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Review

Is stereotactic ablative radiotherapy an alternative to surgery in operable stage I non-small cell lung cancer?

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ABSTRACT

Surgery is the gold therapeutic standard for patients affected with stage I non-small cell lung cancer. Stereotactic ablative radiotherapy is currently considered the preferred treatment option for inoperable patients, representing approximately 25%. Limited data are available directly comparing surgery and SABR in operable patients, none of them prospective. Preliminary results are encouraging, showing that the two treatment modalities are equally effective in terms of tumour control, with expected similar survival projections. Moreover, in elderly patients SABR could represent a valid treatment alternative in comparison to surgery due to the lower morbidity. We here review and discuss the potential role of SABR as an alternative to surgery in operable early stage lung cancer patients.

1. Background

Surgery currently represents the standard treatment option for patients affected with early stage non-small cell lung cancer (NSCLC). Long-term results of surgical resection show survival rates of 60–70% at 5 years, as high as 80% in selected series.[1] Lobectomy or pneumonectomy improves outcomes if compared with sub-lobar resection, but a substantial proportion of patients are ineligible for surgery due to the presence of concomitant medical conditions such as respiratory or cardiovascular comorbidities, associated with a high risk of surgical complications. Moreover, a small group of patients refuse surgery. An observation alone strategy has been shown in the past to obtain worse outcomes if compared to surgery or radiation, and it is now considered inappropriate in the majority of cases.[2] Until recently, patients unfit for surgery typically underwent conventionally fractionated radiotherapy with a total dose of 60–70 Gy delivered over a 6- to 7-week period. The poor outcome achievable with conventional radiotherapy is reflected in the Surveillance, Epidemiology and End Results (SEER) study, showing a global cancer specific 5-year survival rate of 15%.[3] Stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) represents an emerging

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treatment option and a new standard of care for stage I NSCLC in inoperable patients. Due to the long-term efficacy and the low rate of late toxicity,[4] SABR might be considered a valid alternative to surgery also in operable patients.

2. Aim

The present review provides a focus on the scientific basis and clinical data supporting the potential role of SABR as an alternative to surgery in operable patients, as a step towards a more tailored therapy for early stage NSCLC.

3. SABR vs. conventional radiotherapy in inoperable patients

Results of conventional external beam radiation for early stage NSCLC are disappointing,[5] with local relapse as the predominant pattern of failure leading to different 5-year survival rates according to primary tumour dimensions: 38% for patients with tumours < 2 cm, 22% for tumours between 2 and 3 cm, 5% for tumours between 3 and 4 cm and 0% for larger lesions.[6] In order to improve tumour control and, hence, cancer-specific survival (CSS), dose-escalation gained credit as an option, but when considering the dose–response relationship for lung cancer, doses up to 80–90 Gy would be needed to control approximately 50% of the tumours.[7,8] Dose-escalation achieved by conventionally fractionated radiotherapy is limited by 2 main factors: a prolonged overall treatment time, resulting in a considerable amount of tumour repopulation, and an increased radiation dose delivered to the functional lung tissue, with a possible further functional impairment.

SABR, a radiation technique characterised by the use of very accurate repositioning and advanced image-guidance techniques, allows the administration of few large fractions able to kill the neoplastic cells through radio-ablation at very high biologically equivalent doses (BED > 100 Gy). To date, the largest report on the efficacy of SABR in stage I NSCLC is the one from Vrije University in Amsterdam[9]: 676 patients were treated and 124 (18%) had disease recurrence, with a median follow-up time of 32.9 months. Actuarial 5-year rates of local, regional, and distant recurrence were 10.5%, 12.7% and 19.9%, respectively. Of the 124 recurrences, 82 (66%) were distant and 57 (46%) were isolated distant recurrences. Isolated locoregional recurrences occurred in the remaining 42 patients (34%). The median times to local, regional, and distant recurrence were 14.9, 13.1 and 9.6 months, respectively, and CSS at 5 years exceeds 60%. In this series all patients were staged with CT–PET and had either histological confirmation or "proof of malignancy." Delivered doses were 54–60 Gy in 3 fractions to peripheral tumours, 55–60 Gy in 5 fractions for lesions close to chest wall and 60 Gy in 8 fractions for central tumours. This large series confirms, with an adequate follow up time, the promising results of many mono-institutional Phase II clinical trials.[10–13] In 2010, Radiation Therapy Oncology Group (RTOG) 0236 Trial mature results were published, showing an OS rate at 3 years of 55.8%, with a 97.6% LC rate (median follow-up 34.4 months).[14] These favourable clinical outcomes resulted in a significant practice modification in the last years for inoperable patients, mainly represented by elderly patients with comorbidities. Palma et al. showed, in a population-based time-trend analysis, that the proportion of patients aged >75 years with stage I NSCLC treated with radiotherapy with radical intent increased from 26% in the interval 1999–2001 to 32% in 2002–2004 and 42% in 2005–2007. These changes translated into a significant increase in OS rate for stage I lung cancer elderly patients globally treated in 2005–2007 (surgery and/or radiotherapy, $p < 0.001$), and particularly in the subset of patients treated with radiotherapy ($p < 0.056$ at log-rank test comparing 1999–2001 with 2005–2007).[15] As the results achievable with SABR are significantly superior to those achievable with conventional radiotherapy, SABR is currently considered the preferred treatment option for inoperable patients with stage I NSCLC, and efforts towards the confirmation of these findings by a prospective randomised comparison with conventional radiotherapy have been abandoned.

3.1. *Open issues in SABR for inoperable patients*

3.1.1. *Histological diagnosis*

Histological confirmation of lung nodules in SABR series has been a concern since the introduction of this treatment. The majority of patients referred to Radiation Oncology Departments are elderly and/or with comorbidities: hence, in most of them, there is contraindication to CT-guided Fine Needle Aspiration; in adjunct, peripheral nodules may be difficult to reach by bronchoscopy. As a result, in most series a correct histological diagnosis is available in 50–60% of patients. There are several reports comparing the outcomes between patients with or without histological diagnosis: in the series by Takeda et al.,[16] 56 patients without histological diagnosis and 115 patients with confirmed NSCLC were compared, and local control and survival probability at 3 years after SABR were almost identical for patients with or without histological confirmation. In the Vrije University series,[9] histological confirmation before SABR was obtained in 235 (35%) of 676 patients; the remaining patients had a new or growing lesion with a CT appearance consistent with malignancy and local ^{18}FDG-PET uptake, since the likelihood of a benign diagnosis in such patients is less than 4%.[17,18]

3.2. *Central and large tumours*

An increased risk for severe-fatal toxicity was recorded when treating central tumours at high doses per fraction in pioneering studies. Centrally located lesions are in proximity to critical structures such as trachea, bronchial tree or oesophagus, all tissues characterised by a serial architecture, with high risk of toxicity for large doses per fraction. In the Indiana University series, a 11-fold increase risk of severe toxicity was evident for central tumours treated with 60–66 Gy in 3 fractions. Grade 3 or higher toxicity during 2 years of follow-up was noted for 46% of patients with central tumours, with 6 eventual treatment-related deaths occurred.[19] Afterwards, with risk-adapted treatment schedules (60 Gy in 7.5 Gy fractions), excellent rates of controls were reported also in central tumours.[20] Milano et al.[21] reviewed outcomes and toxicity of SABR in 2009, including published experiences with different total dose/fractionation protocols, and showed that with