Chapter 9

General discussion and future perspectives
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The incidence of lung cancer is increasing worldwide. In the United States, it is expected to increase by more than 50% between 2010 and 2030. Of particular concern is the fact that the greatest increase is expected in the elderly, a group with higher levels of comorbidity, which in turn complicates lung cancer treatment.

Current treatment approaches for lung cancer are often not curative, as evidenced by data from the Netherlands showing that there were approximately 10,000 new cases in 2006 but nearly 9,500 deaths from lung cancer. There is growing awareness of the fact that smokers are at increased risk of developing multiple lung tumors, either synchronous or metachronous. If a first cancer treatment has resulted in significant morbidity and has compromised a patient’s quality of life, curative treatment of a second tumor may not be possible. Therefore, when deciding on the best course of treatment for an individual patient, extra consideration should be given to the treatment-related morbidity and to the potential fitness to undergo future treatments.

This thesis addresses several technical issues and the clinical outcomes of stereotactic radiation therapy (SRT) for patients with early stage lung cancer. The current results show that SRT offers superior results compared to conventional radiation therapy, and might even be comparable to surgery, but with much lower toxicity. However, when the technique was first implemented in the VUmc in 2003, clinical outcomes had to be established in larger groups of patients, and simulation and treatment protocols were complex and time consuming. As shown in Chapter 3, adaptive treatment planning does not have clinical benefit for most patients, and the discontinuation of repeating the imaging and planning procedure halfway through treatment greatly reduced departmental workload and treatment costs in 2006.

Some procedures which were investigated did not prove to be useful in treatment planning. The image quality and reproducibility of 4DCT scanning can be improved by using audio-coaching, but work described in Chapter 4 shows that coaching during 4DCT scanning can also lead to geometrical misses of the tumor if it is omitted during treatment delivery. This example of a seemingly
simple measure used to improve image acquisition during the simulation process can create important problems during treatment, illustrating the fact that any change in an SRT treatment protocol can have important consequences and should be evaluated with great care.

Historically, an anatomical resection has been the standard of care for early stage lung cancer for patients who are medically fit. In patients who were unfit for surgery, curative treatment options were limited to conventionally fractionated radiotherapy, and the results were disappointing. In contrast, the current results of SRT are superior to conventionally fractionated radiotherapy, and are even promising when compared to surgery, in particular when one appreciates that the results of surgery are based on a selection of the fittest patient groups, while the results of stereotactic radiation therapy (SRT) are mostly based on unfit and elderly patients (Chapter 5). Non-randomized comparisons of the results of surgery and SRT show comparable local tumor control, and the morbidity of SRT appears lower, even when compared to limited resections or video assisted thoracoscopic surgery (VATS)5. Our results show that SRT is safe and effective even in medically inoperable, elderly patients with multiple comorbidities including severe COPD (Chapter 6), and in patients with tumors arising in the remaining lung after a previous pneumonectomy (Chapter 7). Based on these findings, SRT can be considered the current standard of care for medically inoperable patients instead of conventionally fractionated radiotherapy. In accordance with the guidelines of the American College of Chest Physicians6,7, this new data on the outcomes and morbidity of SRT should also be discussed with all patients who are candidate for a resection, and particularly so in patients who are at increased surgical risk of morbidity and mortality (Chapter 8). A limitation of current SRT data is that due to the poor general health of the patients commonly referred for SRT, the rate of intercurrent deaths is high and thus long-term follow-up data is limited.
Recent developments in SRT
Although the current results of SRT may seem adequate for tumors of up to 6 cm in diameter, new techniques are being implemented rapidly in order to further improve the accuracy and speed of treatment. Optimal patient positioning and dealing with intra- and interfraction shifts is crucial in hypofractionated, high dose SRT. Although Chapter 3 showed that adaptive treatment planning halfway treatment did not show significant benefit in most patients, it also showed that larger deviations in tumor position may occur between treatment fractions in exceptional cases. Since April 2009, a new Novalis Tx™ linear accelerator (Varian Medical Systems) dedicated to stereotactic treatments was available at our department. It is equipped with a conebeam CT scanner (CBCT), a device that allows for imaging of soft tissues immediately before treatment to verify, and when necessary, correct patient position. The quality of images is sufficient to allow for verification of the position of peripheral lung tumors [Fig 1]. Using this approach, treatment setup is currently no longer based on external markers or on bony anatomy, but on the position of the tumor itself.

Figure 1: Example of patient positioning using Conebeam CT. A small tumor was delineated using the planning 4DCT (upper left panel); A Conebeam CT is performed before every treatment, and the target area is projected onto the Conebeam CT images (right panel) to achieve optimal tumor positioning.
The second improvement of the Novalis Tx compared to the older Novalis linear accelerator is the larger maximum field size. The previously used maximum tumor size limit of 6-8 cm for SRT of lung tumors no longer applies as much larger field sizes can now be used on the Novalis Tx [Fig 2]. As little data are currently available on the efficacy and toxicity of SRT for larger tumors, these patient groups will have to be followed with great care.

![Figure 2: Larger T2 tumors can now also be treated by SRT (Planning CT scan: left panel A). The right hand panel (B) shows the first follow-up scan after 4 months showing significant tumor regression](image)

The third development is the use of volumetric intensity-modulated arc therapy or RapidArc (Varian Medical Systems), a new treatment technique that can be used for both conventionally fractionated radiation therapy and for SRT. RapidArc is a form of intensity modulated radiation therapy (IMRT) using arc treatment instead of static beams. The dose is delivered while the gantry of the linear accelerator rotates around the patient with a variable speed, continuously varying the shape of the treatment aperture and continuously modulating the dose rate, to achieve an optimal dose distribution. An advantage of RapidArc over conventional IMRT is that the treatment delivery time itself has been shortened to 12 minutes or less. A recent upgrade of RapidArc software has now made it possible to perform SRT for a stage I lung tumor to a dose of 18 Gy in less than 6 minutes, compared an to average 30 minutes treatment time for the patients described in this thesis. This will greatly reduce the chance of
intrafraction shifts in tumor position, and will allow more patients to be treated per linear accelerator.

**Staging and obtaining a pathological diagnosis**

Just as in all other tumors, obtaining tissue evidence of malignancy is of great importance, particularly as some treatment strategies may be associated with important side-effects. However, a cytohistological diagnosis can often not be obtained in medically inoperable lung cancer patients with peripheral tumors, due to the risks associated with the required procedures in patients with very poor pulmonary function. In cases where no pathological data is available, we accept patients for treatment when a lesion is a FDG-PET positive, new or growing lesion with the CT characteristics of malignancy.

The problem of obtaining histological proof in early stage lung cancer is increasing, as more and more smaller lesions are detected through the increased use of high-resolution multi-slice CT scans. The results of two large randomized screening trials, the Dutch-Belgian Nelson trial and the U.S. National lung screening trial in high risk populations are expected in 2010. A lot of effort is being invested in increasing the predictive value of screening, especially for smaller lesions, as the probability of malignancy is lower and the chance of obtaining histological proof before treatment is small. It should be emphasized that the number of patients in our own SRT series with very small lesions that are typical of screen-detected tumors was extremely low, as less than 1% of patients had a tumor with a diameter of less than 1 cm. In addition, we only accepted patients in our SRT series with new or growing lesions, if no histology was obtained. Preliminary results of the NELSON trial show that a volume doubling time of less than 400 days is an additional predictor of malignancy. Without additional criteria to decrease the chance of inadvertently treating benign disease, the treatment of small, screen detected nodules should be evaluated with great care. Combining CT based screening with new non- or minimally invasive screening techniques may lead to the widespread implementation of lung cancer screening programs. Examples of promising non-invasive techniques that can support the diagnosis of lung cancer are the analysis of protein expression levels in blood, cytopathology combined with gene expression profiling in normal lower airway cells obtained at
bronchoscopy\textsuperscript{15}, analyzing exhaled breath condensate\textsuperscript{16} and the screening of sputum using molecular genetic markers\textsuperscript{17}.

In a number of published reports on SRT, a high percentage of patients did not have biopsy proven NSCLC. Others investigators have included only patients with a biopsy-proven diagnosis, and the reported clinical outcomes were identical. Cyto-histological confirmation of malignancy was available in 40\% of our patients, as the referring pulmonologists were reluctant to perform invasive staging procedures in our mainly frail patient group, where the risks associated with invasive diagnostic procedures were felt to be higher than the likelihood of inducing severe toxicity with SRT. A low percentage of biopsy proven lung cancer before treatment is also common in surgical trials\textsuperscript{18,19}, as transthoracic biopsies are often nondiagnostic\textsuperscript{20}, or are omitted due to the reported 25\% risk of pneumothorax\textsuperscript{21}. An advantage of surgery is that histological proof is always obtained during the surgical procedure itself. It has been suggested that not obtaining histology in all cases is a key limitation of the literature on SRT. However, anecdotal reports of a high incidence of benign lesions at surgery is not supported by the available randomized surgical evidence, as the Dutch PLUS and POORT studies both showed that the incidence of benign lesions in the Netherlands was below 5\% at surgery\textsuperscript{22,23}. International data from the U.S. and Italy with a total number of over 1500 resections also indicate a low incidence of benign disease in cases where the diagnosis of lung cancer is based on a combination of clinical parameters, CT and PET data\textsuperscript{20,24}. Furthermore, a high incidence of benign disease at surgery would be an extra argument against surgery, as a study by Crestanello et al. showed that operative complications occurred in 27\% of patients with screen-detected lesions, and operative mortality was 1.7\%\textsuperscript{25}. This indicates that the potential side effects of SRT are significantly less severe than those with surgery for patients who are inadvertently treated for benign disease.

In our patients, identical outcomes were seen between patients with and without histological proof of malignancy (Chapter 5 and 6), and outcomes are identical to the results of smaller published series with a selection of patients with biopsy proven NSCLC (Chapter 8). Nevertheless, it remains important to obtain a cytological or histological diagnosis whenever possible, especially in countries where infections such as tuberculosis are more common. Additional reasons to obtain a sample of tumor tissue can be to have the opportunity to
identify cases with small-cell histology, or to compare histology when more than 1 lesion is present to differentiate between second primary tumors and metastasis. Tumor tissue is increasingly used to predict the effectiveness of targeted therapy in case of disease progression, and may be used in the future to better predict prognosis or the effectiveness of adjuvant therapy. In our experience, there is a striking difference in the rate of pathology obtained between referring hospitals (unpublished data). An improvement in the techniques and equipment of interventional radiologists and pulmonologists in obtaining pathology using CT guided biopsies or advanced bronchoscopic techniques may be helpful to increase successful biopsy rates in patients who are medically fit to undergo minimally invasive staging procedures.

Operable patients and SRT
The excellent results achieved using SRT raises the question as to whether SRT should also be offered to patients who are fit to undergo surgery. The results regarding local control appear to be equally good, while surgery is associated with a peri-operative mortality in the order of 5% depending on the extent of surgery and on strict patient selection; the morbidity of SRT appears to be lower, and quality of life is generally better preserved. Survival following surgery is shown to correlate with the experience and specialty of surgeons, resection volume and teaching status of hospitals, with highly specialized centers with large patient volumes generally reporting lower mortality and morbidity. Therefore, surgical results might still improve by better training of surgeons, by concentrating lung cancer care in specialized centers and by implementing less invasive surgical techniques. The morbidity of surgery might be reduced by the implementation of VATS, video assisted thoracoscopic surgery. As VATS is less invasive than standard open surgery, it is thought to decrease hospital stay, both acute and chronic chest pain, and time until return to preoperative activity. The survival after VATS lobectomy appears to be similar to that of patients having an open procedure. Although the use of VATS has been advocated during the last 15 years, all large randomized trials comparing VATS to open surgery have unfortunately failed due to lack of accrual. Many retrospective studies reported some degree of patient benefit compared to conventional open thoracotomy, but complication rates are still much higher when compared to SRT. An overview of pooled retrospective data showed that the complication rate of
VATS was 16% compared to 31% for open thoracotomy, with the most important complications being atrial fibrillation, pneumonia and persistent air leak. The mean length of hospital stay was reduced from 13 days for open surgery to 8 days for VATS\textsuperscript{33}. However, data from the SEER database and the ACOSOG Z0030 trial, together comprising data of over 14,000 resections, showed that VATS resection is still only used in less than 10% of patients\textsuperscript{34,35}. The reason for this lack of implementation is unclear, but it is apparent that VATS is not yet available to most patients.

The rate of synchronous or metachronous tumors is increased in patients with lung cancer\textsuperscript{36,37}. Treatment options for second tumors after previous surgery are often limited due to impaired health, and because the extent of lung resections is associated with the level of decline in quality of life\textsuperscript{38}. A theoretical disadvantage of SRT and VATS compared to open thoracotomy is that there is no opportunity to palpate to rest of the ipsilateral lung. A recent study showed that 8% of patients can have synchronous second tumors in a different lobe\textsuperscript{39}, despite pre-operative CT/PET imaging. These second lesions would initially be missed when treating by SRT or VATS, but they can often still be treated when discovered during follow-up. As SRT has little impact on quality of life and lung function, SRT treatment of a first lung tumor should offer more opportunity for the curative treatment of second tumors compared to surgery. SRT of more than a single lung lesion is feasible\textsuperscript{40}. In our series, approximately 6% of patients were treated simultaneously for two synchronous lesions by SRT. Of the patients with a single lung tumor, 4% developed a second lesion during follow-up, and half of these patients were treated for a second time using SRT.
Another difference of surgery compared to SRT is that a mediastinal lymph node dissection can be performed during surgery, although surgical data shows that a complete mediastinal lymph node dissection is only performed in a minority of surgical patients in daily practice\textsuperscript{29,42}. An important question is whether the delayed detection of lymph node involvement can decrease survival. In theory, omitting lymph node dissections could decrease outcomes by the decreased use of adjuvant chemotherapy to treat micrometastasis, or by increasing the rate of regional lymph node recurrences. However, the role of adjuvant chemotherapy is unclear since a recent update on long-term survival in the International Adjuvant Lung Cancer Trial (IALT) showed that the reported survival benefit of platinum-based adjuvant chemotherapy seen at initial analysis vanished at 5-years post treatment follow-up, suggesting late adjuvant chemotherapy-related excess-mortality\textsuperscript{43}. The benefits of mediastinal lymph node dissection to prevent regional recurrences are also unclear. Lymph node dissection does not completely prevent regional recurrences, and surgical series show comparable locoregional control compared to our SRT based results without lymph node dissection.

**Table 1:** differences between surgery and SRT

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>SRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histo-cytological diagnosis</strong></td>
<td>Always (post-surgery)</td>
<td>&lt;50% (VUMC)</td>
</tr>
<tr>
<td><strong>Lymph node dissection</strong></td>
<td>Theoretically: 100% of patients</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Clinical practice: 23% \textsuperscript{[29]}</td>
<td></td>
</tr>
<tr>
<td><strong>Multifocal tumors</strong></td>
<td>4-8%</td>
<td>6% (VUMC)</td>
</tr>
<tr>
<td><strong>In-patient stay</strong></td>
<td>7-17 days \textsuperscript{[33]}</td>
<td>Not required</td>
</tr>
<tr>
<td><strong>Serious Complications</strong></td>
<td>16-32%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td><strong>Mortality (30 days)</strong></td>
<td>3.7-6.9% \textsuperscript{[41]}</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>Hospitalization costs</td>
<td>Outpatient treatment</td>
</tr>
<tr>
<td></td>
<td>Treatment of complications</td>
<td>Treatment of high grade</td>
</tr>
<tr>
<td></td>
<td>Prolonged length of stay in 11%</td>
<td>radiation pneumonitis in &lt;3%</td>
</tr>
<tr>
<td></td>
<td>Extended care facilities in 13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>\textsuperscript{[29]}</td>
<td></td>
</tr>
<tr>
<td><strong>QoL</strong></td>
<td>Decrease in a significant minority \textsuperscript{[38]}</td>
<td>Generally maintained \textsuperscript{[28]}</td>
</tr>
</tbody>
</table>
Table 2: results of surgery for stage I NSCLC

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Local failure (%)</th>
<th>Regional failure (%)</th>
<th>Total of local and regional failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsberg 1995</td>
<td>247</td>
<td>N.R.</td>
<td>N.R.</td>
<td>11.7</td>
</tr>
<tr>
<td>Martini 1995</td>
<td>598</td>
<td>5.8</td>
<td>2.5</td>
<td>8.4</td>
</tr>
<tr>
<td>El-Sherif 2006</td>
<td>784</td>
<td>5.0</td>
<td>4.6</td>
<td>9.6</td>
</tr>
<tr>
<td>Goodgame 2008</td>
<td>715</td>
<td>N.R.</td>
<td>N.R.</td>
<td>16</td>
</tr>
<tr>
<td>Hung 2009</td>
<td>970</td>
<td>12.7</td>
<td>3.1</td>
<td>16</td>
</tr>
<tr>
<td>Kelsey 2009</td>
<td>975</td>
<td>N.R</td>
<td>N.R</td>
<td>14.4</td>
</tr>
<tr>
<td>SRT VUmc (unpublished)</td>
<td>504</td>
<td>3.4</td>
<td>7.7</td>
<td>9.9</td>
</tr>
</tbody>
</table>

The rate of unexpected N2 disease has been reported to be as high as 16% despite preoperative PET-CT, but these studies included patient groups with positive N1 nodes, central tumor locations, and enlarged lymph nodes on CT\(^49\). Patients treated by SRT generally have peripheral lesions which are associated with an incidence of occult N2 disease of less than 3%\(^50\). In case of doubt, a mediastinoscopy can be performed before treatment by SRT, and also less invasive staging techniques such as endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) guided biopsies are emerging rapidly\(^7\). There may be a benefit of mediastinal lymph node staging and adjuvant treatment for patients with large, central T2 tumors, as these patients have a higher rate of occult mediastinal lymph node involvement and especially distant metastasis. A phase I trial combining SRT with adjuvant chemotherapy for patients with T2 tumors was started in the VUmc in 2009. Another option would be a wait-and-see policy, as indirect evidence suggests that there is no decrease in survival after delayed detection of lymph node involvement. A recent study showed that patients with recurrent NSCLC after surgery achieved comparable survival to that of newly diagnosed NSCLC patients when treated with salvage radiotherapy or chemoradiotherapy\(^51\).

Due to the good results of SRT in large groups of inoperable patients and in patients who refused surgery, prospective randomized trials comparing SRT to surgery have been activated. One study is the Dutch “Radiosurgery Or Surgery for operable Early stage non-small cell Lung cancer (ROSEL)”, and the other is the “STARS” study, which is only open to centers who are users of Cyberknife equipment.
A good quality assurance program is crucial when starting a new high-tech image guided radiotherapy technique such as SRT. Surgical studies show that differences in surgical techniques and experience between high volume academic centers and small hospitals can cause poor outcomes, and the same could apply for SRT. The current excellent results of SRT were obtained by experienced, high-tech, university hospitals, but the number of small centers starting an SRT program is growing rapidly worldwide. Centers participating in the ROSEl study will have to comply to the SRT quality assurance guidelines of the ROSEl study. The number of patients referred for SRT outside studies is growing rapidly, as is the amount of non-randomized data on the safety and efficacy of SRT, and it is hoped that the current randomized trials can be
completed before the growing volume of data on retrospective SRT outcomes will bias patients in favor of SRT.

**Conclusions:**
New developments in radiation oncology in the past decade have made it possible to deliver much higher doses of radiation, with much more precision, in less time and with fewer complications than previously thought possible: Stereotactic Radiation Therapy (SRT).

The application of SRT in medically inoperable patients with stage I lung cancer has resulted in excellent outcomes with comparable local control compared to surgery, and with less morbidity. The excellent results of SRT in patients with stage I lung cancer as reported by our group, as well as by a growing number of international groups, has let to the situation that SRT can now be considered standard treatment for patients who are medically inoperable, and for patients at high risk of complications during surgery. Randomized trials have started to compare the results of SRT to surgery in medically fit patients with peripheral stage I lung cancer, as the available evidence suggests that surgery might no longer be the only gold standard.
References


