Developments in early-stage NSCLC: advances in radiotherapy
Chapter 3

Abstract

An increase in the number of predominantly elderly patients with early-stage non-small cell lung cancer is anticipated in many Western populations. Patients often have major co-morbidities and are at increased risk for surgical morbidity and mortality. In the past decade, the use of stereotactic ablative radiotherapy (SABR) has achieved excellent results, with only mild toxicity in such vulnerable patient groups, leading to SABR becoming accepted as a standard of care for unfit patients in several countries. The planning and delivery of SABR has rapidly improved in recent years, particularly with the use of ‘on-board’ imaging at treatment units, and shortened treatment delivery times. Increasingly, more central tumors are being treated using lower doses per fraction (so-called risk-adapted schemes). It is also becoming clear that long-term follow-up should take place at specialist centers in order to distinguish the evolving fibrosis that is frequently observed from the relatively infrequent local recurrences. Given the high local control rates and limited toxicity, increasing attention is being paid to the use of SABR in the subgroup of so-called borderline operable patients, and clinical trials comparing surgery and SABR in these patients are ongoing.
Introduction

Despite declining incidence rates in some Western European populations, the total number of patients diagnosed with non-small-cell lung cancer (NSCLC) continues to increase, largely due to aging populations. While a lobectomy is considered the standard of care for patients diagnosed with stage I and II NSCLC, a substantial number of patients are unable to undergo resection due to co-morbidities or are unwilling to do so. Recent developments in radiotherapy imaging and delivery techniques have facilitated the rapid adoption of stereotactic ablative radiotherapy (SABR) as a treatment for early-stage (T1-2N0M0) NSCLC in patients at high risk for surgical mortality and morbidity.

Epidemiological challenges

Lung cancer is largely a disease of the elderly, with half of all patients aged ≥70 years, and one-third aged ≥75 years. Older patients with lung cancer are more likely to have significant co-morbidities at the time of diagnosis. Furthermore, population-based analyses reveal that the elderly who undergo surgical resection have inferior outcomes compared with younger patients, with an increased risk of early mortality and the inability to resume independent living. Such considerations may continue to influence the decision-making process of elderly patients and their caregivers, as only half of Dutch patients aged ≥75 years diagnosed with stage I NSCLC undergo surgical resection. As conventional radiotherapy for early-stage NSCLC is associated with only modest survival gains, some clinicians have been reluctant to refer frail patients for this treatment, despite the fact that untreated early-stage NSCLC has a 5-year survival of only 2%.

Advances in radiotherapy

Technological advances have facilitated the use of SABR for tumors outside the brain. SABR involves the delivery of a high dose of radiation to precisely target the tumor, while minimizing doses to surrounding healthy tissue. Consequently, a total dose ranging from 50 to 60 Gy can be delivered in three to eight fractions, depending on tumor and delivery system characteristics. This contrasts with a 6-week period typically used to deliver conventionally fractionated radiotherapy in around 30 fractions. The use of few treatment fractions (‘extreme hypofractionation’) in SABR greatly increases the biological effect of radiotherapy, with some schemes doubling the biological effective dose compared with that of conventional radiotherapy. No randomized, controlled trials between conventional
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radiotherapy and SABR have been published so far, but pooled analyses have shown that SABR can achieve superior results compared with conventional radiotherapy.$^{10,11}$

Local control rates exceeding 90% have been reported using SABR in prospective multicenter trials$^{12,13}$, while regional nodal relapses manifest in $<10\%$ of patients$^{10-14}$. These results have led to SABR becoming accepted as the standard of care for unfit patients diagnosed with early-stage NSCLC in countries such as The Netherlands and the UK$^{15,16}$. Recent population-based time-trend studies in The Netherlands have revealed that the use of SABR both increased the number of patients undergoing curative treatment for early-stage NSCLC and improved overall survival for the whole population$^{15,17}$ (Figure 1).

**Figure 1:** Steps in planning and delivery of stereotactic ablative radiotherapy (SABR) at the VU University Medical Center. Treatment planning utilizes four-dimensional computed tomography (CT) scans, capturing tumor motion during the breathing cycle (A), and is used for generating treatment plans ensuring tight coverage of the tumor, while limiting doses to normal organs (B). Before each treatment, the tumor position is verified using a cone-beam CT scan on the treatment couch (C), followed by a ‘volumetric modulated-arc delivery’ technique to deliver the dose in $<5$ min (D).
A key challenge facing SABR is lung tumor motion that can compromise treatment delivery. Respiration-correlated (or four-dimensional, 4D) computed tomography (CT) scans are the recommended approach for assessing the extent of motion for planning SABR\textsuperscript{18}. Besides encompassing all observed motion, other motion-management approaches include continuous tracking of tumor motion using implanted markers, or limiting radiation delivery to specific phases of the respiratory cycle (so-called gating), during which tumor position is predictable\textsuperscript{19,20}. However, the majority of lung tumors show limited mobility\textsuperscript{21}, and results of different approaches for motion management during SABR have been broadly comparable. Imaging on the treatment couch (‘on-board image guidance’) uses cone-beam CT scans which are mounted on many commercial linear accelerators. Such scans allow for the position of the tumor itself to be verified before, and sometimes during, each treatment\textsuperscript{22}. Verification using cone-beam CT scans also removes the need to implant fiducial markers in tumors, a procedure that is not without risks in a population of frail and elderly patients\textsuperscript{23}. In recent years, technological advances have enabled increasingly faster SABR delivery using volumetric intensity-modulated arc therapy\textsuperscript{24}. Even treatment times of <5 min are now routinely achieved using flattening-filter free delivery, an approach which is more patient-friendly\textsuperscript{25}.

**Toxicity of SABR treatment**

The toxicity associated with SABR is usually modest, with between 3% and 10% of patients reporting grade ≥3 toxicity according to Common Terminology Criteria Adverse Events. The most common clinical manifestations include radiation pneumonitis, chest wall pain, rib fractures and skin reaction\textsuperscript{10,26}. When care is taken to restrict doses to the chest wall, the incidence of severe pain and rib fractures is ~2%\textsuperscript{27}.

A concern when delivering high-dose radiotherapy to lung tumors is the potential for damage to healthy lung tissue. However, SABR has been associated with only small decreases in lung function, with greater loss of function observed in patients with a better baseline pulmonary function\textsuperscript{28}. These findings are consistent with clinical outcomes in patients with severe COPD\textsuperscript{29}.

Reports on the quality of life (QoL) after SABR show no substantial decline despite the fact that the subjects studied were mainly inoperable with early-stage NSCLC\textsuperscript{30,31}. In contrast, reports after surgery show substantial, and sometime irreversible, declines in QoL post-treatment particularly in elderly patients\textsuperscript{32,33} (Figure 2).
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Figure 2: Examples of toxicity arising following stereotactic ablative radiotherapy (SABR). (A) The upper panel shows a painful rib fracture which developed (arrow) 1.5 years following the treatment of a tumor located adjacent to the thoracic wall. (B) On the lower panel, a computed tomography (CT) scan carried out 6 months after SABR showing an extensive region of consolidation, with air bronchograms. The patient had symptoms of mild cough (grade I radiation pneumonitis).

Eligibility for SABR

In the early part of the last decade, only patients with small (up to 5 cm in diameter) and peripheral lesions were generally eligible for SABR. In such patients, excellent local control with limited toxicity was seen. Early reports suggested that excessive toxicity might arise when SABR is used for the treatment of centrally located tumors, defined as being <2 cm of the bronchial tree. However, these authors used fraction doses of ≥20 Gy. More recent studies, in which so-called risk-adapted daily fractions of ≤7.5 Gy were used, have shown that even central tumors can be cured with minimal toxicity. Using such schemes,
SABR is now routinely used at experienced centers for tumors located near other organs at risk, such as the aorta or heart (Figure 3).

**Figure 3:** Central lesions treated with stereotactic ablative radiotherapy (SABR). Examples of central lesions treated using SABR despite proximity to the (A) aorta, (B) heart and (C) central hilar location (reproduced with permission from Haasbeek et al.35).

Increasingly, some institutions are treating even more centrally located tumors, using a dose of ≤5 Gy. With small endobronchial tumors, local therapy or even hypofractionated external radiotherapy delivered in 5–6 weeks is preferred instead of SABR. For larger central tumors, surgery and/or chemo-radiotherapy are preferred options in fit patients. Only when such patients are ineligible for standard therapies, or when they refuse these options, should they become eligible for protocols evaluating SABR schemes using dose fractions of ~5 – 7.5 Gy. In addition, as large central tumors have both an increased likelihood of occult nodal metastases and distant failures, the integration of systemic chemotherapy with such tumors will be a growing focus of research.

**Treatment challenges**

A common difficulty in the treatment of frail elderly patients with early-stage NSCLC is the lack of a pre-treatment pathological diagnosis of the tumor, due to an increased risk of complications associated with diagnostic procedures. As rates of benign lesions differ among countries, the risks of a wait-and-see policy with potential tumor growth and metastasizing need to be weighed against the possibility of treatment-induced toxicity in benign disease in every patient individually8,14,37.

Multifocal tumors are not uncommon with NSCLC38,39. In addition, patients treated for early-stage NSCLC have a risk of 2%–7% per year of developing a new lung tumor. These patients can be difficult to treat with surgical resection, especially when the nodules are present in different lobes. Due to the strict dosimetric margins around the tumor, SABR can be used to treat multifocal tumors or patients who develop a second or third primary
tumor, previously treated with surgery, without serious clinical toxicity\textsuperscript{10}.

One of the difficulties with SABR is defining treatment-induced radiological changes and distinguishing these from local recurrences. Focal radiological changes are common after SABR, and these can evolve with time\textsuperscript{41}. SUV-uptake in \textsuperscript{18}FDG-PET-scans after high-dose radiotherapy is not always reliable in distinguishing benign consolidation caused by the radiotherapy from local recurrence\textsuperscript{42}. Obtaining pathological confirmation of a potential local recurrence can be difficult and is not without risks. Studies are undertaken to develop algorithms for these difficult clinical problems, but even with these algorithms differentiating local recurrences from benign changes can be challenging, and expert follow-up is required for patients treated with SABR\textsuperscript{43} (Figure 4).

\textit{Figure 4:} Local recurrence or consolidation? Distinguishing a local recurrence (A) from patients with benign consolidation (B). (A-1) Computed tomography (CT) scan before stereotactic ablative radiotherapy (SABR) treatment. (A2) CT scan 3 months after SABR treatment. (A-3) CT scan 1 year post-SABR led to an FDG-PET scan, which showed increase uptake in the lesion. A trans-thoracic needle biopsy confirmed recurrence, and the patient is now disease-free 1.5 years following a wedge resection of the tumor. (B) Examples of common benign consolidations following SABR (reproduced with permission from Dahele et al.\textsuperscript{41}).
Role of SABR in operable patients

Due to excellent local control rates and low-toxicity profile after SABR for early-stage NSCLC, a shift has been observed in referral patterns for SABR to include patients who have no absolute contraindication to surgery, but are at high risk, the so-called borderline operable patients. When such potentially operable patients are treated with SABR, survival rates comparable with surgery have been reported\textsuperscript{44,45}. Currently, clinical trials are on their way to randomly compare surgical resection with SABR for stage I NSCLC in operable and borderline operable patients. (NCT00840749 and NCT01336894).

Curative options, including salvage surgery, should be considered in patients who develop a local recurrence. Successful surgical resection has been reported in patients who were initially operable, and who developed a local recurrence after being treated with SABR for stage I NSCLC\textsuperscript{46}. This treatment sequence is expected to be increasingly used in patients who are ‘borderline operable’, and who have chosen to undergo SABR instead of surgery for stage I NSCLC.

In summary, the use of SABR represents a major therapeutic advance in patients who present with an early-stage NSCLC, and who are at high risk for post-surgical complications such as those with severe COPD, the frail elderly, and borderline operable patients who do not wish to accept the risk of morbidity and mortality associated with surgery.
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References


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