

Advances in palliative radiotherapy of metastatic non-small cell lung cancer

Rakesh Kapoor, Vijai Simha

Department of Radiation Oncology, Regional Cancer Centre, Post Graduate Institute Of Medical Education and Research, Chandigarh 160012, India

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Correspondence to: Dr. Rakesh Kapoor, Professor. Department of Radiotherapy Post Graduate Institute Of Medical Education and Research Chandigarh 160012, India. Email: drkapoor.r@gmail.com.

Abstract: Radiotherapy has important role in the palliation of metastatic non-small cell lung cancer (NSCLC). Randomized trials tend to suggest that, in general, short regimens give similar palliation though with more long term toxicity compared to longer regimens. Hypofractionated radiotherapy has been the standard of care for the palliative management of lung cancer since decades. Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) are forms of extreme hypofractionation being used more frequently in the treatment of single or oligometastases. In general, they offer good tumor control with little toxicity (at a more expensive cost) compared to the traditionally fractionated radiotherapy regimens. The combination of targeted therapy with radiotherapy is an evolving concept in the management of metastatic lung cancer.

Keywords: Non-small cell lung cancer (NSCLC); hypofractionation; molecular targeted therapy; palliative care; radiosurgery

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Introduction

Patients with metastatic lung cancer have a poor prognosis and the therapeutic options are limited. Controlling their symptoms and maintaining their quality of life should be the principle of treatment. The primary goal of treatment is to use the most effective and the least toxic regimen for the treatment. Radiotherapy has largely been used to palliate non-small cell lung cancer (NSCLC) for this reason (1). Multiple prospective randomized trials using different dose or fractionation schedules have shown that palliative radiotherapy alleviate thoracic and extra-thoracic symptoms in patients with locally advanced or metastatic NSCLC (1-3). Indications for thoracic radiation include hemoptysis, cough, chest pain, dyspnea, obstructive pneumonia, superior vena cava syndrome and hoarseness of voice. Indications for extra-thoracic radiation therapy were initially limited to brain and bone

but has now widened to include adrenal abdominal lymph nodal, liver and re-irradiation for spinal metastases. In a comprehensive review by the Cochrane Collaboration (4), no significant difference among short compared to long radiotherapy regimens in terms of palliation and hypofractionated radiotherapy is the standard of care. The clinical picture and the performance status of the patients must dictate the treatment regimen. Short course and simple treatments must be generally preferred. Our typical palliative dose is 8 Gy in single fraction or 30 Gy in 10 fractions which is simple, well tolerated, efficient and comparable to other regimens (5,6).

Advances in palliative radiotherapy of NSCLC

‘Oligometastatic disease’ is a disease state intermediate between localized disease and metastatic disease (7) where

local treatment modalities have a role in reducing tumour burden and improving the long term survival. Surgery and stereotactic body radiation therapy (SBRT) are the competing modalities; and it is being increasingly recognized that SBRT can provide results equivalent to surgery while being non-invasive and producing minimal complication rates (8). Among the sites favored for the local therapy for oligometastatic tumours are the liver, lung, spine and the adrenal glands. The volume and number of sites of oligometastatic disease are vital in the decision making for aggressive local therapy and affect survival outcomes. Also of increased interest in recent times is the evolving role of reirradiation to metastatic sites to achieve better quality of life (9,10).

SBRT for thoracic disease

SBRT or “stereotactic ablative radiotherapy” is a form of extreme hypofractionated radiation delivery. It utilizes hypofractionated precisely targeted high dose radiation to the tumor while minimizing radiation to adjacent normal tissue.

Stereotactic radiosurgery (SRS) for the lung became possible because of the advent of 3D treatment planning and body immobilization devices to reduce intra- and inter-treatment movement of the tumour. It involves the use of 4DCT scans to manage the pulmonary motion during treatments. This technique allows treatment of small to moderate sized tumors, in either single or limited number of high daily dose fractions, with high chances of local control and little toxicity. Anti-tumour effects of extreme hypofractionation may be due to reasons beyond direct ionizing radiation induced DNA damage such as damage to the tumour vasculature, tumour stroma (11) and enhancement of tumour specific adaptive immune response (12). Clinically the expected results of hypofractionation have clearly overshoot the expected efficacy with hypofractionation as arrived by radiobiological models particularly the LQ model. The role of hypofractionation in lung has been established due to improvement in the therapeutic ratio as the α/β ratio of the tumour is high compared to the α/β ratio of the surrounding lung parenchyma which is relatively higher. Also the fact that the peripheral part of the lung behaves as a parallel organ may be helpful in delivery of high doses per fraction in the treatment of lung tumours. Hypofractionated radiotherapy has shown benefit in clinical trials in the radical treatment of lung cancer (13,14). Even in the setting of highly conformal setting of SBRT, the mean lung dose (>4 Gy) and the volume receiving 20 Gy

($V_{20}>4\%$) has shown maximum correlation with radiation pneumonitis (15). This by itself shows the thin line between control and toxicity in a radiosensitive tissue like lung thus emphasizing the role of SBRT. SBRT also has a role in treating selected patients with painful bone metastases or with oligometastases in, liver spine and adrenals. The COMET study (stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors) (SABR-COMET) is a randomized Phase II Trial open in Europe and Canada, comparing patients with up to five metastatic lesions from any primary tumor site who can receive SABR. Eligible patients are randomized to either standard palliative radiotherapy versus SABR (16).

SBRT for liver oligometastasis

The incidence of metastasis to the liver is in the range of 30-70% of patients with metastatic lung cancer and a subset (10-15%) of patients have been shown to have oligometastatic disease in the liver. There has been gaining interest in surgical or non-surgical treatment of liver oligometastasis (17). Ercolani *et al.* have shown in their case series of survival of as high as 3 years (in one out of three patients) after surgical resection of oligometastatic disease to the liver (18). When radiation is used in the treatment of oligometastasis to the liver, it has been shown that the complication probabilities steeply rise with small increases in the dose. For a dose of 60 Gy delivered in three fractions by SBRT, it is recommended that <700 cc of the normal liver receive >15 Gy (19,20). This calls for accurate and conformal therapies.

SBRT in brain metastases

When brain metastases occur in patients with NSCLC, there is often active disease at the primary site or elsewhere in the body. In few cases, the brain is the only site with active disease (21). There are many guidelines on the treatment of brain metastases showing that therapeutic intervention (radiotherapy or surgery) is associated with improved control of disease in the brain (22).

SRS to the brain involves a single shot of high dose radiotherapy and can control very efficiently one to few metastases either close to the surface or deep in the brain (23). No randomized trials have compared SRS with traditional surgical resection. The traditional whole brain radiotherapy (WBRT) treats the metastases and may also prevent the growth of new metastases, but may

cause side effects such as memory loss. Recent Cochrane review shows that there is low quality evidence that adding upfront WBRT to surgery or to SRS decreases any intracranial disease progression at 1 year. There is also no clear evidence of an effect on overall survival and progression free survival (24). However a phase III trial comparing WBRT and stereotactic boost treatment showed improved functional autonomy performance status for all patients and survival for patients with a single unresectable brain metastasis. WBRT and stereotactic radiosurgery has been as a standard treatment for patients with a surgically unresectable oligometastasis (25).

SRS has become increasingly important treatment technique in the management of brain metastases, but it is not available everywhere and it is more expensive than WBRT. An approach of SRS alone as initial treatment of brain metastases has allowed patients to delay or avoid WBRT and its associated side effects (26). The benefit of SRS in resource poor settings and the cost-benefit ratio is yet to be defined.

Adrenal metastasis

Metastatic disease from a NSCLC to the adrenal gland is common, and systemic treatment is the therapeutic option of choice. However patients with isolated adrenal metastasis have shown good response after surgical resection. The non-invasive option is SBRT (27) which has shown markedly improved progression free survival times and modest improvement in overall survival (28).

Spinal lesions

Durable pain control is one of the primary goals for metastatic spinal lesions which can be achieved by sustained local control. It has been shown that the local control is gradually lost over a period of time after conventional radiotherapy to spinal metastasis (6,29). This lays the foundation for dose escalation for durable pain relief with SBRT by delivery of higher biologically equivalent dose at the time of initial irradiation. Also in re-irradiation of metastases, the margin for error is very small due to the low tolerance of the spinal cord (30). Significant reductions in patient-reported pain and other symptoms were evident 6 months after SBRT, along with satisfactory progression-free survival and no late spinal cord toxicities (31). Radiation Therapy Oncology Group (RTOG) study number 0631 is an open Phase II/III Study of Image-Guided SBRT for

localized spine metastasis comparing one treatment of 16 Gy delivered with SBRT versus a single fraction of 8 Gy.

Targeted therapy with palliative radiotherapy

When used in combination with radiotherapy, molecularly targeted agents aim to increase the effect of the radiation on the tumor. Substantial preclinical data have accumulated to show that these agents can potentially enhance the tumor response to radiotherapy through a variety of mechanisms (32). They offer new but challenging possibilities for clinical practice. There is a growing evidence for combination of radiotherapy and targeted therapies in other cancers (e.g., head and neck cancers) (33,34). However the addition of targeted agents to thoracic radiation so far has not improved outcomes in patients with locally advanced NSCLC (35,36).

The combination of radiotherapy and molecular agents targeting vascular endothelial growth factor (VEGF) mediated angiogenesis may result in synergistic effects leading to enhanced tumor cell killing on the one hand, but to enhanced normal tissue damage on the other hand (37). To date, there are only limited data on the efficacy and toxicity of anti-angiogenic agents given in combination with radiotherapy in lung cancer. Given the strong preclinical rationale for combining Epidermal Growth Factor Inhibitor inhibitors (Cetuximab, Panitumumab, Erlotinib, Gefitinib, Lapatinib, and Trastuzumab) with radiation, additional studies are needed. Phase I/II data and lack of long-term experience suggest that physicians should consider combined modality approaches with caution, considering the possibility of uncommon but potentially severe toxicity (38). With high-precision irradiation techniques (such as SBRT), the combination with targeted agents is feasible with apparent no increase in severe adverse events. Phase III trials involving addition of erlotinib or Temozolomide to radiosensitize WBRT failed to show any benefit (39). In another trial which attempted to substitute erlotinib for WBRT showed that the incidence of intracranial failures was high in the erlotinib arm (40) suggesting that targeted therapies can never substitute for WBRT in NSCLC with brain metastasis. Nevertheless, the addition of molecular targeted drugs to radiotherapy outside of approved regimens or clinical trials warrants careful consideration on a case by case basis.

There is still a debate on the timing of combining targeted agents with radiation and is an open area for future research.

It cannot be assumed that giving the drug concurrently with radiation (as it happens with chemotherapy) is always the optimal treatment strategy. Indeed, drugs that cause cell cycle arrest or prolong cells in the radio-resistant phase of the cell cycle may jeopardize the radiation effect (34).

Brachytherapy

High dose rate (HDR) endobronchial brachytherapy for palliation of hemoptysis or obstruction as these sites are not amenable to ablation by stereotactic techniques (using doses between 6 and 10 Gy at 1 cm). Hypofractionation is the underlying principle in this setting also. However this is not in common use the rarity of the clinical picture meriting brachytherapy. External radiation alone is more effective than endobronchial brachytherapy for symptom palliation in previously untreated patients with endobronchial NSCLC. Endo-bronchial therapy is recommended for symptomatic patients with recurrent endobronchial obstruction previously treated by radiation, provided it is technically feasible (41).

Cost benefit ratio in SBRT

The basic principle of palliative case is to do best with as little as possible. Though these advanced techniques offer conformal and accurate doses with adequate palliation of symptoms and better quality of life, they have to be evaluated in terms of increased costs associated with the treatment particularly in developing countries where the patient himself bears the cost of the treatment. Cost effective analysis from various trials comparing SBRT with other treatment modalities showed that the treatment outcomes are comparable or superior compared to other treatment modalities and are cost effective in the long run (42). SBRT compared to other modalities was more effective in freeing up hospital resources and allowing patients to resume normal activities earlier thus minimizing indirect costs (43,44).

Conclusions

With the newer advancements in radiation delivery techniques allowing a very high precise radiation dose to a well localized target, there is a wealth of data for the practice of evidence based medicine in the palliative management of lung cancer. Advocating aggressive management of oligometastatic disease offers the potential for enhanced

quality and quantity of survival. This has not only widened the scope of palliative radiation in the metastatic setting as well as re-irradiation of previously treated sites.

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