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Tumour Review

The impact of brain metastasis on quality of life, resource utilization and survival in patients with non-small-cell lung cancer

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ABSTRACT

This systematic review aims to improve understanding of the burden of disease associated with brain metastases from non-small-cell lung cancer (NSCLC) in terms of survival, quality of life (QoL) and economic impact. PubMed/MEDLINE, Cochrane collaboration and EMBASE databases were searched for articles published in English from 2000 to 2014. Of 3288 abstracts retrieved, 3156 were eliminated without a full-text review. Of the 132 articles that received a full-text review, a final set of 93 articles was included in an initial literature analysis. In order to homogenize the patient populations evaluated, we included entries that were either entirely composed of NSCLC patients or that had >50% of NSCLC patients in the total study population. From the studies identified in this systematic review, median OS and PFS varied based on the type of treatment received, although whole-brain radiotherapy (WBRT) was associated with the shortest OS and PFS durations. Regimens incorporating targeted therapy in molecularly selected patients were associated with the longest OS and PFS durations. QoL findings varied among studies, generally WBRT resulted in stable or worsening QoL scores rather than improvements. Healthcare costs were increased following diagnosis of brain metastases regardless of treatment. The findings from this review highlight the need for more effective treatments of brain metastases from NSCLC that improve survival function, QoL and potentially decrease costs.

Introduction and rationale

Lung cancer is the leading cause of cancer-related death worldwide [1]. Most non-small-cell lung cancer (NSCLC) patients present with metastatic disease. The site of metastasis affects patients' prognosis, symptoms and therefore quality of life (QoL). The brain or central nervous system (CNS) is a common metastatic site for NSCLC, with 40–50% of patients developing brain metastases during the course of their disease [2–4].

Patients with NSCLC and brain metastases have a poor prognosis, with a median overall survival (OS) between 4 and 9 months with chemotherapy and only 7 months for patients receiving whole-brain radiation therapy (WBRT) [5], which has historically been the standard treatment for brain metastases. Untreated patients have a median survival of just 2 months [5].

Stereotactic radiosurgery (SRS) is a newer treatment option, applied in selected scenarios of relatively limited brain disease. Median OS of more than 12 months has been reported in a series of patients treated with this technique [6,7]. Molecularly targeted therapies including epidermal growth factor receptor (EGFR) inhibitors and anaplastic lymphoma kinase (ALK) inhibitors are being evaluated for the treatment of brain metastases in molecularly selected NSCLC patients, with initial reports of a median survival time around 12 months [5].

In addition to evaluating survival, it is important to measure the impact that brain metastases have on QoL and treatment costs for a complete picture of the disease burden. Symptoms of brain metastasis include headaches, cognitive deficits, ataxia, seizures and visual and speech problems [8], which can impact patients' QoL in addition to the symptoms from their primary tumor. As the literature on QoL impact and the cost of brain metastases is limited, it is difficult to gain a complete picture of the disease burden. One analysis using the Adelphi NSCLC Disease Specific Programme (a patient-record/self-assessment based observational study) surveyed 80 pulmonologists and 40 oncologists and their 1213 NSCLC patients with metastatic disease across France and Germany to assess QoL and health preference scores (indirect utilities using the EQ-5D questionnaire) as well as survival in relation to the sites

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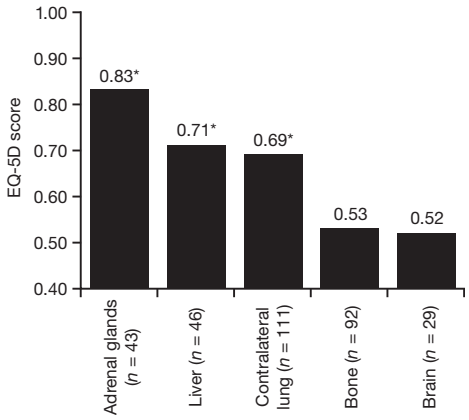

Fig. 1. EQ-5D score for NSCLC patients with one metastatic site [9].

of metastases [9]. Of the 325 patients with one metastatic site who completed the questionnaire, 9% ($n = 29$) had brain metastases. Health-related utilities or preference scores were significantly lower in patients with brain metastases compared with those with adrenal, liver or lung metastases (Fig. 1) [9]. This difference in QoL seen with brain metastases was particularly due to increased difficulty in with usual daily activities, mobility and self-care.

Challenges when evaluating clinical trial data for brain metastases include the varying definitions of clinical endpoints, different schedules and technical modalities for imaging and heterogeneous patient populations [10]. This systematic review aims to improve the understanding of the burden of disease of NSCLC with brain metastases regarding survival, QoL and economic burden, highlighting any unmet clinical needs in these areas. Research questions were developed looking at the effects of treatments on progression-free survival (PFS) and OS in patients with NSCLC and brain metastases, the impact of brain metastases on health-related QoL and the total medical costs associated with brain metastases.

Methods

To identify suitable articles, PubMed/MEDLINE, Cochrane collaboration and EMBASE databases were searched for articles published in English from 2000 to 2014. Search terms for each category are shown in Table 1. The clinical efficacy search focused on studies of patients with NSCLC (primary diagnosis) with brain metastases. Publications were excluded if they did not report OS or PFS data. As a limited number of QoL and economic burden articles were retrieved for NSCLC as a primary diagnosis, studies were considered with other primary cancer sites or studies with mixed populations including NSCLC, as long as the primary cancer diagnosis was not brain cancer. For accuracy and to homogenize the populations studied, we reviewed entries that were either exclusively conducted in NSCLC populations or in which at least

Table 1
Search terms for initial literature search.

Step	Search terms: clinical efficacy	Hits
1	Brain metastas*[Title/Abstract] OR metastatic brain tumor*[Title/Abstract] OR metastatic brain tumour*[Title/Abstract]	7544
2	"Brain Neoplasms/secondary"[Mesh]	10,314
3	#1 OR #2	13,155
4	*non small cell lung[Title/Abstract] OR nsclc[Title/Abstract]	33,840
5	"Carcinoma, Non-Small-Cell Lung"[Mesh]	30,897
6	#4 OR #5	40,657
7	#3 AND #6	1131
8	survival[Title/Abstract] OR overall survival[Title/Abstract] OR progression free survival[Title/Abstract]	591,415
9	(("Disease-Free Survival"[Mesh]) OR "Survival Analysis" [Mesh]) OR "Survival Rate"[Mesh]	282,304
10	#8 OR #9	707,789
11	#7 AND #10	661
12	#11 Filters: Publication date from 2000/01/01 to 2014/12/31; English	488
Step	**Search terms: quality of life**	**Hits**
1	brain metastas*[Title/Abstract] OR metastatic brain tumor*[Title/Abstract] OR metastatic brain tumour*[Title/Abstract]	7544
2	"Brain Neoplasms/secondary"[Mesh]	10,314
3	#1 OR #2	13,155
4	"Quality of life"[Title/Abstract] OR QALY[Title/Abstract] OR quality adjustment[Title/Abstract] OR utility index[Title/Abstract] OR utilities index [Title/Abstract] OR utility valu*[Title/Abstract] OR utilities valu*[Title/Abstract] OR health utility[Title/Abstract] OR health utilities[Title/Abstract] OR EQ-5D[Title/Abstract] OR SF-6D[Title/Abstract] OR HUI[Title/Abstract] OR adversit*[Title/Abstract] OR satisfaction[Title/Abstract] OR satisfied [Title/Abstract] OR patient reported outcome[Title/Abstract] OR patient reported outcomes[Title/Abstract] OR well-being[Title/Abstract] OR well being[Title/Abstract] OR burden[Title/Abstract] OR SF-36[Title/Abstract] OR QLQ-C30[Title/Abstract] OR QLQ-LC13[Title/Abstract]	361,450
5	"Quality of life" [Mesh] OR "Sickness Impact Profile"[Mesh] OR "Patient Satisfaction"[Mesh]	169,797
6	#4 OR #5	428,408
7	#3 AND #6	690
8	#7 Filters: Publication date from 2000/01/01 to 2014/12/31; English	442
Step	**Search terms: economics**	**Hits**
1	brain metastas*[Title/Abstract] OR metastatic brain tumor*[Title/Abstract] OR metastatic brain tumour*[Title/Abstract]	7544
2	"Brain Neoplasms/secondary"[Mesh]	10,314
3	#1 OR #2	13,155
4	Search economic*[Title/Abstract] OR cost*[Title/Abstract] OR pharmacoeconomic[Title/Abstract] OR "costs and cost analysis"[Title/Abstract] OR price*[Title/Abstract] OR financ*[Title/Abstract] OR reimburs*[Title/Abstract] OR "cost of illness"[Title/Abstract] OR economic model*[Title/Abstract] OR cost benefit*[Title/Abstract] OR cost effective*[Title/Abstract] OR utili*[Title/Abstract] OR fiscal[Title/Abstract] OR expenditure*[Title/Abstract] OR quality adjusted life year*[Title/Abstract] OR QALY [Title/Abstract] OR quality adjustment[Title/Abstract] OR disability[Title/Abstract] OR productivity[Title/Abstract] OR budget[Title/Abstract] OR health technology assessment[Title/Abstract] OR absenteeism[Title/Abstract]	1,126,940
5	((((((("Models, Economic"[Mesh]) OR "Economics"[Mesh]) OR "Health Care Costs"[Mesh]) OR "Health Expenditures"[Mesh]) OR "Cost of Illness" [Mesh]) OR "Employer Health Costs"[Mesh]) OR "Drug Utilization"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Length of Stay"[Mesh] OR "Patient Readmission"[Mesh]	552,600
6	#4 OR #5	1,491,651
7	#3 AND #6	490
8	#7 Filters: Publication date from 2000/01/01 to 2014/12/31; English	292