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ORIGINAL ARTICLE - BRAIN TUMORS

# Early postoperative MRI after resection of brain metastases—complete tumour resection associated with prolonged survival

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## Abstract

**Background** This study aimed to investigate the incidence of residual tumour after resection of brain metastases using early postoperative magnetic resonance imaging (MRI) and the influence of residual tumour on overall patient survival.

**Methods** Data from 72 consecutive adult patients undergoing surgery for cerebral metastases over an 18-month study period were retrospectively collected. Early postoperative MRI was used to determine the presence of postoperative residual tumour. Patients were divided into three groups according to the presence of tumour remnant on early postoperative MRI: "no residual tumour", "non-measurable residual tumour" and "measurable residual tumour". Survival analysis (mean estimate survival time) was performed using the Kaplan–Meier and log-rank (mantel cox) tests and compared between groups. Surgical reports were evaluated with regard to the surgeon statement about intraoperative extent of resection (EOR) and compared with the presence of tumour remnant found on the early postoperative MRI.

**Results** Sixty-eight procedures were followed by early postoperative MRI. MRI verified the presence of "measurable residual tumour" following 15 procedures (22%). MRI confirmed complete resection in 57%. Gross total resection was described by the operating surgeon in 85% of the procedures. There was a significant difference in survival time after surgery between the group having no residual tumour on MRI and the group with measurable residual tumour ($p = 0.025$). This difference could not be explained by the differences in postoperative radiation therapy. The longest survival was found in patients with non-measurable and no residual tumour on early postoperative MRI, who also received postoperative radiotherapy.

**Conclusion** Residual tumour was seen on MRI after 22% of the procedures. The intraoperative assessment of EOR performed by the surgeon diverged from the early postoperative MRI in 40% of procedures. Correct assessment of residual tumour thus requires early postoperative MRI. Measurable residual tumour on early postoperative MRI was associated with shorter overall survival independent on postoperative radiotherapy.

**Keywords** Brain metastasis · Brain metastases · Surgery · Postoperative MRI · Resection

**Abbreviations**

| | |
|---|---|
| BrM | Brain metastases |
| MRI | Magnetic resonance imaging |
| EPMRI | Early postoperative magnetic resonance imaging |
| EOR | Extent of resection |
| GTR | Gross total resection |
| OUH | Odense University Hospital |
| MG | Malignant glioma |

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| | |
|---|---|
| NPV | Negative predictive value |
| PPV | Positive predictive value |
| WBRT | Whole brain radiation therapy |
| SRS | Stereotactic radiosurgery |
| KPS | Karnofsky performance score |

## Introduction

Brain metastases occur in a substantial number of patients with cancer [3, 13]. The incidence is growing due to increased surveillance, improved control of systemic disease, improvement in treatment of cancer and prolonged survival [13]. Brain metastases are often seen at a late stage of the disease and are associated with severe morbidity, decreased quality-of-life and a high mortality [2, 4]. There are currently few studies documenting the impact of early postoperative MRI and the presence of residual tumour after surgical resection of brain metastases [5, 8, 10]. There is consensus in the literature regarding the benefits of surgical treatment, where this is indicated [3]. A low preoperative WHO performance score or the Karnofsky performance score (KPS) > 70, age < 65, stable disease, absence of extracranial metastases and postoperative adjuvant radiotherapy are all factors known to be associated with improved survival or reduced recurrence [12, 13, 15, 18]. Previous studies suggest that complete resection of brain metastases is associated with a more favourable outcome in terms of increased survival and a reduced recurrence rate [19, 22].

The importance of complete resection is well known for malignant gliomas [21]. Previous studies on malignant gliomas suggest that the assessment of resection made by the operating surgeon is commonly inaccurate when compared with the results of an early postoperative MRI [2, 7, 16].

In contrast to malignant gliomas, brain metastases have traditionally been considered well-delineated and expansive processes rather than invasive, thereby believed to make gross total resection (GTR) by en bloc resection more achievable [3, 5, 8]. However, in a retrospective review of autopsy material from 57 patients, a well-delimited growth pattern was observed in 50% of the patients only. In 18%, the lesions were found to have perivascular protrusions into the surrounding brain parenchyma, and in 32%, the lesions were found to diffusely infiltrate surrounding brain tissue [6]. Another study described a 20% incidence of residual tumour on early postoperative MRI after surgical resection, and a significant correlation ($p < 0.0001$) between the incidence of tumour progression and residual tumour on the early postoperative MRI [10].

Several methods have been investigated, aiming to improve the surgical methods used for resection of brain metastases. Yoo et al. compared GTR to microscopic total tumour resection and found that the latter method had a significant advantage in terms of reduced local recurrence but was not superior to GTR in terms of survival [22]. Another study by Kamp et al. concluded that the use of supramarginal resection (as suggested by Yoo et al.) is safe, but overall, the possible survival benefit is still unknown [11]. Similarly, fluorescence-guided surgery has been shown to improve surgical resection of brain metastases [9, 20].

The primary objective of this retrospective clinical investigation was to assess the incidence of residual tumour after resection of brain metastases without the use of intraoperative fluorescence and to compare the intraoperative assessment of the extent of resection made by the surgeon with the extent of resection verified at early postoperative MRI. In addition, to investigate the difference in survival between the groups of patients, questioning whether the extent of resection would affect patient survival.

## Method and materials

### Data collection

Patients were identified via the ICD code DC793 in the regional patient record database system. Surgical records from the Department of Neurosurgery at Odense University Hospital (OUH), Denmark, were reviewed in order to identify craniotomies performed during the 18-month study period (August 2014–January 2016), and patient characteristics including information on postoperative radiotherapy treatment were obtained. The study was approved by the Danish Patient Safety Authority (3-3013-1506/1) and by the Danish Data protection agency (16/3499).

Inclusion criteria were:

1. Craniotomy with intended surgical resection of one or more brain metastases
2. Histologically verified metastatic tissue

For inclusion in the statistical analysis regarding EOR, an additional criterion was:

3. Early postoperative MRI performed within 72 h after surgery.

Patients with more than one brain metastasis, where resection was only intended for one lesion, were included. In the data analysis, the extent of resection applied only for the resected lesion.

All patients had preoperative MRI scans.

### Surgical resection

Seventy-two acute and planned craniotomies with intended removal of 75 metastases were performed at OUH during the study period. Neuro-navigation (Medtronic Stealth®) was used for all the procedures. Ultrasonic aspiration is considered a standard procedure in metastasis removal in our institution and all patients underwent ultrasonic aspiration–assisted tumour removal. Fluorescence-guided surgery was not used in this study. The surgeons' intraoperative description of the extent of resection (EOR) was obtained by reviewing surgical notes.

### Verification of extent of resection using early postoperative MRI

Early postoperative (T1-weighted, gadolinium contrast-enhanced) MRIs were performed within 72 h of the surgical procedures. The images were continuously evaluated and described by trained neuroradiologists following the surgical procedures. MRI scans from all included patients and procedures were re-evaluated by a neuroradiologist during the spring of 2017, aiming to reduce the risk of interobserver bias. The observer was blinded to previous descriptions. Any tumour residue was assessed and described based on the RANO group criteria, defining a measurable residual tumour as a "contrast enhancing lesion that can be accurately measured in at least one dimension, with a minimum size of 10 mm" [14]. Patients were categorised into three groups based on their early postoperative MRI-verified EOR:

- No residual tumour (GTR)
- Non-measurable residual tumour (contrast enhancing lesion < 10 mm in one dimension)
- Measurable residual tumour

### Statistical analysis

Statistical analysis was performed using IBM SPSS statistics versions 23 and 24.

Baseline data were collected and entered into SPSS, where calculations of means and median and range were performed using the "descriptive statistics" feature. Categorical variables, such as gender, primary cancer and residual tumour, were analysed using the "frequency" feature. Calculations of negative- and positive predictive value (NPV and PPV) and sensitivity and specificity of the surgeons' intraoperative assessment of EOR were performed using basic descriptive statistics and crosstabs analysis.

Due to the number of censored cases, the Kaplan–Meier method was used to investigate survival and estimated mean survival in the groups. Only patients with postoperative MRI were included in the survival analysis ($n = 64$).

Survival curves were created for the different groups and the log-rank test was used to test for statistically significant differences in survival. Results with $p < 0.05$ were considered statistically significant. A one-way ANOVA was performed post hoc.

Survival was defined as the time from surgery until death and was expressed in months from the time of surgery to death (0.5-month intervals). Patients still alive during the data collection were all censored to a common date (June 03, 2016). If a patient underwent more than one surgical procedure during the study period, the date of the first surgery was used for survival analysis. If a patient had previously undergone surgery for metastatic disease in the brain, survival was calculated from the surgery during the study period.

## Results

Seventy-two surgeries in 68 patients were identified. Early postoperative MRI was performed after 68 procedures (64 individual patients).

### Patient characteristics

Patient characteristics are summarised in Table 1.

Sixty-eight patients suffering from 88 brain metastases underwent 72 surgeries with intended total resection of 75 lesions. The majority (82%) had one brain metastasis prior to surgery. Sixty-nine percent of the patients were female. The mean age was 65 years, with 57% being older than 65 on the day of surgery. The mean KPS at the time of admission was 71, and 72% had an estimated KPS > 70. Eight patients had previously received radiotherapy (including both whole brain radiotherapy (WBRT) and stereotactic brain radiotherapy (SRS)).

The primary cancer causing the brain metastasis was unknown prior to neurosurgical intervention in 31% of the procedures (22 of 72). The most frequent primary cancers were lung cancer (47%), malignant melanoma (13%) and breast cancer (11%).

Four patients underwent surgery twice during the 18-month study period, making the total number of procedures 72 in 68 patients. Two of the patients undergoing a second surgery during the study period had new lesions and two had progression of previously known and resected lesions. One of the four patients underwent two consecutive surgeries 10 days apart with the removal of one supratentorial and one infratentorial lesion. Both procedures were followed by early postoperative MRIs. Five patients had previously received surgical treatment for their metastatic lesions. In total, nine repeated surgeries were included in the study.

### Surgical resection

Removal of one metastatic lesion was the goal in 96% of the procedures. In the remaining three procedures (4%), the

**Table 1** Results of clinical characteristics

| Clinical characteristics | Patients ($n = 68$) $n$ (%) | Measurable residual tumour ($n = 15$) $n$ (%) |
|---|---|---|
| Age (years) | | |
| - Median | 69 | |
| - Mean | 65 | 68 |
| - Range | 43 (42–85) | 37 (47–84) |
| Gender | | |
| - Male | 22 (32%) | 6 (40%) |
| - Female | 46 (68%) | 9 (60%) |
| Primary cancer | | |
| - Lung | 33 (49%) | 7 (47%) |
| - Breast | 8 (12%) | 4 (27%) |
| - Malignant melanoma | 7 (10%) | 2 (13%) |
| - Gastrointestinal (pancreas, colon, rectum) | 9 (13%) | 2 (13%) |
| - Urogenital (cervix, ovary, bladder, kidney) | 11 (16%) | 0 |
| Known primary cancer at the time of surgery | | |
| - Yes | 46 (68%) | 10 (67%) |
| - No | 22 (32%) | 5 (33%) |
| KPS* | | |
| - > 70 | 52 (72%)* | 9 (60%) |
| - Mean | 71* | 67 |
| Location | | |
| - Supratentorial | 47 (69%) | 8 (53%) |
| - Infratentorial | 21 (31%) | 7 (47%) |
| - Eloquent | 16 (24%) | 2 (13%) |
| - Near-eloquent | 9 (13%) | 4 (27%) |
| - Non-eloquent | 18 (27%) | 2 (13%) |
| - Uncertain | 4 (6%) | |
| Number of metastases (preop. MRI) | | |
| - 1 | 55 (81%) | 13 (87%) |
| - 2 | 10 (15%) | 2 (13%) |
| - 3 | 3 (4%) | 0 |
| - Mean | 1.2 | |
| - Sum | 84 | 17 |
| Removed metastases | 71 | 15 |
| Post-op MRI | 64 patients | |
| | 68 procedures | |
| Missing MRI: | 4 (6%) | |
| Postoperative radiotherapy (patients included in the survival analysis (n=64)) | | |
| - Measurable residual tumour ($n = 15$) | 9 | |
| - Non-measurable residual tumour ($n = 14$) | 7 | |
| - No residual tumour ($n = 35$) | 21 | |
| - Overall ($n = 64$) | 37 | |

*KPS prior to 72 surgical interventions, thus $n = 72$

resection of two lesions was intended. Removal of all known lesions was intended for 61 procedures (85%). Severe surgical complications (within 30 days) occurred following six procedures (8%). These were postoperative intracerebral haemorrhage (2 patients, both underwent acute surgical evacuation of the hematoma), problems related to cerebrospinal fluid circulation (2 patients) and ischemic infarction with neurological sequelae (2 patients). Three patients underwent acute surgery due to immediate postoperative complications. One additional patient experienced infection in the skull flap 6 months after the procedure.

No patients had second-look surgery as a result of tumour remnant on the early postoperative MRI.

## Intraoperative assessment of the extent of resection

The operating surgeon described gross total resection (GTR) in 58 of 72 (81%) surgeries. The resection was described as incomplete in 4 procedures (6%) and as uncertain in 4 procedures (6%). In 6 procedures, no statement regarding intraoperative assessment of resection was found.

## Early postoperative MRI

Table 2 provides an overview of the distribution of residual tumour on early postoperative MRI.

Postoperative radiographic assessment of EOR using early postoperative MRI was performed following 68 of the 72 surgical procedures, for 67 within 72 h and one on day 4. In four cases, no early postoperative MRI was performed (2 due to surgical complications, 1 patient was transferred to a local hospital before the MRI was performed, and 1 patient was unaccounted for). Measurable residual tumour according to the RANO criteria [14] (lesion measuring > 10 mm in one dimension) was present on early postoperative MRI after 15 procedures (22%, Table 2).

## MRI-verified extent of resection

Table 3 summarises the difference in surgeon-assessed EOR and early postoperative MRI-verified EOR. For the 15 patients in whom early postoperative MRI described the presence of a measurable residual tumour, 12/15 (80%) were described as GTR by the operating surgeon. Overall, correct intraoperative assessment occurred in 35/62 procedures (56%).

The assessment diverged from the early postoperative MRI in 27 procedures (40%). Early postoperative MRI verified no residual tumour following 39 procedures (57%). According to the surgeon, GTR was obtained in a total 58 procedures.

The sensitivity of the operating surgeon intraoperative assessment of incomplete resection (the number of patients with MRI-verified measurable residual tumour in which the surgeon assessed the resection to be incomplete) was 13% (2/15). Upon including the patients with both measurable- and non-measurable residual tumour, the sensitivity of the surgeon assessment ("complete resection") was 2/25 (8%).

The specificity of the surgeon intraoperative assessment of complete resection (number of patients with MRI-verified complete resection in which the surgeon assessed the resection to be complete) was 85% (33/39).

The positive predictive value (PPV) of the intraoperative assessment (the number of cases in which the surgeon assessed the resection to be incomplete and the patient also had a MRI-verified residual tumour) was 50% (2/4). The negative predictive value (NPV, the number of procedures in which the operating surgeon assessed GTR and the early postoperative MRI-verified complete resection) was 57% (33/58).

## Survival

The groups of patients found to have measurable- or non-measurable residual tumour on the early postoperative MRI had significantly shorter mean estimate survival time after surgery.

From the 64 patients that underwent early postoperative MRI, 66% (42/64) were dead by the end of the data collection period. Twenty-two patients (34%) were still alive by the end of the data collection (censored cases).

Overall mean estimated survival time in this study was 10.4 months (95% CI 8.5–12.2, Table 4). For patients with a measurable residual tumour on the early postoperative MRI, the mean estimated survival time was found to be 5.6 months (95% CI 3.7–7.4 months) versus 12 months (95% CI 9.4–14.5 months) for the group with no residual tumour. In the group found to have a non-measurable residual tumour, the estimated mean survival time was 9.5 months. The overall survival distributions for the different groups were significantly different (log-rank $p = 0.05$, Fig. 1a). There was also a statistically significant longer overall mean estimated survival in the group with no residual tumour versus the group having a measurable residual tumour (log-rank $p = 0.025$, Fig. 1b). A one-way ANOVA was performed post hoc. This confirmed a statistically significant difference in survival between the 3 groups ($p = 0.013$). The one-way ANOVA does, however,

**Table 2** Results of residual tumour on early postoperative MRI and group distribution

| | Measurable, > 10 mm in one dimension | |
|---|---|---|
| | 64 individual patients *n* (%) | 68 procedures *n* (%) |
| Measurable residual tumour | 15 (23%) | 15 (22%) |
| Non-measurable residual tumour | 14 (22%) | 14 (21%) |
| No residual tumour | 35 (55%) | 39 (57%) |

Table 3 Results of MRI-verified EOR vs. EOR assessed by surgeon ($n$ = number of procedures)

| | Assumed complete | Assumed incomplete | No assumption made | Described as uncertain | Total (MRI) |
|---|---|---|---|---|---|
| No residual tumour | 33 | 2 | 2 | 2 | 39 |
| Non-measurable residual tumour | 13 | 0 | 1 | 0 | 14 |
| Measurable residual tumor[1] | 12 | 2 | 0 | 1 | 15 |
| Total (perioperative assessment) | 58 | 4 | 3 | 3 | 68 |

Perioperative assessment vs. MRI-verified extent of resection:

Sensitivity, 13% (2/15); specificity, 85% (33/39); PPV, 50% (2/4); NPV, 50% (33/58)

[1] Measurable, > 10 mm in one dimension

not take into account that several of the patients were alive (censored cases) by the end of the data collection.

## Postoperative radiotherapy

Table 5 comprises an overview of postoperative radiation therapy in the three cohorts as well as the difference in mean estimated survival time.

**Overall** From 64 patients included in the survival analysis, 37 (58%) received postoperative radiotherapy towards the whole brain (WBRT) or stereotactic radiosurgery (SRS) to the tumour cavity. The mean estimate survival time for the 37 patients receiving radiotherapy after surgery was 10.9 months. The mean estimated survival time for the remaining 27 patients (42%) who did not receive postoperative radiotherapy was 8.6 months (Table 5). Overall comparison of survival distributions for these 2 groups (log-rank (Mantel–Cox)) yielded a $p$ value of 0.440.

Included in these 27 patients are 12 patients in whom postoperative radiotherapy was neither planned or initiated, seven patients that received radiotherapy (WBRT or SRS) as treatment of progression at a later stage, two patients in whom radiation was planned but not initiated and six patients that underwent preoperative, but no postoperative radiotherapy. The mean estimated survival time for the 12 patients that did not receive any postoperative radiotherapy was 7.5 months (range, 1.5–16 months), and 6.6 months when including the 2 patients in which radiation was planned but not performed ($n$ = 14). Three patients received both postoperative WBRT or SRS as well as treatment for progression (included in the 37 patients receiving postoperative radiotherapy). Six of the eight patients with a previous history of radiotherapy prior to surgery received no postoperative radiation. One received SRS after surgery and 1 received WBRT due to progression.

**Measurable residual tumour on early postoperative MRI** In the group of patients found to have a measurable residual tumour on early postoperative MRI, 9 out of 15 patients (60%) received postoperative radiotherapy (5 patients received WBRT, 4 received SRS). Those 9 patients had a mean estimated survival time of 5.2 months. The mean estimated survival time for the 6 patients not undergoing postoperative radiotherapy was 5.8 months. Of these 6 patients, 3 received radiotherapy prior to surgery only. Two out of these 6 patients were still alive by the end of the data collection (censored). In one case, the WBRT was planned but not initiated due to short survival time after surgery (1.5 months).

**No residual tumour on early postoperative MRI** In the group with no residual tumour on early postoperative MRI, 21 patients (21/35, 60%) received postoperative radiotherapy (17 patients received WBRT, 3 patients received SRS and 1 patient received WBRT after surgery and SRS as treatment of progression). The mean estimate survival time for these 21 patients was 12 months. The mean estimate survival time for

Table 4 Results of mean estimate survival time

| | Survival time after surgery ($n$ = months) | Std. error | 95% confidence interval (CI) | |
|---|---|---|---|---|
| | | | Lower bound | Upper bound |
| No residual tumour (0 mm), $n$ = 35 | 12.0 | 1.3 | 9.4 | 14.5 |
| Non-measurable residual tumour (1–9 mm), $n$ = 14 | 9.5 | 1.7 | 6.2 | 12.7 |
| Measurable residual tumour, (>/= 10 mm), $n$ = 15 | 5.6 | 1.0 | 3.7 | 7.4 |
| Overall | 10.4 | 1.0 | 8.5 | 12.2 |

Numbers have been rounded to the closest 0.1 decimal

Estimation is limited to the largest survival time if censored

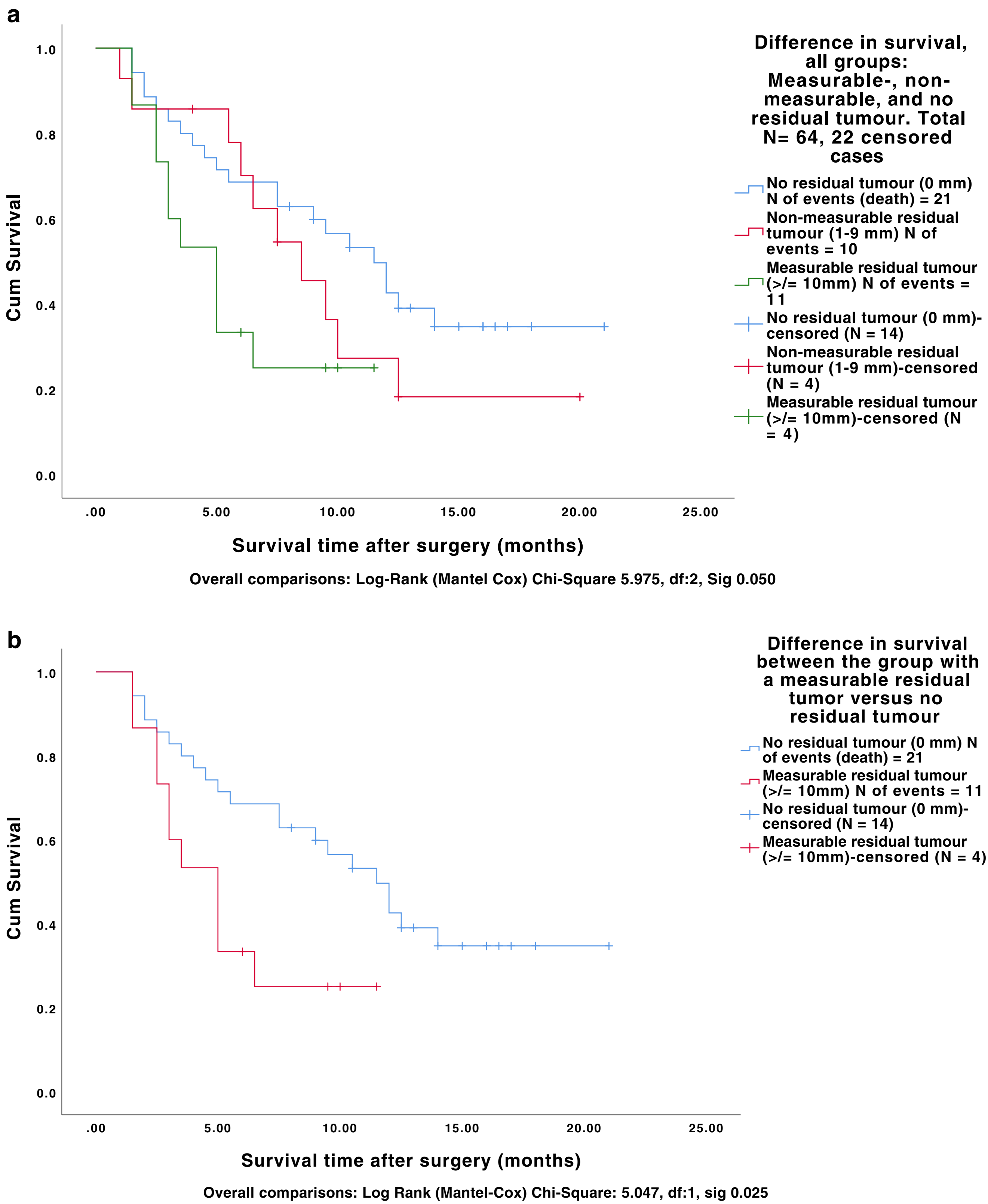


**Fig. 1** Kaplan–Meier survival plots: **a** The difference in survival after surgery ($p = 0.05$) between the three groups of patients (measurable-, non- measurable and no residual tumour). **b** The difference in survival between the group with measurable residual tumour vs. no residual tumour ($p = 0.025$)

**Table 5** Results of postoperative radiotherapy and survival time in the different cohorts

| | N | Mean | | |
|---|---|---|---|---|
| | | Estimate survival time after surgery (months) | Std. error | 95% confidence interval (CI) lower bound/upper bound |
| No residual tumour | | | | |
| - Postoperative radiotherapy | 21 | 12.0 | 1.6 | 8.9/15.2 |
| - Other * | 14 | 10.5 | 1.6 | 7.2/13.7 |
| - Overall | 35 | 12.0 | 1.3 | 9.4/14.5 |
| Non-measurable residual tumour | | | | |
| - Postoperative radiotherapy | 7 | 12.8 | 2.2 | 8.5/17.1 |
| - Other* | 7 | 5.9 | 1.4 | 3.2/8.7 |
| - Overall | 14 | 9.5 | 1.6 | 6.2/12.7 |
| Measurable residual tumour (>/= 10 mm) | | | | |
| - Postoperative radiotherapy | 9 | 5.2 | 1.0 | 3.3 / 7.1 |
| - Other* | 6 | 5.8 | 1.7 | 2.5 / 9.1 |
| - Overall | 15 | 5.6 | 1.0 | 3.7 / 7.5 |
| Overall | 64 | 10.4 | 1.0 | 8.5 / 12.2 |
| Overall comparisons[a]: Log-rank (Mantel–Cox) chi-square 1.015, df. 1, sig 0.314 | | | | |

Numbers are rounded to the closest 0.1 decimal

Estimation is limited to the largest survival time if censored

[a] Test of equality of survival distributions for the different levels of radiotherapy after surgery vs. other*, adjusted for residual tumour on early postoperative MRI

*Other includes patients not receiving postoperative radiotherapy, as well as those receiving radiotherapy towards progression at a later stage. The group also includes patients in which radiotherapy was planned but not initiated, and patients undergoing only preoperative radiotherapy

the 14 patients that did not receive postoperative radiotherapy was 10.5 months.

**Non-measurable residual tumour on early postoperative MRI** From the 14 patients in this group, 7 patients received postoperative radiotherapy, and an additional two received radiotherapy at a later stage due to progression. Five patients did not receive any postoperative radiotherapy. From these 5 patients, 1 was scheduled to receive postoperative radiotherapy but died prior to initiation, and 1 patient only received radiotherapy prior to surgery. The mean estimated survival time for the patients receiving postoperative radiotherapy ($n = 7$) was 12.8 months. For those not receiving postoperative radiotherapy ($n = 7$, including those receiving radiotherapy towards progression at a later stage), the mean estimated survival time was 5.9 months.

Overall, there was no significant difference in survival distributions between the cohorts receiving postoperative radiotherapy or not when adjusted for the presence of residual tumour on early postoperative MRI ($p = 0.314$, Table 5).

## Discussion

The two main findings of this study are (1) early postoperative MRI is a necessity as the intraoperative assessment of EOR performed by the surgeon is frequently incorrect and (2) the survival amongst the group of patients in which GTR was achieved (the group having no residual tumour on early postoperative MRI) was significantly higher than in the group of patients with the presence of measurable residual tumour on early postoperative MRI. This suggests that the gross total resection has a significant impact on improving overall survival in patients with cerebral metastases. This was independent of postoperative radiotherapy.

There are currently few studies investigating the incidence of tumour remnant after surgical resection of brain metastases. Kamp et al. published a retrospective study in 2015, investigating the association between EOR and recurrence after resection of cerebral metastases. They found a 20% (26/130) incidence of residual tumour on early postoperative MRI. The surgeon had assessed GTR in 24 of the 26 cases [10]. The 20% incidence in the study from Kamp et.al corresponds with the 22% incidence of incomplete resections in the present study. This supports the conclusion that the intraoperative assessment made by the operating surgeon is often too optimistic, and early postoperative MRI is recommended. In another retrospective study quantifying the yield of postoperative imaging after resection of brain metastases [5], the overall incidence of residual tumour was 13.7%, and the incidence of *unexpected* residual tumour was 5.4%. The operating surgeon assessed GTR in 166 patients, from which 9 (5.4%) were found to have residual tumour on postoperative imaging [5, 10]. Despite the relatively low number of unexpected residual tumour compared with our study and that by Kamp et al., early postoperative MRI was still superior to the intraoperative assessment alone. This makes us argue for the use of early postoperative MRI as a standard means of assessing postoperative residual tumour. One should also keep in mind that in case of measurable residual tumour, postoperative stereotactic radiation therapy is recommended [15].

Methods aiming to improve surgical resection seem to be of the uttermost importance, especially considering that our data suggests that EOR influences overall survival. The use of intraoperative fluorescent technique may be a promising method, including supramarginal resection if possible [11, 20, 22]. Höne et al. conducted a study in 2012 aiming to improve the surgical technique for the removal of brain metastases. In their study, fluorescein sodium and a yellow 560-nm filter was used as intraoperative contrast enhancement. The use of fluorescein is previously described as markedly enhancing tumour visibility [9, 20], and on early postoperative MRI, measurable residual tumour was found in three patients, whereas GTR was obtained in 25/30 (83.3%) [20]. In the follow-up study published in 2017 (expanded to include 95 patients), GTR was obtained in 83.3%. Obtaining GTR in 83% of patients is an improvement compared with both our study (no residual tumour in 57%) and to that of Kamp et al. (61.5%) [10]. The study does, however, not include investigation on the potential effect of GTR on overall survival. Our study suggests that obtaining complete resection of brain metastases favourably influences overall survival, thus suggesting that the intraoperative use of fluorescein for the improvement of EOR [9, 20, 21] may further contribute beneficially to patient overall survival. Larger prospective studies are, however, needed.

The standard surgical technique for the removal of cerebral metastasis at our institution is the use of ultrasonic aspirator. It has previously been shown that the use of ultrasonic aspiration results in a higher risk of intraoperative tumour seeding, suggesting that this might not the optimal method for the removal of brain metastases [1, 17]. Our present study did not investigate if this also was the case in our study. However, it would not change the conclusion since the same procedure with the usage of ultrasonic aspirator was used in all cases.

Regarding radiotherapy, the largest group with the longest survival was still the group of patients with no residual tumour on early postoperative MRI, also when adjusted for postoperative radiotherapy. Although it did not reach statistical significance in the present dataset, postoperative radiotherapy seems to influence survival in particular in the group with a non-measurable residual tumour on early postoperative MRI. The small group of seven patients with non-measurable residual tumour undergoing upfront postoperative radiotherapy was found to have the highest mean estimated survival time in the study (Table 5). The group with no residual tumour on early postoperative MRI also seemed to benefit from postoperative radiotherapy. The best results in this study, in terms of survival, were achieved in patients with non-measurable or no residual tumour, who underwent upfront postoperative radiotherapy. The mean estimated survival time in these two groups was 12.0 and 12.8 months. In the group of patients with measurable residual tumour, postoperative radiotherapy does not seem to have an impact on survival. This group had the shortest postoperative mean estimated survival time in the study, which is found to be from 5.2 to 5.8 months.

## Limitations

There are several limitations to this study. As a retrospective study, there is always the risk of error due to the collection of data from electronic charts and notes that are not specifically written or designed for the study. The group of patients included in this study represents a selection of patients that are referred to the department within the scope of a certain time frame. Both acute and elective admissions are included. A relatively high number of patients are registered as having an unknown primary tumour prior to surgery. A large percentage of these patients presented a range of neurological symptoms, as well as having a radiologically verified intracranial process. The patients have thus undergone surgery for a brain tumour of unknown aetiology, and postoperative pathology revealed metastatic tissue. In some of these cases, the brain tumour may have been a manifestation of relapse in a previously known and treated primary cancer. To which extent the metastatic disease of the brain represented a relapse or a primary cancer diagnosis is unknown.

There is also a risk of bias in the distribution of patients with regard to age, gender and known primary tumour as well as postoperative radiation therapy. In our study, there is a high female-to-male ratio as well as a difference in adjuvant treatment, extracerebral disease and number of cerebral metastases. Due to the small size of the patient population and the primary aim of the study, we did not exclude patients on the basis of gender, extracerebral tumour activity, previous treatment or comorbidities but included all patients referred to and operated at our department.

Regarding the significance of incomplete resection in terms of survival and oncological outcome, there are multiple potential confounding factors. These include systemic therapy, comorbidities, primary tumour and presence of extracerebral metastases, all factors well known to influence survival [6, 11, 12, 16]. The limited size of the cohort in the present study makes further subgroup analysis of for instance primary tumour and systemic oncological therapy impossible. Further and larger cohort studies are necessary to investigate that.

The follow-up time ranges from 22 months for the first patient undergoing surgery to 4 months and 7 days for the final surgery during the study period. This may in turn affect the survival analysis including censored cases, as mean estimate survival is calculated from the date of the surgery to death, or the last day of data collection.

A multivariate analysis would strengthen the conclusion that EOR influences survival. Such an analysis was not performed due to the small patient population.

Not all patients received postoperative radiation therapy. This is acknowledged as a confounding factor in terms of survival. The group not receiving immediate postoperative radiotherapy is heterogenous in terms of oncological therapy, as some of the patients received radiotherapy at a later stage due to progression and some had previously undergone radiotherapy prior to surgery. The patients suffering from complications to their surgery lived for a short time, and thus did not receive radiotherapy. This study reflects daily practice at our department with consecutive heterogenous patients. For future studies, one might consider a narrower window for inclusion with regard to patients having a history of previous surgery and radiotherapy as well as the status of their primary cancer.

In addition, although the main primary cancer was lung cancer, the relatively limited material makes stratification according to primary cancer impossible, and no further analysis regarding size and localization of the metastatic lesions has been performed in the present study.

## Conclusion

The incidence of measurable residual tumour on early postoperative MRI after resection of brain metastases was 15/68 (22%). The intraoperative assessment of the operating surgeon has a limited value in assessing the extent of resection compared with early postoperative MRI. Despite the limitations in this heterogenous series, we found a significantly shorter postoperative survival time in the group of patients with the presence of measurable residual tumour on early postoperative MRI, compared with the GTR group. The longest survival in the study was found in patients with non-measurable and no residual tumour on early postoperative MRI, who also received upfront postoperative radiotherapy. Our results call for a larger-scale prospective study on the impact of complete surgical resection of cerebral metastases on outcome and survival.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This is a retrospective study. For this type of study, formal consent from the patients is not required.



## References

1. Ahn J, Lee S, Kim S et al (2012) Risk for leptomeningeal seeding after resection for brain metastases: implication of tumor location with mode of resection. J Neurosurg JNS 116(5):984–993 https://thejns.org/view/journals/j-neurosurg/116/5/article-p984.xml. Accessed Nov 2018
2. Albert FK, Forsting M, Sartor K et al (1994) Early postoperative magnetic resonance imaging after resection of malignant glioma; objective evaluation of residual tumor and its influence on regrowth and prognosis. Neurosurgery 34:45–61
3. Al-Shamy G, Sawaya R (2009) Management of brain metastases: the indispensable role of surgery. J Neurooncol 92:275–282. https://doi.org/10.1007/s11060-009-9839-y
4. Arbejdsgruppen for NKR, Hjernemetastaser (Working group for Danish national clinical guidelines brain metastases) (2014) National Clinical guideline Brain metastases (sundhedsstyrelsen): http://www.dnks.dk/fileadmin/user_upload/NKR_hjernemetastaser_klinisk_retningslinje_2014.pdf. Accessed July 2016
5. Benveniste RJ, Ferraro N, Tsimpas A (2014) Yield and utility of routine postoperative imaging after resection of brain metastases. J Neurooncol 118:363–367. https://doi.org/10.1007/s11060-014-1440-3
6. Berghoff AS, Rajky O, Winkler F et al (2013) Invasion patterns in brain metastases of solid cancers. Neuro-Oncology 15:1664–1672. https://doi.org/10.1093/neuonc/not112
7. Danish Neuro Oncological (working) Group (2014) Clinical guidelines for treatment of gliomas: http://www.dnog.dk/assets/files/Retningslinier%20PDF/DNOG-2014-Gliom-Retningslinje.pdf. Accessed july 2016
8. Danish Neurosurgical Society (DNKS) (2015) Guidelines for treatment of brain metastases / Retningslinier vedrørende behandling af hjernemetastaser: http://www.dnks.dk/fileadmin/user_upload/2015/DNKS_retningslinier_hjernemet_version_21_april_20151.pdf. Accessed July 2016
9. Höhne J, Hohenberger C, Proescholdt M et al (2017) Fluorescein sodium-guided resection of cerebral metastases—an update. Acta Neurochir 159:363. https://doi.org/10.1007/s00701-016-3054-3
10. Kamp MA, Rapp M, Buhner J et al (2015) Early postoperative magnet resonance tomography after resection of cerebral metastases. Acta Neurochir 157:1573–1580. https://doi.org/10.1007/s00701-015-2479-4
11. Kamp MA, Rapp M, Slotty PJ et al (2015) Incidence of local in-brain progression after supramarginal resection of cerebral metastases. Acta Neurochir 157:905–911. https://doi.org/10.1007/s00701-015-24-9
12. Lim CSK, Grundy PL (2013) Effectiveness and outcomes of surgery for cerebral metastases. Br J Neurosurg 27:654–657. https://doi.org/10.3109/02688697.2013.771729
13. Lin X, DeAngelis LM (2015) Treatment of brain metastases. J Clin Oncol 33:3475–3484. https://doi.org/10.1200/JCO.2015.60.9503
14. Lin NU, Lee EQ, Aoyama H et al (2015) Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol 16:e270–e278. https://doi.org/10.1016/s1470-2045(15)70057-4]
15. Mahajan A, Ahmed S, McAleer MF et al (2017) Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol 18(8):1040–1048

16. Orringer D, Lau D, Khatri S et al (2012) Extent of resection in patients with glioblastoma; limiting factors, perception of resectability and effect on survival. J Neurosurg 117(5):851–859. https://doi.org/10.3171/2012.8.JNS12234]
17. Preston JK, Masciopinto J, Salamat MS et al (1999) Tumour cell dispersion by the ultrasonic aspirator during brain tumour resection. Br J Neurosurg 13(5):486–489
18. Rogne SG, Ronning P, Helseth E et al (2012) Craniotomy for brain metastases: a consecutive series of 316 patients. Acta Neurol Scand 126(1):23–31. https://doi.org/10.1111/j.1600-0404.2011.01590.x
19. Schackert G, Lindner C, Petschke S et al (2013) Retrospective study of 127 surgically treated patients with multiple brain metastases: indication, prognostic factors, and outcome. Acta Neurochir 155(3):379–387. https://doi.org/10.1007/s00701-012-1606-8
20. Schebesch KM, Hoehne J, Hohenberger C et al (2015) Fluorescein sodium-guided resection of cerebral metastases-experience with the first 30 patients. Acta Neurochir 157(6):899–904. https://doi.org/10.1007/s00701-015-2395-7
21. Stummer W, Pichmeier U, Meinel T et al (2006) Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 7(5):392–401
22. Yoo H, Kim YZ, Nam BH ea (2009) Reduced local recurrence of a single brain metastasis through microscopic total resection. J Neurosurg 110(4):730–736. https://doi.org/10.3171/2008.8.JNS08448