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Original research article

Evaluation of results of linac-based radiosurgery for brain metastases from primary lung cancer☆

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ARTICLE INFO

Article history:
Received 25 October 2011
Received in revised form
13 April 2013
Accepted 23 June 2013

Keywords:
Lung cancer
Radiosurgery
Brain metastasis
Prognostic factors

ABSTRACT

Aim: The purpose of our review was to evaluate results of radiosurgery for patients with brain metastases from lung cancer.
Background: Lung cancer is the leading cause of death from cancer and the most common source of brain metastases. Radiosurgery allows the precise focal delivery of a high single radiation dose to brain metastases and results in high rates of local control.
Materials and methods: 83 patients were treated between 2006 and 2008. We evaluated local control and outcome after radiosurgery and identified prognostic factors.
Results: Median survival in the whole group was 7.8 months from radiosurgery and 11 months from diagnosis. Median survival in classes I, II and III was 13.2, 8.2 and 2.2 months. For 94% of patients symptoms improved or stabilised at the first follow-up visit and this status did not change during 7.1 months. According to the univariate analysis, factors associated with improved survival included: RPA class 1 compared with RPA 2 and 3, RPA class 2 compared with RPA 3, KPS > 70, control of the primary disease, radiosurgery performed more than once, level of haemoglobin >7 mmol/1, absence of extracranial metastases, volume of the biggest lesion <11 cm^3. The multivariate analysis confirmed a significant influence on survival for the following factors: RPA class 1 as compared with RPA 3, KPS > 70, absence of extracranial metastases, multiplicity of radiosurgery.
Conclusions: Stereotactic radiosurgery is a safe and effective treatment. It proved to be effective and safe in older patients. Selection of patients who are likely to benefit most should be based on prognostic factors. KPS proved to be the most important prognostic factor. In the RPA III group (patients with KPS < 70) survival time was similar to that achieved after symptomatic medical management.

1. Introduction

Lung cancer is currently the most prevalent malignancy in the world, accounting for 34% of all cancer deaths. It is also the most prevalent cancer in Poland. Treatment results for lung cancer are still unsatisfactory. This is due to the fact that the disease is usually diagnosed at later stages, with 70% of patients with locally advanced or metastatic cancer. Therefore, a large proportion of patients are not eligible for radical

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http://dx.doi.org/10.1016/j.rpor.2013.06.006

Table 1 – Prognostic factors by RPA classes.

RPA classes	Mean survival in months
RPA class I KPS ≥ 70, age < 65, primary disease controlled, no extracranial metastases	7.1
RPA class II KPS ≥ 70 and at least one of the following: age≥65, uncontrolled primary disease, extracranial metastases	4.2
RPA class III KPS < 70	2.3

therapy and are given palliative treatment instead. Such treatment is aimed to improve their quality of life by mitigating pain and to prolong survival. The five-year survival rate with such patients is only around 10%. In patients with stage IV (metastatic) non-small cell lung cancer, the five-year survival rate is below 5%. In extensive disease small cell lung cancer, it is merely 1–2%. Brain metastases develop in 30% of all non-small cell lung cancer patients.[1] In approximately 10% of SCLC patients, metastases to the central nervous system are found at diagnosis.[2] As the disease progresses, brain metastases occur more often (in 60–80% of patients with two-year survival). Of all cases of brain metastases, those from lung cancer represent 40–50%. Brain metastases have a strong negative impact on prognosis and quality of life. It usually requires urgent treatment. The most important aim of such treatment is to improve neurological performance and prolong survival. The choice of a therapeutic method is based on individual assessment of prognostic factors.

Modern brain metastases therapy is based on individual assessment of prognostic factors.[3,4] These include: age, general status as Karnofsky performance scale, type of primary tumour, number of brain metastases (single or multiple) and progression of extracranial processes. The analysis of those factors based on three clinical trials conducted by the RTOG (1200 patients) allowed to distinguish three prognostic classes.[5] Gaspar[3] used the RTOG database to perform a recursive partitioning analysis (RPA). The Karnofsky performance status proved to be the most significant prognostic factor in an univariate analysis. Among patients with KPS 70 or lower, the primary tumour status was the second key prognostic factor, preceding age and extracranial metastases. Three prognostic classes were distinguished: RPA class I consisted of patients with KPS > 70 and higher, aged 65 or younger with controlled primary cancer and no extracranial metastases, whose mean survival period was 7.1 months. RPA class II consisted of patients who had not been qualified into classes I or III (with KPS > 70 and met one of the following criteria: age > 65, uncontrolled primary disease or presence of extracranial metastases). Mean survival time in class II was 4.2 months. Class III covered patients with performance status <70, mean survival time in that class was 2.3 months.

Prognostic factors by RPA classes are shown in Table 1.

The RPA classification may be used to select a small group of patients for radical local treatment (surgery, radiosurgery). There are several important prognostic factors which are not included in the RPA classification. All prognostic factors should be taken into account while selecting a treatment method. Very intensive treatment methods should be considered for patients with favourable prognostic factors, while less intensive or symptomatic treatment for those with unfavourable prognosis. Quality of life, alongside with the length of life, is an important aspect for assessment of treatment efficacy (particularly in the context of short survival time of brain metastases patients).

Considering a small number of Polish studies concerning prognostic factors in brain metastases radiosurgery, we decided to base this evaluation on treatment results for patients with brain metastases from lung cancer treated with radiosurgery in the period from February 2006 to September 2008.

2. Radiosurgery

Radiosurgery is performed with a so-called gamma knife or with the aid of a linear accelerator (LINAC). This method, in contrast to conventional radiation therapy, involves a one-off delivery of high-dose irradiation to a strictly limited area in order destroy it, wherein it resembles a surgical procedure (hence the name radiosurgery). In radiobiological terms, a delivery of a single high dose prevents a repair of post-radiation damage to cancerous cells occurring between fractions of conventional radiation therapy. Depending on a radiosurgery technique, the focus is supplied with doses with different levels of inhomogeneity (higher with a gamma knife). A high dose not only causes damage to tumorous cells, but also to blood vessels that feed them.[11,12]

The linac system uses photon radiation. Many fields of different angles are focused and dosage is precisely adjusted to the volume of a tumour. The application of a multi-leaf collimator reduces the need to use many isocentres and enables a decrease of dose to critical organs.[13]

In stereotactic radiation therapy, the therapeutic index depends on the size of a tumour. The RTOG study on dose escalation showed that a maximum tolerated dose is relative of the size of a tumour. RTOG researchers determined maximum tolerated doses for particular tumour sizes. For tumours of less than 20 mm, it is 24 Gy; for tumours of 21–30 mm, 18 Gy; for tumours of 31–40 mm, 15 Gy.[14] The study by Mehta et al. showed that local control decreases with the size of tumour.[6] In patients with tumours of less than 2 cm^3 in volume, the complete response rate was 61% and the partial response rate was 17%, for tumours of more than 10 cm^3 in volume, the complete response rate was 10%, and the partial response rate was 40% (Table 2).

3. Side effects of radiosurgery

Radiosurgery is usually well tolerated and can be carried out in an ambulatory setting. Therapy-related complications are relatively rare and moderately severe. The advantage of radiosurgery over traditional methods of radiation lies in the possibility to achieve total conservation of healthy tissues owing to lower toxicity of radiation therapy. Nausea, vomiting, alopecia and headaches are among most prevalent