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### **The evolving role of stereotactic ablative radiotherapy in operable early stage non-small cell lung cancer**

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2015

#### **document version**

Publisher's PDF, also known as Version of record

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#### **citation for published version (APA)**

Verstegen, N. E. (2015). *The evolving role of stereotactic ablative radiotherapy in operable early stage non-small cell lung cancer*.

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## Summary



The aim of this thesis was to investigate the evolving role of SABR as treatment option for potentially operable patients with early stage NSCLC. The first two chapters provide an overview into the introduction of SABR in early stage NSCLC, and describe its impact for medically inoperable patients. Due to changing demographics, increasing numbers of elderly patients are diagnosed with early stage NSCLC, patients who are often medically inoperable or at high risk for surgery due to co-existing comorbidities. **Chapter 2** describes the general aspects of treatment planning and delivery of SABR. SABR is delivered in 8 or fewer fractions, in contrast with the 30- or more fractions used in conventional radiotherapy. Furthermore, reported local control rates after SABR range from 80-95%, and toxicity is generally mild. The introduction of SABR has been associated with improved survival of elderly patients with early stage NSCLC in the Netherlands, and it was also associated with a decrease in the number of untreated patients.

**Chapter 3** addresses the challenges for tumor boards when SABR is implemented, such as difficulties in obtaining a pathological diagnosis before treatment in unfit and elderly patients, tumor motion during treatment delivery, evaluation of radiological changes post-SABR and the diagnosis and treatment of new secondary primary lung tumors after treatment. An important difference between SABR and surgery for early stage NSCLC is that a final pathological diagnosis is always available with surgery, while obtaining a pre-treatment pathological diagnosis can be challenging in unfit patients. Sixty-six percent of our patients undergoing SABR did not have a pathological diagnosis, which in turn raised the question by some as to whether the outcomes reported in patients without pathology could have been a reflection of treatment of non-malignant nodules. In **chapter 4**, we compared outcomes between patients with and without pathological confirmation of malignancy. This analysis revealed no differences in local-, regional- and distant control and overall survival between both patient cohorts. This supports our contention that, in a Dutch population which has a low incidence of benign <sup>18</sup>F-DG-PET positive lung nodules, survival benefits reported after the introduction of SABR are unlikely to be biased by inclusion of benign lesions.

With the excellent local control rates reported after SABR for early stage NSCLC, an increasingly number of fit patients are undergoing SABR. In **chapter 5**, we evaluated outcomes in 177 patients who were treated with SABR for an early stage NSCLC, and who were retrospectively identified as potentially operable. Three-year overall survival was 85% and the corresponding local control rate was 93%, figures which are comparable to outcomes reported following surgery. Although these patients were retrospectively identified as having no contraindication for surgery, it suggests that excellent outcome

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can be achieved with SABR, and the findings support further randomized controlled trials comparing SABR to surgery.

In order to more directly compare outcomes following SABR and surgery for early stage NSCLC, we used propensity score matching to create two comparable patient cohorts, one with SABR patients treated at VUmc and the other with patients treated with a VATS-lobectomy performed at VUmc and five regional hospitals (**Chapter 6**). The analysis showed superior loco-regional control after SABR, with one- and three-year loco-regional control rates following SABR of 96.8% and 93.3%, respectively, as compared to one- and three-year loco-regional control rates following surgery of 86.9% and 82.6%, respectively ( $p=0.04$ ). Distant control, freedom from progression and overall survival were similar in both groups. Treatment related toxicity was also milder following SABR. This report was the first to use propensity score matching to directly compare SABR to VATS-lobectomy, and adds to the equipoise in enrollment to randomized controlled trials.

As surgical patients undergoing VATS-lobectomy in this propensity-score analysis were selected from six different hospitals, it has been suggested that surgical outcome could have been potentially inferior as some participating surgeons may not have completed their learning curve for the procedure. Therefore, we repeated the propensity score matched analysis using surgical patients treated in the Erasmus MC, a tertiary cancer center in The Netherlands (**Chapter 7**). The comparison of the propensity score matched SABR patients with early-stage surgical cases from Erasmus MC revealed no significant differences in tumor control and overall survival between surgery and SABR.

With growing evidence of clinical equipoise of SABR and surgery for early stage NSCLC, as well as the wish of patients to have more say in their treatments, shared decision making should be encouraged such that patients can choose treatments that best reflect their personal preferences. It is important in shared decision making for patients to have access to reliable and understandable evidence on their treatment options. Therefore, we analyzed the quality, usability and readability of online patient information about SABR in the Netherlands, Germany and the United Kingdom (**Chapter 8**). We identified a total of 20 websites, none of which received an excellent or good quality rating for usability and readability, and only two were rated as fair. Fifty-five percent of the websites studied were scored as of poor quality, and 35% as being of very poor quality. This indicates that in spite of the fact that SABR is widely used for early stage NSCLC, only very limited high quality information is available for patients. Work to improve the quality of patient information is clearly a priority in order to increase patient participation in decision-making.

An increasing number of fitter patients are now undergoing SABR, as the growing body of comparative effectiveness research showing similar results after both SABR and surgery in early stage NSCLC. Consequently, there is growing awareness of the need to optimize follow-up schedules after SABR as patients with fewer comorbidities have a better long term overall survival. As the available literature on long-term follow-up after SABR is limited, we analyzed long-term outcomes in 855 patients treated with SABR for T1-2N0M0 NSCLC (**Chapter 9**). Specific attention was paid towards treatment of local recurrences and second primary lung cancers (SPLC), as both may allow for curative treatments. Actuarial 5-year local control was 90.9%, with a median time to local recurrence of 22 months (range 7 to 87 months). The annual risk of a SPLC in our cohort was 2-5% per year. Although radical salvage treatment was performed in only 22% of patients with a local recurrence, this was the case in 80% of patients with a SPLC. The low use of salvage treatments for local recurrences reflects both pre-existing co-morbidities in our patient population, as well as the low incidence of isolated local recurrences. Both the wide range in time to local recurrence and the persistent risk of a SPLC, support long term follow-up with CT for all patients fit enough to undergo any type of salvage treatment.

The literature on salvage surgery for local recurrences following SABR is limited, and concerns exist as intra-thoracic adhesions arising due to SABR may complicate surgery. In **chapter 10**, we report on seventeen patients who underwent a total of 21 surgical procedures for a local recurrence after SABR for primary lung cancer or pulmonary metastases. Only two patients had grade IIIa toxicities (Dindo-Clavien classification) and the 30-day mortality post-surgery was 0%. These findings suggest that surgical salvage for local recurrence post SABR can be safely performed in selected patients.