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An overview on personalisation of radiotherapy prescriptions in locally advanced non-small cell lung cancer: Are we there yet?

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ABSTRACT

Standard of care radiotherapy in LA-NSCLC is 60–66 Gy in 30–33 fractions. However outcomes for these patients are poor with 5-year survival in the range of 10–20%. Randomised controlled trials have shown that dose escalation in a linear fashion does not improve outcomes for all patients, thus there is a need to tailor the prescription to the individual patient. This review assesses the strategies published to personalise the radiation therapy dose prescription in LA-NSCLC. A systematic and scoping search of the literature was performed to identify studies that met the inclusion criteria. 19 relevant studies were identified ranging from prospective clinical trials to mathematically modelled concept studies. Heterogeneity existed between all clinical studies. Nine heterogeneous publications proposed methodology to adapt the dose prescription to the individual patient. A number of encouraging strategies have been identified but fall short of the evidence level required to influence clinical practice.

Non-Small Cell Lung Cancer (NSCLC) is the most common form of lung cancer and with poor treatment outcomes and an age-standardised 5-year survival reported to be 10–20% world-wide [1]. Early stage disease treatment for medically inoperable patients has been revolutionised with the advent of stereotactic ablative body radiotherapy (SABR), which has become a standard of care for patients with medically inoperable NSCLC and which has comparable outcomes to surgery for Stage I disease [2,3]. Outcomes in the locally advanced (LA) setting remain poor with little improvement in overall survival (OS) over the past 40 years [4]. Radiotherapy (RT) is a mainstay of treatment for LA-NSCLC and is delivered either as radiotherapy alone or in conjunction with chemotherapy either concurrently or sequentially. An established dose fractionation of 60–66 Gy in 30–33 fractions remains the RT standard of care [5] for patients with LA-NSCLC.

The benefit of RT dose escalation has been explored and a dose response relationship has been reported in the setting of curative intent RT for NSCLC [6]. Theoretically, dose escalation is key to improving local control (LC), progression free survival (PFS) and OS. The randomised control trial, RTOG 0617, sought to compare outcomes following standard dose RT of 60 Gy versus a higher dose of 74 Gy in LA-NSCLC [7]. Dose escalation was found to be associated with worse outcomes and poorer overall survival. A more recent meta-analysis investigating RT dose response relationships in NSCLC reported survival benefits for escalation in the RT alone setting and no survival benefit in the concurrent chemoradiotherapy (CRT) setting [8].

It has been hypothesised that any potential benefit of dose escalation has not translated clinically in the findings of the RTOG 0617 due, at least in part, to the increased toxicity induced from both the RT and chemotherapy regimens as well as potential variation in RT delivery and quality assurance [9,10]. The overall extension of treatment duration in a conventional 2 Gy per day fractionation schedule, may be a contributing factor to the poorer outcomes given that longer treatment times may facilitate tumour repopulation. As a result adapting the dose fractionation schedule, without extending overall treatment duration, has been suggested as an alternative approach [11].

While the evidence is somewhat conflicting, it seems clear that universal dose escalation in a linear fashion is not the solution for this patient cohort. It thus follows that adopting a personalised, patient specific approach to modifying the radiotherapy prescription may permit safe RT dose escalation [11].

While recent advances in RT technology have been vast, the evolution is now moving away from increasing the geometric capabilities of the equipment and towards personalising and individualising treatment parameters to a patient's specific needs and

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requirements [12]. The poor OS associated with the treatment of LA-NSCLC with RT calls for an urgent need to transform outcomes for patients. Personalisation of radiotherapy dose prescription and safe dose escalation may be one strategy to address this.

Isotoxic treatment planning has been suggested as a method of personalising radiotherapy for each patient based on their individual treatment plan [13]. In isotoxic RT planning, the prescribed dose is increased incrementally until an organ at risk (OAR) maximum tolerated dose is reached. As a result, each patient will have a personalised prescription. However, this approach of dose escalation is not based on any patient or disease specific features.

Several methodologies have been reported in the literature to modify LA-NSCLC prescriptions, which may prove more successful than RTOG 0617 in improving outcomes for these patients. This review aims to assess both the on-going clinical work being carried out in developing modified dose fractionation schedules, as well as evaluate emerging novel proposals to personalise LA-NSCLC radiotherapy prescriptions.

Search strategy methodology

A systematic search of the literature was carried out in PubMed and Embase databases using the key words 'Non-small cell lung cancer' 'Personalised Radiotherapy' 'Dose Optimization' and associated Mesh Terms. See Supplementary Material for complete search strategy. A scoping search of the literature was also performed.

Inclusion criteria were defined as personalised radiotherapy studies relating to NSCLC (including a pre-treatment change in dose per fraction, escalation, de-escalation based on Tumour Control Probability (TCP) or Normal Tissue Complication Probability (NTCP)), modelled personalised radiotherapy studies and studies published after January 2000. Exclusion criteria were defined as any other site (including small cell lung cancer), adaptive studies based on mid-treatment response rather than pre-treatment personalisation, change to chemotherapy prescription, no change to RT prescription, stereotactic radiotherapy studies, protons/carbon ion studies, genetic or biomarker based studies and non-EBRT escalation studies. Studies that reported prescription modification for stratified groups of patients were excluded and only those that individually adjusted the prescription on a per patient basis were included.

Due to heterogeneity between the study types and a limited sample size secondary analysis of the data was not feasible. As a result, the findings were evaluated in a qualitative manner. 19 relevant publications were identified (Fig. 1) [14–32].

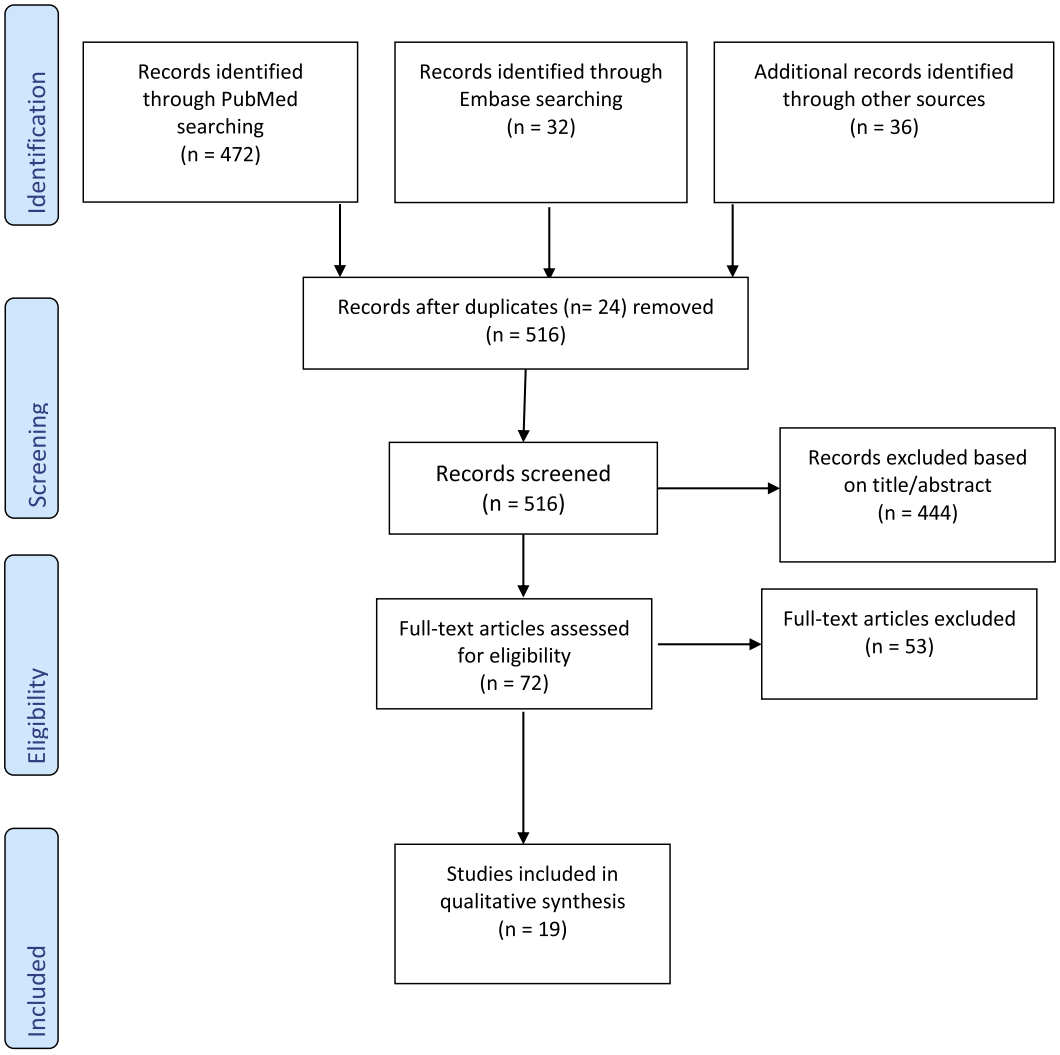

Fig. 1. Flow chart of the literature search process.

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