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Brain metastases from non-small cell lung carcinoma: Changing concepts for improving patients' outcome

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ABSTRACT

The management of Non Small Cell Lung Cancer (NSCLC) brain metastases is challenging, as this frequent complication negatively impacts patients' quality of life, and can be a life-threatening event.

Through a review of the literature, we discuss the main therapeutic options and the recent developments that improved (and complicated) the management of NSCLC brain metastases patients. Most current validated approaches are local with exclusive or combined surgery, whole brain radiotherapy (WBRT) and stereotactic radiotherapy (SRT). At the same time, there is a growing role for systemic treatments that might significantly postpone WBRT. Targeted therapies efficacy/toxicity profile remains to be defined but predictive and prognostic molecular factors integration could help to select treatments fully adapted to life expectancy and progression risk.

1. Introduction

The optimal management of non-small cell lung cancer (NSCLC) brain metastases is challenging as there is a multiplicity of available

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treatments. Ideally, the treatment should be individualized, taking into account each patient's situation, with the integration of molecular factors providing prognosis information and pharmacological targets. We review the main therapeutic indications and the recent developments that improved and complicated the management of NSCLC patients with brain metastases.

2. Prognostic classification

No prognostic classification is currently really suited for the evaluation of NSCLC patients with brain metastases. Regarding the RPA (Recursive Partitioning Analysis) classification, most of NSCLC patients are in the middle prognostic class, and its value in NSCLC seems more limited than in glioblastoma (Gaspar et al., 1997). For patients treated with radiosurgery, the classification has been divided into three subclasses regarding the general condition (Karnofsky Index: 90–100% *versus* 70–80%), the number of metastases (single *versus* multiple), the primary disease status (controlled *versus* progressive), and the presence of extra-cranial metastases (Yamamoto et al., 2012). However, as the NSCLC population is mainly aged of >70 years old, with multiple co-morbidities and poor general condition, more accurate prognosis scales are probably still to be defined. The GPA (Graded Prognostic Assessment) classification assigns a score (0–4) based on four independent clinical factors (Table 1) (Sperduto et al., 2008). For patients with a score of 3.5–4 (*i.e* good prognosis patients), median survival is about 15 months for NSCLC (Sperduto et al., 2012). Unfortunately, this classification ignores molecular factors, such as EGFR activating mutations, KRAS mutations or EML4-ALK rearrangements that are nowadays decision-makers in the NSCLC management because of their predictive value to targeted treatments response.

3. "Classical" benchmark treatments

Historically, studies analyzing brain metastases treatment mainly included NSCLC and breast cancers patients, indiscriminately of primary tumor histological subtypes, much less molecular profiles.

3.1. Surgery

Three randomized clinical trials, excluding the most radiosensitive tumor types (SCLC, lymphomas, germ cell tumors) compared surgical resection followed by whole brain irradiation (WBRT), *versus* exclusive WBRT. Patchell et al. included only patients in good general condition (IK ≥ 70), randomized between biopsy *versus* surgery, both followed by WBRT (36 Gy in 12 fractions). An improvement of OS (10 *versus* 3.8 months), a decrease of local recurrence (20% *versus* 52%) and a rise of the functional independence duration were shown in favor of surgery (Patchell et al., 1990). Noordijk et al. confirmed the OS improvement (10 *versus* 6 months) with a similar methodology, but an unusual radiotherapy fractionation scheme (40 Gy bi-fractionated, 20 fractions). Importantly, excision quality and local control data were not reported (Noordijk et al., 1994). In a study including patients with KI ≥ 50, mainly with a complete resection on CT-scan, the quality of life and the median OS was not improved by a 30 Gy/10 fractions WBRT (6.3 months for WBRT *versus* 5.6 moths for WBRT + surgery). Local outcome was not reported. The absence of benefit might be explained by the high frequency of extra-cranial metastases, the debatable definition of complete resection and by improper selection since MRI was not mandatory (Mintz et al., 1996). Finally, there is a class I evidence showing the beneficial effect of surgery on survival, provided that the following criteria are met: a good condition (KI > 50%) and a controlled systemic disease. Retrospective data suggested that surgery could be performed in case of recurrences, although evidence level is lower (Vogelbaum and Suh, 2006).

3.2. Stereotactic radiotherapy

The stereotactic radiotherapy (SRT) allows high doses gradient to treat tumor and spare surrounding healthy tissues. In case of *invasive* contention (radiosurgery: SRS), delivered dose is usually 15–20 Gy in one fraction with sub-millimeter accuracy. On the other hand, *non-invasive* SRT is accurate to the millimeter and deliver a total dose of 15–33 Gy in 1–5 fractions, depending on the treated volume and on the proximity of high risk organs (trunk, chiasma). With 1–3 metastases not exceeding 3–3.5 cm in major axis, local control rates at 1 year were >90% below 2 cm and around 80% between 2 and 3 cm (Bhatnagar et al., 2006). Interestingly, retrospective data suggested that the "three metastases" threshold was debatable and that survival mainly depended on the metastasis total volume, the general condition and the systemic status of the disease (Bhatnagar et al., 2006). The place of radiosurgery in first intention remains controversial in the case of one small and potentially extricable metastasis since there is no direct comparison between surgery and radiosurgery. However, survival medians were reported to be comparable, with acceptable and mainly asymptomatic acute toxicities (Won et al., 2015; Jeong et al., 2015). Excision is nevertheless often preferred when the lesion is symptomatic, or >2 cm, or carrying a mass effect. When inoperable, a recent study suggested that a five-fraction SRS (total dose = 35 Gy) appeared to be a safe, while a total dose of 40 Gy led to an increased risk of neurotoxicity (Lischalk et al., 2015).

3.3. Whole brain radiotherapy (WBRT)

In situations of multiple metastases and/or when focal therapy is not conceivable, whole brain irradiation (WBRT) is the standard. A systematic review of the literature investigating the optimal WBRT doses and fractionation suggested no difference on survival, intracranial control or quality of life depending on the radiotherapy characteristics (Gaspar et al., 2010). The most frequently used scheme delivers 30 Gy in 10 fractions over 12 days, which is an equivalent biological dose of 39 Gy for normal tissues (alpha/beta = 3 Gy), and provides clinical and radiographic response rate of 50–75% (Priestman et al., 1996). Increasing the global dose did not show benefit regarding relevant clinical end points. To date,

Table 1
GPA classification and median survival for NSCLC patients (Sperduto et al., 2008).

		Score		
		0	0.5	1
Age		>60	50–59	<50
Karnofsky index		<70	70–80	90–100
Cerebral metastases number		>3	2–3	1
Extra-cranial metastases		Yes	–	No
Score	0–1.0	1.5–2.0	2.5–3	3.5–4
Median survival	3.02 months	5.49 months	9.43 months	14.78 months