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Brain metastases from stomach cancer – The role of different treatment modalities and efficacy of palliative radiotherapy

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ABSTRACT

Aim: To evaluate different treatment modalities, sequences, and prognostic factors in patients with brain metastases from stomach cancer.

Background: Brain metastases from gastric cancer are rare and late manifestation of the disease, occurring in less than 1% of gastric cancer patients. The prognosis is poor and median overall survival is 1.3–2.4 months. The standard treatment scheme has not yet been described. Most studies present small sample sizes. The choice of treatment scheme is individually based on performance status, number, location and size of metastases, the status of primary tumor and the presence of other metastases.

Materials and methods: Sixteen patients diagnosed with brain metastases from gastric cancer in Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch.

Patients, mostly men (69%) aged 51–75 years, (median 68.5 years). Thirteen (81.25%) had treatment of primary tumor before diagnosis of brain metastases. Primary metastatic gastric cancer was diagnosed in 6 patients (37.5%), in 3 cases (18.75%) brain was the site of those metastases. Treatment schemes were individually based.

Results: We identified prognostic factors influencing OS: performance status, number of brain metastases, type of treatment. Median OS was 2.8 months. Median time to brain metastases was 12.3 months and it was shorter in patients with pretreatment metastases to other organs. Patients treated with combined treatment had median survival of 12.3 months.

Conclusions: Aggressive treatment schemes are needed to improve the outcome. Prognostic factors such as performance status, number of metastases, dissemination to other organs are helpful in considering the best treatment options.

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1. Background

Stomach cancer is the third most common cause of cancer-related deaths worldwide (740,000 of deaths per year) after lung and breast cancer. The treatment results remain unsatisfactory. Over 30% of patients at the time of diagnosis is in advanced stages of the disease presenting with metastases mostly to the liver, lung or bones. Brain metastases from stomach cancer are uncommon, being diagnosed in 0.47–0.7% of patients; therefore, the standard treatment has not yet been established.[1–3]

Patients with brain metastases from gastrointestinal tract have generally poorer prognosis than patients with brain metastases from other cancers, for example breast or lung, where median survival is 2 months and 7 months, respectively.[2,4]

The symptoms of brain metastases are typical: headache, weakness, altered mental status, focal neurological deficits, gait or visual disturbances, ataxia. Sometimes brain metastases are asymptomatic.

There are several treatment modalities, and the choice of treatment scheme depends on the number and location of brain metastases, the presence of metastatic disease in other organs, the status of primary tumor site, and patient's performance status. In most cases the aim of treating metastases of any location is not to destroy all cancer cells, but to achieve an appropriate relief of symptoms and assure good quality of life.[5–7]

Surgery or stereotactic radiosurgery (SRS) and additional whole brain radiotherapy (WBRT) can be used in patients in good performance status and good prognosis (expected overall survival of 3 months or more), with up to three brain metastases. SRS is a very precise technique that delivers usually a single dose to a well-defined intracranial target with protection of normal surrounding brain tissue. It is a non-invasive method of radiotherapy resembling surgery but without perioperative complications.

SRS can be used for treating rather small tumors (up to 3 cm) and when there are up to three tumors in the brain, it can be also considered as a radiation boost to resection cavity.[6–9]

When the metastases are multiple, patients in good general condition are irradiated using whole brain radiotherapy. In patients in poor general condition, if the expected survival is less than 3 months and the brain metastases are multiple and inoperable, steroids and best supportive care can be used.[8]

The role of chemotherapy and radiosensitizers in the treatment of brain metastases remains undefined mostly because of the blood–brain barrier. WBRT can destroy blood–brain barrier, and consequently facilitate the penetration of cytostatic drugs to the brain tumor.

Brain metastases from stomach cancer are usually late manifestation of the disease and patients are often in severe cachexia and in bad performance status. Modern palliative chemotherapy and immunotherapy lengthen survival by a few months, and possibly the frequency of brain metastases from stomach cancer will rise; therefore, radiotherapy becomes an important treatment modality.

It is known that prognostic factors such as KPS, age, extracranial disease and primary tumor status are useful to choose a tailored strategy of treatment. Other factors, such as number, size, location of intracranial metastases, histology, interval between primary tumor diagnosis and detection of brain disease are also considered.[7]

2. Aim

There are few literature studies concerning treatment and prognostic factors in patients with brain metastases from stomach cancer; therefore, the authors decided to evaluate the efficacy of palliative radiotherapy, to describe different treatment modalities and sequences, and to analyze prognostic factors in this group of patients.

3. Materials and methods

Between 2002 and 2011, a total of 16 patients were diagnosed with brain metastases from stomach cancer at Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Gliwice. The data of all the patients were collected and retrospectively analyzed. The patients ranged in age from 51 to 75 years (median 68.5 years). There were 11 men (69%) and 5 women (31%). All patients had histologically verified gastric cancer. Metastatic gastric cancer was diagnosed during the first clinical examination tests in 6 patients (37.5%), and in half of the patients (18.75%) these were metastases to the brain. The detailed characteristics of patients are presented in Table 1.

Of the 16 patients, 9 (56.25%) underwent primary radical surgery after diagnosis of stomach cancer by biopsy. Four patients (25%) underwent palliative chemotherapy; in 1 case palliative gastrectomy was performed, in 2 cases (12.5%) chemotherapy was added to palliative radiotherapy. Three patients (18.75%) were not treated before diagnosis of brain metastases.

Brain metastases were diagnosed by magnetic resonance imaging (MRI), or contrast-enhanced computed tomography (CT). Having been diagnosed, the patients were proposed with several treatment options according to their prognostic factors. Three main treatment modalities were local, i.e. surgery and radiosurgery or whole brain radiotherapy. They could be used in different sequences.

In WBRT, two opposite fields techniques were used to deliver 20 Gy in 5 fractions with 6 MV photons to the whole brain while sparing critical organs, such as the lenses.

After WBRT, one or two fractions of stereotactic radiosurgery were delivered if patient met the criteria, i.e. regression of metastases to 3 cm of diameter or/and complete regression of some of multiple metastases to a total number of up to three tumors. SRS dose was individually defined based on patient's performance status and tumor volume or technical possibilities that are restricted by critical organs proximity (optic nerves, optic nerves chiasma, brain stem, internal ear).

Areas of incomplete regression were treated with 12–20 Gy in one or two fractions. Stereotactic radiosurgery was used after neurosurgery if there was a tumor mass left or as a boost to the resection cavity. Treated region was relatively small; therefore, the dose could be escalated to 20 Gy using 6 MV photons. The treatment regimens are presented in Table 2.

Table 1 – Characteristics of 16 Patients.

Characteristics	No. of patients (%)
Age (years)	68.5 (51–75)
Sex	
Male	11 (69%)
Female	5 (31%)
Pathology	
Adenocarcinoma no specific type	8 (50%)
Adenocarcinoma intestinal type	4 (25%)
Mucinous adenocarcinoma	2 (12.5%)
Other	2 (12.5%)
Primary metastatic disease	
Distant organs dissemination on diagnosis	6 (37.5%)
No distant organs dissemination on diagnosis of gastric cancer	10 (62.5%)
Pattern of metastases	
Brain only	4 (25%)
Brain and other organs	12 (75%)
Before brain metastases	−9 (56.25%)
Synchronous	−2 (12.5%)
Before other organs	−1 (6.25%)
Leading symptoms of brain metastases	
Muscle weakness	6 (37.5%)
Headache	5 (31.25%)
Lost of consciousness	3 (18.75%)
Epilepsy	2 (12.5%)
Performance status	
0–1	7 (43.75%)
2–3	7 (43.75%)
4	2 (12.5%)
Number of brain metastases	
1	8 (50%)
2–3	5 (31.25%)
>3	3 (18.75%)
Largest tumor size	
<3 cm	10 (62.5%)
≥3 cm	2 (12.5%)
No data	4 (25%)

Table 2 – Treatment of brain metastases.

Treatment of metastases	No. of patients (%)
Single modality treatment	7 (43.75%)
SRS	2 (12.5%)
WBRT	4 (25%)
Surgery	1 (6.25%)
Best supportive care (steroids)	3 (18.75%)
Combined treatment	6 (37.5%)
SRS + WBRT	1 (6.25%)
Surgery + WBRT	3 (18.75%)
Surgery + WBRT + CT	1 (6.25%)
Surgery + SRS + WBRT + CT	1 (6.25%)

SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; CT, chemotherapy.

Overall survival (OS) was analyzed, defined as the interval between diagnosis of brain metastases from gastric cancer and the date of death. Time to brain metastases (TBM) defined as time from diagnosis of gastric cancer to first symptoms of brain metastases was also assessed. Different prognostic factors were evaluated.

The Kaplan–Meier method was used to evaluate overall survival. The comparison of survival curves was made using the Cox-*F* test, *p* value of less than 0.05 was considered statistically significant.

4. Results

Median time to brain metastases (TBM) was 12.3 months (Fig. 1). Median TBM was shorter for patients with pretreatment metastases to other organs compared with patients without metastases (5.5 months vs. 12.6 months, $p = 0.042$). Median TBMs were 12.8 months (range, from 0.8 month to 52 months) and 5.4 months (from 0.8 month to 52 months), respectively, for 9 patients after R0 resection and for the 7 remaining patients ($p < 0.05$). The following clinical features were not prognostic for TBM: gender, age, number, location and largest size of brain tumor, location of other metastases.

The 1- and 2-year OS were 19% and 12.7%, respectively. Median OS was 2.8 months. Amongst different clinical factors influencing OS performance status, number of brain metastases, pattern of metastases (synchronous vs. non-synchronous) and type of treatment were statistically significant (Table 3). There was no statistically significant effect noted on OS for gender, tumor grade, type of neurological symptoms, or location and the largest size of brain metastases. However, patients under the age of 60, and patients with TBM of less than 6 months tended to have a more favorable prognosis ($p < 0.1$).

All patients completed treatment without any serious complications. Tolerance of radiotherapy was fair.

5. Discussion

Radiotherapy brings more possibilities for combined treatment; nevertheless, it is still not easy to identify the best option, as there are no large studies comparing methods of treatment of metastases to the brain from stomach cancer. Type of treatment is the most important factor. In our study, patients who after neurosurgery received WBRT or WBRT and radiosurgery to the residual tumor mass or to resection cavity lived much longer, their median overall survival being 12.3 months.

York et al. divided 19 patients with brain metastases from stomach cancer who were treated at M.D. Anderson during 40 years in three groups: those who received steroids only, surgery and WBRT, and WBRT only. Patients who had surgery and WBRT showed statistically significantly better survival (median 54 weeks) than those who were treated with steroids only (median 7 weeks) but better survival was noted only in younger patients and in those with a good performance status. Median OS of all patients, i.e. 2.4 months, was similar to that in our group.[1]

Patients who had neurosurgery along with adjuvant postoperative treatment had better outcome and that was similar to the study by Kasakura et al. that analyzed the median survival of 11 patients with brain metastases from gastric cancer. Three of them were treated with surgical resection of metastases and, postoperatively, with chemotherapy (2 cases) or radiotherapy (1 case). Patients in the resection group lived longer, i.e. 6 months, than those in the best supportive care group, i.e. less than 1 month ($p = 0.017$).[3] In this study,

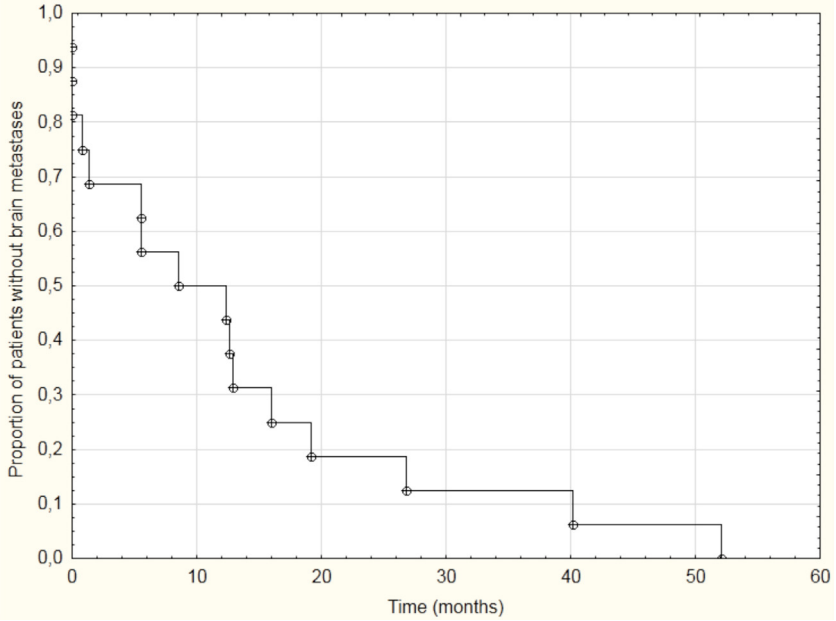

Fig. 1 – Curve of time to brain metastases from gastric cancer for 16 patients.

Table 3 – Prognostic factors influencing overall survival rate.

Prognostic factors	No. of patients	Median OS (months)	1-Year OS (%)	*p* value
Performance status				
0–1	7	8.5	43	0.017
2–4	9	2.5	0	
Number of brain metastases				
1–3	13	3.9	23	0.026
>3	3	1.3	0	
Metastases to other organs				
Yes	12	2.6	8	0.018
No	4	12.7	25	
Pattern of metastases				
Brain only or brain before other organs	5	12.2	60	0.006
Brain and other organs – synchronous	11	2.6	0	
Type of treatment				
Single modality (S,SRS, WBRT)	7	12.5	0	0.017
Best supportive care (steroids)	3	0.9	0	
Combined modality	6	12.3	50	
Chemotherapy				
Yes	2	12.2	100	0.046
No	14	2.6	7	

SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; S, surgery.
Combined modality: SRS + WBRT, S + WBRT, S + WBRT, S + WBRT + CT, S + WBRT + SRS + CT.

postoperative chemotherapy could also play an important role in lengthening survival.[3]

In our study, two patients who received chemotherapy after the diagnosis of brain metastases lived 12.2 months, whereas those without chemotherapy had the median overall survival of 2.6 months ($p = 0.046$). One patient after neurosurgery for brain metastases had palliative radiotherapy and because of cervical lymph node metastases received VI courses of chemotherapy PELF. Another patient after neurosurgery of one brain metastasis received SRS (2× 20 Gy) to a second brain metastasis and WBRT and VI courses of chemotherapy PELF, because of inoperable stomach tumor.

Patients who had surgery only, SRS only or WBRT only, or SRS and WBRT had median survival of 2.8 months. Five patients treated with radiosurgery alone lived 3.04 months after SRS. Nevertheless, patients who received SRS alone had no tumor progression until fifth month after treatment. Aoyama et al. showed that adding WBRT to local treatment improves locoregional control: after 1 year, 53.2% of patients had a good local control in WBRT and SRS arm compared to arm with SRS where only 23.6% of patients maintained local control. There were no differences in overall survival.[6]

The possible explanation of the role of WBRT in this treatment sequence is in destroying micrometastases. The impact

of WBRT on reducing the incidence of brain tumor relapse has been demonstrated in several randomized trials. The omission of WBRT results in a brain relapse risk of 70% versus 18% when WBRT is used.[3,5]

In the study by Park et al., the efficacy of radiosurgery, whole brain radiotherapy and surgery in different sequences was investigated. In that study, 11 patients had RS alone with median survival of 40 weeks. Forty-one patients were treated with WBRT alone and had a significantly shorter median survival of 9 weeks.[9]

The shortest median survival of that of three patients treated with best supportive care (BSC) and steroids. The worst survival in BSC patients may be also explained by a bad performance status of patients that disqualified them for radiotherapy.

In the study by Kasakura, patients treated with BSC lived from 0.5 to 1.3 month,[3] while in the York study it was 7 weeks.[1]

Several studies compared different sequences of treatment and the efficacy of radiosurgery. We found that if we treat with radiosurgery alone the survival could be worse (2.6 months) than with neurosurgery combined with SRS and WBRT, but the small sample size precludes meticulous statistical analysis. The survival time is similar to that from the study by Han et al. that reported 11 patients treated with radiosurgery with or without WBRT. Six patients treated with WBRT and SRS had a tendency to longer median survival time (19 months after SRS) compared to five patients treated with radiosurgery alone (3.04 months after SRS).[2,10,11]

Metastases to other organs did have a significant influence on overall survival rate. Patients who had only brain metastases had median survival of 12.7 months compared to those with dissemination to other organs where median survival was 2.6 months ($p = 0.018$). In the study by Han et al. age, the WHO performance status or the presence of metastases to other organs than the brain did not have a statistically significant influence on survival time.[2]

In the study by Park et al. the investigators evaluated the recursive partitioning analysis as the prognostic factor and found that patients in class 2 had a more favorable prognosis than patients in class 3; therefore, stereotactic radiosurgery was more effective in patients in RPA class 1 and 2 than in class 3.[9]

The recursive partitioning analysis (RPA) classification is useful in determining prognosis in cerebral metastases. Patients in class 2 are those with Karnofsky score (KPS) > 70, older than 65 years, with extracranial spread and uncontrolled primary tumor. Patients in class 3 have KPS < 70. The survival in months is, respectively, 4.2 and 2.3 months.[9,12,13]

Patients with KPS of less than 70% will benefit more from WBRT compared to the other type of brain radiotherapy regardless of the type of brain impairment.[5]

In 2010, Sperduto et al. elaborated Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) identifying prognostic factors in patients with brain metastases considering primary tumor histopathology. In gastrointestinal cancer, KPS status was the only prognostic factor determining DS-GPA score.[13,14]

In our study, the performance status is also an important and strong prognostic value as the median overall survival for patients in good general condition was 8.5 months and those with a poor performance status had the median survival of 2.5 months, and it was statistically significant ($p = 0.017$).

Generally, compared to neurosurgery, radiotherapy, and especially stereotactic radiosurgery, causes less serious complications and fewer deaths connected to treatment. Side effects of the treatment were not observed in patients of this initial series. However, radiotherapy-only based treatment produced poorer outcome than combined aggressive schemes.[9,10,15,16]

6. Conclusions

Brain metastases from gastric cancer are very rare and difficult to treat. The response to radiotherapy is worse than in brain metastases from other cancers and the survival is also shorter. Therefore, more aggressive treatment schemes, such as neurosurgery, combined with stereotactic radiosurgery, palliative radiotherapy and chemotherapy are needed to improve the outcome.

The results of this study show that combining neurosurgery with adjuvant radiotherapy and chemotherapy improves survival. Our study also indicates the prognostic factors, such as performance status, number of metastases and dissemination to other organs, as helpful in considering the best treatment options.

Conflict of interest

None declared.

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None declared.

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