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Do SABR-related toxicities for lung cancer depend on treatment delivery?

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ABSTRACT

Stereotactic ablative radiation therapy for lung cancer is an advanced technique where tumours are ablated with hypofractionated radiation doses, with a high degree of accuracy. The aim of this paper is to review the available literature and to discuss the SABR-induced toxicities for lung malignancies as a function of radiation delivery technique.

A Medline search was conducted to identify the appropriate literature to fulfil the aim of this review and data from all applicable papers were collated and analysed.

The most common techniques of SABR delivery employ linear accelerators, CyberKnife robotic radiosurgery system, TomoTherapy and the Novalis beam surgery system. Linear accelerator-based treatments give rise to a variety of toxicities that are strongly dependent on both patient-related factors and planning/dosimetry-related factors. The limited number of studies using CyberKnife reported low grade toxicities. Grade three toxicities mainly include fatigue and chest pain, usually in less than 10% of patients.

All treatment techniques presented show efficiency in SABR delivery with various toxicities which, at this stage, cannot render one technique better than the other. For more conclusive results, well-designed phase three randomised clinical trials are required with better patient selection criteria, including dose and fractionation, treatment machine and technique, along with the consistent selection of a common toxicity grading criterion.

1. Background

Lung cancer is the most common cancer worldwide, both in new cases and deaths (Ferlay et al., 2012). Non-small cell lung carcinomas (NSCLC) account for approximately 60% of all lung cancers and tend to progress more slowly compared to small cell lung carcinomas (SCLC) (approximately 12% of lung cancers), a more aggressive type of lung cancer, known to metastasise to the brain (Kumar et al., 2013). There are several treatment options to be considered for lung cancer patients and they are: surgery (e.g. thoracotomy, lobectomy, wedge resection), chemotherapy, radiation therapy, targeted therapies and immunotherapy. As recommended by the European Society of Medical Oncology (ESMO) in the 2017 Clinical Practice Guidelines for early-stage and locally advanced non-small cell lung cancer, for patients with stage 1–2 NSCLC without comorbidities, lobectomy is the most preferred treatment modality, whereas stereotactic ablative radiation therapy (SABR) is recommended for stage 1–2 patients that are medically inoperable (Crino et al., 2010). ESMO is in favour of adjuvant cisplatin-based chemotherapy for patients with stage 2–3 radically resected NSCLC and recommends a two-drug combination of a platinum-based agent (Crino et al., 2010). A third-generation drug can be considered for patients with advanced NSCLC or stage 3A-N2 NSCLC. For patients with inoperable locally advanced stage 3 NSCLC, ESMO recommends adding platinum-based chemotherapy with chest radiotherapy (Crino et al., 2010). For patients with localised SCLC and a favourable outcome, surgery is the recommended treatment modality (Fruh et al., 2013). All other patients with localised T1-4 N0-3 M0 SCLC and a good performance status should be treated with concurrent chemotherapy and radiation therapy, while patients with metastatic disease need to be managed with four-to-six cycles of platinum-based chemotherapy (Fruh et al., 2013).

1.1. Radiation therapy for lung cancer

Radiation therapy for lung cancer is a viable treatment modality which can be used to cure lung cancer, or as palliation of symptoms. Radiation therapy is the standard of care for patients with SCLC, occurring in 70–90% of patients with localised disease and 60–70% in patients with advanced disease (Siegel et al., 2012). For patients with NSCLC, approximately 18% receive radiation therapy (Siegel et al.,

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2012). In both histological types of cancer, radiation therapy can be coupled with chemotherapy, ultimately depending on the severity of disease (Siegel et al., 2012).

There are several techniques which can be used to deliver radiation therapy. These include three-dimensional conformal radiation therapy (3DCRT), intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and proton beam therapy (PBT). IMRT, when compared to 3DCRT, has demonstrated significant advantages in lowering the mean lung dose, the volume of lung receiving 20 Gy, and decreased doses to the spinal cord and heart, while improving target volume conformity (Baker et al., 2016; Teoh et al., 2011). As a result, the use of IMRT for lung cancer is increasing (Baker et al., 2016). While there are several benefits of modulated delivery techniques, such as increased conformity to a target volume and conformity of dose across the target volume, IMRT and VMAT plans are more complex and, hence, warrant more time spent on planning (Teoh et al., 2011). IMRT also has a higher monitor unit count which gives rise to increased amounts of low dose radiation (Teoh et al., 2011). An advantage of VMAT is increased efficiency in delivery time compared to IMRT, due to the use of one or two arcs (Teoh et al., 2011). Proton beam therapy (PBT) is a novel technique which uses pencil-beams and scattered protons to treat lung tumours with a high degree of conformity (Baker et al., 2016). PBT takes advantage of the physical properties of high energy protons traversing through a medium, with protons delivering most of their energy at a point known as the Bragg peak. After the Bragg peak, the protons do not deliver an exit dose.

SABR is a highly accurate technique that delivers radiation through a hypofractionated radiotherapy scheme which can be applied to all of the treatment modalities listed above (Teoh et al., 2011). Hypofractionated radiation therapy is given over a shorter period of time than standard radiation therapy and the total dose is divided into doses larger than the standard 2 Gy per fraction.

1.2. Stereotactic ablative radiation therapy

SABR was developed in the 1990s at the Karolinska Hospital, Sweden, stemming from the work completed in intra-cranial stereotactic radiosurgery (Adjei et al., 2015; Nagata, 2014; Ricardi et al., 2015). SABR is an advanced radiotherapy technique, whereby tumours are ablated using hypofractionated radiotherapy schemes (Benedict et al., 2010; Marks et al., 2010; Timmerman et al., 2014). In opposition to stereotactic radiosurgery, SABR is used exclusively for extra-cranial tumours, in sites such as the lung, liver, prostate cancer and adrenal glands (Ricardi et al., 2015; Timmerman et al., 2014). SABR is delivered with a high degree of accuracy accomplished by the integration of modern imaging, such as four-dimensional computed tomography, accurate immobilisation and delivery techniques (Benedict et al., 2010; Marks et al., 2010; Timmerman et al., 2014).

SABR is typically delivered in doses greater than 8 Gy per fraction, occasionally reaching 20–30 Gy per fraction (Adjei et al., 2015; Zhang et al., 2011). In SABR, the biologically effective dose (BED) is significantly higher than the BED utilised in 3DCRT (Zhang et al., 2011). A meta-analysis by Zhang et al., (2011) tentatively concluded that patients treated with medium and medium to high BED (146 Gy > BED > 83.2 Gy) were more likely to have a greater overall survival rate than those treated with low or high BED. The challenge in SABR is to encompass the entire target volume and accurately ablate the target while simultaneously avoiding the surrounding critical structures (i.e. heart, bronchus, oesophagus, etc.) (Ricardi et al., 2015).

As previously mentioned, there are several treatment techniques which can be used to deliver SABR. These include IMRT, VMAT (linear accelerator-based arc and tomotherapy) and 3DCRT (Lo et al., 2016). These can be delivered with a variety of treatment machines – either via robotic radiosurgery (CyberKnife), TomoTherapy or linear accelerator (linac) based methods (Ricardi et al., 2015; Lo et al., 2016; Xhaferllari et al., 2016). VMAT-based SABR has demonstrated effectiveness in reducing the patient bed-time and hence intra-fraction motion (Lo et al., 2016). Studies cited by (Teoh et al., 2011) have shown that SABR delivered with VMAT resulted in an increase in conformity and increased sparing of lung parenchyma. All studies showed an improvement in treatment delivery efficiency (Teoh et al., 2011). VMAT plans, compared to IMRT plans, also showed a lower monitor unit count, which however, was still higher than that of 3DCRT SABR plans (Teoh et al., 2011).

Linear accelerator-based SABR is more commonly used as they are adequate to deliver complex SABR plans (Benedict et al., 2010). Modern linear accelerator-based SABR is more time efficient compared to robotic radiosurgery delivery techniques, which also require more sophisticated planning (Lo et al., 2016). A 6 MV photon beam is a suitable energy for lung SABR, allowing for a compromise between beam penetration and penumbra (Benedict et al., 2010). CyberKnife is a robotic radiosurgery accelerator which delivers high-energy 6 MV photon beams isocentrically or non-isocentrically (Ding et al., 2010). When comparing CyberKnife and standard linear accelerator SABR, both provide adequate dose distributions over the target volume (Ding et al., 2010). CyberKnife, however, was found to deliver a decreased dose to healthy lung when treating anterior tumours. Conversely, linear accelerator-based therapy was found to deliver decreased lung dose when treating the posterior tumours (Ding et al., 2010). CyberKnife SABR requires more monitor units in comparison to linear-accelerators, to deliver similar prescriptions (Ding et al., 2010). TomoTherapy combines the idea of a linear accelerator and a CT scanner. Helical TomoTherapy is achieved by synchronising the movement of the CT couch and the rotation of the x-ray tube to produce radiotherapy delivered in an arc around the patient (Xhaferllari et al., 2016). The development of such techniques and modalities, along with other technological advances, has allowed SABR to be implemented in clinics worldwide.

The primary objective of the large number of studies reported on SABR for lung treatment was to assess the safety, clinical efficacy and disease control of the primary cancer and oligometastases. Few studies on SABR comprehensively report on the toxicities experienced by the patients. ***This integrative review aims to summarise the toxicities*** reported in the literature, based on the treatment delivery technique. Given that the majority of the clinical studies did not report on the statistical significance (i.e. p-values and confidence intervals) of the toxicities experienced by the patients, statistical analyses cannot be provided.

2. Methods

A search was conducted on Medline to identify the appropriate literature to fulfil the aim of this review (see the appendix for search strategy). The data from all applicable papers (n = 30) were collated and analysed as indicated in the data tables.

3. Results and discussion

A. Type of radiation treatment delivery

Of all reports identified, a total of 30 studies specified the type of machine utilised in the stereotactic ablative treatment of lung cancers, all of which were reports on NSCLC or lung metastases. The studies were divided into those using:

(1) Linear accelerators,
(2) The CyberKnife robotic radiosurgery system,
(3) TomoTherapy and
(4) The Novalis beam surgery system.

The studies described acute toxicities which included pulmonary toxicity, radiation pneumonitis, myositis, dermatitis, oesophagitis, fatigue, dyspnoea, thoracic pain, pleural effusion, pulmonary fibrosis,