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Review article

Brain metastasis in lung cancer: Building a molecular and systems-level understanding to improve outcomes

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ABSTRACT

Lung cancer is a clinically difficult disease with rising disease burden around the world. Unfortunately, most lung cancers present at a clinically advanced stage. Of these cancers, many also present with brain metastasis which complicates the clinical picture. This review summarizes current knowledge on the molecular basis of lung cancer brain metastases. We start from the clinical perspective, aiming to provide a clinical context for a significant problem that requires much deeper scientific investigation. We review new research governing the metastatic process, including tumor cell signaling, establishment of a receptive tumor niches in the brain and evaluate potential new therapeutic options that take advantage of these new scientific advances.

Lung cancer remains the largest single cause of cancer mortality in the United States (Siegel et al., 2015). This continues to be the clinical picture despite significant advances in therapy, including the advent of targeted molecular therapies and newly adopted immunotherapies for certain subtypes of lung cancer. In the vast majority of cases, lung cancer presents as advanced disease; in many instances, this advanced disease state is intimately associated with micro and macrometastatic disease (Goldberg et al., 2015). For both non-small cell lung cancer and small cell lung cancer patients, the predominant metastatic site is the brain, with up to 68% of patients with mediastinal lymph node metastasis eventually demonstrating brain metastasis (Wang et al., 2009).The frequency (incidence) of brain metastasis is highest in lung cancers, relative to other common epithelial malignancies (Schouten et al., 2002). Other studies have attempted to predict the risk of brain metastasis in the setting of previously non-metastatic disease. One of the largest studies to do this, analyzing historical data from 1973 to 2011 using the SEER database revealed a 9% risk of patients with previously non-metastatic NSCLC developing brain metastasis over the course of their disease, while 18% of small cell lung cancer patients without previous metastasis went on to develop brain metastasis as their disease progressed (Goncalves et al., 2016).The reasons underlying this predilection for the central nervous system, as well as the recent increase in the frequency of brain metastasis identified in patients remain important questions for both clinicians and basic scientists. More than ever, the question of how brain metastasis develop and how they can be treated and managed requires the involvement of interdisciplinary teams—and more importantly—scientists who are capable of thinking like clinicians and clinicians who are capable of thinking like scientists. This review aims to present a translational perspective on brain metastasis. We will investigate the scope of the problem of brain metastasis and the current management of the metastatic disease process in lung cancer. From this clinical starting point, we will investigate the literature surrounding the molecular underpinnings of lung tumor metastasis and seek to understand the process from a biological perspective to generate new hypotheses.

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1. Brain metastasis in lung cancer

The phenomenon of lung cancer metastasis to the brain is not a new one; it has long been noted that lung tumors have a predilection to spread to and within the central nervous system (Goldberg et al., 2015; Wang et al., 2009; Schouten et al., 2002; Goncalves et al., 2016). However, as imaging modalities have improved and as clinicians have worked to anticipate the spread of disseminated lung cancer to the brain, the instance of lung cancer metastasis in the brain has increased dramatically in recent decades. It is unclear whether this increase is related in to changing treatment options and modalities or whether it can be attributed solely to improved diagnostics. Increasingly, evidence suggests that the increased incidence of clinically validated lung tumor metastases to the brain is the result of a confluence of factors, including improved detection owing to improved imaging modalities and clinical awareness as well as changes in the treatment of lung cancers, particularly those susceptible to targeted molecular therapies.

2. Current clinical management of lung tumor brain metastasis

Clinical management of lung metastasis to the brain and CNS is currently guided by a number of factors, including the performance status and the overall health of the patient. Aggressive clinical management, typified by surgical interventions, whole brain radiation and stereotactic radiosurgery improve survival times for patients, although these interventions themselves are also associated with morbidities (Baykara et al., 2014). Other studies however, such as the recent QUARTZIII trial failed to reveal significant improvements in survival or quality of life in non-small cell lung cancer patients receiving whole brain irradiation. However, these results have not yet been parsed by stratifying patient data based on disease subtypes, and the results represent an interim study endpoint; the possibility remains that patients with certain performance status or disease characteristics could still benefit from whole brain irradiation. Other studies have evaluated a broader subset of cancers, defined histologically. One recent study found a slight, but statistically non-significant increase in survival in small cell lung cancer patients receiving whole brain irradiation (Nieder et al., 2013). In all cases where brain metastases are symptomatic, management with corticosteroids is the current standard of care, although steroids by themselves do not significantly prolong survival times (Gallego Perez-Larraya and Hildebrand, 2014). The goal in this instance is to manage the vasculogenic brain edema associated with lung tumor cell infiltration of brain and CNS tissues and to provide relief to patients.

Typically, patients present with headache or occasionally with altered mental status and even more rarely with personality changes or increased emotional lability. Many of the latter are highly subjective and can be difficult to assess clinically, especially given the traumatic nature of a cancer diagnosis in and of itself. However, frequent headaches or severe headaches can often be an early warning sign of potential brain metastasis in cancer patients that warrants diligent clinical follow up.

2.1. Detecting brain lesions

Clarifying actual brain lesions from generalized brain edema can be difficult; to that end, multiple imaging modalities are often preferred. Currently, magnetic resonance imaging with contrast enhancement represents the gold standard for the detection of brain metastasis, although this may be supplemented with other modalities and techniques, including diffusion tensor imaging (DTI) to increase confidence in the diagnosis (Fink and Fink, 2013). In some instances, biopsy of the lesion is indicated, although open brain biopsy is also associated with risks and potential morbidity. Early studies revealed that MRI, and longitudinal monitoring with MRI may represent a more sensitive approach than CT scan alone (Yokoi et al., 1999). In the case of lung cancers, brain lesions are typically multiple and disseminated, although interestingly, they do tend to localize in different regions of the brain than other cancer types- a fact that can have diagnostic significance. Specifically, lung cancer metastases to the brain tend to develop focal lesions in "watershed" regions of the brain- these are the regions where the vasculature is finest and most narrow (Takano et al., 2016). This suggests a potential role for hematogenous spread of lung tumor cells to the brain and their subsequent entrapment in fine vessels and extravasation into the tissue. Although it has generally been assumed that dissemination of lung tumor cells to the brain is mediated hematogenously, new evidence that a robust lymphatic system may actually exist in CNS tissues may lead to future work that could potentially indicate other mechanisms (Louveau et al., 2015). Generally speaking, lung tumor metastasis presents as multiple focal lesions, rather than distinct solitary lesions which may be indicative of a different tumor type, although if detected early, lesions can be solitary in nature—and this is associated with better response to surgical resection (Ali et al., 2013).