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Characteristics of long-term survivors of brain metastases from lung cancer

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ABSTRACT

Background and aim: Long-term survival of lung cancer patients with brain metastases (BM) is very rare. Our aim is to report the characteristics of patients who survived for at least three years after a BM diagnosis.

Materials and methods: Nineteen lung cancer patients who had survived ≥3 years after a BM diagnosis were identified in our database. Seven (37%) had undergone whole-brain radiotherapy (WBRT) only, five (26%) BM surgery + WBRT, three (16%) BM surgery + WBRT + BM radiosurgery, and four (21%) no WBRT (one, surgery; one, radiosurgery; two, BM surgery + radiosurgery). Their characteristics were compared with historical data for 322 lung cancer patients with BM (control group, CG), who had received WBRT between 1986 and 1997.

Results: Median survival from BM in long survivors group was 73 months (in CG – 4 months). Characteristics comparison: median age 55 vs. 58 (CG), $p = 0.16$; female sex 68% vs. 28% (CG), $p = 0.003$; RTOG/RPA class 1 – 75% vs. 13% (CG), $p = 0.00001$; adenocarcinoma histology 84% vs. 24% (CG), $p < 0.00001$; control of primary tumor 95% vs. 27% (CG), $p < 0.00001$; extracranial metastases 0 vs. 26% (CG), $p = 0.01$; single BM 63% vs. 9% (CG), $p = 0.00001$; surgery of BM 53% vs. 14% (CG), $p = 0.00001$.

Conclusions: Beside prognostic factors already recognized as favorable in patients with BM, the adenocarcinoma histology and female sex were prevalent in long-term survivors of BM from lung cancer.

1. Background and aim

Approximately 15–30% of lung cancer patients develop brain metastases (BM), according to epidemiological studies.[1,2] The incidence is higher in more advanced disease stages and with small-cell lung carcinoma (SCLC) and adenocarcinoma histology. There has been an increasing incidence of BM over the last few decades. A population-based Swedish study showed that the rate of age-adjusted hospital admissions

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for BM doubled between 1987 and 2006.[2] This increase is related to the better diagnostic methods available and some progress in the treatment of locally advanced non-small cell lung carcinoma (NSCLC). A review of the Radiation Therapy Oncology Group (RTOG) data showed that longer survival with locally advanced NSCLC is associated with a higher incidence of BM.[3]

Despite advances made in surgery, radiation oncology and systemic treatments, the prognosis of lung cancer patients with BM remains dismal. The median survival has not improved with time and is still about three months.[2] Survival may be increased to 7–13 months in selected patients when surgery[4,5] or stereotactic radiotherapy[6] is used to complement whole-brain radiotherapy (WBRT). WBRT, which is commonly used in the treatment of BM, has never correlated with improvement of survival in randomized trials.[7,8] However, the prognosis of patients with BM is determined by variables other than therapeutic strategies. RTOG recursive partitioning analysis (RPA) identified a good performance status, control of the primary tumor, no extracranial metastasis, and younger age as factors associated with improved survival.[9] However, the median survival of these favorable patients is still only about six months. Therefore, a question arises about the additional factors to offer chance for long survival in BM from lung cancer. To answer this question, we searched for long-term survivors of BM from lung cancer in our database and compared the characteristics of these patients with those of the whole cohort of patients with BM from lung cancer.

2. Materials and methods

A review of the database at the Department of Radiation Oncology of the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw (Poland) identified 19 patients (long-term survivors) who had survived for at least 3 years after the diagnosis of BM from histologically confirmed lung cancer, who had been treated and/or followed up between 1986 and 2006. Three hundred twenty-two patients with BM from lung cancer were treated between 1986 and 1997 and an additional 600 such patients were treated between 1998 and 2006. We do not have complete data for patients treated between 1998 and 2006, so it is probable that there were more three-year survivors, but they were not followed up in our centre. However, for the period between 1986 and 1997, we had five such patients. This allows us to speculate that the proportion of three-year survivors from BM in the entire cohort of such patients is about 2%. The presence of BM was confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). The medical records of all 19 patients were available for review. Their records were compared with the records of 322 lung cancer patients with BM (the control group, CG) treated with WBRT between 1986 and 1997. We chose this control group because of the completeness of their data in terms of prognostic factors, treatment, and survival, as the results of their treatments have been published previously.[10]

The characteristics of the patients in both groups were compared with regard to age, sex, Karnofsky performance status (KPS), RTOG/RPA class (outline 1),[9] histology, control of the primary tumor at the time of BM diagnosis, presence of extracranial metastasis at the time of BM diagnosis, interval from diagnosis of the primary tumor to the development of BM (metachronous vs. synchronous [BM diagnosed within one month of the primary tumor]), number of BM (single vs. multiple), the use of surgery in the treatment of BM, and the use of radical surgery in the treatment of the primary tumor.

Outline 1. RTOG/RPA prognostic classes of patients with brain metastases.

RTOG/RPA prognostic classes[9]
Class 1: Patients younger than 65 with control of the primary tumor and no extracerebral metastases and Karnofsky performance status (KPS) at least 70%
Class 3: Patients with KPS less than 70%
Class 2: All others

All the patients in the CG underwent WBRT for the management of BM; 105 (33%) received 20 Gy in 4 Gy fractions, 183 (57%) received 30 Gy in 3 Gy fractions, and 32 (10%) received 40 Gy in 2 Gy fractions. Only 44 (14%) patients had undergone previous surgery for BM. Stereotactic radiosurgery (SRS) was not available at that time. Among the 19 long-term survivors, seven (37%) underwent whole-brain radiotherapy (WBRT) only, five (26%) had BM surgery and WBRT, three (16%) had BM surgery and WBRT followed by SRS for residual tumor, and four (21%) had no WBRT at all (one, BM surgery only; one, SRS only; and two, BM surgery and SRS). The WBRT dose was 30 Gy in 10 fractions in 13 patients (81%); three other patients received different schedules (36 Gy in 12 fractions, 37.5 in 15 fractions, and 56 Gy in 28 fractions). The doses of linac-based SRS varied between 15 and 26 Gy in one fraction. The relative frequencies of the prognostic factors were compared between the control group and long-term survivors with a χ^2 test.

Survival was calculated from the date of diagnosis of BM. It was estimated using the Kaplan–Meier method.

3. Results

3.1. *Survival and pattern of failure in long-term survivors*

The median survival for 19 long-term survivors was 73 months (range: 36–137 months), whereas that for the entire cohort of 322 CG patients was four months ($p = 0.00001$). Seven patients remained alive at the time of the last follow; two of them experienced successfully salvaged intracranial recurrence (one with SRS and one with surgery), both outside the primary tumor bed. Of the 12 patients who died, six experienced an intracranial recurrence. For three of them, the brain recurrence was successfully salvaged with SRS. The causes of death of 12 patients were: three, brain relapse; two, progression of the lung cancer outside the brain; two, second primary (pancreatic adenocarcinoma and anaplastic thyroid cancer); one, stroke in a patient with a history of cerebral vascular incidents preceding WBRT; and four, unknown (at 38, 52, 62, and 68 months of follow-up). In five of the eight patients diagnosed with intracranial recurrence, no WBRT was given as the primary treatment.

3.2. *Comparison of characteristics between long-term survivors and control group (CG)*

The results of comparison of the characteristics of the long-term survivors vs. controls are reported in Table 1. There was a significant difference in the RTOG/ RPA class distributions ($p = 0.0001$): class 1, 75% vs. 13% in CG; class 2, 25% vs. 67% in CG. There were no RPA class 3 patients among the long-term survivors. All the RPA/RTOG class 1 components, except age, were significantly associated with long-term survival. Of the long-term survivors, 68% were female, whereas only 28% of the CG were female ($p = 0.003$). No patient with BM from SCLC survived for three years. The histological comparison showed a high incidence of adenocarcinoma in the long-term survivors (84% vs. 23% in CG; $P < 0.00001$). The proportion of patients whose primary tumor was treated surgically was much higher among the long-term survivors (58% vs. 9% in CG, $p = 0.00001$). Surgery for BM was also related to long-term survival (53% vs. 14% in CG, $p = 0.00001$).

Table 1 – Characteristics of 322 patients from control group and 19 long-term survivors (patients surviving for at least 3 years with brain metastases).

Characteristics (p-value)	Control group [number (%)][a]	Long-term survivors [number (%)][a]
Gender ($p = 0.003$)		
Male	232 (72)	6 (32)
Female	90 (28)	13 (68)
Age ($p = 0.16$)		
Median [range]	59 [31–79]	55 [42–71]
<65 years	241 (75)	15 (79)
≥65 years	81 (25)	4 (21)
Histology		
SCLC ($p = 0.0004$)	132 (41)	0 (0)
Squamous carcinoma	67 (20)	3 (11)
Adenocarcinoma ($p < 0.00001$)	76 (24)	15 (84)
Large cell carcinoma	3 (1)	0 (0)
NSCLC without type specification	44 (14)	1 (5)
RTOG/RPA prognostic class ($p = 0.0001$)		
Class 1	41 (13)	14 (75)
Class 2	215 (67)	5 (25)
Class 3	66 (20)	0
KPS ($p = 0.03$)		
>70	256 (80)	19 (100)
≤70	66 (20)	0
Presence of extracranial metastases ($p = 0.01$)		
Yes	83 (26)	0
No	229 (71)	19 (100)
Unknown	10 (3)	0
Control of the primary tumor ($p < 0.00001$)		
Yes	88 (27)	18 (95)
No	222 (69)	1 (5)
Unknown	12 (4)	0
Number of BM ($p = 0.00001$)		
Single	124 (39)	12(63)
Multiple	190 (59)	7(37)
Unknown	8 (2)	0
Interval from diagnosis of the primary to development of BM ($p = 0.44$)		
Synchronous	147 (46)	7(37)
Metachronous	175 (54)	12(63)
Surgery of BM ($p = 0.00001$)		
Yes	44 (14)	10 (53)
No	278 (86)	9 (47)
Surgery in the treatment of the primary ($p = 0.00001$)		
Yes	30 (9)	11 (58)
No	292 (91)	8 (42)

[a] Unless otherwise stated.

4. Discussion

We have demonstrated that only about 2% of patients survived for three years in this entire cohort of patients with BM from lung cancer. This confirms that the prognosis for patients with BM from lung cancer is very poor, and that only selected patients will survive in the long term. Reports of other series confirm that long-term survivors are rare: 5–13% of patients live for two years and 2–2.5% for five years.[11–13] In contrast, the results of aggressive treatment of the primary lung tumors with surgery or radiochemotherapy and of brain metastases with surgery or SRS have been reported as promising, with five-year survival rates of 11–21%.[14–16] Although BM surgery was also associated with improved survival in our previous study,[10] three-year survival was extremely rare. Some incompleteness in our data should be acknowledged, as stated in Section 2, so we cannot exclude the possibility that some additional patients survived for three years but were not recorded. However, we do not think that there were many such cases, because all the patients treated with SRS and practically all those treated with BM surgery and WBRT, or who deliberately refused WBRT, were followed up at our institution. Regardless of the possible bias caused by some missing data, we were able to gather information about the characteristics of long-term survivors.

The confirmation of recognized favorable prognostic factors, such as the RTOG/RPA class 1 components, including the control of the primary tumor, the absence of extracranial dissemination, and a good performance status, was expected. However, the median survival of RPA class 1 patients is only about 6–7 months. Aggressive local treatment of BM with surgery or SRS may prolong survival.[4–6] Additional factors, other than the therapeutic strategy used, may relate to long-term survival. In our group of 19 three-year survivors, about one-third were treated with WBRT only, which emphasizes the role of the biology of the tumor and other patient-dependent factors in survival. In randomized trials, WBRT did not improve survival,[7,8] but did improve intracranial control. In our series, the limited number of events and the varied treatment strategies do not allow us to draw any firm conclusions about the relationships between the treatment, the relapse pattern, and long-term survival.

We identified two additional factors related to long-term survival in BM from lung cancer: female sex and histological type, which are not included in the RTOG/RPA prognostic classes, enclosing BM from all solid tumors. Female sex

appears to be an independent favorable prognostic factor in lung cancer patients.[17,18] It has also been confirmed as such in patients treated with radiation[19] and in patients with BM.[10,20] Possible explanations of the better prognosis in females include the influence of social, hormonal, or tumor-related factors. In a recently published study by McGovern et al.,[19] the authors concluded that survival differences between men and women with NSCLC occur because the disease develops and progresses differently according to inherent biological differences between the sexes. For women with NSCLC, pathology examinations more frequently reveal an adenocarcinoma than a squamous cell carcinoma. In a prospective study of 4618 patients with stage I–IV NSCLC at the Mayo Clinic, 60% of women and 48% of men had adenocarcinoma, whereas 22% of women and 32% of men had squamous cell carcinoma ($p < 0.01$).[18] We found a significantly higher incidence of adenocarcinoma in long-term survivors (84% vs. 23% in CG). Adenocarcinoma histology has been associated with a better prognosis in some series of patients with BM from lung cancer,[21] but not in others.[10,22,23] However, long-term survivors have a predominant adenocarcinoma histology.[24] We hypothesize that some types of BM from lung adenocarcinoma have different molecular characteristics, which make them a different and curable clinical entity, as opposed to the large majority of BM cases, which appear incurable. Some data already suggest that the genetics of BM from lung cancer may affect treatment results. In a study by Gow et al.,[25] patients with epidermal growth factor receptor (EGFR) mutations had a higher response rate to WBRT than patients with wild-type EGFR.

No patient with BM from SCLC survived for three years in our series and no long-term survivors were reported in other series,[11–13] which confirms a particularly poor prognosis of such patients. This can be explained by the biology of SCLC, because the occurrence of BM is usually a sign of the progression of the extracranial disease in these patients.[26]

In conclusion, long term survival in patients with BM from lung cancer is rare. Very few selected patients from RTOG/RPA class 1 may survive in the long-term, and more aggressive treatment is related to longer survival. However, RTOG/RPA class 1 and aggressive treatment are not sufficient to ensure long-term survival. Additional unidentified factors, probably indicative of biological differences, which are very likely to be related to female sex and adenocarcinoma histology, should be considered. Further research is required to precisely identify the female patients with BM and/or patients with BM from adenocarcinoma who have such a favorable prognosis.

Conflicts of interest

There were no financial and/or personal relationships with other people and organizations that could inappropriately influence (bias) this work.

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