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

Verstegen, N.E.

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Conclusions and future directions

Curative treatment of early stage NSCLC

Lung cancer surgery was first introduced by Graham and Slinger in 1933, and it has been considered to be the treatment of choice for operable patients with early stage NSCLC ever since[1–3]. In 1950, Churchill et al. reported a series of patients with long term survival following lobectomy for lung cancer, leading to the replacement of the pneumonectomy as treatment of choice[4]. A report in 1973 on the use of sub-lobar resections in early stage NSCLC raised the possibility that surgical cure may not be compromised by the omission of a lobectomy[5]. A subsequent randomized controlled trial comparing lobectomy to more limited resections reported more local recurrences, and decreased survival, in patients who underwent a sub-lobar resection[6]. Therefore, the recommended extent of surgical resection remained a lobectomy[1,2]. However, more recent retrospective studies have suggested that sub-lobar resections using modern surgical techniques may result in better outcomes than those observed in older literature. A recent meta-analysis concluded that a sub-lobar resection produces similar survival as a lobectomy in patients stage IA tumors measuring ≤2 cm in size[7–9]. In view of the rapidly increasing population of elderly patients with early stage NSCLC, surgeons have a renewed interest in sub-lobar resections, especially in these elderly patients[10]. However, as no new results from randomized controlled trials are available, no definite recommendations can be made.

The rationale for surgery as the recommended treatment comes primarily from retrospective studies and database registries, showing higher survival rates after surgery as compared to other treatment modalities[2]. The solitary randomized controlled trial supporting the role of surgery in early stage NSCLC was published more than 50 years ago and compared surgery with radiotherapy[11]. The study reported an improved overall survival after surgery for squamous cell carcinoma.

Surgical resection can be associated with significant risks. When the post-operative recording period for surgical mortality is extended to 90 days, death rates are substantial and can be double the rates reported over 30 days[12–14]. Furthermore, the risk of surgery-associated morbidity is high, with readmission rates of 23% within the first 90-days, and a remaining impaired quality of life especially in elderly[15,16]. Due to the lack of supportive randomized evidence and the risks involved with surgery, its role in early stage NSCLC has been questioned[17,18].

The use of stereotactic radiotherapy for lung tumors was first reported in the literature in 1995[19]. High local control rates have been achieved in medically inoperable patients, and the introduction of SABR was associated with improved survival for elderly patients with early stage lung cancer in the Netherlands[20–23]. With these excellent results, the role of SABR for potentially operable patients has gained considerable interest. However, randomized controlled trials comparing both treatments failed to accrue patients, and were therefore prematurely closed [24].

In recent years, many comparative effectiveness studies have been published comparing surgery and SABR for early stage NSCLC, including two chapters in this thesis[24,25]. In general, these studies found no clear advantage of one treatment over the other. Most importantly, local control was found to be similar following both treatments. Furthermore, treatment-related toxicity is milder post-SABR, a finding of interest especially for older patients, who have more co-morbidities. These studies also suggested a potential overall survival benefit following surgery, a finding that may be attributed by the fact that patients who undergo surgery are fitter, and as non-randomized comparisons involving patient matching for known variables may not eliminate all baseline differences between populations[25]. Recently, a pooled analysis of two randomized controlled trials comparing surgery with SABR, both of which failed to accrue sufficient numbers of patients, became available[26]. This analysis reported a significantly higher overall survival following SABR as compared to surgery, representing the first randomized data suggesting SABR might lead to better overall survival for operable early stage NSCLC. The results of this study are consistent with the above mentioned comparative effectiveness studies. Nevertheless, additional data from well-powered randomized clinical trials are warranted.

Randomized controlled trials (RCT's) are considered the highest form of evidence in evidence-based medicine. Most of the substantial improvements in treatment and outcome of patients with cancer over the past four decades have been established using RCT's[27]. However, patients participating in RCT's are strictly defined and highly selected, and especially elderly patients are underrepresented in trials, even though most cancer patients are of advanced age[28]. Therefore, outcome of RCT's may not be representative for the entire population of patients, and especially so for lung cancer patients, who have a median age of 70 years at time of diagnosis and often have other comorbidities[29–31]. In the absence of data from RCT's comparing surgery and SABR, other forms of comparative effectiveness research are valuable, such as population-based observational studies, propensity score matching, Markov modeling, cost-effectiveness studies and meta-analytic methodologies. The results of observational studies rank lower than RCT's in the hierarchy of evidence based medicine, due to potential inclusion bias and the often complicated statistical methods (see Table 1). However, in the absence of RCT's, the findings of observational studies should not be overlooked.

Table 1: *Strengths and limitations of RCT's and observational studies (Reprinted with permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society)*

	RCTs	Observational Studies
Strengths	Randomization balances baseline characteristics (as prognostic factors)	Rigor of observational studies is enhanced by specific methodological strategies
	"Prospective" infrastructure collects pertinent data	Observational studies and RCTs with same focus provide consistent results
	Methods of analysis can be simple and straightforward	Treatments evaluated in non-randomized studies are safe and effective
Limitations	RCTs on the same topic are often contradictory	Baseline characteristics (as prognostic factors) are usually imbalanced
	Meta-analyses and large RCTs often disagree	Quality of data pertinent to research question can be variable
	RCTs can have limited generalizability (applicability to broader populations)	Accompanying methods of analysis can be complex and obscure

Definition of abbreviation: RCT = randomized controlled trial.
The main text of this article focuses on limitations of RCTs and strengths of observational studies.

At present, new trials comparing surgery and SABR are in preparation, namely VALOR in the USA and SABRtooth in the UK. Both studies involve an initial approach to patients by a more neutral party consisting of a pulmonologist and research nurse. This reduces any bias that may be introduced if the patient is initially seen by either a surgeon or radiation-oncologist. Furthermore, prospective registration of patient data nationwide has become mandated, such as by the Dutch Institute of Clinical Auditing (DICA). These databases can help provide more reliable observational data and reduce inclusion bias.

Shared decision making

Shared decision making is a process in which clinicians and patients work together to select the optimal treatment, based on all the clinical evidence and the patient's preferences[32]. In situations where two treatments appear to have clinical equipoise, as appears to be the case for surgery and SABR in early stage NSCLC, shared-decision making has been encouraged to incorporate patients' preferences and values in medical management[33]. In order to succeed in shared decision making, doctors need to be aware of all relevant comparative effectiveness research, so that they can provide patients with the information they are entitled to [34]. Specifically, patients need to be aware of the pro's and con's of each treatment. Patients considering surgery need to be informed about the advantages of having a pathological diagnosis and lymph node dissection, but also about the mortality rates following surgery outside of clinical trials, data on quality of life post treatment, and financial burden of treatment[35,36]. Similarly, patients considering SABR need to be informed of the similar cancer-related outcomes as for surgery and the low toxicity profile, but also on the challenges in the evaluation of follow-up CT-scans and uncertainties in diagnosis and salvages of rare local recurrences. Only when patients receive all the information, they can make a well-informed decision, tailored to their specific preferences.

Treating operable patients with early stage NSCLC with SABR

With growing evidence that SABR and surgery yield comparable results in early stage NSCLC, our data shows increasing numbers of potentially operable patients undergo SABR[37]. With fitter patients undergoing SABR, new areas of further research emerge.

Topics of further research in operable patients treated with SABR
Improve pre-treatment pathological diagnosis of lung cancer in different global populations
Optimize detection of occult lymph node metastases using endoscopic techniques in ^{18}FDG-PET staged patients
Implement optimal follow-up regimen for potentially salvageable disease recurrences and second primaries
Develop techniques for distinguishing local recurrences from fibrosis
Study the safety of surgical resections after SABR, especially in more central hilar lesions
Implement programs for smoking cessation in survivors

Pre-treatment pathological diagnosis

Although establishing a pathological confirmation before any local treatment is recommended, it may not always be feasible, especially in less superficial lesions or in patients with severe COPD[38]. In the Netherlands, the likelihood of a final diagnosis of benign disease in Dutch patients who undergo surgery for suspected NSCLC, is generally less than 5%[39–41]. In chapter 4 of this thesis, we have shown that is unlikely that the results published on SABR in the Dutch population have been significantly biased by patients with benign lesions undergoing SABR[42]. In general, attempts should be made to obtain pathology, but it is important to weigh the likelihood of malignancy against the risks of the diagnostic procedure and/or treatment. The Dutch-Belgian NELSON screening trial reported that 17% of the major complications, and 21% of minor complications, arose in subjects who underwent surgery for benign disease[43]. Both guidelines, as well as a decision analysis, have suggested a 85% likelihood of malignancy as threshold prior to proceeding with treatment, without pathological confirmation, in cases where there are concerns about morbidity related to biopsy[44–46]. Models to predict the probability of malignancy using clinical, CT, and FDG-PET features have been developed[47,48]. However, caution is advised if such models have not been validated for specific geographic regions, as the specificity and sensitivity of FDG-PET-scans to detect lung cancer varies widely in different geographic regions[4950].

Lymph node staging

One of the presumed advantages of surgery over SABR for early stage NSCLC is the possibility to perform lymph node dissection, thereby identifying patients who might benefit from adjuvant chemotherapy[1,2]. Nodal upstaging occurs in approximately 15% of patients and the estimated survival benefit of adjuvant therapy in these selected patients is 5%[51]. Although it is guideline-recommended, not all surgical patients actually undergo a complete lymph node dissection, with even less lymph nodes harvested in patients treated with a VATS-lobectomy[2,52–54]. Furthermore, not all patients benefit from the advantages of lymph node staging, as only two thirds of all patients who are upstaged at surgery are finally able or willing to undergo adjuvant treatment[55]. When this is taken into account, the potential survival improvement is quickly diluted: If 100 patients with clinical stage I NSCLC undergo resection, approximately 15 will have nodal disease, of whom 10 would receive chemotherapy and an excess of 0.5 patients would be alive 5 years later[24]. Furthermore, in long-term follow-up in trials that have investigated the benefits of adjuvant therapies in local-advanced disease, the initial survival benefits of approximately 5% are lost after 5 years, due to an increased risk of death due to non-cancer related causes[56].

Currently, guidelines state that staging for patients with suspected early stage NSCLC consists of CT- and ^{18}FDG-PET scans. In case of pathological ^{18}FDG-uptake in regional lymph nodes, further investigations such as endobroncial or endoscopic ultrasound with fine needle biopsy or mediastinoscopy are used to determinate the nodal status. However, the sensitivity, specificity and accuracy of ^{18}F-FDG-PET scans for assessing mediastinal lymph node metastasis with a short-axis diameter of less than 15 mm is still limited, as is reflected by the fact that up to 15% of all clinical stage I patients are upstaged after lymph node dissection[57]. Even though SABR patients do not undergo lymph node dissection, most studies comparing SABR and surgery have found comparable or even lower loco-regional recurrence rates, although rates do vary depending on definition of local and regional recurrence[58–60]. It is hypothesized that the low loco-regional recurrence rates observed could be due to a boost in immune function following SABR[61,62]. A recent study using propensity score matching, however, found a trend towards more nodal recurrences after SABR and significantly more loco-regional tumor recurrences[39]. In order to improve loco-regional tumor control in SABR patients, minimally invasive mediastinal staging using endobronchial or endoscopic ultrasound or mediastinoscopy may need to be explored in patients at in high-risk of occult nodal disease, even when ^{18}FDG-PETscans are negative. One such trial, the STAGE study, is currently accruing patients out our center.

Follow-up post SABR

The optimal follow-up regimen for patients treated with SABR was unclear. Clinical guidelines recommend CT-imaging every 3-6 months for a period of up to 3 years post radiotherapy, followed by annual CT-imaging[63]. In chapter 9 of this thesis, we describe long-term results of patients treated with SABR, focusing on follow-up regimens. Based on these results, we recommend that all patients eligible for any type of salvage undergo 6-monthly follow-up CT-scans for a period of three years post SABR, followed by annual CT-scans thereafter. However, it is not clear if such scans should always be performed using intravenous contrast. The advantage of a contrast-enhanced scan is the more accurate evaluation of the mediastinum and better identification of regional recurrences. However, administration of contrast is not without risks[64]. As the peak incidence of regional recurrence is in the first 2 years post treatment[65] and CT-follow-up in later years is more focused on peripheral second primary lung cancers, that have an incidence rate of 2-5% per year, limiting the number of contrast-enhanced scans to early follow-up appears reasonable. Further research is needed to determine if fitter patients, in whom salvage of a recurrence might be feasible, merit a different follow-up scheme[66].

Detection and salvage of local recurrence

An important clinical problem is the follow-up imaging after SABR, where local recurrences have to be distinguished from focal fibrosis. This is especially of importance in fitter patients, who are more likely to have longer follow-up and might be eligible for salvage treatment in case of local recurrence. High risk radiological features have been identified to aid with distinguishing local recurrence from fibrosis[67] but these criteria require validation in larger groups of patients with pathological confirmed local recurrences. New techniques, such as quantitative image feature analysis, are also being explored[68]. However, local recurrences post-SABR are only seen in approximately 10% of patients, and ongoing multi-center collaborations with experienced investigators are underway in order to gather enough information for reliable assessments.

Fitter patients treated with SABR might also be candidates for surgical salvage of isolated local recurrences. In chapter 10, we reported the largest case-series to date of patients undergoing salvage surgery for a local recurrence after SABR to date. Of seventeen patients who underwent a total of 21 resections, only two patients had complications exceeding > grade 2, and 30-day mortality was 0%. This suggests that salvage surgery can be safely performed after SABR. However, the number of reported salvage procedures for local recurrences following SABR is still limited and restricted to specialist centers. If our results on the safety and efficacy of salvage surgery are confirmed by additional studies, patients who are at increased risk for surgical complication can opt to have SABR as initial treatment, while still having the option of surgery if salvage is required[69].

Smoking cessation

Smoking is well established as a risk factor for several types of cancer, most importantly lung cancer[70]. However, continuing smoking after completion of curative treatment decreases overall survival and cancer-specific mortality, as well as increasing the risk of disease recurrence and development of second primary lung cancer[71,72]. Smoking may also lead to an additive risk for the development of a second primary lung cancer when combined with chemotherapy or radiotherapy[73]. Smoking cessation is challenging and often ignored in the doctor's office. Reports have shown that only 40% of oncologists regularly provide assistance to patients to quit smoking[74]. The American Society of Clinical Oncology provides a guide to aid oncologists in this task, which includes behavioral counseling and advice on pharmacotherapy, mostly nicotine-replacement[75]. Furthermore, several notable programs in the USA have been initiated, such as in MD Anderson and Memorial Sloan Kettering, where smoking cessation rates of more than 30% have been reported by means of active intervention[76,77]. The routine implementation of such programs in the

Netherlands merits further study.

When Dr Evarts Graham, who first performed a one-stage pneumonectomy for lung cancer, was awarded the Lister Medal by the Royal College of Surgeons of England in 1947, he stated in his oration that "perhaps in the future some non-surgical method will be discovered which will be not only more simple in its execution but more reliable in its results than a surgical operation" [78]. Recent outcomes of SABR suggest that maybe the future envisaged by Dr Graham has now arrived.

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