebral distant metastatic disease.[6] A small retrospective study compared staging PET-CT with CT alone and found major therapy changes based on the PET-CT findings, particularly with regard to surgical management.[8]

Stages 0, I and II

Routine radiological staging for asymptomatic patients with stage 0 (MIS), I and II disease is generally not recommended, due to low rates of true positive findings and comparatively high rates of false positive findings.[9–13] A reasonably large percentage of the recurrence seen in patients with stage 0 (MIS), I and II disease is local (nodal, satellite or in-transit) and is often detected by the patient or clinician.[14] Therefore, for patients with stage 0 (MIS), I or II disease, and excluding sentinel node biopsy (where indicated), baseline cross-sectional imaging is not routinely recommended in asymptomatic patients.

In those with thick melanomas (eg, T4, stage IIB and IIC disease) there are conflicting views in the literature, with currently little evidence to support a significant benefit of initial staging with PET-CT or CT, due to low yield and high false positive rates.[15,16] However, in certain high-risk clinical situations, such as thick T4 tumours, baseline PET-CT may add value with regard to altering the proposed treatment or therapy. Therefore, in patients with high-risk stage II disease with thick melanomas (eg, T4, stage IIB and IIC disease), initial staging with PET-CT can be considered and should be discussed at a multidisciplinary meeting (MDM). Also consider PET-CT staging if sentinel node biopsy failed or was declined.[17]

Stage IIIA

For patients with stage IIIA disease (positive sentinel lymph nodes with low nodal tumour volume), there is little evidence to support the value of baseline cross-sectional imaging. In particular, staging imaging in this group has a high false positive rate, which may lead to inappropriate further investigation and/or interventions.[18] However, the rate of relapse in this group is not negligible, but it may be that the volume of locoregional or distant metastatic disease is below the threshold for imaging detection at the initial diagnosis.[19] Follow-up surveillance imaging should be considered at an appropriate time interval based on the risk of recurrence. However, for patients with positive sentinel lymph nodes where therapeutic lymphadenectomy is planned (which is not considered the standard of care), baseline PET-CT is recommended instead.

Therefore, for patients with stage IIIA disease under clinical or ultrasound observation, baseline cross-sectional staging imaging such as PET-CT is not routinely indicated in asymptomatic patients. PET-CT is recommended for patients with a positive sentinel node where therapeutic lymphadenectomy is planned.

Stages IIIB, IIIC and IIID

In patients with high-risk stage III disease (stage IIIB, IIIC and IIID disease), baseline PET-CT detection of occult metastasis may upstage the patient, which can have significant implications for further management.

A small retrospective study by Groen et al reported that 18% of patients with stage III disease were upstaged to stage IV.[20] Therefore, baseline PET-CT is recommended for patients with stage IIIB, IIIC or IIID disease, as potential upstaging may influence a change in treatment.[13]

Stage IV

Patients with stage IV disease may present clinically or as an unexpected finding on imaging with or without a history of melanoma. For patients with stage IV disease, PET-CT is recommended if the result will change management. Baseline PET-CT for stage IV disease should be guided by the MDM and recommended in certain clinical circumstances, such as if there is oligometastatic disease demonstrated on conventional CT that would be amenable to surgery or radiotherapy, as a baseline for systemic therapy or if there are equivocal findings on conventional CT that could potentially change treatment decisions. Otherwise, contrast-enhanced staging CT of the chest, abdomen and pelvis should be performed. Neck CT should be added if the primary malignancy is in the head, neck or upper trunk.

Brain imaging

The AJCC recognises patients with central nervous system metastases as having the worst prognosis of all melanoma patients with distant metastatic disease (M1d category).[5] The incidence of developing brain metastases increases with TNM stage. The risk of cerebral metastasis in stage I and II disease is low, and routine staging is generally not recommended. For patients with stage III disease, macroscopic nodal and in-transit disease has been associated with an increased risk of brain metastases.[21] In stage IV disease, the risk of concurrent cerebral and extracerebral metastasis at diagnosis has been described as being present in up to a third of patients, and there is also a small group where the brain is the only site of metastatic disease.

It is widely accepted that contrast-enhanced magnetic resonance imaging (MRI) is superior to contrast-enhanced CT for the detection of cerebral metastases and is therefore preferable due to improved diagnostic accuracy.[6] If low-dose CT is performed as part of the PET-CT examination, it may not be of diagnostic quality for the detection of brain metastases, and additional diagnostic-quality brain imaging may therefore be required.

Given the prognostic implications and treatment options now available, staging high-resolution brain imaging is recommended for patients with stage IIIB, IIIC, IIID and IV disease.[22]

Lymph node ultrasound

An ultrasound of the lymph node basins draining the primary site may be considered in selected clinical situations. Examples include high-risk stage II patients with equivocal clinical examination or when

Table 1: Initial staging imaging recommendations for melanoma by AJCC stage.

AJCC stage	Staging imaging
0, I, II	Not routinely indicated in asymptomatic patients. Regional lymph node ultrasound in selected clinical situations.
IIB, IIC	Consider baseline PET-CT for high-risk T4 tumours, following MDM discussion.
IIIA	Not routinely indicated in asymptomatic patients. PET-CT is recommended if therapeutic lymphadenectomy is planned.
IIIB, IIIC, IID	PET-CT and high-resolution brain imaging recommended (MRI preferable over contrast-enhanced CT).
IV	PET-CT, if the result will change clinical management or therapy, and MDM discussion. Otherwise, baseline CT chest, abdomen and pelvis +/- neck. High-resolution brain imaging recommended. MRI preferable over contrast-enhanced CT.

clinical examination is limited by patient body habitus or when sentinel node biopsy has failed or was declined. There is evidence that ultrasound can detect lymph node metastasis with a reasonable degree of accuracy, with literature to support increased sensitivity of ultrasound compared to clinical examination.[23,24] Although the sensitivity of ultrasound is higher than clinical examination, it is no substitute to sentinel node biopsy.

Follow-up and surveillance imaging

Cross-sectional body imaging

In conjunction with intensive clinical follow-up, the addition of routine cross-sectional imaging does allow earlier detection of recurrent disease, but the impact on overall survival is still unclear.[25] Cross-sectional imaging follow-up should be guided by the probability of recurrence at any stage and determined by stage, symptoms, clinical findings and suitability for therapy. With emerging systemic therapies, routine follow-up cross-sectional imaging also provides assessment of therapeutic response. In particular, the apparently high negative predictive value of PET-CT seems to be reasonably consistent and notably reassuring.[26]

The optimal cross-sectional imaging (PET-CT or CT) surveillance regime for high-risk melanoma remains controversial, and there is currently no international consensus. Even in high-risk melanoma patients, there is no high-quality data to support improved survival outcomes following routine follow-up cross-sectional imaging. It is generally agreed that PET-CT has superior diagnostic accuracy over conventional CT.[6] In those clinical settings where CT findings are equivocal or there are clinical findings highly suspicious for recurrence, PET-CT results may alter the treatment course, particularly when surgery is being considered.[8] There is, however, no prospective data that directly compares the two modalities with regard to the magnitude of differences in survival outcomes.

Stages 0, I, IIA and IIB

For patients with stage 0, I, IIA and IIB disease, routine surveillance imaging is not recommended if the patient is asymptomatic.

Stage IIC

For patients with thick melanomas (eg, T4 tumours), baseline staging with PET-CT is controversial due to low yield and high false positive rate. However, there are significant relapse rates, particularly in patients with stage IIC disease. In a retrospective study of pathologic stage II patients by Lee et al, 46% of stage IIC patients relapsed, and of those, 52% of first relapses were systemic. Imaging detected relapse in 31% of these patients.[27] Stage IIC patients notably relapsed earlier with a higher proportion of systemic metastases (especially lung and brain) when compared to other stage II subgroups.[27] Therefore, for patients with stage IIC disease, CT chest, abdomen and pelvis +/- neck and brain MRI or CT head at six months and then at twelve months is recommended. Consider annual surveillance imaging in years 3–5 following diagnosis. If there are equivocal findings on routine CT surveillance, PET-CT should be considered if it would influence a treatment change.

Stage IIIA

From the limited data available, baseline staging cross-sectional imaging in patients with a positive sentinel lymph node (stage IIIA with low nodal tumour volume) appears to be of limited benefit, with low yield and high rates of false positive tests.[18,28,29] This can lead to further unnecessary investigations, some of which may be invasive/morbid. However, the rate of recurrence in this group is not insignificant. Although a high percentage of first relapses are locoregional and often detected by the patient or clinician, less frequent surveillance cross-sectional imaging in this group has been shown to detect asymptomatic recurrence/progression.[28] Therefore, for patients with stage IIIA disease, CT chest, abdomen and pelvis +/- neck at six months and then at twelve months, and then annually thereafter until three years following diagnosis, is recommended.

Stages IIIB, IIIC, IIID and IV

The approach to cross-sectional imaging surveillance of patients with higher stage III disease and stage IV disease varies widely. For example, the National Comprehensive Cancer Network suggests follow up PET-CT or CT every 3–12 months.[13] Regarding salvage curative surgery, radiotherapy or emerging systemic therapies,

there is an impression that treatments are more effective in the setting of low tumour volume, making early detection of recurrence and/or distant metastatic disease relevant.[26,30] For patients with asymptomatic stage IIIB, IIIC, IIID or IV disease, more frequent cross-sectional imaging (eg, 3–6 monthly in the first three years) should be considered, when the rates of recurrence are highest. Particularly in stage III disease, a substage approach to follow-up regimes may indeed be beneficial.[28] This approach acknowledges that, although the actual benefit of earlier imaging detection on survival outcomes is not yet known, there are now more treatment options available.

Therefore, in asymptomatic patients with stage IIIB, IIIC, IIID and IV disease, routine follow-up with contrast-enhanced CT of chest, abdomen and pelvis +/- neck can be considered at 3–6 monthly intervals for the first three years. Annual follow-up imaging in years 3–5 following diagnosis is recommended. If there are equivocal findings on routine CT surveillance, PET-CT should be considered if it would influence a treatment change. If there is biopsy proven local (nodal, satellite or in-transit) recurrence or oligometastatic disease, PET-CT should be considered if the patient is a candidate for surgery, radiotherapy or systemic therapy. The PET-CT imaging request should be discussed at the MDM.

For patients with stage III and IV disease on active treatment (systemic therapy or radiotherapy), the follow-up imaging schedule will be determined by the oncology team, who will likely base their decision on individual patient symptoms and/or the need to assess treatment response. The above schedule may be a useful guide to the minimum frequency of imaging.

Brain imaging

MRI is superior to contrast-enhanced CT for the detection of cerebral metastases and is preferred (particularly if there is prior documented metastatic brain disease). As with relapse at other sites, development of brain metastases generally occurs in the first three years.[21,31] Patients with stage IIC disease have been found to relapse earlier, with a higher proportion of systemic metastases compared to other stage II subgroups.[27] For stage III patients, macroscopic nodal and in-transit disease has been associated with an increased risk of brain metastases.[21] There has also been an association between primary tumour ulceration and development of brain metastasis.[32]

Previously, the poor prognosis of those with brain metastases may have precluded routine surveillance for those at risk. However, given the prognostic implications and recent advances in surgery, stereotactic radiotherapy and systemic therapy, there are improved treatment outcomes (particularly in the setting of smaller tumour volume and asymptomatic lesions). This would suggest that earlier detection increases the treatment options available to patients, although there remains little evidence to directly support this. Therefore, surveillance high-resolution brain imaging (brain MRI or contrast-enhanced CT head) should also be considered in high-risk patients (stages IIC, IIIB, IIIC, IIID or IV) at 3–6 monthly intervals in the first three years, with less frequent surveillance following this.

Lymph node ultrasound surveillance

Ultrasound of the draining regional lymph node basins may provide a useful adjunct to clinical examination, particularly when clinical examination is limited (such as obese patients), when sentinel node biopsy (SNB) has failed or not performed when indicated or as surveillance of SNB positive nodal stations when therapeutic lymphadenectomy is not performed. Following the results of the MSLT-II trial, local surveillance with ultrasound is likely to increase.[33] There is evidence that ultrasound can detect lymph node metastasis with a reasonable degree of accuracy, with literature to support an increased sensitivity of ultrasound compared to clinical examination.[34,35]

Sonographic features suspicious for nodal malignancy, as defined by Vassallo et al, remain as consistent criteria in the literature for lymph node malignancy and include longitudinal to transverse diameter ratio <2, echogenic central hilum narrowed or absent (suggesting diffuse hypoechogenicity) and concentric or eccentric widening of the peripheral cortex.[36] Nodal size alone is not a good discriminator, as small nodes may have

malignant features and benign reactive nodes may be notably enlarged. Other suspicious features include peripheral vascularity on colour Doppler sonography and intranodal necrosis.[37] A combination of more than one suspicious finding has been shown to increase the sensitivity of detection.[38] The success of sonographic nodal assessment therefore relies on the expertise of the sonographer, who requires a certain level of technical skill and knowledge. Equivocal sonographic findings may need short-interval follow-up ultrasound or fine needle aspiration (FNA).

Therefore, ultrasound imaging of the draining nodal basins should be performed in a select group of patients, in conjunction with routine clinical follow-up and appropriate cross-sectional imaging as per TNM stage. Ultrasound imaging should be performed in patients with stage IB, IIA, IIB or IIC disease where SNB is not performed

Table 2: Surveillance imaging recommendations for melanoma by AJCC stage.

AJCC stage	Surveillance imaging
0, IB, IIA, IIB	Not routinely indicated in asymptomatic patients. For patients with stage IB, IIA, IIB or IIC disease where SNB is not performed when clinically indicated, or where SNB has failed or clinical examination is limited, regional lymph node ultrasound is recommended 6 monthly for 2 years.
IIC	CT chest, abdomen and pelvis +/- neck and brain MRI or CT head 6 monthly for 3 years. Consider annual surveillance CT imaging in years 3–5. Consider PET-CT if there are equivocal findings on CT that would influence treatment change. If SNB was not performed, regional lymph node ultrasound is recommended 6 monthly for 2 years.
IIIA	CT chest, abdomen and pelvis +/- neck at 6 months and then at 12 months and annually thereafter until 3 years from the initial diagnosis. Regional lymph node ultrasound 6 monthly for 2 years for patients with SNB positive stage III disease where therapeutic lymphadenectomy is not performed.
IIIB, IIIC, IID, IV	CT chest, abdomen and pelvis +/- neck and brain MRI or CT head 3–6 monthly for 3 years and annually in years 3–5 following diagnosis. Consider PET-CT if there are equivocal findings on CT surveillance and if it would influence a treatment change. Consider PET-CT if there is biopsy proven local recurrence or oligometastatic disease and the patient is a candidate for surgery, radiotherapy or systemic therapy.

when clinically indicated, and in patients with SNB positive stage III disease where therapeutic lymphadenectomy is not performed and where SNB has failed. Ultrasound imaging should also be considered for patients where clinical examination is limited. The recommended frequency of ultrasound imaging is six monthly for two years. For those patients undergoing ultrasound surveillance and who have not had SNB, baseline ultrasound is also advised.

There may be more than one draining nodal basin. For example, a primary tumour in the central torso may drain to either axillary or inguinal stations, and ultrasound assessment should include all relevant nodal stations. For primary tumours in the head and neck, bilateral neck ultrasound is advised.

Conclusion

Although the available literature is limited with regard to the effect on overall survival, radiological staging and surveillance imaging plays an integral role in guiding decision making with respect to management of melanoma. With the emergence of new and targeted therapies for melanoma, there is now even more need to accurately stage and restage disease. As of yet, there is no international consensus to guide the mode or interval of imaging and there is significant variability in clinical practice. The imaging recommendations outlined above are based on a review of the current literature and clinical consultation with the aim to provide a pragmatic and standardised approach to radiological imaging for patients with melanoma in New Zealand.

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REFERENCES

1. Schadendorf D, Van Akkooi ACJ, Berking C, et al. Melanoma. The Lancet. 2018; 15;392(10151):971-84.
2. Liang JJ, Robinson E, Martin RC. Cutaneous melanoma in New Zealand: 2000–2004. ANZ J Surg 2010; 80: 312–316.
3. New Zealand Ministry of Health. Cancer: new registrations and deaths 2016. Wellington: Ministry of Health; 2016. [cited 30 July, 2020]. Available from: www.health.govt.nz
4. Tas F. Metastatic behavior in melanoma: timing, pattern, survival, and influencing factors. J Oncol. 2012;2012:647684. doi:10.1155/2012/647684.
5. Amin MB, Edge S, Greene F, et al. AJCC Cancer Staging Manual (8th edition). Springer International Publishing: American Joint Commission on Cancer. 2017.
6. Xing Y, Bronstein Y, Ross MI, et al. Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis. Journal of the National

Cancer Institute. 2011 19;103(2):129-42.

7. Cancer Council Australia Melanoma Guidelines Working Party. Clinical practice guidelines for the diagnosis and management of melanoma. Sydney: Cancer Council Australia. 2019. [cited 30 July 2020]. Available from: https://wiki.cancer.org.au/australia/Guidelines:Melanoma
8. Schüle SC, Eigentler TK, Garbe C, et al. Influence of 18 F-FDG PET/CT on therapy management in patients with stage III/IV malignant melanoma. European journal of nuclear medicine and molecular imaging. 2016; 1;43(3):482-8.
9. Barsky M, Cherkassky L, Vezeridis M, Miner TJ. The role of preoperative positron emission tomography/computed tomography (PET/CT) in patients with high-risk melanoma. Journal of surgical oncology. 2014;109(7):726-9.
10. Bikhchandani J, Wood J, Richards AT, Smith RB. No benefit in staging fluorodeoxyglucose-positron emission tomography in clinically node-negative head and neck cutaneous melanoma. Head & neck. 2014;36(9):1313-6.
11. Orfaniotis G, Mennie JC, Fairbairn N, Butterworth M. Findings of computed tomography in stage IIB and IIC melanoma: a six-year retrospective study in the South-East of Scotland. Journal of plastic, reconstructive & aesthetic surgery. 2012;1;65(9):1216-9.
12. Topuz ÖV, Görtan FA, Döner ZR, et al. Usefulness of 18F-FDG PET/CT in Cutaneous Melanoma Patients with Negative Sentinel Lymph Nodes and High Clark Levels. Molecular Imaging and Radionuclide Therapy. 2018;27(2):66.
13. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology (NCCN Guidelines). 2019. [cited 30 July 2020]. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx
14. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. Journal of the American Academy of Dermatology. 2019;1;80(1):208-50.
15. Arrangoiz R, Papavasiliou P, Stransky CA, et al. Preoperative FDG-PET/CT is an important tool in the management of patients with thick (T4) melanoma. Dermatology research and practice. 2012;1;2012.
16. Danielsen M, Kjaer A, Wu M, et al. Prediction of positron emission tomography/computed tomography (PET/CT) positivity in patients with high-risk primary melanoma. American journal of nuclear medicine and molecular imaging. 2016;6(5):277.
17. NICE guidelines. National Collaborating Centre for Cancer – Melanoma: assessment and management. 2015. [cited 30 July 2020]. Available from: https://www.nice.org.uk/guidance/ng14/evidence/full-guideline-pdf-250314589
18. Holtkamp LH, Read RL, Emmett L, et al. Futility of imaging to stage melanoma patients with a positive sentinel lymph node. Melanoma research. 2017;1;27(5):457-62.
19. Wagner T, Meyer N, Zerdoud S, et al. Fluorodeoxyglucose positron emission tomography fails to detect distant metastases at initial staging of melanoma patients with metastatic involvement of sentinel lymph node. British Journal of Dermatology. 2011;164(6):1235-40.
20. Groen LC, Lazarenko SV, Schreurs HW, Richir MC. Evaluation of PET/CT in patients with stage III malignant cutaneous melanoma. American journal of nuclear medicine and molecular imaging. 2019;9(2):168.
21. Samlowski WE, Moon J, Witter M, et al. High frequency of brain metastases after adjuvant therapy for high-risk melanoma. Cancer medicine. 2017;6(11):2576-85
22. Vosoughi E, Lee JM, Miller JR, et al. Survival and clinical outcomes of patients with melanoma brain metastasis in the era of checkpoint inhibitors and targeted therapies. BMC cancer. 2018;1;18(1):490.
23. Bafounta ML, Beauchet A, Chagnon S, Saiag P. Ultrasonography or palpation for detection of melanoma nodal invasion: a meta-analysis. The lancet oncology. 2004;1;5(11):673-80.
24. Machet L, Nemeth-Normand F, Giraudeau B, et al. Is ultrasound lymph node examination superior to clinical examination in melanoma follow-up? A monocentre cohort study of 373 patients. British journal of dermatology. 2005;152(1):66-70.
25. Podlipnik S, Carrera C, Sánchez M, et al. Performance of diagnostic tests in an intensive follow-up protocol for patients with American Joint Committee on Cancer (AJCC) stage IIB, IIC, and III localized

primary melanoma: a prospective cohort study. Journal of the American Academy of Dermatology. 2016;1;75(3):516-24.

26. Leon-Ferre RA, Kottschade LA, Block MS, et al. Association between the use of surveillance PET/CT and the detection of potentially salvageable occult recurrences among patients with resected high-risk melanoma. Melanoma research. 2017;1;27(4):335-41.
27. Lee AY, Droppelmann N, Panageas KS, et al. Patterns and timing of initial relapse in pathologic stage II melanoma patients. Annals of surgical oncology. 2017;1;24(4):939-46.
28. Lewin J, Sayers L, Kee D, Walpole I, et al. Surveillance imaging with FDG-PET/CT in the post-operative follow-up of stage 3 melanoma. Annals of Oncology. 2018;1;29(7):1569-74.
29. Scheier B, Lao CD, Kidwell KM, Redman BG. Utility of pre-operative PET/CT staging in sentinel lymph node-positive melanoma. Journal of Clinical Oncology. 2015;20; 33(15).
30. Freeman M, Laks S. Surveillance imaging for metastasis in high-risk melanoma: importance in individualized patient care and survivorship. Melanoma management. 2019;18;6(1).
31. Fife KM, Colman MH, Stevens GN, et al. Determinants of outcome in melanoma patients with cerebral metastases. Journal of Clinical Oncology. 2004;1;22(7):1293-300.
32. Zakrzewski J, Geraghty LN, Rose AE, et al. Clinical variables and primary tumor characteristics predictive of the development of melanoma brain metastases and post-brain metastases survival. Cancer. 2011;15;117(8):1711-20.
33. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. New England Journal of Medicine. 2017;8;376(23):2211-22.
34. Bafounta ML, Beauchet A, Chagnon S, Saiag P. Ultrasonography or palpation for detection of melanoma nodal invasion: a meta-analysis. The lancet oncology. 2004;1;5(11):673-80.
35. Machet L, Nemeth-Normand F, Giraudeau B, et al. Is ultrasound lymph node examination superior to clinical examination in melanoma follow-up? A monocentre cohort study of 373 patients. British journal of dermatology. 2005;152(1):66-70.
36. Vassallo P, Wernecke K, Roos N, Peters PE. Differentiation of benign from malignant superficial lymphadenopathy: the role of high-resolution US. Radiology. 1992;183(1):215-20.
37. Ahuja AT, Ying M, Ho SY, et al. Ultrasound of malignant cervical lymph nodes. Cancer Imaging. 2008;8(1):48.
38. Moehrle M, Blum A, Rassner G, Juenger M. Lymph node metastases of cutaneous melanoma: diagnosis by B-scan and color Doppler sonography. Journal of the American Academy of Dermatology. 1999;1;41(5):703-9.