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전이성 뇌종양 치료에서 수술적 절제의 역할: 17 년간의 종단연구

The role of surgical resection in managements of brain metastasis: A 17-year longitudinal study

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서울대학교 대학원
의학과 신경외과학 전공
이 창 현

A thesis of the Degree of Master of Medicine

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The Department of Neurosurgery,
Seoul National University, College of Medicine
Chang-Hyun Lee

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지도교수 김 동 규

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의학과 신경외과학 전공

이 창 현

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위 원 장 백 선 하 (인)

부위원장 ____________ (인)

위　　원 이 세 훈 (인)

The role of surgical resection in managements of brain metastasis: A 17-year longitudinal study

by
Chang-Hyun Lee
(Directed by Dong Gyu Kim, M.D., Ph.D.)

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Approved by Thesis Committee:

Professor Sun Ha Paek Chairman
Professor Kim Dong Gyu Vice chairman
Professor 이상훈 S H Lee

Abstract

The role of surgical resection in managements of brain metastasis: A 17-year longitudinal study

Objective

Advancement during the last decade has yielded several new treatment options for the management of brain metastases such as radiotherapy, chemotherapy, and stereotactic radiosurgery (SRS). However, surgical resection still remains the mainstay and is especially performed in the necessity of cases of decompression. The goal of this study is to evaluate the role of surgical resection for the patients with brain metastases by overall survival, recurrence, and functional outcome.

Methods

Between March 1995 and June 2011, a total of 194 consecutive patients had undergone surgical resection of brain metastases. The indications of surgical resection were to control intracranial pressure, to confirm pathological diagnosis, cystic lesions or intratumoral

hemorrhage, intractable seizures, and large metastasis. The postoperative adjuvant treatment was decided by the extent of surgical resection, and histology. Whole brain radiotherapy (WBRT) was usually administered at a conventional dose of 30 Gy in 10 fractions. SRS administered a dose in the range 15–24 Gy.

Surgical resection as the initial treatment was performed in 157 patients. Remaining 37 patients were excluded in this study because they had undergone other treatments such as SRS and/or radiotherapy before surgical resection. Among 157 patients, 109 (69.4%) and 17 (10.8%) patients underwent WBRT and SRS. Thirty one (19.7%) patients did not undergo adjuvant treatment. The extent of surgical resection was assessed by postoperative magnetic resonance imaging and operation record. Overall survival was defined as the interval from the date of metastasectomy through the date of death. The tumor-control was evaluated by local recurrence and distant metastasis. Functional status was evaluated by change of Karnofsky performance status (KPS) and recursive partitioning analysis (RPA).

Results

In total 157 patients, gross total resection (GTR) and subtotal resection (STR) were achieved in 119 (75.8%) and 38 (24.2%) cases, respectively. Neurogenic death accounted for 25% and non-neurogenic

death accounted for 75%. The overall median survival was 19.3 months. Median survival by surgical extent accounted for 20.4 and 15.1 months in the GTR and the STR group, respectively (*P*=.016). The patients with stable primary extracranial cancer showed significant longer overall survival than in patients of synchronous detection of extracranial cancer (*P*=.032). The RPA I class showed longer survival than the RPA II class (*P*=.047). This difference is prominent in the GTR group rather than the STR group (GTR, *P*=.022; STR, *P*=.075). There were no significant survival differences by clinical characteristics (age, gender, number of lesion, and histology of systemic disease). Overall local recurrence occurred in 15.7% of these patients. The local recurrence rate was 14.6% in GTR and 18.2% in STR (*P*=.589). Overall distant metastasis was detected in 43 patients (29.5%). The KPS score in the GTR group was changed from 82.3 to 87.0, and that in the STR group changed from 79.2 to 77.1 (*P*=.001). Postoperative complications occurred in 7 patients (4.5%). Two STR cases (1.3%) expired due to uncontrolled brain swelling and intracerebral hemorrhage.

Conclusion

Surgical resection shows favorable outcome in aspect of survival and clinical outcome. The extent of surgical resection, RPA class, and the status of extracranial condition are important prognostic factors in overall survival. Even in advancement of adjuvant therapies, surgical resection plays a major role in management of brain metastasis.

Keywords: brain, metastasis, surgery, survival, outcome

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Introduction

The American Cancer Society Registry 2008 indicates that more than 1.4 million people are diagnosed of cancer each year. Of these people, more than 40% are expected to have metastatic lesions in the brain, which is more than 10 times the number of individuals who will be diagnosed of a primary brain tumor.[1] Besides, the incidence of brain metastases is believed to be increasing, due to greater numbers of systemic cancer patients, improved treatment outcome of systemic tumors, leading to prolonged survival, and evolving imaging techniques with increased ability to detect smaller tumors.[12, 19]

Traditionally, brain metastases had been considered as a dismal disease with rapid neurological decline and gloomy prognosis with median survival of 4-6 weeks without any treatments.[2] It was not until the application of whole brain radiation therapy (WBRT) and corticosteroid, median survival was prolonged just a few months.[2] In that time, surgical resection [18] had a limited role for patients with brain metastases because of trivial survival improvements and unacceptable postoperative mortality until the 1980s.[9] However, the paradigm of brain metastases treatment recently has shifted from rare, dismal, and palliation to common, not disappointing, and disease control due to the advancement of neurosurgical techniques, radiosurgery, radiotherapy, and chemotherapy.

WBRT, together with corticosteroid administration, has played a key role in brain metastases treatment since the 1920s.[5, 8, 11] From 1971 to 1976, the Radiation Therapy Oncology Group (RTOG) conducted 2 phase III prospective randomized trials in an attempt to evaluate several treatment schedules. From those studies, 30Gy doses in 10 fractions emerged as the standard treatment for brain metastases patients. Until now, WBRT has been a mainstream of therapeutic strategies for brain metastases. Since stereotactic radiosurgery (SRS) was developed by Lars Leksell in the early 1950s, it has been applied to many intra- and extracranial lesions as a primary or secondary treatment. Recently, the National Comprehensive Cancer Network (NCCN) guidelines recommend SRS as a primary treatment for limited metastatic lesions (1 to 3 lesions).[13] However, the indication and timing of SRS for brain metastases have been controversial.

The first surgical series of brain metastases was published in 1926.[8] Prior investigators had reported that surgical resection for brain metastases, whether radical or palliative, is of no ultimate benefit insofar as prolongation of life is concerned. The reason was that median survival was under 6 months and operative mortality was as high as 30%.[8] Since a publication reported long-term survivors of brain metastases after surgical resection in 1933[14], and more studies began to report favorable outcomes following surgical resection.[3, 16] As imaging techniques, including computed tomography (CT) and magnetic resonance [17] imaging, became available and surgical techniques improved, surgical resection was reconsidered as an important modality for brain metastases.[2,7]

Surgical resection is strongly advocated in some situations. First, obtaining a biopsy specimen remains the gold standard for pathological diagnosis. This argument is supported by Patchell et al.,[16] who stated that approximately 11% of patients radiologically diagnosed with brain metastases actually had a different pathological diagnosis, such as brain abscess or primary brain tumor. Second, patients classified as recursive partitioning analysis (RPA) class I with solitary brain metastases need to undergo aggressive surgical resection followed by WBRT to promote survival, superior local control, and less recurrence.[7] Third, surgical resection is the only way to decompress emergent or critical mass lesions.

Many clinical investigations have attempted to find optimal treatment strategies for brain metastases. Unfortunately, level I recommendation is rare because there are many confounding factors, such as histology, status of extracranial cancer, tumor location, size, number, and resection state. In spite of many confounding factors, the clarification of surgical role and the remedy for shortcoming of surgical resection were needed because surgical resection can play an important role for brain metastases. They can be accomplished through thorough investigation. The goal of this study is to evaluate the role of surgical resection for the patients with brain metastases by overall survival, recurrence, and functional outcome.

Materials and Methods

Patient population

All consecutive patients who had undergone surgical resection for metastatic brain tumors at Seoul National University Hospital and Seoul National University Bundang Hospital from March 1995 through June 2011 were retrospectively investigated. The patients with malignant lymphoma, hematological tumors, or the patients who underwent brain biopsy only were also excluded in this study. A total of 194 consecutive patients had undergone surgical resection of brain metastases. The medical records and radiological images of the patients were reviewed. The indications of surgical resection were the following: 1) patients who needed to control intracranial pressure (ICP) and brain edema, 2) patients with an unidentified primary tumor who needed pathological confirmation, 3) patients with cystic lesions, including intratumoral hemorrhage, 4) patients with medically uncontrollable seizures due to brain metastases, and 5) patients with a large metastasis (>30 mm in maximum diameter). The patients who underwent other treatments as an initial treatment such as radiotherarpy and/or radiosurgery were excluded. Surgical resection as the initial treatment was performed in 157 patients. Remaining 37 patients were excluded in this study because they had undergone other treatments such as SRS and/or radiotherapy before surgical resection and might act confounding factor to investigate the surgical role.

The status of extracranial cancer was evaluated by historical review and divided into five groups: 1) no evidence of disease (NED), 2) stable systemic cancer, 3) progressive or uncontrolled primary cancer, 4) synchronous detection both brain metastases and extracranial cancer or systemic cancer detection by further evaluations followed by brain metastases diagnosis, and 5) unknown origin of brain metastases (primary extracranial cancer could not be detected despite full radiologic and nuclear medical studies). A retrospective RPA was performed based on three consecutive RTOG trials that included approximately 1200 patients with brain metastases.[6] All postoperative complications were investigated during the medical record review.

Treatment protocol

Multimodal treatments were categorized as SR+observation, SR+WBRT, and SR+SRS. Among 157 patients, 31 (19.7%), 109 (69.4%), and 17 (10.8%) patients underwent SR+observation, SR+WBRT, and SR+SRS, respectively. The extent of surgical resection was assessed by postoperative MR imaging and operation record and classified into the gross total resection (GTR) or subtotal resection (STR). The adjuvant modality was decided by the extent of surgical resection, tumor characteristics, and histology. WBRT was usually administered at a conventional dose of 30 Gy in 10 fractions. WBRT was given at 20 Gy in 10 fractions in elderly patients and those who had previously undergone WBRT.

SRS was performed using a Leksell Gamma Knife (Elekta Instrument AB, Stockholm, Sweden) models B, C, or Perfexion and the Leksell Gamma Plan^{TM} system (Elekta Instrument AB) based on 1.0-1.5-mm slices of MR images with contrast enhancement. The radiosurgery isodose, maximum dose, and dose to the margin were determined on the basis of the contrast-enhanced lesion volume, which was calculated during dose planning by use of the best-fit isodose method. The metastatic lesions usually received a dose in the range 15–24 Gy and the

Radiation Therapy Oncology Group 95-08 dosing guidelines were usually followed. [20]

Outcome measurement

Overall survival was defined as the interval between the date of metastasectomy and the date of death. Tumor control was evaluated by local recurrence and distant metastasis. Local recurrence was defined as a metastatic tumor recurrence at the surgical bed. Distant metastasis included the detection of new brain metastases other than those occurring at the surgical site. Preoperative functional status was evaluated by Karnofsky performance status (KPS) and RPA. Postoperative KPS was also measured at postoperative 4 weeks.

Statistical analysis

Each variable of three groups (SR+observation, SR+WBRT, and SR+SRS) were compared using chi-square tests. Chi-square tests and hazard ratios and corresponding 95% confidence intervals (CI) were calculated. Fisher's exact tests were used to calculate the significance of relationships between dichotomous variables. The reference point for survival was the date of treatment for brain metastases. Endpoints were death or the end of this study. Survival lengths were estimated using the

Kaplan-Meier method and were compared by a log-rank test. Univariate and multivariate analyses using the Cox proportional hazard model were performed to identify relevant factors affecting survival. The numeric factors analyzed in the Cox analyses were dichotomized according to the median number. All data were analyzed using SPSS version 17 for Windows (SPSS, Inc., Chicago, IL, USA). A *P*-value of less than 0.05 was considered statistically significant for all analyses.

Results

Patient characteristics

A total of 157 patients (82 males and 75 females) who underwent surgical resection for brain metastases enrolled in this study. Patient characteristics are described in Table 1. The average age at the time of surgical resection was 53.7 years (range 23-78 years). Single metastasis was diagnosed in 96 patients, and 61 patients had more than one lesion. The goal of neurosurgical treatment was ICP control in 49.7%, histological confirmation in 21.0%, and both in 29.3%. Tumor characteristics were cystic lesion in 22.3%, solid lesion in 51.0%, and mixed lesion in 22.9%. The brain metastases were divided into well-marginated (134 patients, 69.1%) and irregular (52 patients, 26.8%). In our series, 40 patients (25.5%) were RPA class I, 108 patients (68.8%)

Table 1. Patient demographics (n=157)

Characteristics	Number	% or range
Gender		
Male / Female	82/75	52.2% / 47.8%
Mean age (range)	53.7	(23-78)
Multiplicity		
Single / Multiple	96 / 61	61.1% / 38.9%
Tumor characteristics		
Cystic / Solid	35 / 80	22.3% / 51.0%
Mixed	36	22.9%
Mean diameter	40.06 mm	(11.50-80.14)
Extracranial cancer		
Lung	73	46.5%
Adenocarcinoma	46	29.3%
Squamous cell carcinoma	12	7.6%
Small cell carcinoma	10	6.4%
Etc.	6	3.2%
Breast	21	13.4%
Genitals	14	8.8%
Liver	7	4.5%
Kidney	4	2.5%
Aim of surgical resection		
Control ICP	78	49.7%
Confirm histology	33	21.0%
Both	46	29.3%
Recursive partitioning analysis (RPA)		
Class I / II / III	40 / 108 / 9	25.5%/68.8%/5.7%
Status of extracranial cancer		
NED	7	4.5%
Stable	70	44.6%
Progression	33	21.0%
Synchronous presentation	42	26.8%
Unknown	5	3.2%

Abbreviations: ICP, intracranial pressure; NED, No evidence of disease were class II, and 9 patients (5.7%) were class III. The average of KPS at admission was 81.3. Brain metastases were from lung (73 patients, 46.5%); breast (21 patients, 13.4%); genitals, including ovary, uterus, vagina, and prostate (14 patients, 8.8%); liver (7 patients, 4.5%); and kidney (4 patients, 2.5%). The extracranial primary cancer was undiscovered in 5 cases. The cause of death was identified in 44 patients. Neurogenic death such as brain swelling accounted for 25% and non-neurogenic death accounted for 75%.

In 157 patients, GTR was achieved in 119 cases (75.8%) and STR was achieved in 38 cases (24.2%), as determined by postoperative MR images. Among 157 patients, 31, 109, and 17 patients underwent SR+ observation, SR+WBRT, and SR+SRS, respectively. This information is listed in Table 2. GTR was accomplished in 73.8% of solid metastases, 74.3% of cystic metastases, and 80.6% of mixed tumors (*P*=.720).

Table 2. The patients distribution by the surgical extent and adjuvant treatments

	WBRT	SRS	NAT
GTR (119)	86	5	28
STR (38)	23	12	3
Total	109	17	31

Abbreviations: WBRT, whole brain radiotherapy; SRS, sterotactic radiosurgery; NAT, no adjuvant treatment; GTR, gross total resection; STR, subtotal resection.

Survival and relating factors

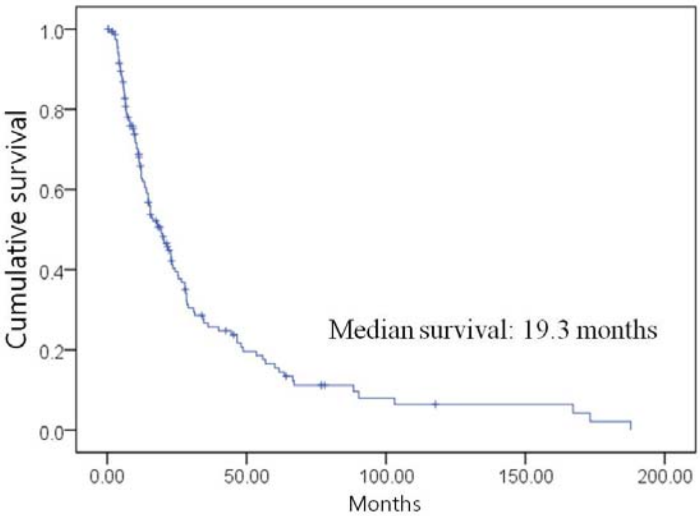

Figure 1. Overall survival plot for surgical resection patients. The median survival was 19.3 months.

The overall survival plot of this surgical series is depicted in Figure 1. The median survival of all 157 patients was 19.3 months. The survival curve by tumor characteristics is shown in Figure 2. The median survival was 12.3, 15.3, and 11.3 months in cystic, solid, and mixed brain metastases, respectively (*P*=.54). The survival plot according to preoperative state is illustrated in Figure 3. Median survival was 28.1, 23.3, 15.4, 13.5, and 187.8 months in NED, stable, progression, synchronous detection, and unknown origin, respectively (*P*=.071). The stable state group showed significant prolongation of overall survival more than the synchronous detection group (*P*=.032) The reliability of survival in the unknown primary cancer group because only 5 patients were enrolled in the group. The survival plot by treatment protocols is depicted in Figure 4. The median survival time was 15.5, 22.9, and 12.2

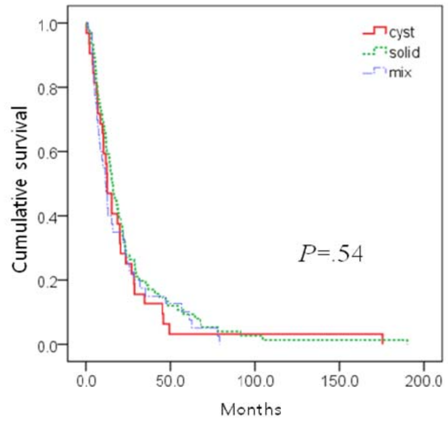

Figure 2. The survival plot by tumor characteristics. There were no significant relationships between survival and characteristics, such as cyst or solid.

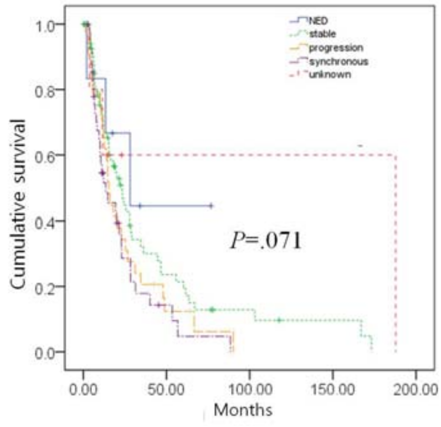

Figure 3. The survival plot by extracranial cancer status. There was no significant relationship between survival and extracranial cancer status.

months in SR+observation, SR+WBRT, and SR+SRS, respectively (*P*=.059). Median survival times by surgical extent are shown in Figure 5. Survival time was 20.4 months in the GTR group and 15.1 months in the STR group (*P*=.016).

Figure 6 illustrates the survival curves by adjuvant treatments in the GTR group; median survival was 15.5 months in the GTR+observation group and 25.5 months in the GTR+WBRT group (*P*=.155). Figure 7 demonstrates that the survival curve by adjuvant treatments in the STR group, which was 15.4 months in the STR+WBRT group and 12.2 months in the STR+SRS group (*P*=.371).

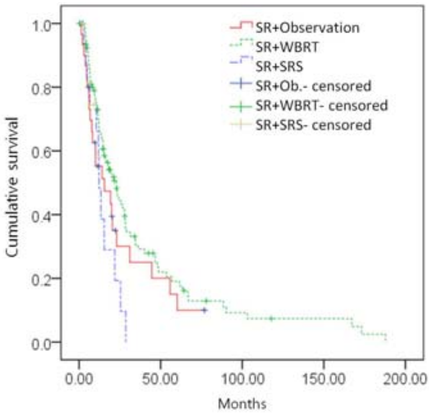

Figure 4. The survival plot by treatment method. There was no significant relationship between survival and treatment method.

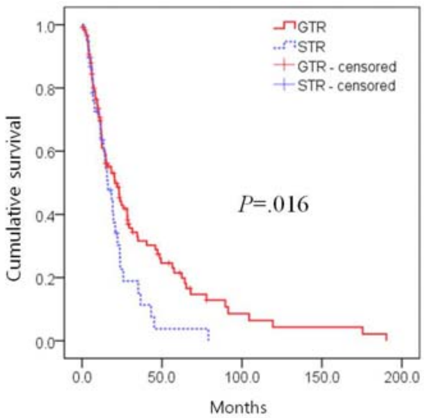

Figure 5. The survival plot by surgical resection extent. Patients that underwent GTR showed significantly longer survival times than patients who underwent STR. Median survival by surgical extent was 20.4 months in the GTR group and 15.1 months in the STR group (*P*=.016).

Multivariate analyses using the Cox proportional hazard model revealed that the extent of surgical resection significantly correlated with survival (hazard ratio, 1.675; 95% CI, 1.054-2.663; *P* =.029). No other factors related with overall survival, including histology (*P*=.57), extracranial primary cancer (*P*=.88), and multiplicity (*P*=.45). In the GTR group, overall survival did not differ (95% CI, 15.5 to 25.4; *P*=.45) between the two groups; median survival was 15.5 months (95% CI, 6.5 to 23.4 months) in the GTR+observation group and 25.5 months (95% CI, 14.8 to 31.6 months) in the GTR+WBRT group. In the STR group, overall survival did not differ (95% CI, 11.0 to 13.5; *P*=.89) between the

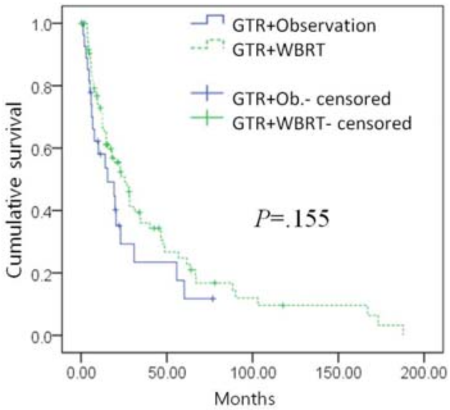

Figure 6. The survival plot by adjuvant treatment in the GTR group. Median survival was 15.5 months in the GTR + observation group and 25.5 months in the GTR + WBRT group (*P*=.155).

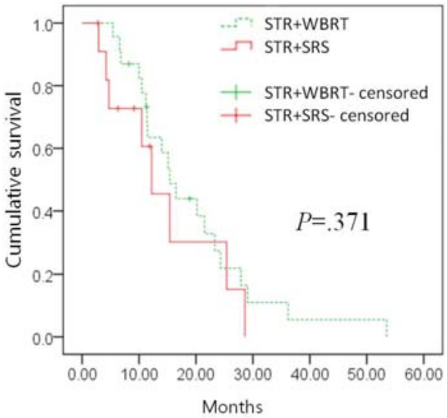

Figure 7. The survival plot by adjuvant treatment in the STR group. The median survival time was 15.4 months in the STR + WBRT group and 12.2 months in the STR + SRS group (*P*=.371).

two groups with a median survival of 12.2 months (95% CI, 0 to 34.1 months) in the STR+SRS group and 15.4 months (95% CI, 10.8 to 13.8 months) in the STR+WBRT group.

The median survival by RPA class was 10.9, 7.7, and 6.5 months in RPA class I, II, and III, respectively (I vs II, *P*=.047; I vs III, *P*=.635; II vs III, *P*=.412) in figure 8. In GTR group, the median survival by RPA class I, II, and III was 20.0, 10.0, and 4.5 months, respectively (RPA I vs II, *P*=.022; I vs III, *P*=.309;II vs III, *P*=.475). In STR group, the median survival by RPA class I, II, and III was 9.3, 7.5, and 18.0, respectively (I vs II, *P*=.075; I vs III, *P*=.102;II vs III, *P*=.230).

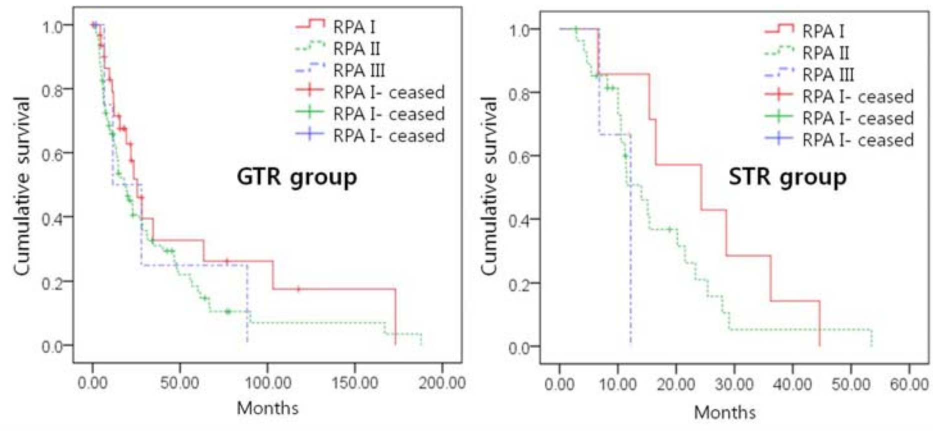

Figure 8. The survival plot by RPA class and the surgical extent. The RPA I group showed more prolonged survival than the RPA II (*P*=.047). In the survival difference between RPA I and II group patients, GTR showed a statistical significance (*P*=.022) and STR did not showed significance (*P*=.075)

Local recurrence and distant metastasis

Table 3. Local recurrence and distant metastasis by methods

	Local recurrence	*P*	Distant metastasis	*P*
GTR + Observation	5 (20.8%)	.463	4 (17.4%)	.196
GTR + WBRT	8 (13.1%)		30 (36.1%)	
STR + SRS	2 (18.2%)	.680	1 (10%)	.243
STR + WBRT	5 (21.1%)		7 (31.8%)	

Abbreviations: GTR, gross total resection; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; STR, subtotal resection.

Among 157 cases, local recurrence happened in 19 patients (15.7%); the compiled results are shown in Table 3. The local recurrence rate occurred in 14.6% and 18.2% in the GTR and STR groups, respectively (*P*=.589). Among the patients who underwent GTR, the local recurrence rate was 20.8% in SR+observation and 13.1% in SR+WBRT (*P*=.463).

In patients who underwent STR, local recurrence occurred in 18.2% in the SR+SRS group and 21.1% in SR+WBRT group (*P*=.680). When stratifying by tumor characteristics, the local recurrence was 11.5% for pure cystic tumors and 6.0% in solid tumors (*P*=.304). The local recurrence rate was 13.5% in adenocarcinoma of lung, 5.6% in infiltrating ductal carcinoma of breast, and 40.0% in renal cell carcinoma of kidney (*P*=.186). Local recurrence was not related to multiplicity, aim of surgical resection, the status of extracranial cancer, or tumor location.

In 157 patients, overall distant metastasis was detected in 43 patients (29.5%). Distant metastasis by tumor characteristics occurred in 31.4% of cystic tumors and 21.2% of solid tumors (*P*=.415). When stratifying by histology, distant metastases occurred in 23.5% of lung adenocarcinomas, 22.2% of breast infiltrating ductal carcinomas, and 0% in hepatocellular and renal cell carcinomas (*P*=.525). The mean age of patients with distant metastasis was 51.9 years, and patients without distant metastasis were 53.6 years old on average (*P*=.446). Distant metastasis occurred in 19.2% and 28.2% of controlled and progressed extracranial cancer cases, respectively (*P*=.346). Distant metastasis was not associated with multiplicity, aim of surgical resection, extracranial cancer, or tumor location.

Postoperative complications and functional outcome

Postoperative complications occurred in 7 of 157 patients (4.5%). The STR group accounted for 6 patients. The number of mortality case accounted for 2 cases (1.3%) and all 2 cases are on the STR group. One patient had visited emergency department due to seizure. Despite metastasectomy and decompressive lobectomy, they expired because of malignant brain swelling. One patient suffered from a huge metastasis with cerebral herniation. The patient died after surgical resection because of uncontrolled ICP. The other patients expired due to postoperative intracerebral hemorrhage. Postoperative brain swelling was observed in 5 patients and they recovered finally except one. One patient suffered from postoperative infection.

The postoperative KPS score improved in 36.3% of patients, was unchanged in 54.8%, and aggravated in 8.9% of patients. The KPS score in the GTR group was changed from 82.3 to 87.0, and that in the STR group changed from 79.2 to 77.1 (P=.001). In the GTR group, the change in KPS score was 3.9 (85.0→88.9) and 4.9 (81.1→85.9) in the GTR+observation and GTR+WBRT groups, respectively (P=.691). In the STR group, the change in KPS score was 0.0 (78.3→78.3) and -2.6 (79.6→77.0) in the STR+SRS and STR+WBRT groups, respectively (P=.465).

Discussion

Medical advances have introduced several new treatment options for managing metastatic brain lesions. Although the best management depends on the patient's individual prognostic factors, surgery remains an effective method in the treatment of these patients.[2] Prior authors suggested that surgical resection is currently recommended not only emergency decompression but also elective metastasectomy.[7] Despite the advantages of SRS or radiotherapy as local treatment, the studies relating surgical resection have demonstrated that surgery is beneficial for improving neurological status and survival.[12] Prior investigators reported that median survival time ranged from 10-16.4 months in surgical resection and mortality was <2%.[2] In this study, the median survival of surgical series patients in the last 17 years was 19.3 months, and mortality was 1.5%. Although near 80% of patients had to undergo surgical resection due to severe brain edema, survival and complications of surgical resection are comparable with those of other surgical series and other treatment combinations.[3,17] Besides, 5-ALA fluorescence-guided surgery has helped distinguish tumor from peritumoral tissue, which improves complete GTR.[21] With more advances in surgical techniques, intraoperative imaging and the risk of misdiagnosis without histological diagnosis, surgical resection is still a promising and reasonable treatment for brain metastases.

Survival and relating factors

We investigated factors that improve survival in the surgical resection group. In this study, *en bloc* GTR resulted in more favorable survival outcomes than STR. The median survival of the GTR group was significantly longer than that of the STR group (*P*=.016). Although GTR was recommended, it could not be always performed. Because surgeons consider functional outcome, they sometimes decide to perform STR and adjuvant treatment in some cases. In comparing STR followed by WBRT versus SRS, there was not a significant difference with regard to median survival time (*P*=.371). A review of the literature and the Guidelines for the Management of Brain Metastases also showed that no class I study has compared the use of SR+WBRT to SR+SRS.[7] Additional studies in this population are needed to consider optimal treatment protocols. However, KPS in STR+SRS was improved from 77.3 to 78.2. Conversely, KPS in STR+WBRT aggravated from 76.8 to 75.3 (*P*=.23). Although both adjuvant SRS and WBRT control residual tumor with similar efficacy, SR+SRS may be more favorable than SR+WBRT in aspect of postoperative KPS and treatment compliance of the patient. In the GTR group, adjuvant WBRT did not improve survival (*P*=.122) or KPS change (*P*=.67) between GTR+observation and GTR+WBRT. Therefore, the extent of surgical resection may be a key determinant of prognosis. In single brain metastases, GTR+observation may be a reasonable protocol.

Systemic cancer status can be defined by primary tumor activity and is known as a significant determinant of clinical outcome in the literature.[2] In this study, the patients in stable state of systemic cancer survived longer than the patients in synchronous detection of extracranial cancer (*P*=.032). The brain metastases patients with synchronous detection of extracranial cancer usually demonstrated progressive cancer stage, which may relate with short survival. The current trend that has emerged is to offer surgical resection only in cases when there is reasonable control of systemic cancer, and patients are expected to survive for more than 3-4 months.[2] In this investigation, the median survival of progressive state of extracranial cancer was 15.4 months. Clinicians may consider surgical resection of brain metastases with generous surgical indications even the patients in progressive systemic cancer state.

Preoperative RPA Classifications was known to related with overall survival. In this study, RPA I and II showed significant difference of survival.[7] However RPA III did not reveal any significance, which may be originated from few cases. Only 9 patients (6 GTR, 3 STR) belong to RPA III group. RPA classification helps to estimate the survival of brain metastases patients.

Local recurrence and distant metastasis

A previous study reported that local recurrence in SR+observation was higher than SR+WBRT patients; they stated that local control is essential and can be achieved with adjunct therapies following surgical resection.[15] Conversely, other authors reported that there was no significant difference in the local recurrence rate between the "microscopic total resection" alone and the GTR+WBRT.[22] The authors recommended aggressive surgical resection because tumor cell lay on the peritumoral tissue that look like normal tissue. In this study, we compared the GTR+observation and GTR+WBRT groups to evaluate the efficacy of WBRT. The GTR+WBRT group showed a tendency of better local control and survival than the GTR+observation group, but the result was not statistically significant (P=.463).

Local recurrence of pure cystic metastases was almost twice as frequent as that of solid metastases (11.5% versus 6.0%) (P=.304). Although this difference was not statistically significant, surgeons may perform more aggressive removal of cystic tumors. Local recurrence rate by tumor histologies ranged 5% - 40% without statistical significance. However, additional large studies are needed because local recurrence shows the tendency to be proportional to malignant potential of extracranial cancer.

Prior authors reported that distant metastasis-free survival was positively correlated with old age and absence of extracranial metastasis and negatively correlated with extracranial cancer progression in patients diagnosed of lung cancer and underwent SRS.[10] In this study, distant metastasis was not correlated with age or extracranial cancer. It might be associated with multiplicity and extracranial cancers. In spite of bias, the efficacy of adjuvant WBRT for preventing distant metastasis was still obvious. In patients who underwent STR, adjuvant WBRT did not affect the occurrence distant metastasis. Regardless of the extent of surgical resection, WBRT did not significantly decrease distant metastases.

Functional outcome

The postoperative KPS change in the GTR group was better than that in the STR group. Regardless the extent of surgical resection, the patient underwent WBRT showed worse KPS change than the others. The influence of radiation therapies on cognitive function is a matter of recent study due to the progressive increase in survival and treatment efficacy.[18] Both SRS and WBRT are related to cognitive impairment. In particular, WBRT is characterized by several adverse reactions (classified as acute, subacute, and delayed) due to exposure of high-dose radiation.[4] In this study, the patients underwent adjuvant WBRT slightly deteriorated KPS. SRS may be a preferable choice rather than WBRT in terms of quality of life.

This study has several limitations, heterogeneous population in terms of extracranial cancer and systemic condition and retrospective study design, all of which must be considered when interpreting the results. Chemotherapy was not considered in the study. One reason is anticancer agents showed diverse penetration rate of blood-brain barrier. The other reason is most patients need to use chemotherapy. However, chemotherapy usually irregularly stopped and halted due to poor general condition. The mixed nature of the patient population means that the results of the present study are more informative for physicians managing patients because they represent the general population of patients with brain metastases. A larger and more sophisticated randomized controlled study should be conducted to define the roles of surgical resection and adjuvant treatment.

Conclusion

Surgical resection shows favorable outcome in aspect of survival and clinical outcome. In this surgical resection series for brain metastases, the extent of surgical resection, RPA class, and the status of extracranial cancer are important prognostic factors in overall survival. Even in advancement of adjuvant therapies, surgical resection plays a major role in management of brain metastasis.

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국문 초록

전이성 뇌종양 치료에서 수술적 절제의 역할: 17년간의 종단연구

목적

지난 10년동안 전이성뇌종양의 치료는 방사선치료, 항암치료, 정위적 방사선수술(stereotactic radiosurgery [SRS])등의 발전을 보였다. 그러나 수술적 치료는 여전히 치료의 중심이고 특히 응급 뇌감압술이 필요한 경우에는 가장 중요한 치료이다. 이 연구는 전이성 뇌종양환자의 치료에 있어서 수술적 절제의 역할을 생존기간, 재발, 기능적 결과들의 면에서 평가하기 위함이다.

방법

1995년 3월부터 2011년 6월까지 총 194명의 수술을 받은 전이성뇌종양 환자들을 조사하였다. 수술은 뇌압조절이 필요한 환자, 병리진단이 필요한 환자, 낭성병변이나 종양내출혈, 조절되지 않는 경련발작, 거대종양의 경우에 시행되었다. 부가적인 치료는 수술적절제의 정도와 종양의 조직학적 소견에 따라 결정되었다. 전뇌방사선치료 (whole brain radiation therapy [WBRT])는 통상적인 30Gy, 10 fractions 의 방법으로 시행되었고 SRS는 권고사항에 따라 15-24Gy를 조사하였다.

종양의 치료로 수술을 가장 먼저 선택한 환자는 총 157명이었다. 나머지 37명은 수술전 방사선치료나 방사선 수술을 받아서 이 연구에서 배제되었다. 총 157명중 109명 (69.4%)는 수술 후 전뇌방사선치료(WBRT), 17명(10.8%)은 방사선수술(SRS)을 받았다. 31명(19.7%) 수술 후 부가적인 치료를 받지 않았다. 수술적절제의 정도는 전절제 (gross total resection)와 아전절제 (subtotal resection)로 분류하였다. 총생존기간은 전이암을 절제한 시점부터 사망할 때까지로 정의하였다. 종양조절의 결과는 국소재발과 원격전이로 분류하였다. 기능적인 평가는 Karnofsky performance status

(KPS)와 Recursive Partitional Analysis (RPA)로 측정하였다.

결과

총 157명중 전절제는 119명(75.8%) 이었고 아전절제는 38명(24.2%)이었다. 신경학적 사망은 25%였으며, 나머지 75%는 비신경학적 사망이었다. 평균생존기간 (median survival)은 19.3개월이었다. 평균생존기간은 전절제군에서 20.4개월이었고 아전절제군에서 15.1개월이었다 (P=.016). 두개외 원발종양의 상태에 따른 평균생존기간은 안정적인 상태인 경우가 원발종양과 전이뇌종양이 동시에 발견된 경우보다 의미있다 길었다 (P=.032). RPA I 환자군은 RPA II 환자들보다 더 생존기간이 길었다 (P=.047). 이 차이는 아전절제군 환자들보다 전절제군 환자들에서 의미있는 차이를 보였다 (GTR, P=.022; STR, P=.075). 그외 다른 인자들(나이, 성별, 병소의 개수, 원발종양의 종류)에 따라서는 평균생존기간에 의미있는 차이를 보이지 않았다. 국소재발은 총 15.7%에서 발생하였다. 전절제군에서는 14.6%가

발생하였으나 아전절제군에서는 18.2%가 발생하였다 (P=.589). 원격전이는 43명의 환자 (29.5%)에서 발생하였다. 수술 후 KPS는 전절제군에서 82.3에서 87.0으로 호전되었으나 아전절제군에서는 79.2에서 77.1로 악화되었다 (P=.001). 수술 후 합병증은 7명(4.5%) 에서 발생하였고 그 중 사망한 환자는 2명(1.3%)으로 모두 아전절제군의 환자였다. 사인은 조절되지 않는 뇌부종과 뇌출혈이었다.

결론

전이성 뇌종양환자의 치료에서 수술적 절제는 생존기간과 임상적 결과면에서 양호한 성적을 보였다. 수술적 전절제의 여부, RPA 분류, 두개외 원발종양의 상태에 따라 평균생존기간이 의미있는 차이를 보였다. 비록 부가적인 치료가 발달했다고 할지라도 수술적 절제는 전이성 뇌종양의 치료에 중요한 역할을 하고 있다.