Is whole brain radiotherapy needed for treatment of inoperable brain metastases from non-small cell lung cancer?

Inoperable brain metastases from non-small cell lung cancer

Lung cancer is the most common cancer worldwide, and the third most common cancer in the UK, with around 45,500 new cases each year. Most (87%) of these cases are classified as non-small cell lung cancer (NSCLC). Around 30% of people with NSCLC will have (or go on to develop) brain metastases. Survival rates for most people with NSCLC after the development of brain metastases are poor, ranging from two to six months. This briefing paper examines the evidence around the use of whole brain radiotherapy for patients with inoperable brain metastases from NSCLC (those who are not suitable for neurosurgery or stereotactic radiosurgery).

Key points

• Whole brain radiotherapy, combined with steroids (now usually dexamethasone) and supportive care, has been a commonly used treatment for patients with inoperable brain metastases from non-small cell lung cancer for over 50 years. The QUARTZ trial is the first large randomised controlled trial to test whether it is beneficial, in terms of overall survival and quality of life.

• In QUARTZ, all 538 patients received optimal supportive care (including dexamethasone), with half of the patients also receiving whole brain radiotherapy.

• In patients unsuitable for surgery or stereotactic radiosurgery, the potential added benefit (in terms of quality adjusted life years) of treatment with whole brain radiotherapy is estimated to be around four days, and is no more than two weeks.

• There is no evidence that the addition of whole brain radiotherapy makes a significant difference to overall survival.

• In particular, patients in Recursive Partitioning Analysis classes II and III, and older patients (particularly those over 70 years old) did not benefit from whole brain radiotherapy.

• There may be some benefit (around 3 weeks longer median survival) from whole brain radiotherapy for younger patients, <60 years old.

• There is some evidence that patients with good performance status (Karnofsky Performance Status ≥70), and a controlled primary non-small cell lung cancer, may do better with whole brain radiotherapy, but the evidence is not strong enough to say it should be given routinely in this group of patients.

• This evidence should inform discussions with patients and their families on the potential value of whole brain radiotherapy.

• QUARTZ demonstrates that trials that include patients with very poor prognoses are possible, and can still provide high quality information; QUARTZ had excellent adherence to trial follow-up and completeness of data.

Treatment options for inoperable brain metastases from NSCLC

All patients diagnosed with brain metastases receive supportive care, which will include access to palliative care services and medications (such as painkillers) to help manage their symptoms. Symptomatic patients are generally started on a course of steroids (in most cases dexamethasone), with doses tapered to reach the lowest possible dose that maintains symptom relief.
In addition, some patients with brain metastases from NSCLC who are unsuitable for neurosurgery or stereotactic radiosurgery are also given systemic treatments, including chemotherapy, targeted treatments, or whole brain radiotherapy.

**Systemic treatments, including targeted treatments**

Most patients do not receive systemic treatments because they do not have the driver mutations that new targeted treatments are aimed at, or there is lack of access to these new treatments. Currently approved targeted treatments relate to patients with epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangement, each of which affect only 5-10% of patients. Patients who do receive these agents may still go on to be considered for treatment with whole brain radiotherapy.

**Whole brain radiotherapy**

The use of whole brain radiotherapy with steroids for patients with brain metastases was developed in the latter half of the twentieth century. It continues to be an accepted option where other treatments (eg. surgery or stereotactic radiosurgery) are not indicated. Whole brain radiotherapy often involves patients having five to ten fractions of radiotherapy, delivered over five to twelve days. This is costly to patients in terms of time and travel, as well as having a cost to the NHS. Treatment may shrink the tumour and relieve symptoms, but may also have side effects such as fatigue, hair loss, sickness and drowsiness.

To date, there have been no large randomised controlled trials to test whether whole brain radiotherapy offers benefits in addition to optimal supportive care (including steroids) in terms of patient survival or quality of life. The QUARTZ trial addressed this lack of evidence by investigating whether whole brain radiotherapy could be omitted from the treatment of patients with brain metastases from NSCLC.

The 2011 NICE Lung Cancer guidelines recommend that palliative whole-brain radiotherapy is considered for patients with symptomatic brain metastases with good performance status (WHO 0 [asymptomatic] or 1 [symptomatic but completely ambulatory]). In practice, there is a lack of consensus with regards to the use whole brain radiotherapy. A survey of 60 UK clinicians involved in treating lung cancer, carried out in 2015, found that some clinicians

**The QUARTZ trial**

QUARTZ was a phase III randomised controlled trial, looking at whether optimal supportive care (including steroids) alone was non-inferior to whole brain radiotherapy (20 Gy in five fractions) plus optimal supportive care, in terms of quality adjusted life years (QALYs), overall survival and quality of life. It included 538 patients from the UK and Australia with NSCLC with brain metastases unsuitable for surgical resection or stereotactic radiosurgery. It recruited patients from 2007 to 2014.

**Quality-adjusted life years**

A quality-adjusted life year (QALY) is a measure that combines the duration of survival and quality of life. In QUARTZ, quality of life was measured using the EQ-5D-3L tool. This is a questionnaire that patients complete about their mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

**Non-inferiority trials**

Non-inferiority trials aim to test whether a new treatment approach is not clinically worse than the current standard treatment with regards to a specified endpoint. The pre-specified non-inferiority margin is the maximum tolerable difference if the new treatment is not to be considered (clinically) inferior. In the case of QUARTZ, the non-inferiority margin was a difference in QALY of no more than seven days. If the trial’s confidence interval does not include (or exceed) the non-inferiority margin, we can conclude that the new treatment approach is non-inferior.

Non-inferiority designs are often used when the new treatment approach is unlikely to be better than the current standard treatment in terms of the primary outcome, but may have other advantages (for example, fewer side-effects or lower cost). In the case of QUARTZ, this is appropriate as whole brain radiotherapy was considered the current standard treatment, and we were assessing its omission. Omitting whole brain radiotherapy could have advantages for patients through reducing the time they need to spend in hospital, and the associated travel time and costs, and avoiding the side-effects of radiotherapy.
use it for most patients with inoperable brain metastases (who were not suitable for stereotactic radiosurgery), while others rarely use it. 16% of respondents reported treating at least 60% of these patients with whole brain radiotherapy at some point during their treatment, while around 42% of respondents used whole brain radiotherapy for less than 20%.

How does whole brain radiotherapy compare to optimal supportive care alone?

Quality adjusted life years

Those patients in the whole brain radiotherapy plus optimal supportive care group had an average QALY of 46.4 days, compared to 41.7 days for those in the optimal supportive care alone group: a difference of -4.7 days (the same as the number of days over which the whole brain radiotherapy group were receiving radiotherapy). The 90% confidence interval for this difference ranged from 12.7 days lower QALY to 3.3 days higher QALY in the optimal supportive care alone group. The largest expected detriment with supportive care alone was 12.7 QALY days, which is larger than our pre-specified non-inferiority limit of seven days.

Overall survival

QUARTZ also found no evidence of a significant difference in overall survival between the two groups. Those in the whole brain radiotherapy plus optimal supportive care group had a median survival of 9.2 weeks, while those in the optimal supportive care alone group had a median survival of 8.5 weeks. This short survival was consistent with other study results in similar patient populations.

Quality of life

The Quality of Life measured over time was similar for the two groups.

Were there any groups who did benefit significantly from whole brain radiotherapy?

The only subgroup which gained a statistically significant benefit from whole brain radiotherapy was patients under 60 years old. In those, the benefit in median survival was three weeks. There was some evidence that patients with good performance status (Karnofsky Performance Status ≥70), and controlled primary NSCLC, may derive some benefit with whole brain radiotherapy, but the evidence is not strong enough to say it should be given routinely in this group of patients.

What does this mean in practice?

Overall, the QUARTZ results suggest that whole brain radiotherapy can be omitted (in patients not suitable for neurosurgery or stereotactic radiosurgery), and patients can be treated with optimal supportive care (including steroids) alone, without a clinically significant reduction in overall survival or quality of life.

QUARTZ found younger patients, particularly those less than 60 years old, did have improved survival with whole brain radiotherapy. Trends towards whole brain radiotherapy being beneficial for patients with good performance status, and a controlled primary NSCLC, were also seen, although there was no clear statistical difference in these two groups. Outside these groups, (ie. for older patients, those with poor performance status, with extra-cranial sites of metastatic disease or an uncontrolled primary NSCLC) whole brain radiotherapy appears to offer no benefit in terms of either survival or quality of life. The QUARTZ results could have far-reaching implications for the almost 500,000 patients diagnosed with brain metastases from NSCLC each year worldwide. Conversations about treatment options for patients with inoperable brain metastases from NSCLC are not easy, but the views of patients and their families are important factors in the choice of treatment approach. With the QUARTZ results, these discussions can, at last, be informed by good quality evidence on the level of benefit likely from whole brain radiotherapy, to set against the costs in terms of time, travel and side-effects.

Further information


Credits

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