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Surgical treatment of cerebellar metastases in elderly patients: A threshold that moves forward?

Stefano Telera [a,*], Roberto Gazzeri [b], Veronica Villani [c], Laura Raus [a], Francesca Romana Giordano [d], Alessandra Costantino [d], Catia Pompea Delfinis [a], Francesca Piludu [e], Isabella Sperduti [f], Andrea Pace [c]

[a] UOSD Neurosurgery, IRCCS National Cancer Institute Regina Elena, Rome, Italy
[b] UOSD Pain Therapy, San Giovanni Addolorata Hospital, Rome, Italy
[c] UOSD Neuro-Oncology, IRCCS National Cancer Institute Regina Elena, Rome, Italy
[d] UOC Anesthesia and Intensive Care, IRCCS National Cancer Institute Regina Elena, Rome, Italy
[e] UOC Radiology and Diagnostic Imaging, IRCCS National Cancer Institute Regina Elena, Rome, Italy
[f] UOC Biostatistics, IRCCS National Cancer Institute Regina Elena, Rome, Italy

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ABSTRACT

The impact of surgery for cerebellar brain metastases in elderly population has been the object of limited studies in literature. Given the increasing burden of their chronic illnesses, the decision to recommend surgery remains difficult.

All patients aged ≥65 years, who underwent surgical resection of a cerebellar brain metastasis from May 2000 and May 2021 at IRCCS National Cancer Institute "Regina Elena", were analyzed. The study cohort includes 48 patients with a mean age of 70.8 years. 7 patients belonged to the II Class according to the RPA classification, 41 to the III Class; the median GPA classification was 1.5. Median pre-operative and post-operative KPS was 60. Median Charlson Comorbidity Index (CCI) was 11; median 5-variable modified Frailty Index was 2. Overall, 14 patients (29%) presented perioperative neurologic and systemic complications. 34 patients (71%) were able to perform adjuvant therapies as RT and/or CHT after surgery. A higher CCI predicted complications occurrence ($p = 0.044$), while significant factors for a post-operative KPS ≥70, were i) hemispheric location of the metastasis, ii) higher pre-operative KPS, iii) RPA II classification. Median Overall Survival was 7 months. A post-operative KPS <70 ($p = 0.004$) and a short time interval between diagnosis of the primary tumor and cerebellar metastasis appearance, were predictive for a worse outcome ($p = 0.012$). Our study suggests that selected elderly patients with cerebellar metastases may benefit from microsurgery to continue their adjuvant therapies, although a high complications rate should be taken in account.

1. Introduction

Brain Metastases occur in 10–40% of cancer patients and their incidence have progressively increased over the years in relation to the improved diagnosis of neoplastic diseases, advancements in therapy and aging of the population, at least in developed countries.[1–7]

Current treatments for brain metastases include surgery, stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT) and to a lesser extent, chemotherapy and target therapies. The combination of longer life expectancy of the general population, the higher incidence of cancer in elderly and the extended survival afforded by modern antiblastic therapies, have also led to an increase volume of older patients requiring surgical evaluation for brain metastatic lesions.[1,7,8]

The United Nations have defined people aged older than 60 years as *older people*, and people aged older than 80 years as *oldest-old.* However, the definition of elderness remains unclear: traditionally subjects older than 65 years are considered elderly, although significant differences can be recognized among such patients.[6,8,9]

The impact of surgery for brain metastases in this population, which carry an increasing burden of chronic illnesses and cognitive dysfunctions, has been the object of limited studies in the literature and given the lack of unquestionable evidences about perioperative morbidity and

* Corresponding author. Neurosurgery, IRCCS National Cancer Institute Regina Elena , Rome, Italy.
E-mail address: stefano.telera@ifo.it (S. Telera).

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mortality, the decision to recommend surgery remains difficult.[2,6,8]

In this setting, cerebellar metastases, which represent about 20% of all surgically treated brain metastases, appear poorly tolerated due to intracranial hypertension, brain stem compression, tonsillar or upward herniation of the cerebellar tissue and hydrocephalus. Such lesions, although generally considered to portend a poorer prognosis and to be associated to a higher risk of complications, than those in the supratentorial compartment, often require urgent surgical decision, even in older patients.[4,6,9–13]

The aim of this study is to retrospectively analyze the inpatient mortality and post-operative complications trends in a series of elderly patients (≥65 years), submitted to surgical resection of cerebellar brain metastases and to compare our findings to those available in the literature, which include subjects of all ages.

2. Materials and methods

All patients aged ≥65 years, who underwent surgical resection of a cerebellar brain metastasis, from May 2000 and May 2021 at the Neurosurgical Department of IRCCS National Cancer Institute "Regina Elena", were analyzed.

Surgery was considered in symptomatic lesions, due to mass effect, significant perilesional edema or hydrocephalus ≥2 cm in size and in asymptomatic lesions ≥3 cm in size.

Independent patient variables examined included i) patient's age (divided in ≥65 and < 75 years; and ≥75 years of age); ii) sex; iii) histology of the primary tumor; iv) time elapsed between cerebellar metastasis appearance and primary tumor diagnosis; v) anatomic location (vermian-paramedian vs hemispheric); vi) size and number of brain metastases (patients with hydrocephalus or cystic tumors were not analyzed differently); vii) Gross Total Resection Rate (GRT) vs Subtotal Resection Rate (SRR); viii) Recursive Partitioning Analysis (RPA) Score; ix) Graded Prognostics Assessment (GPA) Score; x) 5-variable modified Frailty Index (mFI-5); xi) Charlson Comorbidity Index (CCI); xii) preoperative Karnofsky Perfomance Status (KPS) after glucorticoid therapy was introduced; xiii) post-operative KPS; xiv) Clavien Dindo Complication Classification, xv) Overall Survival (OS) after surgery.

Risk stratification scores have been devised to guide treatment strategies. Among them, the Recursive Partition Analyses (RPA) and the Graded Prognostic Assessment (GPA) have been introduced to predict survival in cancer patients with brain metastases, based on objective and easily measurable parameters such as i) age, ii) KPS, iii) controlled disease for RPA and i) age, ii) KPS, iii) number of cerebral lesions and iv) presence of extracranial lesions for GPA.[14–16]

The CCI provides a score accounting for the age of the patients plus 16 medical comorbidities (3 of them stratified, according to their severity). The total score ranges from 0 to 37. The mFI-5, based on few variables that are easily retrieved in the clinical setting, provides an objective measurement of patient's frailty with a low interobserver variability. It stratifies patients on a scale from 0 (not frail) to 5 (maximum frailty) on the basis of the presence of five comorbidities (Table 1).[17–20]

Functional outcomes were assessed using post-operative KPS score, evaluated within 4 weeks from surgery to balance the effects of recent surgery on one side, and of disease progression locally or systemically, chemotherapy or radiation therapy on the other side.

In all patients, except those with neurologic complications, steroid therapy was progressively tapered and suspended within 3 weeks after surgery.

The resection grade was determined by intraoperative judgment of the surgical team and intraoperative echography, or early post-operative contrast enhanced MRI and/or CT scans (within 48 h from surgery). Gross total resection (GTR) was defined as no visible residual tumor, as opposed to subtotal resection (STR).[21,22]

The study was approved by the Ethic Committee of our Institution (number 1635/21) and informed consent were waived due to the retrospective nature of the study.

Table 1

Charlson Comorbidity Index (CCI)		**5 variable modified Frailty Index (mFI-5)**	
Comorbidity	**Score**	**Frailty**	**Score**
Miocardial Infarction	1	Diabetes Mellitus	1
Congestive Hearth Failure	1		
Peripheral Vascular Disease	1	Increased blood pressure requiring medication	1
Cerebrovascular Disease	1		
Dementia	1	Status (non-independent functional status)	1
Chronic Obstructive Pulmonary Disease	1		
Connective tissue disease	1	Respiratory Pathology (history of COPD or pneumonia)	1
Peptic ulcer	1		
Diabetes	not complicated = 1 complicated = 2	Failure of hearth (congestive heart failure within 30 days	1
Renal Disease	2		
Paralysis	2		
Leukemia	2		
Lymphoma	2		
Solid Tumor	localized = 1 metastatic = 6		
Liver disease	mild = 1 severe = 3		
AIDS	6		
Age	0-40 = 0 41-50 = 1 51-60 = 2 61-70 = 3 >70 = 4		

3. Statistical analysis

Descriptive statistics was used to summarize pertinent study information. Associations between categorical variables were analyzed according to the Pearson chi square test or Fisher exact test, when appropriate. The impact of the different analyzed variables on complications occurrence, post-operative KPS and Overall Survival was evaluated using the logistic regression and Cox regression model. The Odds Ratio (OR), Hazard Ratio (HR) and the 95% Confidence Interval (95% CI) were estimated for significant variables at univariate analysis. A multivariant logistic regression and proportional hazard model were developed using stepwise regression (forward selection, enter limit and remove limit, $p = 0.10$ and $p = 0.15$, respectively), to identify independent predictors of outcomes, considering the variables significant at univariate analysis. The assessment of interactions between significant investigational variables was taken into account when developing the multivariate model.

The receiver operating characteristics (ROC) was applied to the continuous variable in order to estimate the most appropriate cut-off value, able to split patients into groups with different outcome probabilities.

The SPSS (version 21.0; SPSS, Inc., Chicago, IL), a licensed statistical program was used for all analyses.

4. Results

From May 2000 to May 2021, 48 patients ≥65 years of age, affected by cerebellar metastases from solid tumors were operated upon at the Neurosurgical Department of the National Cancer Institute "Regina Elena".

The patients included 27 males (56.3%) and 21 females (43.8%) with a mean age of 70.8 years ± 4.6 years. 39 patients aged ≥65 and < 75 years (81.3%); 9 aged ≥75 years (18.8%). Primary tumors were: non-

small cell lung carcinoma (NSCLS) 20 cases; breast carcinoma 9 cases; colorectal carcinoma 8 cases; ovarian carcinoma 2 cases; kidney carcinoma 2 cases; melanoma 2 cases; bladder tumor 2 cases; salivary glands 1 case; gastric carcinoma 1 case; uterine carcinoma 1 case. In 10 cases (21%) the metastases were synchronous with the discovery of the primary tumor. In 38 cases they were metachronous with a median time between primary tumor diagnosis and cerebellar metastases appearance of 26 months (range 3–324 months). The main symptoms complained by the patients were ataxia and gait disturbances (45% of the cases); dysmetria and adiadochokynesia (21%); nausea (17%); vertigo and dizziness (15%); headache (15%); altered mental status (6%). No symptoms were observed in 4 patients (8%).

All patients had been assessed with total body and/or PET CT scan, brain MRI and any other investigation that might help stage the disease and in six cases the presence of other small supratentorial metastases, amenable to SRS treatment, were diagnosed preoperatively. A preoperative symptomatic hydrocephalus was observed in 3 patients (6%).

The median size of the operated cerebellar metastases was 3 cm (range 2–6 cm; larger diameter).

As far as the anatomic location is concerned, in 39 cases the cerebellar metastasis was categorized as hemispheric (81.3%), in 9 cases as vermian-paramedian (18.7%).

A standard suboccipital craniotomy or craniectomy, in the prone position (46 cases) or the occipital trans-tentorial approach (2 cases) were employed. All the patients but two, were reported to have a GTR of their lesions. The resection grade was determined by intraoperative judgment of the surgical team and intraoperative echography in 7 cases (before 2003), early post-operative contrast enhanced CT scan in 28 cases and/or MRI scans in 13 cases (after 2003) (Figs. 1 and 2).

7 patients belonged to the II Class according to the RPA classification, 41 to the III Class.

The median GPA classification of the patients was 1.5 (range 0.5–2.5).

Median pre-operative KPS, evaluated after glucorticoid therapy was introduced for at least 24 h, was 60 (range 20–80), median post-operative KPS was 60 (30–90). Post-operatively, KPS improved in 31 patients (64.6%), remained stable in 12 (25%) and deteriorated in 5 (10.4%).

Median length of stay in the hospital (LOS) was 9 days (5–90 days).

The median CCI was 11 (range 9–14); the median mFI-5 was 2 (range 1–4) (Table 2).

4.1. Post-operative complication and mortality

Overall, 14 patients out of 48 (29%) presented perioperative complications. Some patients presented more than one complication: 7 cases of post-operative hematoma in the surgical cavity requiring reoperation (all of them with lesions $\geq$ 3 cm of diameter), 4 cases of acute hydrocephalus requiring an external ventricular drainage (DVE), 4 cases of CSF fistula all of them resolved with lumbar drainage; one case of wound infection requiring revision surgery, 2 cases of lung infection, one case of urinary infection, one case of melaena due to a bleeding metastasis of the rectum (Fig. 3). According to Clavier Dindo Classification 1 patient belonged to Grade V, seven patients to Grade IV, 3 patients to Grade III and 3 patients to Grade II.

Patients with complications presented a median CCI of 12 (range 10–14) and a median mFI-5 of 2 (range 1–4). Based on the ROC curve analysis a threshold score of CCI >10, was associated to an increased complication risk. 38.7% of the patients with post-operative complications presented a CCI >10 vs 11.8% with a CCI $\leq$10 (p 0 0.05).

Perioperative mortality (within 3 months from surgery) included 11 patients (23%), 5 of them died as a direct consequence of post-operative complications, 6 due to progressive metastatic disease or systemic complications.

34 patients (71%) were able to perform adjuvant therapies as RT and/or CHT after surgery.

At univariate and multivariate analysis, the only significant factor which predicted complications occurrence was a higher CCI ($p = 0.044$) (Table 3).

At univariate analysis, significant factors for a post-operative KPS $\geq$70, were i) the hemispheric location of the metastasis, ii) a higher preoperative KPS, iii) a higher GPA classification and iv) a RPA II classification. All of them, except a higher GPA classification, remained significant at multivariate analysis. As far as RPA classification is concerned, all 7 patients with a preoperative RPA II classification presented a post-operative KPS $\geq$70, therefore the odds ratio was not calculated (Table 4).

4.2. Follow up and overall survival

The median follow-up in 48 patients was 6 months (range 1–120 months). Median Overall Survival was 7 months (CI 5.4–8.6). 3 patients were still alive at the last follow-up; the 1-year survival rate was 24%, the 2-year survival rate 13.5%.

The cohort of patients has been further divided in two subgroups since molecular target and immune-therapies significantly came in to use in our Institute after 2010. However, we did not find significative differences as far as OS is concerned: between 2000 and 2010, the OS in 30 patients was 7 months (CI 95% 4.3–9.7), while between 2011 and 2020, the OS in 18 patients was 6 months (CI 95% 3.5–8.5, $p = 0.39$). Median

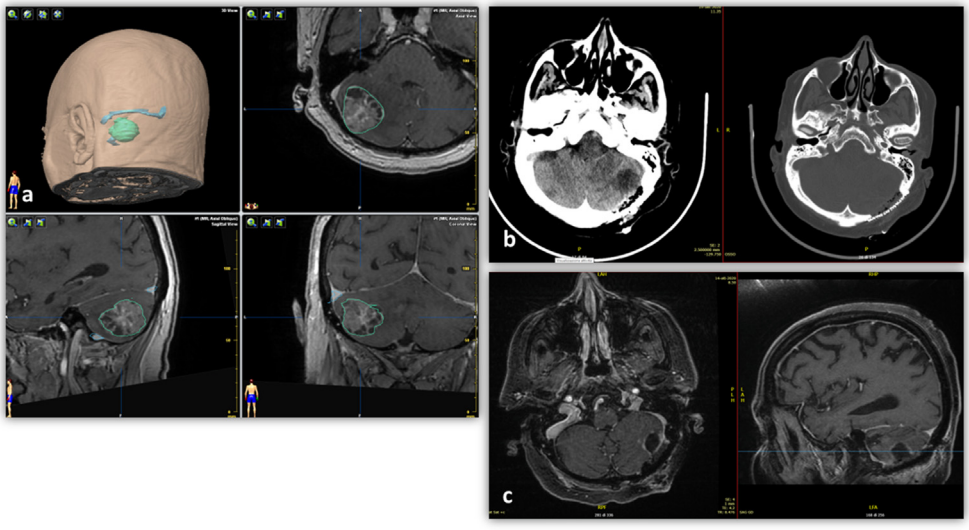

Fig. 1. a: 3D reconstruction and axial, sagittal and coronal T1 weighted MR images with Gadolinium of a large hemispheric right cerebellar metastasis in an 80-year-old female affected by ovarian cancer (RPA Class III, GPA score 1). **b:** post-operative axial CT scan with contrast showing an apparent complete removal of the lesion. **c:** axial and sagittal T1 weighted MR images with Gadolinium after SRS treatment, 4 weeks after surgery demonstrating local disease control. The patient died 8 months after surgery due to progressive systemic disease.

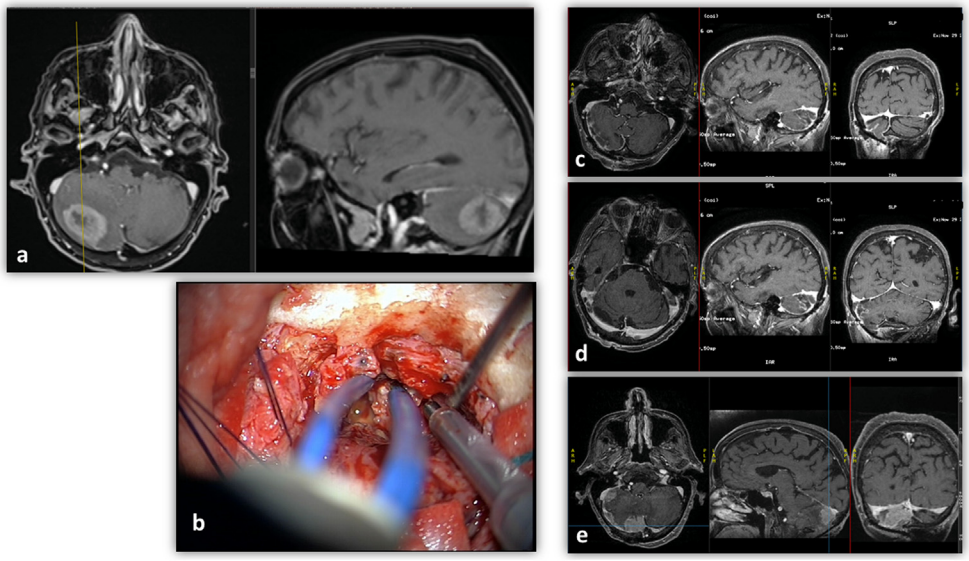

Fig. 2. a: axial and sagittal T1 weighted MR images with Gadolinium of a hemispheric right cerebellar metastasis in an 82-year-old female affected by breast cancer (RPA Class III, GPA score 2). **b:** intraoperative image during tumor removal. **c:** post-operative T1 weighted MR images with Gadolinium, demonstrating complete removal of the lesion. **d:** post-operative T1 weighted MR images at seven months after surgery showing a significant recurrent lesion with involvement of the cerebellar-pontine angle. The patient died 8 months after surgery due to local disease progression.

Table 2
Summary of the demographic and clinical characteristics of the cohort of patients.

Operated patients	48
Median Age	70.8 Years
≥ 65 yrs < 75 yrs	39 (81.3%)
≥ 75 yrs	9 (18.8%)
Sex	
Male	27 (56.3%)
Female	21 (43.8%)
Primary Tumor	
lung	20
breast	9
colorectal	8
ovarian	2
kidney	2
melanoma	2
bladder	2
salivary glands	1
gastric	1
uterus	1
Metachronous metastases	38
Synchronous metastases	10
Median Tumor Size	3 cm (2–6 cm)
Tumor location	
Emispheric	39 (81.3%)
Vermis-Paramedian	9 (18.8%)
RPA Score	
II	7 (14.6%)
III	41 (85.4%)
Median GPA Score	1.5 (0.5–2.5)
Median pre-operative KPS	60 (20–80)
Median post-operative KPS	60 (30–90)
Median Lenght of Stay	9 days (5–90)
Median Charlson Comorbidity Index	11 (9–14)
Median 5-variable mFI	2 (1–4)

Survival in the last 5 years was 6 months (CI 95% 3–9 months).

At univariate OS analysis, significant negative factors included the male sex of the patient ($p = 0.032$), the occurrence of complications ($p = 0.039$), the post-operative KPS <70 ($p = 0.005$) and a short time interval between diagnosis of the primary tumor and cerebellar metastasis appearance ($p = 0.015$).

At multivariate analysis, only a post-operative KPS <70 ($p = 0.004$) and a short time interval between diagnosis of the primary tumor and cerebellar metastasis appearance, remained significantly predictive for a worse outcome ($p = 0.012$) (Table 5).

5. Discussion

At present, more than 25% of the patients with brain metastases from solid tumors, are older than 65 years. Besides, there are clinical observations indicating that frequency of brain metastases tends to increase with age.[1,2]

The post-operative outcomes after surgery for brain metastases in elderly population has been seldom reported in literature in the past, and only recently the topic has gained more interest, due to the increased number of cancer patients requiring neurosurgical advice at this age.[1,2,6,8]

In epidemiological studies a mortality rate between 4% and 18% and a significant association between comorbidity burden and survival have been reported in patients ≥65 years old.[2,6,23–25] Compared with supratentorial tumors, infratentorial ones were almost 1.5 times more likely to have complications.[26,27] Recently Proescholdt et al compared the results of surgery and adjuvant therapies between 325 older (≥65 years) and 492 younger patients showing that median survival after brain metastases resection differed significantly: 5.81 vs 8.12 months. In both groups patients who received postoperative systemic treatment showed significantly longer overall survival. However, elderly patients less frequently received systemic treatment unless they presented a higher postsurgical KPS score. Only in patients receiving also systemic treatment, age was no longer a negative prognostic factor.[1] Frati et al also analyzed two cohort of patients affected by cerebral metastases: the first included 135 patients <45 years old (20% of them with cerebellar metastases); the second 174 patients >70 years old (17.2% of them with cerebellar metastases). Notably, they did not observe significant differences between the two groups in term of post-operative KPS and complications (5.5% of patients presented complications). The preoperative KPS score was an important predictor of the post-operative functional status and of the patients' access to further adjuvant treatments, regardless of their age.[8]

Cognitive impairment, although often unrecognized, is also common in elderly patients and should be taken in to account in selecting surgery. In different epidemiologic surveys, the prevalence of cognitive impairment or dementia in elderly patients over 65 years of age was reported between 23% and 50% and some reports have showed that such impairments may also contribute to increased post-operative morbidity, post-operative cognitive dysfunction (PND) and mortality.

Therefore, it has been suggested that the inclusion of a multi-domain assessment of cognitive impairment in elderly patients in routine preoperative risk assessment and decision making, may be important for tailoring the type of surgery, adequate perioperative monitoring and

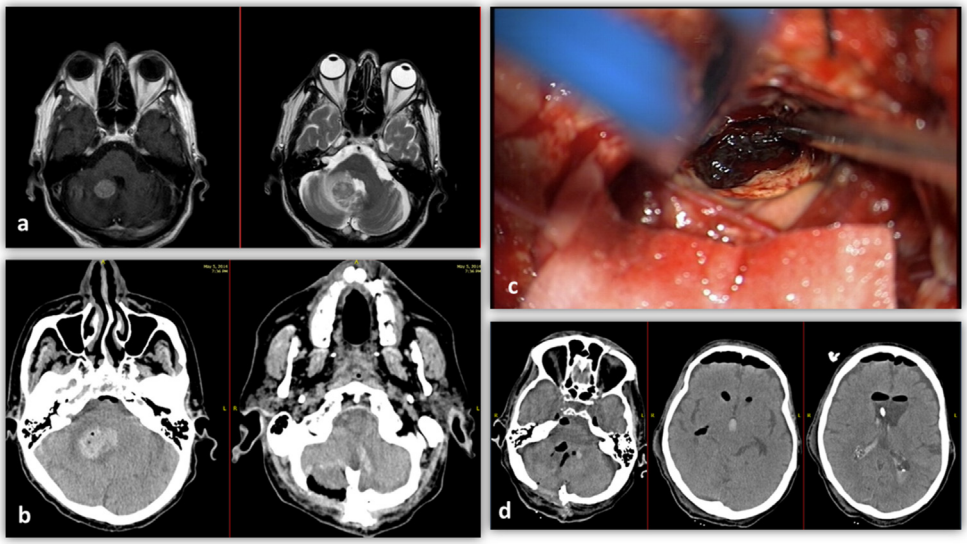

Fig. 3. a: preoperative T1 with Gadolinium and T2-weighted MR images showing a paramedian cerebellar metastasis in a 77-year-old male affected by melanoma (RPA class III, GPA score 1) associated to progressive consciousness deterioration. **b:** axial CT scan showing a post-operative hematoma in the surgical bed causing coma. **c:** intraoperative view during hematoma removal. **d:** post-operative CT scan after removal of the hematoma and external ventricular catheter positioning. The patient recovered only partially from his comatose state and died 15 days after surgery, due to nosocomial lung infection.

Table 3
Cox-regression analyses of Complications: univariate and multivariate analyses (n = 48).

Complications	Univariate Analysis	
	OR (CI95%)	p value
Age >75 yrs vs < 75 yrs	2.320 (0.518–10.381)	0.271
Sex Male vs Female	2.154 (0.608–7.627)	0.234
Primary Tumor	–	0.289
Lung vs Breast	1.143 (0.168–7.762)	0.891
Other histologies vs Breast	2.909 (0.700–12.092)	0.142
Tumor location hemispheric vs vermian	1.273 (0.270–6.005)	0.761
Tumor Size	1.260 (0.655–2.426)	0.489
Time to metastases	1.003 (0.995–1.012)	0.425
RPA Score II vs III	2.789 (0.303–25.544)	0.365
GPA Score	0.437 (0.146–1.302)	0.137
Charlson Comorbidity Index	**1.689 (1.013–2.814)**	**0.044**
5-variable mFrailty Index	1.841 (0.816–4.154)	0.142
Pre-operative KPS	0.969 (0.908–1.034)	0.343

Table 4
Cox-regression analyses of Post-operative KPS ≥70: univariate and multivariate analyses (n = 48).

KPS ≥ 70	Univariate Analysis		Multivariate Analysis	
	OR (CI95%)	p value	OR (CI95%)	p value
Age >75 yrs vs < 75 yrs	1.458 (0.339–6.265)	0.612	–	–
Sex Male vs Female	1.021 (0.326–3.199)	0.971	–	–
Primary Tumor	–	0.705	–	–
Lung vs Breast	0.595 (0.168–2.113)	0.422		
Other histologies vs Breast	0.655 (0.134–3.186)	0.600		
Tumor Location hemispheric vs vermian	**10.353 (1.178–90.952)**	**0.035**	**11.895 (1.129–125.347)**	**0.039**
Tumor Size	1.058 (0.576–1.942)	0.855	–	–
Time to metastases	0.999 (0.991–1.0107)	0.749	–	–
GPA Score	**4.283 (1.460–12.568)**	**0.008**	**-**	**ns**
Charlson Comorbidity Index	1.004 (0.658–1.534)	0.986	–	–
5-variable mFrailty Index	1.075 (0.518–2.228)	0.847	–	–
Pre-operative KPS	**1.218 (0.1074–1.382)**	**0.002**	**1.256 (1.085–1.453)**	**0.003**

predicting the prognosis of elderly patients.[28–33]

5.1. Surgery for infratentorial metastatic lesions

Cerebellar metastases by nature of their location, pose specific issues, since their clinical picture may dramatically worsen in a matter of few days or even hours, due to intracranial hypertension from hydrocephalus and direct brain stem compression.

In this setting, surgery is potentially able i) to provide immediate symptomatic relief removing the mass effect of the lesion, ii) to possibly avoid the requirement of a definitive V–P shunt, iii) to shorten the need for corticosteroid therapy, iv) to provide tissue samples for further molecular analysis and, in combination with radiation, v) to improve the overall prognosis of the patients.[5,7,9,12,34]

Indication to surgery is usually based on the neurological clinical conditions and comorbidities of the patients, the control of the primitive tumor, the location, mass effect and tumor size of the metastatic lesions.[21]

In any case, the main target should be to preserve the eligibility of the patient to the adjuvant therapies treatments, which are hampered by the presence of a lesion with a significant mass effect in the posterior cranial fossa, causing a worsened KPS or a major neurologic deficit.

In a recent multicenter retrospective analysis of 3500 adult patients (826 with cerebellar lesions), who underwent craniotomy for resection of brain metastasis, infratentorial location was associated with an increased odds for multiple medical complications (surgical site infections, pneumonia and reintubation), reoperation and unplanned readmission.[35]

Commonly cited positive prognostic factors in terms of overall survival, included the association of surgical resection and radiotherapy, preoperative KPS score >70, younger age, solitary lesions and absence of post-operative complications.[7,13,34]

5.2. Surgery for infratentorial lesions in general population vs in elderly population

5.2.1. Perioperative morbidity and mortality

A comparison among the most recent surgical series for cerebellar

Table 5
Cox regression analyses of Overall Survival: univariate and multivariate analyses (n = 48).

Overall Survival	Univariate Analysis		Multivariate Analysis	
	HR (CI95%)	p value	HR (CI95%)	p value
Age >75 yrs vs < 75 yrs	1.0102 (0.506–2.400)	0.807	–	–
Sex Male vs Female	**1.972 (1.059–3.673)**	**0.032**	**-**	**ns**
Primary Tumor Lung vs Breast	– 2.127 (0.883–5.120)	0.153 0.092	–	–
Other histologies vs Breast	0.577 1.287 (0.530–3.127)			
Complications Yes vs No	**1.988 (1.035–3.818)**	**0.039**	**-**	**ns**
Tumor location hemispheric vs vermian	1.639 (0.751–3.578)	0.215	–	–
Tumor Size	1.122 (0.837–1.504)	0.471	–	–
Time to metastases	**0.993 (0.988–0.999)**	**0.015**	**0.993 (0.988–0.998)**	**0.012**
RPA Score II vs III	1.081 (0.477–2.450)	0.853	–	–
GPA Score	0.726 (0.434–1.212)	0.220	–	–
Charlson Comorbidity Index	1.205 (0.946–1.534)	0.130	–	–
5-variable mFrailty Index	1.470 (0.945–2.266)	0.081	–	–
Pre-operative KPS	0.981 (0.949–1.015)	0.270	–	
Post-operative KPS	**0.966 (0.941–0.990)**	**0.005**	**0.964 (0.940–0.988)**	**0.004**
Lenght of Stay LOS	**1.019 (1.001–1.038)**	**0.039**	**-**	**ns**

metastases in the general population and ours in elderly population, is reported in Table 6. In all studies, the most common primary site of tumors were lung and breast, followed by gastrointestinal and genito-urinary carcinomas.

In our cohort of older patients, the rate of complication (29%) appeared higher than that reported by studies on general population (4–22%), but in line with that reported by Song et al in a large cohort of patients ≥65 years affected by CNS tumors (39%). Of note, half of the complicated cases were related to the occurrence of a post-operative hematomas in the surgical cavity, requiring reoperation.

Wronsky et al reported that 19% of 74 patients affected by colorectal cancer cerebral metastases (26 of them with cerebellar metastases) required reoperation.[11]

As comparison, Pompili et al in their series of 44 operated patients with cerebellar metastases with an average age of 58 years (range 39–83) observed 18% of post-operative hematomas requiring reoperation, 20% of overall complication rates and 9% perioperative mortality. The constant feature that was related with complications was tumor dimension: all the complicated cases were >3 cm in diameter.[5]

A technical explanation may be that cerebellar tissue is more fragile than brain, and that a contusion and/or hematoma in the narrow posterior cranial fossa may lead more frequently to severe neurological deterioration while, in the supratentorial compartment a 2–3 cm hematoma/contusion may be clinically neglectable. Therefore, a meticulous surgical technique avoiding excessive cerebellar contusion and/or retraction must be pursued and careful hemostasis appeared to be crucial for a satisfactory result especially in older subjects. Moreover, a strict post-operative monitoring and pharmacologic control of blood pressure seems to be advisable to prevent hypertensive crisis and hematoma formation, especially in elderly patients.[5,7,35]

Sunderland et al reported in their series of 92 patients, a post-operative complication rate of 22.8% and a mortality rate of 7.6%. 14 cases (15%) of post-operative hydrocephalus were observed, half of which required permanent CSF diversion.[12]

On the contrary, Ghods et al performed a retrospective analysis in 50 patients affected by cerebellar metastases (average age 54 years) and reported no perioperative mortality and only 4% morbidity. No post-operative hematoma was observed in his series after meticulous intra and post-operative control of blood pressure[7]

In our cohort of patients, a higher CCI was the only predictive factor significantly associated to post-operative complications, as also reported by Grossmann et al and Stark et al in their retrospective analyses of brain metastases operated in elderly people.[2,6]

5.2.2. *Preoperative functional status*

At multivariate analysis, we observed that significant factors which predicted an improved KPS score post-operatively (KPS ≥70), were a higher pre-operative KPS score, the hemispheric location of the metastasis and RPA II classification. These results find correspondence with different other reports in which lower preoperative functional status appeared to be strongly associated with unfavorable post-operative performance, underlying the fact that early surgery, before functional deterioration takes place, may be associated to a better oncological outcome.[1,7,10,11,35] As far as the better post-operative results in patients with hemispheric location of the lesion vs those with vermian ones is concerned, we hypothesized that removal of a hemispheric metastasis is usually better tolerated with lesser risks of cerebellar symptoms and dysphagia, which may have an impact on post-operative functional status. Location in the vermis compared to hemispheric cerebellar metastatic lesions, predicted in Ersoy's series of 73 patients with cerebellar metastases and an average age of 60 years (range 30–82), the occurrence of surgical complications (45.5% vs 8.1%; p = 0.005), but this was not confirmed in our study.[9]

5.2.3. *Overall survival and adjuvant therapies*

The median survival of our cohort of patients was 7 months which is in line with what observed in a general population with cerebellar metastases. At multivariate analysis, only the post-operative KPS and the time interval between diagnosis of the primary tumor and cerebellar metastasis appearance, maintained a prognostic value. Similar results were also obtained by Proescholdt et al showing that in elderly patients, a better post-operative KPS leads to a higher chance of receiving adjuvant treatment and attaining a longer OS.[1]

The reason of the second finding is not clear, but it may be related to intrinsic biologic characteristics of the primitive tumor which allow a greater susceptibility to oncologic therapies and a favorable local and systemic disease control, before and after removal of brain metastases.

At present, this remains a controversial issue since some studies confirmed the prognostic role of a longer time latency between primary tumor and development of brain metastases, especially in breast cancer, while others were unable to replicate these results.[1–3,6,36,37]

Pompili et al reported a median survival of 8 months (range 5–9). Factors associated to a better outcome, were KPS ≥70 before surgery, RPA class I-II vs III, suboccipital surgical approach vs occipital-transtentorial, absence of complications and KPS at discharge. Time to metastases did not reach statistical significance.[5]

Sunderland et al observed a median survival of 6 months after surgery, in 92 patients with a median age of 59 years.[11] More recently, Ersoy et al observed a median survival of 9.2 months (range 3.2–21.7) and a perioperative mortality of 6.8%.[9]

Calluaud et al documented a significant prognostic role of the edema/tumor ratio calculation in 120 patients affected by posterior fossa metastases. Their median OS was 8.9 months, while factors relevant on outcome included gross total resection, performance status at diagnosis, GPA class and adjuvant therapies. Time to metastases reached significance at univariate analysis only. To note, age did not appear to be prognostic of a worse outcome in all the last three studies.[9,12,38]

Table 6
Comparison of recent studies on surgically treated cerebellar metastases.

	N° patients	Median age (range)	Synchronous metastases %	Single metastases %	Complications rate%	Peri-operative mortality	OS	Time to metastasis	Adjuvant therapy
Pompili et al. 2008	44	58 (39–83)	23%	93%	20%	9% (1 mo)	8 mo	30 mo	36%
Yoshida et al. 2009	73	57 (42–77)	NR	32%	NR	NR	single met 35 mo multiple met 8.4 mo	13.5 mo	48%
Ghods et al. 2011	50	54 (29–81)	34%	64%	4%	0%	NR	17 mo	NR
Sunderland et al. 2016	92	59 (37–76)	36%	79%	22.8%	7.6% (1 mo)	6 mo	NR	73%
Calluaud et al. 2018	120	62 (55–89)	48%	65%	19.1%	1.7%	9 mo	4 mo	82%
Ersoy et al. 2021	73	60 (30–82)	26%	53%	17.8%	6.8% (1 mo)	9 mo	NR	73%
Telera et al. 2023	48	69.5 (66–87)	21%	87.5%	29%	23% (3 mo)	7 mo	26 mo	71%

Although it is difficult to provide a reliable" quantitative measure" from the literature, elderly patients appear to be more fragile with respect to their younger counterpart.[27,35]

This factor may be due not only to the aging of the brain, but also to their multiple comorbidities and often longer oncologic history. However, at present there is no solid and reliable guideline about the "exact age" at which surgery could be performed with benefit.[5,9]

34 patients (71%) in our series were able to perform adjuvant therapies as RT and/or CHT after surgery, which has been recognized as a significant prognostic factor for OS in all elderly patients with brain metastases, especially considering recent advances in radio-oncological and target therapies.[1] Our results compare favorably with those reported in adult population, in which multimodal treatments after neurosurgical resection of the cerebellar lesion, were possible within the range of 36% and 73% of cases.[5,9,12,34]

Accurate surgical technique and post-operative care are paramount, since occurrence of any complications, especially in advanced age, may severely affect the prognosis and ability of the patient to obtain any advantage from surgery.[1,9]

Upfront SRS have also been considered in oligometastatic elderly patients, with large brain metastases. In this setting, radiological oncologists are usually cautious, especially in posterior cranial fossa, since SRS may enlarge peritumoral edema, leading to severe neurological complications. However, a small number of studies have shown that both single session or fractioned SRS can be feasible and safe in treating large brain lesions, especially in radiosensitive cancers. A delay or even prevention of neurologic death can be achieved with reported OS between 5 and 13 months.[39,40] Recently Lai et al have reported their experience in treating with SRS 44 adult patients, affected by large (3.5 cm of median diameter) cerebellar metastasis from lung cancers. Two patients worsened after treatment, one of them requiring emergency life-saving surgery, while in 83.7% pre-treatment neurologic symptoms improved. The OS rate at 6 and 12 months were 79.5% and 43.2% respectively.

6. Limitation

As far as we know, the present study is the first specifically addressing the results of surgery in elderly patients with cerebellar metastases. However it has also several limitations: i) this cohort of patients is heterogeneous in terms of different primary tumors and adjuvant therapies; ii) as a single-center retrospective study, institutional bias and limited generalizability cannot be excluded; iii) the number of analyzed patients is limited, even if data published on this topic are also quite sparse; iv) only two comorbidity and frailty indexes have been exploited in this series, compared to the many others available in the literature; v) due to the retrospective nature of this study an assessment of cognitive functions preoperatively and post-operatively was not performed; vi) finally, the present cohort may be affected by selection bias as indicated by the relatively low CCI compared to the general cancer population >65 years old. This may have artificially improved outcomes.

7. Conclusions

Our results suggest that selected elderly patients with cerebellar metastases may benefit from microsurgery, to continue their adjuvant therapies, although a high complications rate should be taken in account. Comorbidities evaluation, location of the tumor, pre-operative KPS, time interval between diagnosis of the primary tumor and cerebellar metastasis appearance and prognostic assessment scales may help to appropriately select patients to submit to surgery. Outcomes were associated in our series with cerebellar tumor location and preoperative functional status.

On the contrary, we observed that in older patients belonging to RPA Class III, with a short interval between tumor first diagnosis and cerebellar metastases or with a high comorbidity burden, surgical indication could be questionable, even if good results may still be obtained.

Given the concomitant advances in SRS treatments, comparative prospective studies are strongly needed and more data should be gathered to standardize therapeutic options. Both neurosurgeons and radiotherapists are called to explore what their disciplines can offer, to the benefit of this subgroup of patients.

Credit authorship statement

Stefano Telera Conceptualization; Writing – review & editing, Supervision.Roberto Gazzeri Conceptualization; Writing – review & editing, Validation.Veronica Villani Data curation, Writing – review & editing, Laura Raus Data curation, Writing – review & editing, Francesca Romana Giordano Investigation.Alessandra Costantino Investigation, Catia Pompea Delfinis Investigation, Francesca Piludu Writing – review & editing.Isabella Sperduti Methodology, Formal analysis.Andrea Pace Supervision, Formal analysis, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Nomenclature/Abbreviations

SRS: Stereotactic radiosurgery
WBRT: Whole brain radiotherapy
RT: Radiotherapy
GRT: Gross Total Resection Rate
SRR: Subtotal Resection Rate
RPA: Recursive Partitioning Analysis
GPA: Graded Prognostics Assessment
KPS: Karnofsky Perfomance Status
OS: Overall Survival
CCI: Charlson Comorbidity Index
mFI-5 5-variable: modified Frailty Index
CHT: Chemotherapy
LOS: length of stay in the hospital
CSF: Cerebrospinal fluid