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Original Article

# The Role of Radiotherapy in Epidermal Growth Factor Receptor Mutation-positive Patients with Oligoprogression: A Matched-cohort Analysis

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## Abstract

*Aims:* Almost all patients with epidermal growth factor receptor (EGFR) mutations will develop resistance to first-line EGFR tyrosine kinase inhibitors (TKIs). The management of oligoprogression on EGFR TKI is controversial. Irradiating progressing tumours may potentially eradicate the resistant clone and allow continuation of EGFR TKI, but the clinical data remain sparse. We aimed to assess the effect of radiotherapy on survival outcomes in patients with oligoprogression in a matched-cohort study.

*Materials and methods:* This was a retrospective matched-cohort study comparing patients with EGFR mutation-positive stage IV non-small cell lung cancer receiving radiotherapy versus chemotherapy for progression. Patients in the radiotherapy group received radiotherapy (mainly stereotactic ablative radiotherapy) for oligoprogression, whereas the chemotherapy group received only systemic chemotherapy upon progression. Key prognostic factors including gender, age, performance status, time to first progression and mutation subtypes were matched.

*Results:* Twenty-five patients with oligoprogression (radiotherapy group) were identified, and a matched chemotherapy group with the same number of patients was generated. The median duration of follow-up was 24.3 and 34 months for the radiotherapy and chemotherapy groups, respectively. The median overall survival of the radiotherapy group was significantly longer than the chemotherapy group, 28.2 versus 14.7 months ($P = 0.026$). The median progression-free survival (PFS) was 7.0 and 4.1 months after radiotherapy and chemotherapy, respectively ($P = 0.0017$). The use of radiotherapy was an independent predictive factor of overall survival and PFS in multivariate analysis. Only one patient had ≥grade 3 toxicity after radiotherapy. The frequency of secondary T790M mutation and subsequent Osimertinib exposure were similar in both groups.

*Conclusion:* Radiotherapy may effectively extend EGFR TKI therapy for patients with oligoprogression on TKI. Improved PFS and overall survival were observed, although potential biases should not be overlooked. Further randomised studies are warranted.


*Key words:* Non-small cell lung cancer; oligoprogression; stereotactic ablative radiotherapy; tyrosine kinase inhibitors

## Introduction

The advent of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and the identification of the predictive biomarkers, EGFR mutations, have revolutionised the management of advanced stage non-small cell lung cancer (NSCLC) [1–4]. However, almost all patients will eventually develop resistance to EGFR TKIs at a median time of 9–13 months [5–10]. Although the mechanisms of resistance may vary, clinical progression usually manifests in three distinct patterns that include isolated central nervous system progression, oligoprogression or widespread systemic progression [11]. The management of oligoprogression is controversial owing to the paucity of clinical data. The resistant clone progresses clinically but the non-progressing clone may still be sensitive to TKIs. Local therapy of progressing tumour may eradicate the resistant clone and allow continuation of EGFR TKI [12,13].

There are various types of local therapy and each has its own merits and drawbacks. Among them, stereotactic

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ablative radiotherapy (SABR) is a non-invasive way to eliminate progressive clones. SABR can deliver a high radiation dose to selective target sites precisely in a few fractions. Local control rates after SABR are high (70–90%) [14]. Severe toxicities are uncommon and the procedure can be carried out in an out-patient setting [14]. Weickhardt *et al.* [15] reported the experience of using SABR to treat oligoprogression in oncogene addicted NSCLC from a single centre. This single arm study suggested that SABR prolonged the disease control by a median of 6 months. Another single arm phase II study reported that the combination of SABR and erlotinib altered the pattern of failure as well as resulted in high progression-free survival (PFS) and overall survival compared with historical patients who received systemic treatment alone. Of note, no known positive EGFR mutants were included in that study [16].

The benefit of radiotherapy in oligoprogression after EGFR TKI has not been explored in a randomised study. Considering the potential ethical implication, a randomised comparative study can be challenging. Here we report a matched-cohort study comparing patients who were treated with radiotherapy for oligoprogression with patients who received only systemic chemotherapy.

## Materials and Methods

This was a retrospective study on patients with histologically confirmed EGFR mutation-positive stage IV NSCLC from two hospitals in Hong Kong (Pamela Youde Nethersole Eastern Hospital and Queen Mary Hospital). Patients were retrospectively identified and included in the analysis if they fulfilled the three major criteria. First, they had three or fewer foci of radiological progression upon EGFR TKI therapy, detected by either computer tomography or positron emission tomography with integrated computed tomography (PET-CT). Second, these foci were treated with radiotherapy. Third, the same systemic therapy was continued after radiotherapy. A matched cohort of patients who received EGFR TKI therapy at a similar period and switched to platinum-based doublets with or without bevacizumab upon progression was generated from the hospital database. Criteria for matching included: gender, age, performance status, time to first treatment progression and mutation subtypes. The patients were classified into two groups, namely the radiotherapy group and the chemotherapy group.

### *Radiotherapy*

In total, 25 patients fulfilling the inclusion criteria were identified in the clinical database. Radiotherapy, mainly SABR, was delivered to the oligoprogressive foci. Detailed information on SABR treatment planning and delivery in thoracic lesions were previously reported [17] and they abided by the recommendation of the European Organization for Research and Treatment of Cancer and the International Atomic Energy Agency [18–20].

In brief, patients were immobilised by BodyFIX® (Elekta) or an alpha-cradle. Head and neck casts were used for cranial lesions. Contrast axial computed tomography imaging was obtained at 1.25–2.5 mm slice thickness. Motion control and characterisation were carried out either using the breath-hold technique or by four-dimensional computed tomography (General Electric Medical System) for thoracic and intra-abdominal lesions. The gross tumour volume (GTV) was contoured in appropriate window settings and fusion of diagnostic magnetic resonance imaging or PET-CT imaging was carried out to assist target delineation if necessary. The internal target volume (ITV) was derived by summation of GTVs in 10 respiratory phases in four-dimensional computed tomography simulated lesions. The clinical target volume (CTV) was identical to the GTV (or ITV in four-dimensional computed tomography simulated lesions), except for vertebral lesions in which abnormal marrow signal and an adjacent normal bony expansion were included per an international consensus [21]. A 3–8 mm margin was added to the CTV to form the planning target volume for extra-cranial lesions.

Dose fractionation for thoracic, abdominal and vertebral lesions was 50–60 Gy in three to five fractions, 35 Gy in five fractions and 24–35 Gy in two to five fractions, respectively. The treatments were typically completed within 2 weeks. The dose was prescribed in the 60–90% isodose level. Single fraction stereotactic radiosurgery of 15–20 Gy was delivered to intracranial lesions, prescribed at the 80–90% isodose level. Six patients received hypofractionated conformal radiotherapy as those lesions were considered not suitable for SABR or facilities were unavailable at that time.

Most of the treatment planning was carried out using the Eclipse® treatment planning system (Varian Medical Systems) using the anisotropic analytic algorithm with tissue heterogeneity correction. Some treatments for intracranial lesions were planned using iPlan® radiotherapy (BrainLAB AG) using the pencil beam algorithm.

Treatments were delivered with a Varian linear accelerator using 6 MV photons. Image guidance with either onboard cone beam computed tomography (Varian Medical Systems) or the ExacTrac® frameless radiosurgery system (BrainLAB AG) before each fraction of therapy was used to ensure high precision.

PET-CT was preferred but not mandatory to confirm the status of oligoprogressive disease and to assist target delineation. In total, 16 (64%) patients had PET-CT and 10 (40%) had dedicated brain imaging. EGFR TKI was withheld 1 day before radiotherapy and resumed the day after treatment. Follow-up imaging including computed tomography or PET-CT was usually arranged every 3–4 months. Repeated radiotherapy to the same or other new progressing sites was offered at the discretion of the treating oncologists.

This study was approved by the institution review board.

### *Statistical Analysis*

The study end points of this analysis were to assess if the use of radiotherapy upon oligoprogression may prolong the use of EGFR TKI and thus improve overall survival. The time to progression and the overall survival time after

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