

Review

Recent Trends in Epidemiology of Brain Metastases: An Overview

EMELINE TABOURET^{1,3}, OLIVIER CHINOT^{1,3}, PHILIPPE METELLUS^{1,3},
AGNÈS TALLET², PATRICE VIENS^{2,3} and ANTHONY GONÇALVES^{2,3}

¹AP-HM, Timone Hospital, Departement of Neuro-oncology and Neuro-surgery, Marseille, France;

²Institut Paoli-Calmettes, Departement of Medical Oncology, Marseille, France;

³Aix-Marseille Université, Marseille, France

Abstract. Brain metastases (BM) are the most common intracranial neoplasm in adults. Initially considered as an essentially terminal stage of advanced cancer, BM are increasingly being recognized as an emerging area of clinical interest. Their epidemiological characteristics have changed significantly, including an increased incidence in tumors frequently associated with BM, such as lung and breast cancer or melanoma, but also a more frequent occurrence with other primary tumor entities such as renal, colorectal and ovarian cancer. BM are more commonly diagnosed in multiple intracerebral sites, but in the context of controlled extracranial disease. Accordingly, progress in the development of systemic treatments, together with the rationalized use of surgical resection, radiosurgery and whole-brain radiotherapy, have led to an increase in the number of long-term survivors and in median survival. The recent emergence of targeted therapies and growing knowledge regarding the specific biology of BM should allow further improvements in prognosis of this devastating disease.

Brain metastases (BM) are the most common intracranial neoplasms in adults (1, 2). Classically, diagnosis of BM was considered to represent a poor prognosis event for patients,

frequently corresponding to the initiation of the terminal phase of the disease. The estimated overall survival was short and therapeutic options were often palliative and with limited, intent (3). Improvements in local procedures combined with the increasing availability of systemic treatments, including emerging targeted therapeutics, have substantially modified the prognosis and survival of patients with BM (4). Indeed, the number of potentially active therapeutic lines is increasing and available therapies may control many metastatic tumors for months or even years (5). Accordingly, although the incidence of cancer is generally stable, mortality rates are declining, while the median survival duration has been improved in advanced stages (3, 6-8). Such progress in systemic treatments, as well as improvement in imaging detection, has both lead to an increased incidence of BM and changed the characteristics of corresponding patients.

In this context of more frequently stable and controlled systemic disease, BM management now represents an emerging area of interest in organ-specific metastasis research. Thus, evidence from randomised controlled trials make it possible to propose standard guidelines for local management, including the rationalized use of surgical resection, radiosurgery and adjuvant or exclusive whole-brain radiotherapy (9, 10). In addition, the concept of the blood brain barrier (BBB), which was thought to exclude most systemic therapeutics from the brain, thereby creating a putative sanctuary for metastatic tumors, is now increasingly being challenged and systemic therapeutics may have antitumor activity at the central nervous system (CNS) level (11).

The objective of this work was to review literature data in order to provide an overview of the most recent trends in epidemiology, clinical characteristics, therapeutic management and outcome of BM (excluding the specific topic of leptomeningeal disease).

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Correspondence to: Dr. Anthony Gonçalves, Medical Oncology Department, Institut Paoli-Calmettes, 13009, Marseille, France. Tel: +33 491223537, Fax +33 491223670, e-mail: goncalvesa@ipc.unicancer.fr

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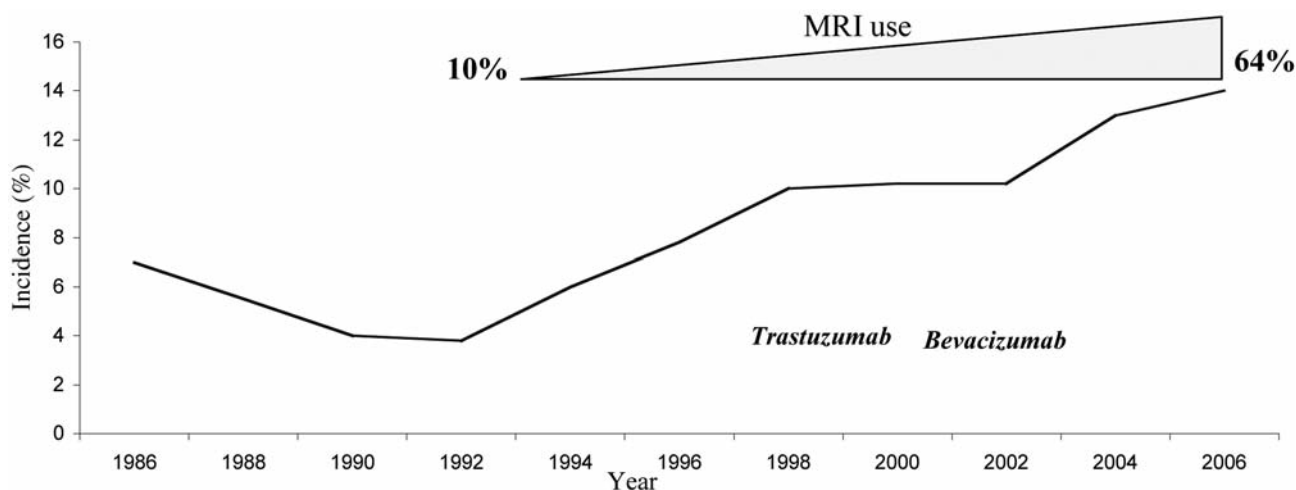


Figure 1. Incidence of brain metastases from 1986 to 2006 [according to Smedby *et al.* (14)] and MRI use [according to Nieder *et al.* (15)].

Global Incidence and Prevalence of BM

The estimated number of new cases of BM diagnosed each year in the USA is 170,000 (12) per year. The incidence of BM is hypothesized to have increased during the last 20 years (Figure 1). However, there are only two studies actually examining such time trends and their results are not very clear. Thus, Schouten *et al.* (13) used the Maastricht Cancer Registry to select patients that were at risk of developing BM ($N=2724$) from 1986 to 1995. This cohort was linked to the Neuro-oncology Registry of the University Hospital Maastricht. A diagnosis of BM was found in 232 patients (8.5%). The cumulative incidence of BM was 32.5% in patients with small cell lung cancer diagnosed in the period 1986-1990, and 26% for patients diagnosed in 1991-1995. Similar results were observed for breast cancer (6.5% *versus* 3.9% in 1986-1990 and 1991-1995 periods, respectively). The authors concluded that there was no evidence of an increasing incidence of BM in patients with breast and lung cancer. Conversely, a more recent survey by Smedby *et al.* (14) identified a cohort of 15,517 patients with BM in the Swedish National Patient Registry 2009. In this study, the annual age-adjusted incidence rate of hospitalization for BM doubled between 1987 and 2006, from 7 to 14 patients per 100,000. Primary malignancies behind the increase of BM were mainly lung cancer, irrespective of gender, and breast cancer in women. The discrepancy between these two studies could be attributed to three main parameters: a different definition of the population at risk when computing incidence estimates, a smaller sample size, as well as a shorter time period of observation in the study of Schouten *et al.*, which was stopped in 1995, before the emergence of most of the changes detected in the study by Smedby *et al.*

Such an increase in BM incidence could be explained by the improvements in the quality of neuroimaging staging, particularly the more frequent use of Magnetic Resonance Imaging (MRI). To date, MRI is the most widely used examination for BM detection (64% today *versus* 14% 20 years ago) (15). Another potential explanation could be the global increase in cancer incidence with time. Indeed, in the period analyzed by the Swedish study, the incidence and prevalence of solid malignancies in the country increased from 490 to 530 per 100,000 individuals and from 3,236 to 4,130, respectively (14). In addition, for many cancer types, there has been a parallel improvement in prognosis due to an earlier detection of indolent tumors, as well as the use of more effective treatments. For example, improvement in the prognosis of breast cancer provides a basis for the substantial increase of patients with breast cancer being hospitalized for BM. The introduction in the adjuvant setting of trastuzumab, a targeted therapy with low presumed efficiency in the CNS, may have altered the natural history of patients with HER-2-positive breast cancer and unmasked CNS as a potential sanctuary site (5).

Incidence and Prevalence of BM According to the Primary Tumor

Several studies have also questioned the incidence and prevalence of BM according to the primary cancer (Figure 2). In a population-based study from the Metropolitan Detroit Cancer Surveillance System, Barnholtz *et al.* (16) collected data from 16,210 patients diagnosed with BM from various primary tumors between 1973 and 2001. The estimated global BM incidence was 9.6%, in descending order arising from lung (19.9%), melanoma (6.9%), renal (6.5%), breast (5.1%) and colorectal cancer (1.8%). In other studies, the incidence

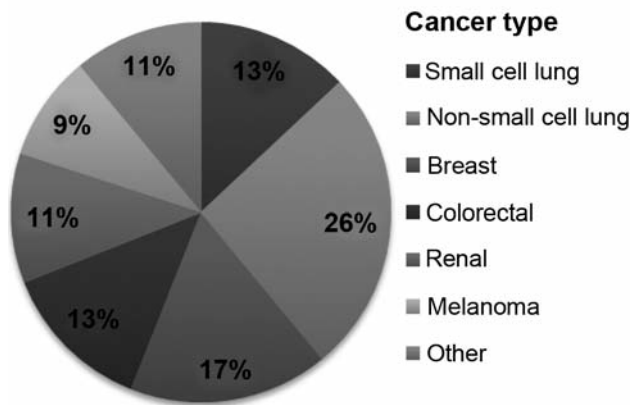


Figure 2. Partitioning of primary cancer in patients with brain metastases [according to Nieder *et al.* (15)].

of BM ranged from 5% to 20% in breast cancer (17-20). Recent reports suggest that the incidence and prevalence of BM from breast cancer are increasing (21, 22). Pelletier *et al.* (23) evaluated the epidemiology and economic burden associated with BM from breast cancer. Data were obtained for 13,845 patients from the PharMetrics Patient-Centric Database between January 2002 and December 2004, showing an increase in prevalence of BM from breast cancer between 2002 (6.61%) and 2004 (11.78%). In another study by Nieder *et al.* (15) comparing two cohorts of patients with BM, the first treated between 2005 and 2009 and the second between 1983 and 1989, i.e. approximately 20 years earlier, BM from breast cancer cases were equally common (17% in both cohorts). The contemporary cohort contained slightly fewer patients with primary lung cancer (40% versus 52%) and slightly more melanoma (9% versus 5%), but differences was not significant. However, a significant higher number of patients with colorectal and kidney primaries (24% vs. 8%, $p=0.002$) as observed in the most recent cohort. A similar increase in prevalence of BM from colorectal cancer was found in another study (24). Again, these changes could be explained by a general improvement in detection, treatment and prognosis of these two cancer types (25-27). Of note, Kolomainen *et al.* (28) performed a study examining 3,690 patients with epithelial ovarian cancer and described an increase in incidence of BM from 0.3% between 1980 and 1994 to 1.3% between 1995 and 1999 ($p<0.001$). These data could also result from improvements in ovarian cancer management leading to a survival advantage, such as aggressive surgical resection and taxanes incorporation (29), and therefore an increased potential for cerebral dissemination.

Currently, the global prevalence of BM ranges from 8.5% to 9.6% (13, 16). These data are likely to underestimate the true BM prevalence, due to asymptomatic BM or

symptomatic but ignored BM in a seriously ill patient with otherwise symptomatic advanced cancer. Although Pickren *et al.* (30) found a similar rate of BM in their study (8.7%), most other autopsy series reported higher rates: thus, Posner and Chernik (31) published data regarding 2,375 autopsies of patients with cancer and found 15% of patients with BM, while a US study from Rochester, Minnesota, demonstrated that 41% of the cancer patient population had BM. However, this study was not restricted to autopsy data (autopsy was carried out on only 70% of patients) (32). Moreover, autopsies of patients with melanoma revealed 40% of patients with BM (31) and autopsies of breast cancer patients found rates of BM ranging from 16% to 30% (33). Of note, these series of autopsy data are more than 20 years old. If the incidence of BM is increasing, the true prevalence may be even higher. However, new autopsy data are unlikely to be forthcoming because autopsy rates in the USA are now only about 5% (34, 35).

Patients' Characteristics

At the time of BM diagnosis, the performance status of patients was most frequently preserved, with a median Karnofsky Performans Status (KPS) at 70 and this characteristic has remained unchanged (3, 15, 36-38).

According to some US studies, the frequency of BM could be influenced by race (16, 39) since the incidence of BM in African-Americans was significantly higher compared to the white population for lung, melanoma and breast cancer, but was lower for renal cancer. However, these data may be impacted by social inequalities in healthcare access.

The median age at diagnosis ranged from 57 to 63 years (14, 16, 36-38, 40). This characteristic seems to have remained stable during the past 20 years. Age at diagnosis was influenced by primary cancer (14). The incidence of BM was highest for those diagnosed between the age of 40 to 49 years with primary lung cancer, 50 to 59 years with primary melanoma, renal or colorectal cancer and 20 to 39 years with breast cancer (41). It is noteworthy that there was no correlation between the age of peak incidence of BM and the age of peak incidence of the corresponding primary, especially for breast cancer. In fact, the higher frequency of BM in younger and/or African-American patients with breast cancer could be explained by the higher frequency in this population of triple-negative [ER, PR and HER2] tumors (42), in which an increased risk of CNS metastasis was demonstrated (43).

There were significantly more female than male patients in the contemporary cohort of patients with BM (15, 36), whereas male patients represented the majority of patients twenty years ago (2). This is likely to result from the increasing number of lung cancer cases diagnosed among women, as well as an increase in the incidence of BM in

patients with breast cancer. Moreover, a distinct susceptibility in the development of BM according to gender could exist. Thus, in Barnholtz-Sloan *et al.* study (16), men had similar or higher (for melanoma) incidence of BM compared to women, whereas men with primary lung cancer had significantly less BM than women. Yawn *et al.* (44) looked at the rate of BM in patients diagnosed with primary lung or breast cancer between January 1988 and December 2001 in Olmsted County, Minnesota, and noted that women were twice as likely as men to have BM detected following primary lung cancer. However, these results remained controversial, and in another study (45), gender was not a predictive factor for brain progression in non-small cell lung carcinoma.

Disease Characteristics

The highest incidence for BM occurred for individuals diagnosed with advanced-stage disease (16, 36). This has remained unchanged with time. However, BM have become more often diagnosed as associated with multiple extracranial metastases [from 14 to 44% (15)] and the current proportion of patients with BM without extracranial disease has been decreasing [from 52% to 23% (15)] during the past 20 years (3, 37, 38). The number of patients with a single BM is also decreasing (3, 37, 40, 46), [from 63% to 29% (15)] whereas the proportion of patients with three or more BM has increased (38, 47) [from 17% to 36% (15)]. Simultaneous detection of BM and primary cancer was also more common [from 18% to 30% (15)] (38, 48-50) likely due to the more frequent use of brain imaging (including brain MRI) in the initial staging procedure (51). However, the median time interval from the diagnosis of the primary tumor to development of BM has increased significantly in the current decade (8 months *versus* 3 months) (3, 15). Such a time interval is actually dependent on, and strongly linked to, the primary cancer. Thus, the median time interval from primary to BM diagnosis ranged from 2.6 to 7 months (16, 52, 53) for lung cancer, but may reach 39 to 47 months for breast cancer (54-56).

There were significant changes in the distribution of prognostic classes. Fewer patients than twenty years ago are currently assigned to the most favorable (7% *versus* 19%) and most unfavorable (31% *versus* 44%) RPA prognostic classes (3, 15, 47). This could be the result of the already mentioned increase in concomitant extracranial metastases at BM diagnosis (since this directly participates in the RPA class allocation), even though systemic disease is increasingly being controlled.

Treatment

The use of surgical resection ranges between 16% and 18% (57-59). Its use has dramatically increased with time, with currently three times more surgical procedures being carried

out for BM and a 79% relative increase in the annual number of surgical resections for BM (60). Stereotactic radiosurgery has also been developed and is now widely used (61). Currently, conventional surgery and/or stereotactic radiosurgery take part in the treatment of BM for 27% to 31% of patients (47). During the same time, the use of whole-brain radiotherapy (WBRT) did not decrease and is administered to two out of three patients (62-64). Finally, an increase in the total number of local procedures was observed (12, 62).

Another significant change has been in the more frequent use of systemic treatment (11, 55, 65). Systemic treatment and the number of lines administered before the BM onset was higher in the most recent patients. Currently, only 35% of patients have never received systemic treatment before the onset of BM, whereas this figure was 75% twenty years ago. Moreover, 13% of patients were found to receive three or more lines of systemic therapy before the diagnosis of BM. In addition, systemic treatments were more frequently administered after the onset of BM (45% *versus* 24%) (11, 15).

Accordingly, treatment of BM may increase financial costs. Thus, the total one-year cost of BM from breast cancer management was estimated at \$99,899 in 2006 whereas it was \$ 47,719 for the treatment of breast cancer without BM (23). Indeed, the diagnosis of BM was associated with more hospital stays, for a longer period, with more physician visits and pharmacy claims.

Survival

Nieder *et al.* (15) found that the median survival was only minimally improved in the most recent patients (from 3.2 to 3.9 months). In contrast, the one-year survival rate increased from 15% to 34% and some long-term survivors were observed. Survival was shown to be dependent on presentation of BM and on administered treatments. The median overall survival ranged from 8 to 13 months after surgery (57, 59, 66, 67), and from 8.5 (68) to 12.1 (69) months after stereotactic surgery. When focal procedures were not performed, the median survival was 3.2 to 3.6 months after WBRT alone (70) and 1.3 months with best supportive care only (12).

The impact of systemic therapies (chemotherapy and targeted therapy) is not really known at present (12, 55, 65, 71, 72). A retrospective study compared survival of patients with BM from breast cancer treated either with WBRT alone or WBRT followed by systemic treatment. The median survival was 3, 8 and 11 months for patients treated with WBRT alone, WBRT followed by chemotherapy and WBRT followed by systemic treatment including targeted therapies, respectively (73). These results support the use of systemic treatments in the management of BM from breast cancer.

Survival is also dependent on the nature of the primary cancer. Thus, the median survival for patients with BM

Table I. Time trends in clinical characteristics of brain metastases (BM).

Disease characteristic	
Primary	Prevalence of renal and colorectal cancer increasing (15)
Status of disease	Incidence and prevalence of BM in breast, lung and ovarian cancer increasing (16, 25, 30) Presence of visceral metastases increasing (15, 50) Multiple BM increasing (38, 47) Concomitant diagnosis increasing (47, 51)
RPA classes	Classes I and III decreasing; class II increasing (3, 36, 47)
Time from initial diagnosis to BM	Increasing (3, 15)
Patient characteristic	
Gender	Predominance of female gender (15, 36)
Therapy and survival	
Local procedures	Stereotactic surgery (61) Focal treatments increasing (47)
Systemic therapy	In development (11, 12, 55, 65, 71-73)
Costs of cares	increasing (23)
Survival	Median survival increasing (15) Long term survivors appeared (40, 81)
RPA	Fewer patients assigned to the most favorable class (3, 15, 47)

ranges from 2.7 to 6.3 months (16, 74, 75) for lung cancer, from 5.1 (75, 76) to 6 months (24) for colorectal cancer and from 4.8 to 10 months for melanoma (16, 75, 77). Survival of patients with BM from breast cancer varied with clinic pathological and molecular subtypes. Thus, the median survival was estimated to be 2.9 months for inflammatory breast cancer, a rare and aggressive form of the disease (78). For the triple-negative subtype, the median survival was 4.9 months (79), whereas it ranged from 11.3 (80) to 26.3 months (40, 43, 81, 82) in HER2-overexpressing tumors receiving trastuzumab and from 19 to 24 months (81,83) for hormone receptor-positive tumors.

Conclusion

BM was classically thought to appear in a context of uncontrolled systemic disease and was considered as a terminal phase of the disease. The usual treatment was surgery when possible, and/or WBRT. Systemic treatments were rarely used and were believed to have little or no efficacy. As shown in this review, important changes have recently been noted in the epidemiology of this disease (Table I). An increase in incidence and prevalence has been observed. On initial diagnosis, BM are more often multiple and occur later in the context of a more frequently controlled extracranial disease. Surgery, stereotactic radiosurgery and radiotherapy are still the mainstays of BM management, but the combined or sequential use of each of these approaches is increasingly selected based on expected probabilities of overall survival, local control and potential neurocognitive toxicities. In addition, the impact of systemic therapy is

increasingly suggested. This emphasizes the need for developing specific clinical trials of therapy in BM, in order to increase both cerebral control and overall survival. Combined with the growing knowledge of the specific biology of BM, it is anticipated that these studies will result in significant progress in this devastating disease.

Competing Interests

The Authors declare that they have no competing interest.

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