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Review

Normal tissue considerations and dose–volume constraints in the moderately hypofractionated treatment of non-small cell lung cancer

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ABSTRACT

Hypofractionated radiation therapy (RT) regimes in non-small cell lung cancer (NSCLC) have become increasingly popular with a number of international trials currently underway. The majority of the dose–volume-constraints (DVCs) published in the literature refer to conventional 2 Gy per fraction deliveries. Here relevant organs-at-risk (OARs) are identified and available dose–volume constraint data discussed and summarised for moderately hypofractionated NSCLC regimes. The OARs examined include lung, brachial plexus, heart, oesophagus, airway and spinal cord. Where available the toxicity rates are also reported with all data summarised tabulated to aid its use in the clinic.

In Europe lung cancer represents 15.9% and 7.4% of all invasive cancers diagnosed in males and females respectively and remains a leading cause of cancer deaths accounting for 26.1% in males and 12.7% in females [1]. Stereotactic Ablative Body Radiation Therapy (SABR) has demonstrated the ablative ability of very large doses (>100 Gy biological effective dose (BED)) in small tumours [2]. However, in some cases these dose levels cannot be safely delivered in locally advanced (LA) non-small cell lung cancer (NSCLC) due to the size of the target volumes and proximity to nearby structures. Thus, with standard prescription of 60 Gy/30# (fractions) [3] 5-year survival rates remain in the region of 10–15% [4–6].

An analysis of a number of RTOG (Radiation Therapy and Oncology Group) trials demonstrated overall treatment time (OTT) to be significantly associated with poorer survival [7]. OTT can be reduced through hypofractionation (>2 Gy per #). Thirion et al. have published their experience of 72 Gy/24# in 60 patients, with 1-year overall survival of 68% and thoracic-progression-free survival of 72% [8]. A dose of 55 Gy/20# is a NICE (National Institute for Health and Care Excellence) approved schedule in the UK (United Kingdom) [9]. A review of this regime demonstrated 97% of patients received the prescribed dose (PD), demonstrating deliverability to the majority of patients [10]. Low levels of toxicity (no grade 3+ toxicities and radiation pneumonitis rates <20%) suggest that there is space for dose escalation within 20# schedules [10]. Long term follow-up of this schedule has shown local tumour control at 3 years of 74.1% [11]. There are a number of current trials in hypofractionated NSCLC treatment, including RTOG 11-06 (30#) [12], I-START (20#) [13] and IDEAL-CRT (30#) [14], while the results of NCIC CTG BR.25 (60 Gy/15#) have recently been published [15].

In 2010 the QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) review of the literature on normal tissue effects was published, summarising tolerance data on an organ-by-organ basis [16]. However, it is primarily focussed on conventional fractionation and the lack of established constraints for hypofractionated treatment of NSCLC was highlighted in a recent study from Swanick et al. [17]. A number of authors have also summarised tolerance doses for SABR [18,19]. In a dose escalation planning study by Warren et al. the proximal bronchial tree and great vessels limited escalation [20], organs that are not typically contoured or considered in conventional NSCLC radiation therapy (RT). At doses above 80 Gy EQD_2 (Equivalent Dose in 2 Gy) toxicities can be observed related to high point-doses (oesophageal fistula, bronchial stenosis) [8,21–23]. In accelerated hypofractionated schedules in LA-NSCLC there are additional organs-at-risk (OARs) and toxicities to be considered. The motivation of this systematic review is to discuss and

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summarise dose–volume constraints (DVCs) for moderately hypofractionated (2.1–5 Gy per #) regimes in LA-NSCLC in order to aid those intending to treat with a hypofractionated regime to select appropriate evidence based DVCs.

Materials and methods

A literature search was performed using PubMed, Science Direct, Google Scholar and ClinicalTrials.Gov including the terms 'hypofractionation', 'lung cancer,' 'NSCLC', 'DVCs', 'dose volume constraints', 'toxicity' and incorporated Boolean logic to narrow the results. Secondary related articles were selected from the reference lists of articles found to be relevant. The search yielded both clinical trial schema and publications on clinical treatment. The organs-at-risk identified include lung, brachial plexus, heart, oesophagus, airway and spinal cord. Particular attention has been paid to reported cases of grade 4 and 5 toxicities and their relationship to dose delivered. Only studies including 3DCRT (3-dimensional conformal radiation therapy) or IMRT (intensity modulated radiation therapy) were included. Schedules other than 5# per week, greater than 5 Gy per #, where patients had previous thoracic RT or where a scheduled break was present in RT were also excluded. A CONSORT diagram illustrates the number of papers identified and how the inclusion/exclusion criteria resulted in the final number of studies (see Fig. 1).

Results

Lung

V_{20Gy} (% volume receiving 20 Gy) <30–35% is commonly used in conventional fractionation [24] and many of the studies analysed here have used this metric without accounting for differences in fraction number, fraction size or dose distribution due to delivery technique [8]. A number of the studies use a mean lung dose (MLD) constraint as detailed in the QUANTEC report [16], with five utilising a LQ (linear quadratic) correction on the DVH (dose–volume histogram) before generating a MLD or $rNTD_{mean}$ (mean fraction-normalised lung dose divided by the normalised prescription dose) [13,14,25–27]. In three studies the lung dose is the basis for deciding the prescription dose level [26–28]. A summary of the data gathered is presented in Tables 1 and 2, this represents data from 1845 patients and there were 13 deaths as a result of toxicity (crude rate 0.7%). Two patients with T4 disease died during treatment; they had received 12 Gy/5# and 31.2 Gy/13# respectively [29]. Three patients died from lung toxicity within 90 days of RT, one of these received 59 Gy of 70.5 Gy, the second died after completing RT (70.5 Gy/30#) with autopsy revealing the presence of radiation fibrosis [30] and the third received 63.25 Gy/25# [26]. Three deaths were reported by Kepka et al., two of these were at their highest dose level of 58.8 Gy/21# leading them to reduce the dose to the previous level of 56.7 Gy/21# [31]. None of these three patients had exceeded the DVCs (V_{20Gy} < 35% and MLD < 20 Gy) [31]. Three patient deaths were reported at 60 Gy/25# [32], and one at both 54/18# [33] and 60 Gy/15# [15]. There is considerable heterogeneity in the reporting of toxicity across the studies, with some only reporting toxicity by group (e.g. grade 2+), others did not distinguish between acute and late lung toxicity or by chemotherapy schedule. Thus not all data could be included in overall toxicity summaries. The crude incidence of grade 3+ toxicity in the sequential studies reported here was 2.9% (15/516) for acute and 4.7% (24/516) for late toxicity. In the concurrent studies the crude incidences of grade 3+ acute and late toxicity were 6.3% (10/158) and 10.1% (16/158) respectively. Three of the concurrent studies did not distinguish between acute and late toxicity and they reported grade 3+ rate of 3.3% (13/400) [32,34,35].

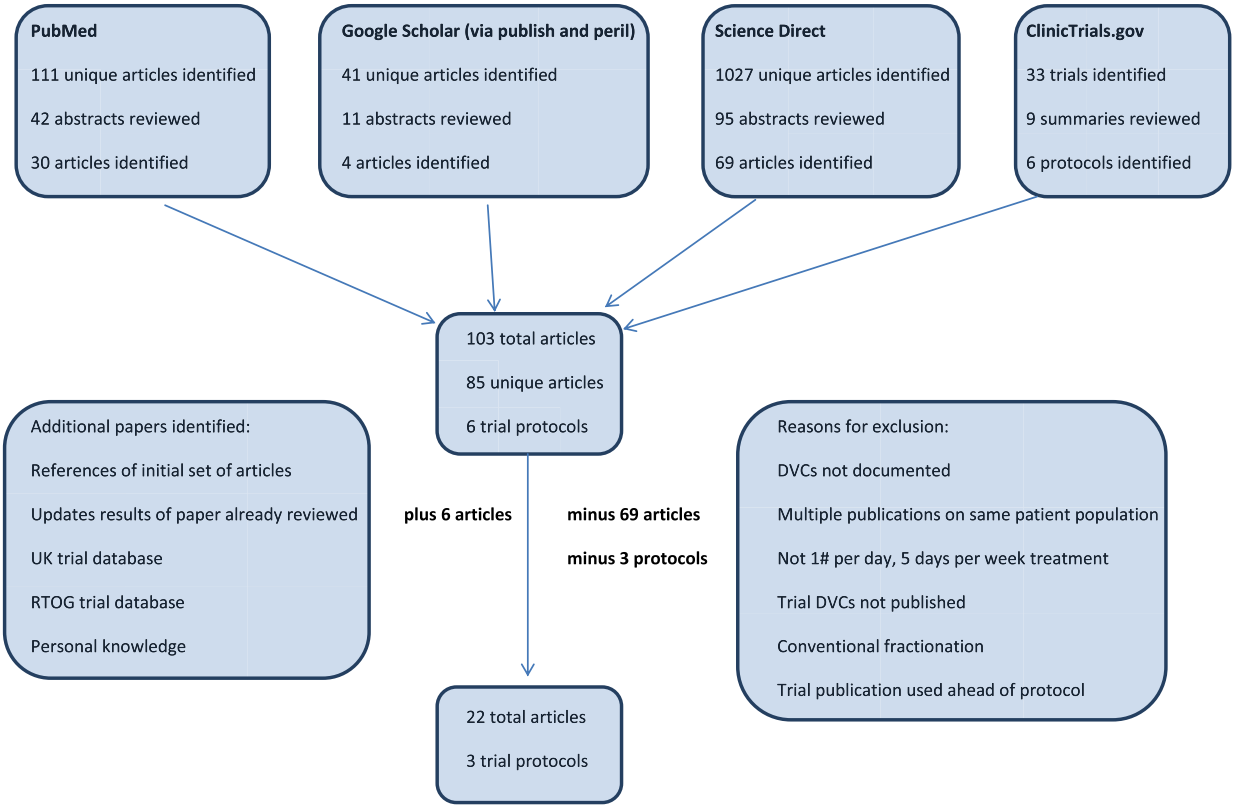

Fig. 1. CONSORT diagram indicating the selection process for including papers/protocols in this review.

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