Radiotherapy and Oncology 106 (2013) 276–282

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Outcomes of stereotactic ablative radiotherapy for central lung tumours: A systematic review

Sashendra Senthi *, Cornelis J.A. Haasbeek, Ben J. Slotman, Suresh Senan

Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 2 November 2012
Received in revised form 9 January 2013
Accepted 14 January 2013
Available online 22 February 2013

Keywords:
Lung cancer
Stereotactic
Inoperable
Central
Toxicity
Mortality

ABSTRACT

Background and purpose: Stereotactic ablative radiotherapy (SABR) has improved the survival for medically inoperable patients with peripheral early-stage non-small cell lung cancer (NSCLC). We performed a systematic review of outcomes for central lung tumours.
Material and methods: The systematic review was performed following PRISMA guidelines. Survival outcomes were evaluated for central early-stage NSCLC. Local control and toxicity outcomes were evaluated for any centrally-located lung tumour.
Results: Twenty publications met the inclusion criteria, reporting outcomes for 563 central lung tumours, including 315 patients with early-stage NSCLC. There was heterogeneity in the planning, prescribing and delivery of SABR and the common toxicity criteria used to define toxicities (versions 2.0–4.0). Tumour location (central versus peripheral) did not impact overall survival. Local control rates were $\geqslant$85% when the prescribed biologically equivalent tumour dose was $\geqslant$100 Gy. Treatment-related mortality was 2.7% overall, and 1.0% when the biologically equivalent normal tissue dose was $\leqslant$210 Gy. Grade 3 or 4 toxicities may be more common following SABR for central tumours, but occurred in less than 9% of patients.
Conclusions: Post-SABR survival for early-stage NSCLC is not affected by tumour location. SABR achieves high local control with limited toxicity when appropriate fractionation schedules are used for central tumours.
 Radiotherapy and Oncology 106 (2013) 276–282

Anatomic surgical resection is the treatment of choice for patients diagnosed with early-stage non-small cell lung cancer (NSCLC) [1,2]. For tumours that are centrally located, more extensive surgical procedures are required due to tumour invasion into the major bronchi and/or vessels [3,4], which is associated with a higher mortality and morbidity [5]. Thus, the treatment of central tumours represents a high-risk clinical scenario in which the risks associated with surgery have been deemed acceptable.

As the global population ages, the proportion of elderly lung cancer patients and those with comorbidities will also increase [6–9]. For the unfit elderly with peripheral early-stage NSCLC, stereotactic ablative radiotherapy (SABR) is considered the preferred treatment [2], offering improved survival and quality of life over conventional radiotherapy [10,11]. In an early SABR trial, fractions of 20–22 Gy, delivering total doses of 60–66 Gy to central tumours were associated with a greater than 10-fold increased risk of high-grade toxicity or death [12]. This led to an ongoing Radiation Therapy Oncology Group (RTOG) phase I/II trial (0813) specifically for central tumours, to determine the maximum tolerated dose which can be delivered in five fractions [13]. Similarly, it has lead others to suggest that the risks associated with SABR for central tumours may be prohibitive and high-dose accelerated radiotherapy be the subject of further research [14].

As reports from Japanese and Dutch investigators have reported favourable outcomes in early-stage tumours using daily fractions of 6.0–7.5 Gy to total doses of 48–60 Gy [15,16], many centres have continued to use SABR for central tumours. We performed a systematic review of published literature on the clinical outcomes of SABR for central lung tumours.

Methods

A systematic review was performed according to the PRISMA guidelines [17]. We searched for English-language papers published from January 2000 to August 2012. The inclusion criteria were:

1. Studies reporting clinical outcomes following SABR for primary NSCLC or metastatic lung tumours and,
2. Studies specifically reporting clinical outcomes for centrally located tumours.

* Corresponding author. Address: Department of Radiation Oncology, VU University Medical Center, De Boelelaan 1118, 1081 HV Amsterdam, The Netherlands.
E-mail address: s.senthi@vumc.nl (S. Senthi).

0167-8140/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.radonc.2013.01.004

Studies were excluded if:

1. They were review articles or case reports,
2. They were not the most recently published outcomes, in instances of multiple publications from the same study cohort.

Using PubMed, the search was completed in August 2012. The search strategy was (sabr[tw] OR sbrt[tw] OR srt[tw] OR stereotactic[tw]) AND lung[tw] AND (central[tw] or centrally[tw]), which identified 86 studies. Two clinicians reviewed these and the reference lists of selected articles to determine which were suitable for inclusion. Survival outcomes were restricted to patients with central early-stage NSCLC [18]. Local control and toxicity outcomes included those reported for any central tumour receiving SABR. Toxicity outcomes were included when graded using the Common Toxicity Criteria (CTC) protocol version in place at the time. The prescribed tumour doses were converted into a biologically equivalent dose (BED) to enable comparison between studies, acknowledging the limitations of this approach [19,20]. The BED was calculated using the assumption that tumour and normal tissue alpha/beta ratios were 10 Gy (BED_{10}) and 3 Gy (BED_3), respectively [21]. BED_{10} calculations were made using the dose delivered to at least 95% of the planning target volume (PTV). BED_3 calculations were made using the prescribed dose schedules and the maximum organ at risk doses received when studies provided this detail. BED calculations did not take into account tumour doubling time or the length of treatment.

Results

A total of 20 studies were found suitable for inclusion. Four of these were prospective [22–25], including two Phase II studies [23,24]. Seven studies reported clinical outcomes for NSCLC together with metastatic tumours [26–32] and one reported outcomes restricted to central early-stage NSCLC alone [32]. From these 20 studies, a total of 563 central tumours (including 315 early-stage NSCLC patients) received SABR. The radiotherapy details of these studies are summarized in Table 1. In these studies toxicities were described using CTC versions 2.0, 3.0 and 4.0.

Survival

The only prospective survival outcomes ($n = 22$) specific to central early-stage NSCLC were reported by Fakiris et al. [24], updating the initial report from Timmerman et al. [12]. The median overall survival was 24 months (95% CI 18–42), which was not statistically different ($p = 0.697$) from that of peripheral tumours. Haasbeek et al. reporting outcomes from the largest retrospective cohort, found the 3-year overall survival for central ($n = 63$) and peripheral ($n = 445$) early-stage NSCLC was statistically no different, 64% vs. 51% ($p = 0.09$) respectively [32]. Bradley et al. reported a 2-year overall survival of 75% for all early stage NSCLC and found central (vs. peripheral) location did not impact survival on both univariate ($p = 0.429$) and multivariate analyses [33]. Similarly, Janssen et al. found fractionation schedule, which depended on tumour location alone, did not impact survival on both univariate and multivariate analyses [31], while Andratschke et al. found tumour location did not impact survival on univariate analysis for histologically proven early-stage NSCLC ($p = 0.653$) [34]. Cause-specific survivals for central early-stage NSCLC have been reported to be greater than 80% at 2–3 years [30,33,35]. Table 2 details all reported survival outcomes.

Local control

After a median follow-up of 16 months, a prospective trial by Bral et al. found that tumour location did not impact recurrence, with the crude local control for central tumours being 94% (1/17) [23]. Retrospective studies have reported similar local control outcomes, with 2 and 3-year rates typically exceeding 85% [23,26,31–33,36–38], as shown in Table 2. However, six studies have reported poorer local control, of between 60–76% [27,29,30,34,35]. In two of these, SABR was prescribed to the isocentre, leading to a significantly lower peripheral tumour doses being delivered [29,35]. In the third study, 23% (12/53) of patients had stage II, III or recurrent stage III disease and 10% (6/63) of lesions had SABR delivered as a radiotherapy boost following conventional radiotherapy [27]. Although stage-specific local control outcomes were not reported, in the latter study the 2-year survival for non-stage I patients was 12%. In the fourth study reporting poorer local control, only 64% (37/58) of tumours had planning target volume coverage above 95% as under-dosage was permitted to meet normal organ constraints [30]. Additionally, in this study multiple fractionation schedules were utilized, and local control was 85% when the BED_{10} was $\geqslant$100 Gy and 60% when the BED_{10} was <100 Gy. In the last two studies, the modal prescribed doses were 35 Gy [34] and 40 Gy [27] in five fractions, resulting in a respective BED_{10} of 60 and 72 Gy.

The importance of maintaining a BED_{10} of at least 100 Gy to the tumour periphery was evident from a number of studies. Using a schedule of five fractions, Olsen et al. reported a 100% 2-year local control using a total dose of 50 Gy (BED_{10} 100 Gy) and 50% using 45 Gy (BED_{10} 86 Gy) [38]. Here, fractionation schedule was the only factor found to impact local control on multivariate analysis ($p = 0.019$). Similarly, Rowe et al. reported a 2-year local control of 94% with a BED_{10} $\geqslant$100 Gy and 80% when <100 Gy, ($p = 0.02$) [37]. Using a SABR schedule of four fractions, Chang et al. reported a crude local control of 100% with a total dose of 50 Gy (BED_{10} 113) vs. 57% using 40 Gy (BED_{10} 80 Gy) [26]. Two additional studies in which central and peripheral tumours were analysed together, also found that a BED_{10} above 100 Gy improved local control [15,25].

The post-SABR regional and distant control rates specifically for central early-stage NSCLC have been infrequently reported. Haasbeek et al. reported 2-year regional and distant control rates of 91% and 73%, respectively, which were no different from peripheral tumours treated by the authors using SABR over the same period, 86% ($p = 0.47$) and 75% ($p = 0.72$), respectively [32]. Two additional studies reported a crude distant recurrence rate of approximately 15%, which was the predominant pattern of recurrence [26,36].

Treatment-related mortality

In a prospective study utilizing a SABR fractionation with a BED_3 of 460 Gy, Fakiris et al. reported 18% (4/22) of patients with central tumours had potential treatment-related deaths [24]. Although an independent committee defined these, they included infective pneumonia and haemoptysis in the setting of local recurrence. Bral et al. reported the only other prospectively defined treatment-related death, a case of fatal haemoptysis after stent insertion for bronchial stricture [23]. Milano et al. reported 8.7% (4/46) mortality rate using SABR for central non-stage I NSCLC and no mortalities treating central stage I tumours [27]. It must be noted that in three (75%) of these cases, the authors could not exclude respiratory infection as the cause of death. Onimura et al. and Unger et al. each reported one treatment-related death, which were caused by an oesophageal ulcer (BED_3 154 Gy) and bronchial fistula (BED_3 209 Gy) respectively [15,28]. The latter two cases are the only cases of treatment-related death observed when the prescribed BED_3 was $\leqslant$210 Gy.

Table 3 details all treatment-related mortality reported for centrally located tumours. The overall treatment-related mortality rate from central tumours receiving SABR was 2.8% (16/563). For