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

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What is already known about this topic?

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

What does this study add?

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

Abstract

Background

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

Objective

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

Methods

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

Results

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

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

Conclusion

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

Introduction

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

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

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

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

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

Material and Methods

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

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

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

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

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

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

Results

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

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

66 patients were diagnosed with brain metastases (41 males), median age 63.4 years (IQR 50.5-75.0). Breslow index at diagnosis was available for 48 out of 66 patients with a median Breslow index of 2.7 mm (IQR 1.6-4.5). By analyzing the initial stage (AJCC 2017) at the first diagnosis of melanoma of the patients presenting brain metastases, 7 patients were in stage I (10.6%), 16 in 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 in IV (37.9%).

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

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Figure legends

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

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

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

		Latest/highest stage												P*
		IIC		IIIA		IIIB		IIIC		IIID		IV		
		N=24	%	N=31	%	N=65	%	N=83	%	N=10	%	N=179	%	
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%	

* Pearson's X^2 test

Table 2 - Overall survival, metastasis-free survival and brain metastasis free survival estimates in 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)	-	
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)	-	

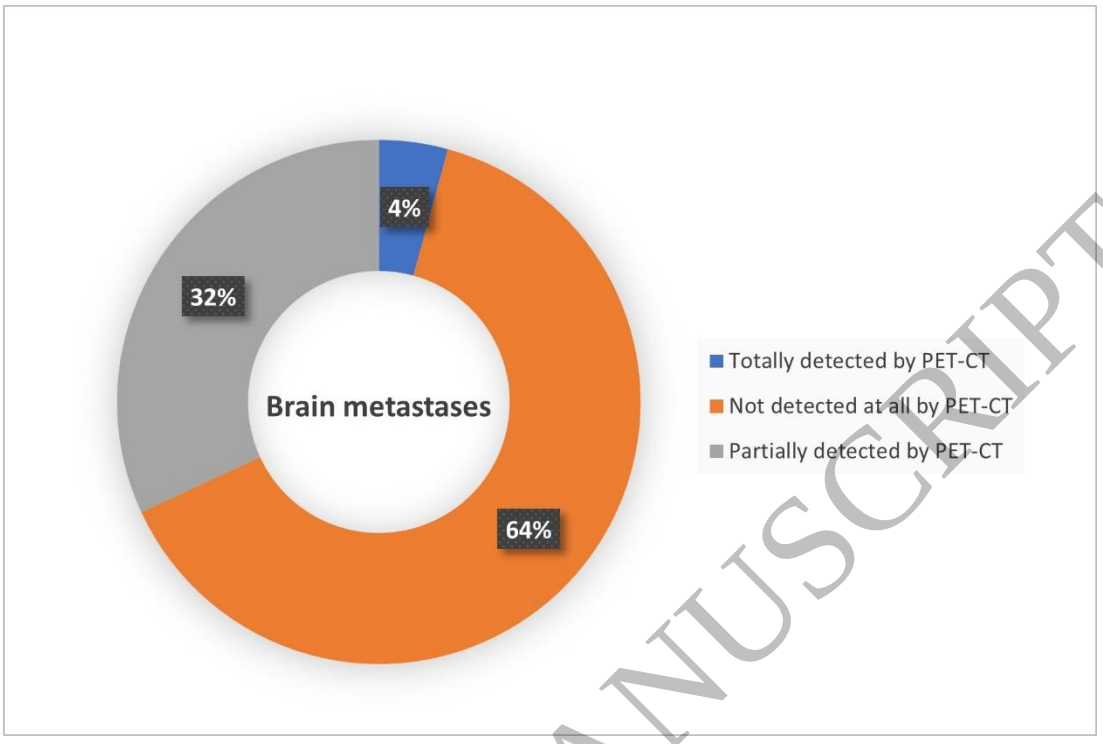

Figure 1
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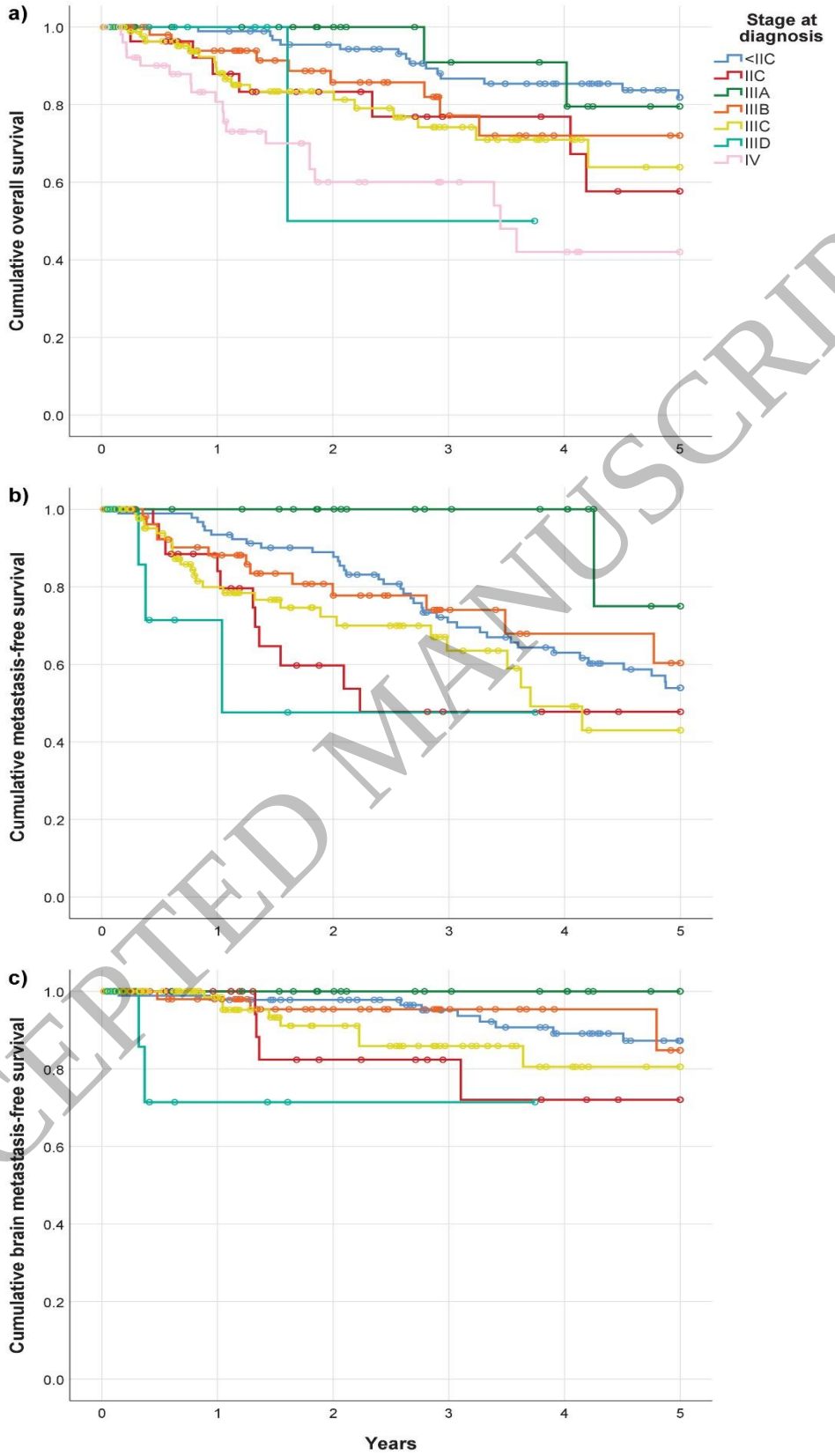

Figure 2
123x247 mm (DPI)