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Curative radiotherapy in patients inoperable for medical reasons
Chapter 2

Abstract

Due to changing demographics, increasing numbers of elderly patients are being diagnosed with an early-stage non-small cell lung cancer. These patients may be difficult to treat due to coexistent illnesses and poor performance. Stereotactic radiotherapy is a new and promising treatment option, particularly in the frail elderly. However, the high local control rates and favorable toxicity profile make it also an increasingly attractive treatment for patients who are at increased risk for operative mortality.
Epidemiology

Lung cancer is a leading cause of cancer-related death in both men and women in Western countries\(^1\). Although incidence rates are stable or falling in many Western countries, the growing proportion of the elderly in the population has resulted in an overall increase in the number of elderly lung cancer patients\(^2\). In the USA, for example, more than two thirds of all patients diagnosed with lung cancer are older than 65 years, with the median age at diagnosis exceeding 70 years\(^3\). Approximately 80% of lung cancers can be classified as non-small cell lung subtype, and about 20% of elderly patients diagnosed with NSCLC present with early-stage disease (stages I–II)\(^4,5\). Between 25 and 40% of elderly patients with stage I and II disease do not undergo a curative treatment\(^4,6,7\). Reasons for the latter include the fact that nearly 70% of elderly patients diagnosed with lung cancer have significant comorbidities, and concerns about comorbidity, frailty, or efficacy result in the elderly being less likely to receive protocol-specified treatment\(^2,4,8-10\). A lack of evidence-based decision making in elderly patients is also due to the fact that they are less likely participate in clinical trials\(^11,12\). Current guidelines recommend surgical resection as standard treatment in early stage NSCLC\(^13-15\). When guidelines assessing a patient’s fitness to undergo surgery are applied, up to 20% of patients with early-stage NSCLC are considered medically inoperable\(^4,16\). Common reasons for inoperability include a poor lung function, cardiovascular comorbidity as assessed by the American College of Cardiology guidelines, low American Society of Anesthesiologists score, and low general performance as assessed, for example, by using the WHO performance score\(^13,15\). As untreated early-stage NSCLC has a 5-year survival of 2%, alternative curative treatments should be considered in patients who are ineligible for surgery or refuse it\(^17\).

Conventional Radiotherapy

Until recently, conventional radiotherapy has been considered as treatment of choice only for patients either who are medically inoperable or who had refused surgery\(^14\). Modest improvements in survival are achieved using conventional radiotherapy, when compared with patients who receive no treatment\(^18\). An analysis of 6,065 patients with histologically confirmed unresected stage I–II NSCLC diagnosed between 1992 and 2002 revealed a median overall survival after radiotherapy of 13 months (95% confidence interval (CI) of 13–14 months) versus 7 months (95% CI 6–8 months) in untreated patients\(^19\). No differences in either acute or late radiation toxicity were observed between patients aged older or younger than 70 years\(^20\). However, delivery of high radiation doses using conventional techniques may carry the risk of more severe side effects\(^21\).
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Stereotactic Radiotherapy

In recent years, stereotactic ablative radiotherapy (SABR or SBRT) has emerged as a highly effective new treatment modality for patients who are unfit for surgery or who refuse surgery. Modern lung SABR is characterized by 4D imaging to account for individual tumor motion, accurate image-guided setup prior to and during each treatment fraction, and treatment delivery times of 10 min or less, depending on equipment used (Figure 1)\(^2\). No randomized clinical trials comparing conventional radiotherapy and SABR have yet been reported. However, a meta-analysis of studies in early-stage NSCLC reported significantly higher 5-year overall survivals after SABR, compared with conventional radiotherapy (42% vs. 20% respectively). Disease-specific survival 2 years after treatment was 67% for conventional radiotherapy versus 83% for SABR\(^2\). The lower overall survival in nonsurgically treated patients reflects the fact that non-cancer-related deaths are very common in such patients\(^16\).

*Figure 1: Features of SABR*
Curative radiotherapy for inoperable patients

**Figure 2:** (A) 4D CT scan study showing the position of a tumor in the right upper lobe in a single phase of the respiratory cycle (B) The corresponding reconstructed image showing tumor position in all positions of the respiratory cycle illustrated in a maximum intensity projection.

The total doses used in lung SABR are typically between 50 and 60 Gy, and treatment is delivered in 3–8 fractions\(^ {22,24}\). Planning target volumes are currently derived using 4-dimensional CT scans (Figure 2)\(^ {25}\). In order to ensure treatment accuracy, patients are comfortably positioned and monitored during SABR. At some centers, techniques to manage tumor motion, such as abdominal compression, respiratory gating, breath holding, or tumor tracking systems, are also applied. However, there is no evidence to suggest that patient fixation or active management of tumor motion leads to improved tumor control. Sophisticated image devices, either present in the treatment room or mounted on-board modern linear accelerators, allow verification of the tumor position prior to daily treatment\(^ {22,26}\). At present, cone-beam computed tomography scans that are acquired just before SABR delivery are a widely used approach for ensuring accurate delivery (Figures 3 and 4). A drawback of some techniques used for SABR delivery is the long treatment durations of up to 1.5h\(^ {27}\). Elderly patients, in particular, might better tolerate delivery using volumetric-intensity-modulated arc therapy, which takes less than 7 min at present\(^ {28}\).

The dose fractionation schedules used can vary depending on tumor size and location, and a minimal biologically effective dose (BED) of 100 Gy is considered necessary for optimal local control\(^ {22,24,29}\). Commonly, a more fractionated scheme is used for tumors in close proximity to critical structures such as the mediastinum, chest wall, hilus, or heart. Limiting the volume of irradiation to adjacent normal structures reduces the risk of toxicity. For example, limiting volumes of the chest wall receiving 30 Gy or more can decrease the risk of rib fractures posttreatment\(^ {30}\). Other critical organs include the bronchial plexus and esophagus, and dose constraints have been recommended for such structures\(^ {31}\).
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Local control at 3 years after SABR ranges from 80 to 95%\textsuperscript{29,32–34}, control rates which are much higher than generally reported after conventional radiotherapy. These local control rates are also similar to those reported after surgery\textsuperscript{35–37}. However, despite high local control rates, patients do remain at risk of recurrence due to systemic relapse. As has been reported in the surgical literature, distant metastases are the main site of recurrences after SABR, occurring in approximately 20% of patients\textsuperscript{29,32,33,38}. Regional recurrences following SABR are observed in less than 10% of patients\textsuperscript{29,32,38–40}.

**Acute and late toxicity**

Acute toxicity in SABR is usually mild, with the majority of patients not experiencing any adverse effects. Common complaints after SABR are chest wall pain, skin reactions, esophagitis, and general malaise, such as fatigue or dyspnea\textsuperscript{24,29}. Late toxicity usually arises 3–6 months after treatment. Common manifestations include radiation pneumonitis, chest pain, and rib fractures. Severe (grade 3 CTCAE) toxicity is uncommon and seldom seen in more than 10% of treated patients\textsuperscript{24,29}. These low rates of toxicity are similar in both younger and elderly patients\textsuperscript{41}. SABR is a safe and effective treatment alternative for patients with severe COPD and even in elderly patients with severe COPD\textsuperscript{41,42}. In patients with poor lung function, a systematic review of the literature revealed SABR to have comparable outcomes to surgery\textsuperscript{43}. Cause-specific survival after SABR ranges between 67 and 88% at 3 years post treatment\textsuperscript{32,33,39,44,45}. However, SABR is commonly performed in patients who are medically inoperable due to extensive comorbidities, and many patients die from other causes than lung cancer. Consequently, overall survival rates usually range between 36 and 70%, but it can be as high as 90%\textsuperscript{32,38,44–46}. An early study on SABR for centrally located tumors, which used high fraction doses typically administered to peripheral lesions, reported high incidences of severe treatment-related toxicity\textsuperscript{47}. However, other authors have performed SABR for central lesions using lower doses per fraction, and results indicate this to be a safe and effective approach\textsuperscript{48,49} (Figure 5).

Care should be paid to restricting doses to critical adjacent structures\textsuperscript{48,51}, and optimal SABR schemes for use in central tumors remain under investigation (RTOG 0813 NCT013170560). Radiation-induced changes in lung parenchyma are common, making it important to distinguish benign fibrosis from disease progression, in order to minimize the risk of invasive diagnostic procedures or inappropriate salvage therapy (Figure 6)\textsuperscript{32}. Response evaluation using the RECIST criteria may be inappropriate after SABR due to the frequent presence of extensive fibrosis in the high-dose area\textsuperscript{52}. Furthermore, moderate to intense FDG uptake observed shortly after SABR is also not a good indicator of residual
Figure 3: Images of a small lung tumor as seen in all three axes of a planning CT scan. The yellow contour represents tumor position in all phases of the respiratory cycle and the red contour a planning target volume that incorporates an additional ‘safety’ margin of 5 mm.

Figure 4: Patient positioned at a linear accelerator (or treatment unit). Adjustable armrests, neck cushioning, and mattress ensure patient comfort. Imaging detector panels mounted in the ceiling (A) and X-rays sources in the floor (B) allow for real-time kilovoltage imaging. A retractable cone-beam CT scan (C) allows for volumetric images to be acquired.
Consequently, the evaluation of such radiological findings can be challenging and needs to be addressed in a multidisciplinary team with experience in interpreting post-SABR findings.

**Population Impact of Introducing SABR**

The recent introduction of SABR has impacted the survival of elderly patients with early-stage lung cancer, with studies showing an increased use of radiotherapy in elderly patients. A large population-based study performed in the Netherlands explored outcomes in three time periods: one in which SABR was not available, one in which SABR availability was limited, and finally when SABR became fully available. During the study period, the introduction of SABR was associated with a decrease in the proportion of untreated patients and a corresponding increase in the proportion of patients treated with radiotherapy. This increase in treated patients has led to a significant improvement of overall survival in the entire population, a finding that reached statistical significance only for patients who underwent radiotherapy.

**Role of SABR in Medically Operable Patients**

The high local control rates obtained by using SABR in patients who were medically inoperable, as well as the low toxicity profile, have increased interest in SABR as an alternative to surgical resection in medically fit patients. Recently an increase has been observed in referrals for SABR in the Netherlands for patients in whom no absolute contraindication to surgery was present. Two single-arm phase II trials of SBRT in patients who are fit to undergo surgery have been completed, and the mature results of JCOG 0403 (NCT00238875) and RTOG 0618 (NCT00551369) are awaited. Several observational studies have reported on the outcomes of SABR for patients who were medically fit but who declined to undergo surgery. The results of these studies reveal that survival comparable with that after surgery can be achieved. A study using Markov modeling indicated that outcomes after either SABR or surgical resection are likely to be similar, with any advantage of surgery being lost as soon as the risk of operative mortality exceeds 4%. These results are especially important for elderly patients who, even after careful selection, experience more postoperative mortality and morbidity compared to younger patients. A study using Markov modeling indicated that outcomes after either SABR or surgical resection are likely to be similar, with any advantage of surgery being lost as soon as the risk of operative mortality exceeds 4%. Recent reports suggest that salvage surgical resections are feasible after SABR, in patients who were fit for surgery but chose instead to undergo SABR. If surgical salvage becomes an established treatment option, it may increase the preference...
Figure 5: Examples of central lung tumors that are currently being treated outside study protocols using a risk-adapted SABR fractionation scheme delivered in 8 fractions of 7.5 Gy (From Ong et al. 50)

Figure 6: Classification of radiological changes after SABR (a) Acute radiological pneumonitis within 6 months of treatment (b) Late radiological fibrosis after more than 6 months from the time of treatment (From Dahele et al. 52)
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of elderly patients to consider SABR as their preferred treatment option. In conclusion, due to changing demographics, increasing numbers of elderly patients are being diagnosed with an early-stage non-small cell lung cancer. These patients may be difficult to treat due to coexistent illnesses and poor performance. Stereotactic radiotherapy is a new and promising treatment option, particularly in the frail elderly. However, the high local control rates and favorable toxicity profile make it also an increasingly attractive treatment for patients who are at increased risk for operative mortality.
Figure 7: Overall survival in patients aged 75 years or older, who were diagnosed with early-stage NSCLC in a Dutch hospital. Outcomes in untreated patients were poor and the significant increase in survival after radiotherapy was observed following the introduction of SABR in 2003 (From Palma et al.’)

Figure 8: Overall survival following SABR in both potentially operable and inoperable patients who underwent SABR for stage I NSCLC. The overall survival observed in potentially operable patients is similar to that reported after surgery.
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