Cancer Treatment Reviews 56 (2017) 8–15

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Systematic or Meta-analysis Studies

Nodal recurrence after stereotactic body radiotherapy for early stage non-small cell lung cancer: Incidence and proposed risk factors

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ARTICLE INFO

Article history:
Received 14 September 2016
Received in revised form 30 March 2017
Accepted 2 April 2017

Keywords:
SBRT
SABR
NSCLC
Regional recurrence
Lymph node
Early stage

ABSTRACT

Stereotactic body radiotherapy (SBRT) is an alternative to surgery for patients with early stage non-small cell lung cancer (NSCLC) who are inoperable due to comorbid disease or who refuse surgery. SBRT results in an excellent local control rate of more than 90%, which is comparable to surgery, while short and long-term overall toxicity is low. Surgically treated patients are often more extensively staged pre-operatively, e.g. with endobronchial ultrasound and/or mediastinoscopy, and typically undergo intra-operative lymph node dissection or sampling. Occult nodal metastases (ONM), detected by lymph node dissection, have been shown to increase the incidence of regional recurrence (RR) after surgery, which is associated with poor outcome. In patients undergoing SBRT, however, definite pathological nodal staging is lacking and so other ways to identify patients at high risk for ONM and RR are desirable.

The aim of this systematic review is to summarize the incidence of, and risk factors for, RR after SBRT and compare these to those after surgery. The available evidence shows the incidence of RR after SBRT or surgery to be comparable, despite more elaborate pre- and intra-operative lymph node evaluation in surgical patients. However, the fact that this finding is based on mostly retrospective studies in which the majority of patients treated with SBRT were inoperable, needs to be taken into consideration. For now, there is no evidence that inoperable clinical stage I patients with no indication of pathological lymph nodes on PET/CT will benefit from more invasive lymph node staging prior to SBRT.

Background

The standard treatment option for patients with early stage non-small cell lung cancer (NSCLC) without lymph node involvement is a surgical tumor resection with a systematic hilar and mediastinal lymph node dissection (MLND). If patients are inoperable due to their age or comorbidities, or they refuse surgery, stereotactic body radiotherapy (SBRT) is an alternative treatment option. SBRT is the term describing the administration of high precision, high dose radiotherapy in a limited number of treatment fractions. Due to the high dose per fraction and the short overall treatment time, the radiobiological effectiveness of SBRT is high (biologically effective dose [BED] >100 Gy) resulting in excellent local control rates of over 90%, comparable to surgery [1,2]. Unfortunately, no randomized trials on the outcome of SBRT *vs.* surgery in operable patients have been successfully conducted, most closing early due to poor accrual. However, a recently published pooled analysis of two of these randomized trials suggests an improved survival and better treatment tolerability for SBRT compared to surgery [1]. The overall toxicity is low and does not seem to adversely affect long-term lung functionality and quality of life, making it a suitable treatment option, especially for patients with a poor pulmonary function [3–6].

Since the introduction of SBRT more than a decade ago, the number of patients treated with this modality has increased over time [7]. Its use for early stage NSCLC has resulted in a decrease in the number of untreated elderly patients and an improved survival in this group [8].

An essential difference between stereotactic radiotherapy and surgery for early stage NSCLC is the evaluation of the regional

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http://dx.doi.org/10.1016/j.ctrv.2017.04.001
0305-7372/

lymph node stations. In patients who are fit enough to undergo a surgical resection, extensive preoperative staging of regional lymph nodes is performed [9]. If nodal involvement is diagnosed on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), endobronchial ultrasound (EBUS), esophageal ultrasound (EUS) and/or mediastinoscopy is subsequently performed. For medically inoperable patients undergoing SBRT, staging is more often limited to an FDG-PET/CT scan, where small lymph node metastases are likely to be missed [10–12]. Nevertheless, in cT1-2N0 patients, the probability of having mediastinal (N2) lymph node disease is only ~5% [13,14]. Besides elaborate pre-operative staging, surgically treated patients routinely undergo either intra-operative lymph node sampling or a systematic hilar/mediastinal lymph node dissection. This procedure leads to nodal upstaging in 10–20% of the patients [11,13,15]. Conversely, the regional lymph node stations of patients undergoing SBRT are not sampled and left untreated, except for incidental dose to the lymph nodes close to the planning target volume (PTV) and/or in the beam path [16].

Patients undergoing surgery who have (unexpected) regional lymph node involvement are known to have a worse prognosis, even when the involved nodes contain only microscopic disease [17]. Therefore, adjuvant chemotherapy and/or radiotherapy are considered in patients diagnosed with occult lymph node disease following surgery [18,19].

The clinical relevance of not performing pathological lymph node staging for clinical stage I patients undergoing SBRT is unclear. Does it result in more regional recurrences (RR) than in patients who had their lung tumor resected? Should more invasive staging prior to SBRT be performed to diagnose nodal involvement?

The aim of the current systematic review is to shed more light on the outcome of SBRT with respect to the regional lymph nodes. Studies on the incidence of, and risk factors for, regional failure following SBRT will be discussed. These findings are compared to the incidence of RR after surgery and risk factors derived from surgical studies.

Material and methods

Defining regional recurrence

To minimize heterogeneity in outcomes due to variable definitions of RR, only articles with a clear and comparable definition were included in this systematic review. The revised RECIST guideline (version 1.1) includes criteria for measuring pathological lymph nodes, whereas the original version does not [20–22]. However, the assessment of lymph node recurrence in patients with previously clinically node negative disease (as is the case in the current review) remains somewhat unclear. The lack of a measurable lymph node of at least 1.5 cm at baseline means the 20% growth in diameter cannot be used to define progressive disease. According to RECIST, the growth of an existing lymph node to $\geq$1 cm in diameter or the occurrence of a 'new' lymph node $\geq$1 cm is pathological. However, we disagree that the diagnosis of a lymph node recurrence should be based solely on the diameter of a regional lymph node on CT. In clinical practice, we always require more 'proof' of recurrence to avoid unnecessary treatments with a risk of toxicity. For the purpose of the current review, we achieved group consensus on how to define RR during follow-up for patients who were clinically node negative before SBRT. We agreed upon the following criteria: (1) a new or growing lymph node on CT combined with FDG-PET avidity, and/or (2) biopsy confirmed regional recurrence, and/or (3) continuing lymph node enlargement on serial CT scans. Studies not meeting one of these three criteria were excluded.

Search strategy

The PubMed database was searched for relevant articles up to August 2016, using the following search terms: 'non-small cell', 'NSCLC', 'lung cancer', 'lung neoplasm', 'lung tumor', 'early stage', 'stage 1', 'stage 2', 'failure(s)', 'recurrence(s)', 'outcome(s)', 'follow-up', 'progression', 'stereotactic radiotherapy', 'SBRT', 'SABR', 'radiosurgery', 'regional', 'nodal', 'mediastinal', 'lymph node(s)'. The literature search yielded 157 articles, which were all screened for eligibility by one of the authors (KW). Articles deemed relevant

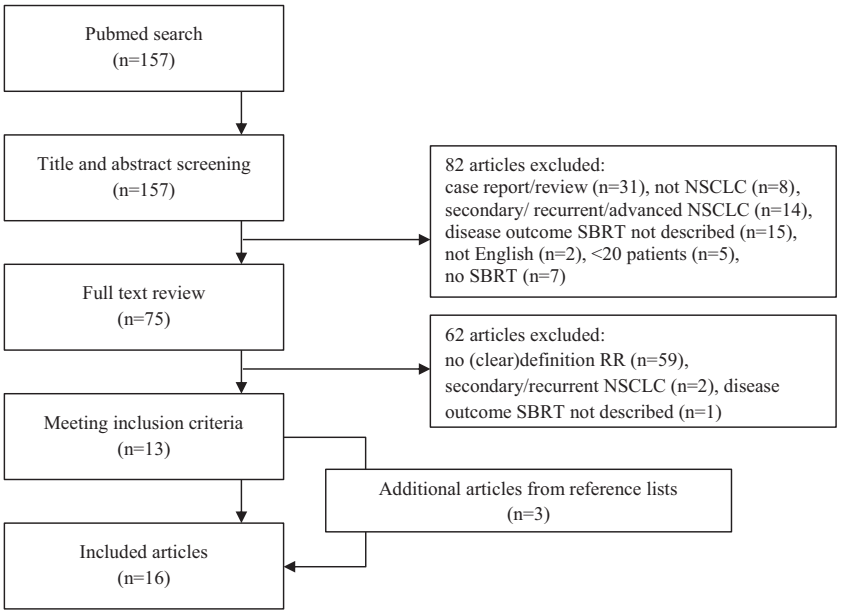

Fig. 1. Flowchart outlining the search and research process. NSCLC = non-small cell lung cancer, RR = regional recurrence, SBRT = stereotactic body radiotherapy.