

1 **PET-CT vs brain MRI for the detection of cerebral metastases of melanoma, a 5-year**  
2 **retrospective study**

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21 publication of their case details.

22  
23 **What is already known about this topic?**

- 24
- Although PET-CT has seen improvement in detecting brain metastases it is unclear how it  
25 performs compared to the cerebral MRI, the current gold standard.

## 1 **What does this study add?**

- 2 • Despite the increasing performance of PET-CT, brain MRI remains the most efficient  
3 diagnostic tool to detect melanoma cerebral metastases and should always be performed  
4 in addition to PET-CT in patients with high-risk melanoma from stage IIC.

## 5 **Abstract**

### 6 **Background**

7 Melanoma patients present a high risk of developing extra cutaneous metastases. PET-CT is one  
8 of the preferred examinations for the staging of oncological patients. It is not the method of  
9 choice to detect brain metastases, but this technique has shown significant improvement and  
10 allows the detection of some of them, although it is unclear how it performs compared to the  
11 MRI, the current gold standard for diagnosing brain metastases.

### 12 **Objective**

13 To compare the accuracy of PET-CT and cerebral MRI to detect brain metastases in melanoma  
14 patients.

### 15 **Methods**

16 We retrospectively included all patients diagnosed with melanoma stage IIC-IV (AJCC 8<sup>th</sup>  
17 Edition-2017) presented at the skin tumor board of the University Hospital of Bern between  
18 01/2018 and 12/2022. All radiological reports extracted from the patient management system  
19 were analyzed to assess a discrepancy between the visibility of brain metastases on PET-CT and  
20 brain MRI.

### 21 **Results**

22 In this study including 393 patients, brain MRI demonstrated significantly higher performance  
23 than PET-CT in detecting brain metastases. Cerebral metastases were detected completely,

1 partially or were not detected by PET-CT in respectively 2 patients (4%), 15 patients (32%) and  
2 30 patients (64%) out of 47.

### 3 **Conclusion**

4 Despite the increasing performance of PET-CT, this study highlights the crucial role of brain  
5 MRI, which remains the gold standard to detect cerebral metastases. Brain MRI should be  
6 performed on patients with high-risk melanoma from stage IIC to exclude brain metastases.  
7

### 8 **Introduction**

9 Malignant melanoma is the 6<sup>th</sup> most common cancer in Europe (after breast, colon, prostate, lung,  
10 and bladder cancers). Its incidence is constantly rising (1, 2), with about 108'000 new diagnoses  
11 every year and 17'000 cases of mortality (3). Risk factors for the development of melanoma are  
12 mainly UV exposure, personal or family history of melanoma, multiple naevi,  
13 immunosuppression, and fair skin phototype (4, 5). Although survival rates are constantly  
14 increasing due to improved detection and treatment (6), melanoma is responsible for the highest  
15 number of skin cancer deaths per year and presents a high risk of developing metastases. Thus,  
16 early diagnosis, staging and close follow-up are essential.

17 Regarding the risk of developing brain metastases of melanoma, a recent systematic literature  
18 review found 33% of brain metastases at the diagnosis of stage IV cutaneous melanoma. Among  
19 patients with stage IV cutaneous melanoma without brain metastases at diagnosis, 25% of  
20 patients will develop some later (7).

21 Positron emission tomography and computed tomography (PET-CT) is currently one of the  
22 preferred examinations for the staging of oncological patients and the search for metastases (8-

1 10). It is not the method of choice to detect brain metastases (11, 12), but this technique has seen  
2 significant improvement over the years and allows the detection of some brain metastases (13-  
3 15). Magnetic resonance imaging (MRI), the gold standard for diagnosing brain metastases (16-  
4 18), could be contraindicated in some patients and represent an additional source of stress (19,  
5 20). Common contraindications include cardiac implantable electronic devices, cochlear  
6 implants, intraocular foreign bodies, and other metallic objects (21). MRI also has limitations, as  
7 different post-treatment artefacts can be challenging to differentiate from metastases (22, 23).

8 Regarding the current literature, it was necessary to compare the accuracy of the latest generation  
9 PET-CT and cerebral MRI to detect brain metastases in a large cohort of melanoma patients.

10

## 11 **Material and Methods**

12 We conducted a retrospective study of melanoma patients presented at the skin tumor board at the  
13 University Hospital of Bern in Switzerland, between 01/2018 and 12/2022.

14 Patients were included if their cases were discussed at least once at the skin tumor board and if  
15 they had a histopathological diagnosis of malignant melanoma stage IIC-IV (according to the  
16 American Joint Committee on Cancer (AJCC) 8<sup>th</sup> Edition 2017) (24). Additional inclusion  
17 criteria include age over 18 and a signed consent. This study was reviewed and approved by the  
18 ethics committee of the canton Bern (ID 2022-01620).

19 Data were extracted from the patient management system of the University Hospital of Bern. All  
20 radiological reports (whole body PET-CT and brain MRI) performed between 01/2018 and  
21 12/2022 were analyzed for the study. Brain MRI were conducted with a Siemens MRI from 1.5

1 Tesla. From 01/2018 to 11/2020, PET-CT were performed with a Siemens Healthineers Biograph  
2 Vision 600, and then from 12/2020 to 12/2022 with a Siemens Healthineers Biograph Vision  
3 Quadra.

4 To assess a discrepancy between the visibility of brain metastases on PET-CT and brain MRI, a  
5 maximum period of 3 months between examinations was determined. The discrepancy was  
6 classified into three groups: totally detected (all the brain metastases diagnosed on cerebral MRI  
7 were visible on PET-CT); partially detected (only some, but at least one, brain metastases  
8 diagnosed on MRI were visible on PET-CT); not detected (no metastases diagnosed on MRI were  
9 detected on PET-CT).

10 For descriptive purposes, continuous data were presented as medians with interquartile ranges  
11 (IQR) while nominal data as absolute numbers with percentages. Pearson's  $X^2$  test was used to  
12 compare the frequency of patients who had PET-CT/MRI according to melanoma stage.  
13 Cumulative survival estimates were calculated using Kaplan-Meier estimator and presented with  
14 their 95% confidence interval (CI). For the overall survival (OS), metastasis-free survival (MFS)  
15 and brain metastasis-free survival (BMFS), patients were grouped depending on their initial stage  
16 at diagnosis. Patients with unknown initial stage or no follow-up were excluded. Patients with  
17 metastasis at diagnosis were also excluded for the MFS and BMFS estimates. Log-rank test was  
18 used to assess survival differences across tumor stages. Stratified Cox regression analysis,  
19 accounting for within-patient repeated measures, was used to compare detection rates of BM  
20 according to the type of exam performed. All tests were considered statistically significant at p-  
21 value  $<0.05$ . Analyses were performed with SPSS v.26.0 (IBM Corp, Armonk, NY, US).

22

## 1 **Results**

2 This study included 393 patients (248 males), median age 66.7 years (IQR 55.6-76.2). For stage  
3 IIC, IIIA, IIIB, IIIC, IIID and IV, respectively 24, 31, 65, 83, 11, and 179 patients were included.  
4 For 2018, 2019, 2020, 2021, and 2022, respectively, 71, 60, 73, 104 and 85 patients were  
5 included.

6 179 patients were diagnosed with stage IV melanoma (114 males), median age 66.2 years (IQR  
7 54.8-76.0). 56 patients were directly in stage IV upon initial diagnosis. For the remaining 123  
8 patients, metastases appeared at a median of 2.4 years (IQR 0.9-5.3) after initial diagnosis.

9 66 patients were diagnosed with brain metastases (41 males), median age 63.4 years (IQR 50.5-  
10 75.0). Breslow index at diagnosis was available for 48 out of 66 patients with a median Breslow  
11 index of 2.7 mm (IQR 1.6-4.5). By analyzing the initial stage (AJCC 2017) at the first diagnosis  
12 of melanoma of the patients presenting brain metastases, 7 patients were in stage I (10.6%), 16 in  
13 stage II (24.2%), 1 in IIIA (1.5%), 4 in IIIB (6.1%), 11 in IIIC (16.7%), 2 in IIID (3.0%), and 25  
14 in IV (37.9%).

15 Cerebral MRI demonstrated significantly higher performance than PET-CT in detecting brain  
16 metastases. At 5 years, the estimated cumulative detection rates of cerebral metastases by PET-  
17 CT and MRI were respectively 24.7% (95% CI: 11.0-36.2) and 76.7% (95% CI: 63.7-85.0)  
18 ( $p < 0.001$ ). 19 patients out of 66 were excluded from the analysis due to an excessive time lapse  
19 (more than 3 months) between PET-CT and brain MRI. PET-CT detected all brain metastases in  
20 only 2 patients out of 47 (4.3%). In 30 patients (63.8%), brain metastases were not detected at all  
21 with PET-CT; in 15 patients (31.9%), they were partially detected (Fig. 1).

1 Table 1 indicates the distribution of patients examined through PET-CT and cerebral MRI per  
2 stage. Across the different stages, PET-CT and cerebral MRI were performed respectively in  
3 100% vs 37.5% of patients in stage IIC, 87.1% vs 19.4% in IIIA, 93.8% vs 40% in IIIB, 95.2% vs  
4 61.4% in IIIC, 100% vs 81.8% in IIID and 94.4% vs 81.6% in IV. Contraindications for MRI  
5 were specified for 3 patients; 2 patients had a non-compatible pacemaker, and 1 patient had a  
6 non-compatible cerebral aneurysm clip. For all the other patients who did not undergo the MRI,  
7 no information was specified in the reports.

8 OS, MFS and BMFS are shown in Table 2 and Figure 2a, 2b and 2c respectively, median follow-  
9 up was 2.1 years (IQR 0.8-4.2 years).

10

## 11 **Discussion**

12 Our study confirmed that the performance of brain MRI was superior to PET-CT in the detection  
13 of cerebral metastases. Therefore, it should be systematically recommended for patients with  
14 stage IV melanoma but also to patients with high-risk melanoma from stage IIC, to rule out any  
15 cerebral metastases.

16 Numerous studies have evaluated the clinical relevance of PET-CT brain imaging in the detection  
17 of metastases of solid extracranial malignancies and have questioned the impact on management  
18 and staging. These retrospective studies evaluated PET-CT examinations from oncological  
19 patient databases and found that 1.2% to 6.7% of patients were positive for brain metastases on  
20 PET-CT. 97.5% to 99.6% of these brain metastases were already known prior to PET-CT,  
21 suggesting that PET-CT scanning of the brain of all oncological patients has a limited clinical  
22 value (14, 15, 25, 26).

1 Even though PET-CT is not the method of choice for the detection of brain metastases, including  
2 the head in the scanning field can be of clinical value. Three studies reviewing PET-CT scans of  
3 melanoma patients found brain or head metastases in 8.4 % (27), 6.7% (14) and 3.3% (28) of  
4 patients suggesting that including the head in the scanning field, not only to visualize the brain  
5 but also the skull and the soft tissue can change the clinical management.

6 Various studies have compared the efficiency of PET-CT versus brain MRI for different  
7 malignancies, using MRI as the gold standard. In 2003, Rohen *et al.* found brain metastases with  
8 PET-CT in 12 out of 16 patients (75%) with various extracranial tumors, with only 61% of the  
9 total lesions being seen on PET-CT (29). In 2008, Kitajima *et al.* detected through MRI 20 brain  
10 metastases in patients with non-central nervous system malignancies, none of those being  
11 melanoma. PET-CT detected brain metastases in 9 out of the 20 patients (45%) (11). A 2015  
12 study by Hjorthaug *et al.* about patients with lung carcinoma showed that PET-CT detected brain  
13 metastases on 31 patients out of 66 (46%) (30).

14 In 2020, Oldan *et al.* showed that PET-CT could detect melanoma brain metastases over about  
15 2.0 cm, with hot lesions potentially visible from a size of 0.9 cm (13).

16 In our study performed between 2018 and 2022, brain metastases were partially or completely  
17 detected through PET-CT in 17 out of 47 patients (36.2%). These rates are lower than those  
18 found in other extracranial malignancies and suggest that the visibility of melanoma metastases is  
19 poorer than for other tumors.

20 Despite the increased performance of PET-CT, the literature shows insufficient detection of brain  
21 metastases. It is therefore the medical duty to perform a brain MRI in melanoma patients from  
22 stage IIC.



1 In 2019, the European Society for Medical Oncology (ESMO) issued guidelines on the use of  
2 imaging for the staging and follow-up of melanoma patients. They suggested that brain MRI and  
3 PET-CT both should be conducted in high-risk patients (from pT3b and/or stage III) (31). In  
4 2022, an interdisciplinary European expert team published consensus-based guidelines  
5 suggesting that PET-CT and cerebral MRI should be both performed from stage IIC (32).

6 In the US, the American Academy of Dermatology (AAD) and the National Comprehensive  
7 Cancer Networks (NCCN) released guidelines in 2019 and 2023, respectively. The AAD  
8 proposed imaging from stage III but highlighted the importance of extensive and thorough  
9 anamnesis and physical examination for the lower stages to search for signs or symptoms of  
10 metastasis, in which cases imaging should be done for lower stages (33). For the initial staging,  
11 the NCCN recommended PET-CT from stage III, whereas brain imaging with MRI was only  
12 suggested from stage IIIB. For the follow-up, they recommended a brain MRI on asymptomatic  
13 patients only from stage IIIC (34).

14 Our study showed that the cumulative 5-years OS, MFS, and BMFS were poor in stages IIC, IIIC  
15 and IIID, highlighting the necessity of an early detection of brain metastases in these stages and  
16 the use of the most accurate radiological examination. These results support the European  
17 guidelines of ESMO and the interdisciplinary European Expert team, suggesting that brain MRI  
18 should be performed from stage IIC for the initial staging and the follow-up.

19 Melanoma stage IIC is classified as high risk since overall survival and recurrence-free survival  
20 are poor, especially compared to stage IIIA (35). Data suggests that adjuvant immunotherapy  
21 should be used in stage IIC as for stage III as it shows a significant improvement in distant  
22 metastases-free survival and a reduction of the risk of recurrence (36-38).

1 Studies about cumulative OS, MFS and BMFS by stage are highly diverse in terms of study  
2 population and treatment, and the comparison between the results should be interpreted carefully.  
3 A study comparing the survival rates for stage IIIA-IIID of AJCC 8<sup>th</sup> edition, the German central  
4 malignant melanoma registry and 2 studies from the European Organization for Research and  
5 Treatment of Cancer have rates comparable to our study except for AJCC 8<sup>th</sup> edition, compared  
6 to which they are poorer (39). A literature review by Michielin *et al.* analyzing the survival rates  
7 of stage IV melanoma patients treated with immunotherapy and targeted therapy found 5-year OS  
8 between 43% and 64% depending on prognostic factors and treatment, compared to 34% in the  
9 general population (40), these numbers are comparable to our study. When comparing with the  
10 American national cancer institute and the Netherland cancer registry, our study had better  
11 survival in all stages (41, 42).

12 Our study has several limitations. Since the radiological reports were analyzed between 01/2018  
13 and 12/2022, the patients presented at the skin tumor board in December 2022 could have  
14 benefited from PET-CT or brain MRI after the time limit of 31/12/2022. Therefore, the results in  
15 Table 1 could be slightly underestimated. All the data were retrospectively issued from patient  
16 records and could be incomplete. No statistical data about the size and the localization of brain  
17 metastases could be obtained because of the incompleteness of some radiological reports. Finally,  
18 Kaplan Meier curves can have unstable results due to the small number of patients in certain  
19 stages.

20 This study includes a higher percentage of men (approximately 60%), which is consistent with  
21 the current epidemiology. Several studies suggest that male sex is associated with an increased  
22 risk of developing melanoma and melanoma brain metastases (7, 43). These disparities are not

1 totally understood but the implication of gender related behavioral patterns as well as genetic and  
2 epigenetic aspects have been found (44).

3

#### 4 **Conclusion**

5 Despite the increasing performance of PET-CT, this study highlights the crucial role of brain  
6 MRI, which remains the most efficient diagnostic tool to detect cerebral metastases. Our results  
7 support the European guidelines suggesting that brain MRI should be performed on all patients  
8 with a diagnosis of stage IV melanoma but also on patients with high-risk melanoma from stage  
9 IIC for the initial staging and the follow-up, to exclude brain metastases.

10

#### 11 **References**

- 12 1. Ahmadi F, Karamitanha F, Ramezanzpour A. Clustering trends of melanoma incidence and  
13 mortality: A worldwide assessment from 1995 to 2019. *Australasian Journal of Dermatology*.  
14 2022.
- 15 2. Bulliard J-L PRG, Levi F. *Epidemiologie und Prävention des Hautmelanoms in der*  
16 *Schweiz: Update 2010*2010. 408-13 p.
- 17 3. System E-ECI. Estimates on cancer incidence and mortality in 2022, for all cancer sites  
18 2023 [Available from: <https://ecis.jrc.ec.europa.eu>].
- 19 4. Rastrelli M, Tropea S, Rossi CR, Alaibac M. Melanoma: epidemiology, risk factors,  
20 pathogenesis, diagnosis and classification. *In Vivo*. 2014;28(6):1005-11.
- 21 5. Longvert C, Saiag P. [Melanoma update]. *Rev Med Interne*. 2019;40(3):178-83.

- 1 6. Tichanek F, Forsti A, Hemminki A, Hemminki O, Hemminki K. Survival in melanoma in  
2 the nordic countries into the era of targeted and immunological therapies. *Eur J Cancer*.  
3 2023;186:133-41.
- 4 7. Tan XL, Le A, Tang H, Brown M, Scherrer E, Han J, et al. Burden and Risk Factors of  
5 Brain Metastases in Melanoma: A Systematic Literature Review. *Cancers (Basel)*. 2022;14(24).
- 6 8. Pfannenber C, Schwenzer N. [Whole-body staging of malignant melanoma: advantages,  
7 limitations and current importance of PET-CT, whole-body MRI and PET-MRI]. *Radiologe*.  
8 2015;55(2):120-6.
- 9 9. Danielsen M, Hojgaard L, Kjaer A, Fischer BM. Positron emission tomography in the  
10 follow-up of cutaneous malignant melanoma patients: a systematic review. *Am J Nucl Med Mol*  
11 *Imaging*. 2013;4(1):17-28.
- 12 10. Arrangoiz R, Papavasiliou P, Stransky CA, Yu JQ, Tianyu L, Sigurdson ER, et al.  
13 Preoperative FDG-PET/CT Is an Important Tool in the Management of Patients with Thick (T4)  
14 Melanoma. *Dermatol Res Pract*. 2012;2012:614349.
- 15 11. Kitajima K, Nakamoto Y, Okizuka H, Onishi Y, Senda M, Suganuma N, et al. Accuracy  
16 of whole-body FDG-PET/CT for detecting brain metastases from non-central nervous system  
17 tumors. *Ann Nucl Med*. 2008;22(7):595-602.
- 18 12. Galldiks N, Langen KJ, Albert NL, Chamberlain M, Soffiatti R, Kim MM, et al. PET  
19 imaging in patients with brain metastasis-report of the RANO/PET group. *Neuro Oncol*.  
20 2019;21(5):585-95.
- 21 13. Oldan JD, Glaubiger SA, Khandani AH, Jewells VL. Detectable size of melanoma  
22 metastases to brain on PET/CT. *Ann Nucl Med*. 2020;34(8):545-8.
- 23 14. Webb HR, Latifi HR, Griffeth LK. Utility of whole-body (head-to-toe) PET/CT in the  
24 evaluation of melanoma and sarcoma patients. *Nucl Med Commun*. 2018;39(1):68-73.

- 1 15. Tasdemir B, Dostbil Z, Inal A, Unal K, Yildirim S, Simsek FS. Evaluation of clinical  
2 contributions provided by addition of the brain, calvarium, and scalp to the limited whole body  
3 imaging area in FDG-PET/CT tumor imaging. *Biomed Res Int.* 2014;2014:129683.
- 4 16. Pope WB. Brain metastases: neuroimaging. *Handb Clin Neurol.* 2018;149:89-112.
- 5 17. Galldiks N, Lohmann P, Albert NL, Tonn JC, Langen KJ. Current status of PET imaging  
6 in neuro-oncology. *Neurooncol Adv.* 2019;1(1):vdz010.
- 7 18. Chen W. Clinical applications of PET in brain tumors. *J Nucl Med.* 2007;48(9):1468-81.
- 8 19. Tischler V, Calton T, Williams M, Cheetham A. Patient anxiety in magnetic resonance  
9 imaging centres: Is further intervention needed? *Radiography.* 2008;14(3):265-6.
- 10 20. Hudson DM, Heales C, Meertens R. Review of claustrophobia incidence in MRI: A  
11 service evaluation of current rates across a multi-centre service. *Radiography (Lond).*  
12 2022;28(3):780-7.
- 13 21. Ghadimi M, Sapra A. Magnetic Resonance Imaging Contraindications. StatPearls.  
14 Treasure Island (FL)2023.
- 15 22. Galldiks N, Kocher M, Ceccon G, Werner JM, Brunn A, Deckert M, et al. Imaging  
16 challenges of immunotherapy and targeted therapy in patients with brain metastases: response,  
17 progression, and pseudoprogression. *Neuro Oncol.* 2020;22(1):17-30.
- 18 23. Langen KJ, Galldiks N, Hattingen E, Shah NJ. Advances in neuro-oncology imaging. *Nat*  
19 *Rev Neurol.* 2017;13(5):279-89.
- 20 24. American Joint Committee On C, Amin MB, Edge SB, Greene FL, American Joint  
21 Committee on C. *AJCC cancer staging manual. Eighth edition ed.* New York: Springer; 2017.  
22 xvii, 1032 pages : illustrations (black and white, and colour) p.

- 1 25. Ludwig V, Komori T, Kolb D, Martin WH, Sandler MP, Delbeke D. Cerebral lesions  
2 incidentally detected on 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography images  
3 of patients evaluated for body malignancies. *Mol Imaging Biol.* 2002;4(5):359-62.
- 4 26. Manohar K, Bhattacharya A, Mittal BR. Low positive yield from routine inclusion of the  
5 brain in whole-body 18F-FDG PET/CT imaging for noncerebral malignancies: results from a  
6 large population study. *Nucl Med Commun.* 2013;34(6):540-3.
- 7 27. Niederkohr RD, Rosenberg J, Shabo G, Quon A. Clinical value of including the head and  
8 lower extremities in 18F-FDG PET/CT imaging for patients with malignant melanoma. *Nucl*  
9 *Med Commun.* 2007;28(9):688-95.
- 10 28. Salvatore B, Caprio MG, Fonti R, D'Amico D, Fraioli F, Salvatore M, et al. Is 2-deoxy-2-  
11 [(18F)]fluoro-D-glucose PET/CT acquisition from the upper thigh to the vertex of skull useful in  
12 oncological patients? *Transl Med UniSa.* 2015;11:34-8.
- 13 29. Rohren EM, Provenzale JM, Barboriak DP, Coleman RE. Screening for cerebral  
14 metastases with FDG PET in patients undergoing whole-body staging of non-central nervous  
15 system malignancy. *Radiology.* 2003;226(1):181-7.
- 16 30. Hjorthaug K, Hojbjerg JA, Knap MM, Tietze A, Haraldsen A, Zacho HD, et al. Accuracy  
17 of 18F-FDG PET-CT in triaging lung cancer patients with suspected brain metastases for MRI.  
18 *Nucl Med Commun.* 2015;36(11):1084-90.
- 19 31. Michielin O, van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U,  
20 [clinicalguidelines@esmo.org](mailto:clinicalguidelines@esmo.org) EGCEa. Cutaneous melanoma: ESMO Clinical Practice Guidelines  
21 for diagnosis, treatment and follow-up dagger. *Ann Oncol.* 2019;30(12):1884-901.
- 22 32. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguín N, et al.  
23 European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics: Update  
24 2022. *Eur J Cancer.* 2022;170:236-55.

- 1 33. Swetter SM, Tsao H, Bichakjian CK, Curiel-Lewandrowski C, Elder DE, Gershenwald  
2 JE, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad*  
3 *Dermatol.* 2019;80(1):208-50.
- 4 34. Network NCC. NCCN Guidelines Version 3.2023 Melanoma: Cutaneous 2023 [Available  
5 from: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492>.
- 6 35. Kanaki T, Stang A, Gutzmer R, Zimmer L, Chorti E, Sucker A, et al. Impact of American  
7 Joint Committee on Cancer 8th edition classification on staging and survival of patients with  
8 melanoma. *Eur J Cancer.* 2019;119:18-29.
- 9 36. Long GV, Luke JJ, Khattak MA, de la Cruz Merino L, Del Vecchio M, Rutkowski P, et  
10 al. Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma  
11 (KEYNOTE-716): distant metastasis-free survival results of a multicentre, double-blind,  
12 randomised, phase 3 trial. *Lancet Oncol.* 2022;23(11):1378-88.
- 13 37. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, et al.  
14 European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update  
15 2022. *Eur J Cancer.* 2022;170:256-84.
- 16 38. Garbe C, Keim U, Amaral T, Berking C, Eigentler TK, Flatz L, et al. Prognosis of  
17 Patients With Primary Melanoma Stage I and II According to American Joint Committee on  
18 Cancer Version 8 Validated in Two Independent Cohorts: Implications for Adjuvant Treatment. *J*  
19 *Clin Oncol.* 2022;40(32):3741-9.
- 20 39. Garbe C, Keim U, Suci S, Amaral T, Eigentler TK, Gesierich A, et al. Prognosis of  
21 Patients With Stage III Melanoma According to American Joint Committee on Cancer Version 8:  
22 A Reassessment on the Basis of 3 Independent Stage III Melanoma Cohorts. *J Clin Oncol.*  
23 2020;38(22):2543-51.

- 1 40. Michielin O, Atkins MB, Koon HB, Dummer R, Ascierto PA. Evolving impact of long-  
2 term survival results on metastatic melanoma treatment. *J Immunother Cancer*. 2020;8(2).
- 3 41. U. S. National Institutes of Health NCI. Five-Year Survival Rates [Available from:  
4 <https://training.seer.cancer.gov/melanoma/intro/survival.html>].
- 5 42. Leeneman B, Schreuder K, Uyl-de Groot CA, van Akkooi ACJ, Haanen J, Wakkee M, et  
6 al. Stage-specific trends in incidence and survival of cutaneous melanoma in the Netherlands  
7 (2003-2018): A nationwide population-based study. *Eur J Cancer*. 2021;154:111-9.
- 8 43. Diaz MJ, Mark I, Rodriguez D, Gelman B, Tran JT, Kleinberg G, et al. Melanoma Brain  
9 Metastases: A Systematic Review of Opportunities for Earlier Detection, Diagnosis, and  
10 Treatment. *Life (Basel)*. 2023;13(3).
- 11 44. Bellenghi M, Puglisi R, Pontecorvi G, De Feo A, Care A, Mattia G. Sex and Gender  
12 Disparities in Melanoma. *Cancers (Basel)*. 2020;12(7).

### 13 **Figure legends**

14 **Figure 1** - Discrepancy between PET-CT and cerebral MRI in detection of brain metastases.

15 **Figure 2** - Kaplan-Meier plot of cumulative overall survival (a), cumulative metastasis-free  
16 survival (b) and cumulative brain metastasis-free survival (c) in the first 5 years by tumor stage at  
17 initial diagnosis.

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1 **Table 1** - Distribution of melanoma patients examined through PET-CT / MRI per stage (AJCC  
 2 8<sup>th</sup> Edition 2017).

	Latest/highest stage												P*	
	IIC		IIIA		IIIB		IIIC		IIID		IV			
	N=2 4	%	N=3 1	%	N=6 5	%	N=8 3	%	N=1 0	%	N=17 9	%		
PET-CT	No	0	0.0%	4	12.9%	4	6.2%	4	4.8%	0	0.0%	10	5.6%	0.49
	Yes	24	100.0%	27	87.1%	61	93.8%	79	95.2%	11	100.0%	169	94.4%	
MRI	No	15	62.5%	25	80.6%	39	60.0%	32	38.6%	2	18.2%	33	18.4%	<0.001
	Yes	9	37.5%	6	19.4%	26	40.0%	51	61.4%	9	81.8%	146	81.6%	

3 \* Pearson's X<sup>2</sup> test

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1 **Table 2** - Overall survival, metastasis-free survival and brain metastasis free survival estimates in  
 2 the first 5 years, in total and by tumor stage at diagnosis.

	N*	Cumulative survival (95% CI)		P**
		3 years	5 years	
OS	383	59, 77.7% (72.6-83.0)	71, 69.4% (63.2-76.1)	
Stage <IIC	91	86.7% (79.7-94.4)	81.9% (73.5-91.1)	<0.001
Stage IIC	42	76.9% (60.5-97.7)	57.7% (36.2-91.9)	
Stage IIIA	29	90.9% (75.4-100.0)	79.5% (57.7-100.0)	
Stage IIIB	57	77.2% (63.6-93.7)	72.0% (56.9-91.2)	
Stage IIIC	95	74.2% (63.5-86.6)	63.9% (48.6-83.9)	
Stage IIID	11	50.0% (12.5-100.0)	-	
Stage IV	55	60.0% (46.0-78.2)	42.0% (25.9-68.2)	
MFS	328	68.2% (62.2-74.8)	53.1% (45.9-61.5)	
Stage <IIC	91	70.8% (61.8-81.2)	53.9% (43.8-66.4)	0.007
Stage IIC	42	47.8% (30.0-76.1)	47.8% (30.0-76.1)	
Stage IIIA	29	100% (nc)	75.0% (42.6-100.0)	
Stage IIIB	57	74.1% (61.5-89.2)	60.3% (42.8-85.0)	
Stage IIIC	95	63.5% (51.3-78.6)	43.0% (27.5-67.2)	
Stage IIID	11	47.6% (18.8-100.0)	-	
Stage IV	55	60.0% (46.0-78.2)	42.0% (25.9-68.2)	
BMFS	328	91.9% (88.3-95.6)	84.7% (79.0-90.9)	
Stage <IIC	91	95.1% (90.6-99.9)	87.3% (79.7-95.5)	0.005
Stage IIC	42	82.4% (66.1-100.0)	72.1% (51.2-100.0)	
Stage IIIA	29	100% (nc)	100% (nc)	
Stage IIIB	57	95.4% (89.3-100.0)	84.8% (66.7-100.0)	
Stage IIIC	95	85.9% (76.5-96.5)	80.5% (67.8-95.6)	
Stage IIID	11	71.4% (44.7-100.0)	-	
Stage IV	55	60.0% (46.0-78.2)	42.0% (25.9-68.2)	

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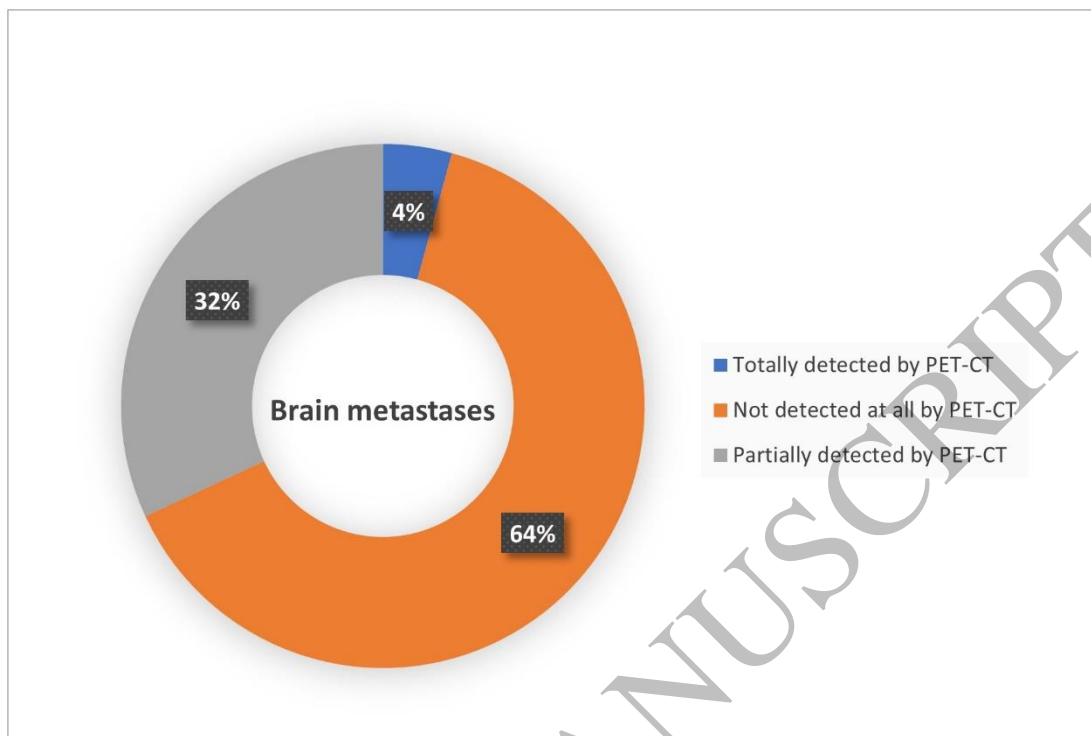
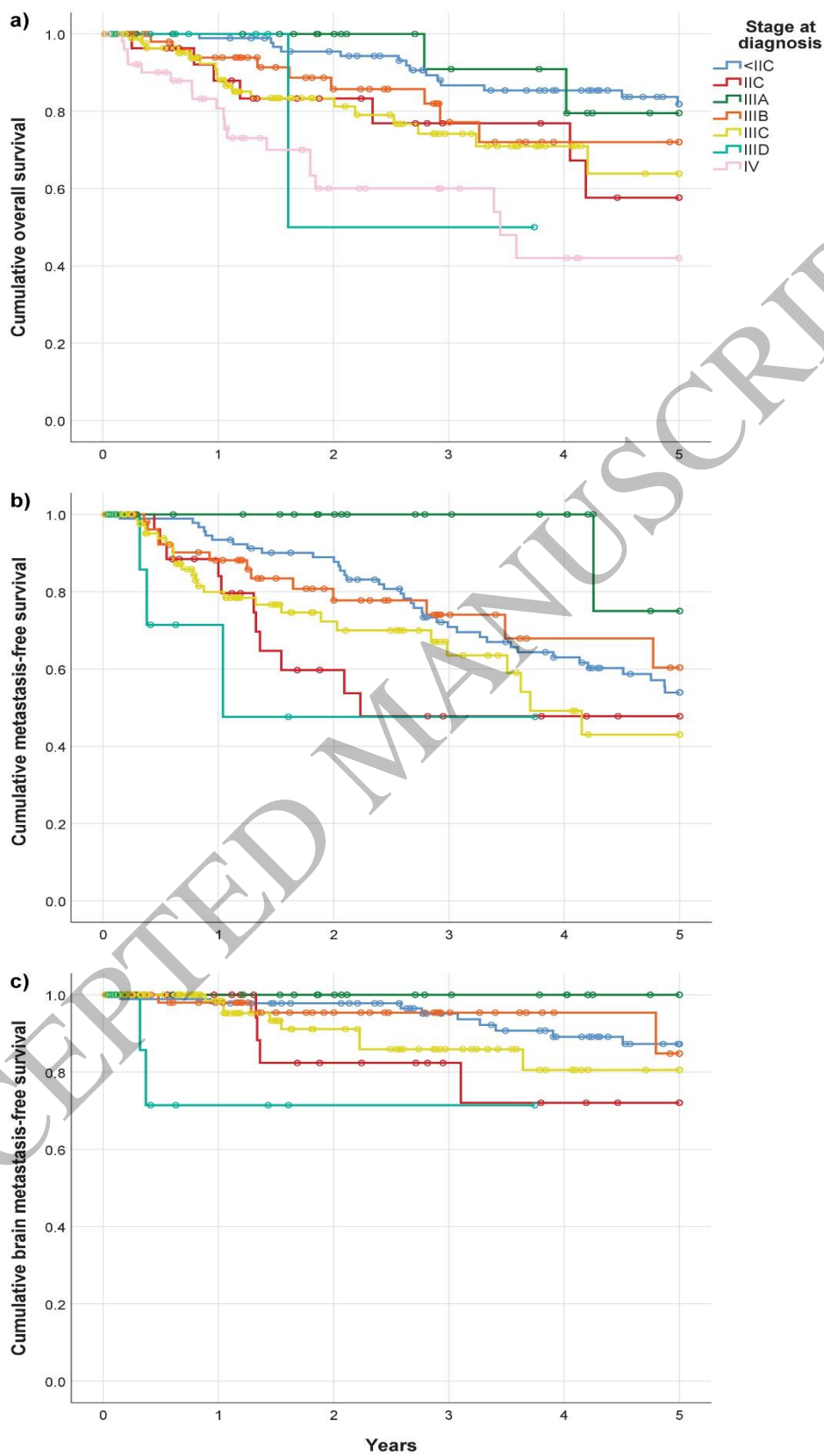


Figure 1  
145x97 mm (DPI)

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3  
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ACCEPTED MANUSCRIPT



1  
2  
3

Figure 2  
123x247 mm (DPI)