Stereotactic radiation therapy for stage I non-small cell lung cancer

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Summary

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This thesis examines outcomes after SBRT at the population level and at the individual patient level. The introductory chapters contrast the pre- and post-SBRT eras, in terms of efficacy and treatment utilization, particularly in the elderly. **Chapter 2** examines treatment patterns and outcomes for patients with inoperable early stage lung cancer. Although all patients had early stage lung cancer that was theoretically curable, based on tumor size and location, co-morbidities were common and led to only one-third undergoing curative-intent treatment, with the rest receiving palliative-intent treatment or no treatment. However, the delivery of curative-intent treatment, or high dose palliative radiotherapy, was found to be associated with improved survival. The finding that that higher doses of radiation result in improved outcomes supports dose escalation, with SBRT representing the highest level of dose-escalation achievable. **Chapter 3** examines outcomes in elderly patients with stage I lung cancer selected for curative-intent treatment with either surgery or SBRT. Elderly patients are much less likely to undergo surgical treatment than their younger counterparts. After treatment, elderly age was not a predictor of survival in either the surgical group or the radiotherapy group, whereas clinical factors such as the performance status and sex were predictive. This suggests that for elderly patients, treatment decisions should be based on clinical and pathological features rather than age, and that advanced age alone should not be considered a contraindication for radical treatment.

The following two chapters illustrate the results of a shift from conventional radiotherapy to SBRT in North Holland. **Chapter 4** is a population-based study that examined changes in treatment patterns and survival in elderly patients after the implementation of SBRT. As might be suggested by the findings of the earlier chapters, the implementation of SBRT was associated with a decrease in the proportion of patients going without treatment and an increase in the proportion of patients undergoing RT. This shift was associated with a 5-month median improvement in overall survival, a benefit seen only in patients undergoing radiotherapy, but not in those undergoing surgery or receiving no treatment. **Chapter 5** describes a comparison of outcomes between surgeryand SBRT in a matched cohort of elderly patients from North Holland. The results do not show a difference in long term mortality, although 30-day mortality was high after surgery. This suggests that there is clinical equipoise as to which treatment should be considered the standard of care in elderly patients. In another high-risk patient population, those

with severe COPD, a systematic review carried out in **Chapter 6** similarly demonstrates that SBRT and surgery result in comparable survival outcomes, but that short-term complications are higher in patients treated with surgery, specifically 30-day mortality.

The second half of this thesis, Chapters 7-14, narrows the focus of study to the individual patient level. **Chapter 7** is a review of volumetric modulated arc therapies (VMAT), a new development in radiation oncology. VMAT provides advantages over standard static-beam radiation techniques, in terms of dose distributions and treatment times. Particular advantages include the fact that VMAT can be delivered on a standard linear accelerator and results in faster treatment times. Minimizing treatment times has several important implications, both for patients (in terms of comfort and minimizing intrafraction motion), cancer centers (by increasing patient throughput) and potentially a radiobiological benefit (by avoiding repair of sublethal DNA damage by tumor cells).

Chapters 8 and 9 assess benign CT density changes after SBRT, both in early and late time frames after treatment. **Chapter 8** is a comparison of early CT density changes after VMAT and standard 3D-conformal techniques for lung SBRT. Although CT density changes occurred in more than half of patients, there were no differences between the two techniques in the type or severity of radiological or clinical pneumonitis arising after SBRT, and clinical pneumonitis rates were low. In **Chapter 9**, long-term CT density changes were assessed after SBRT in patients who had a minimum of 2 years of CT follow-up. Nearly all patients developed CT density abnormalities at some time in follow-up, and the patterns of CT density changes continued to evolve more than 1 year after treatment in many patients. This has important implications in helping to distinguish between benign CT density changes and recurrence: even CT changes arising years after treatment can be benign fibrosis and do not necessarily represent malignancy.

The clinical assessment of fibrosis after SBRT is subjective and qualitative, and **Chapter 10** describes a new technique that objectively measures CT Hounsfield unit density changes, using a deformable registration technique for image matching. Deformable registration is much more accurate than traditional rigid registration techniques, and CT density measurements correlate well with physician-assigned radiological pneumonitis severity scores. In **Chapter 11**, this new technique is used to correlate dose-distributions with CT density changes after SBRT. CT density changes were found to increase with dose, target size, and time after SBRT. Most CT

density changes were noted in regions receiving more than 20 Gy; however, after treating large tumors (with PTV >100cc), late CT density changes were evident even in low-dose region.

The finding that normal tissue toxicity is higher in patients with larger tumors was confirmed in **Chapter 12**, which correlated dosimetric factors with early toxicity after SBRT in patients with large target volumes, ranging from 87-283 cc. Rates of pneumonitis were higher (28%) than that reported with smaller tumors, and pneumonitis correlated best with the dose of radiation delivered to the contralateral lung. Two patients died of causes that may have been related to treatment. However, for these patients with large tumors who are not candidates for surgery or chemo-radiotherapy, SBRT provides the only chance for long-term disease control. Although these patients may be at higher risk of SBRT-related complications than patients with smaller tumors, these complications should not discourage treatment, since the alternative option of remaining untreated would likely be associated with substantial complications arising from local progression. **Chapter 13** is a discussion covering some of the issues pertaining to tumor targeting with SBRT, and whether fiducial markers implanted in the tumor are necessary for treatment. Although radio-opaque fiducial markers may enhance targeting in some cases, insertion of the markers is associated with a small risk of complications, and even after implantation there is a risk of migration. Current treatment strategies without fiducial markers rely on cone-beam CT scanning to image the tumor prior to treatment, which confirms the position of the tumor before treatment.

Chapter 14 is a summary of many of the SBRT issues addressed in this thesis, describing the development of SBRT, oncologic and toxicity outcomes, and controversies about the role of SBRT in relation to surgery for first-line treatment. This chapter describes how SBRT has changed treatment paradigms for stage I NSCLC, and outlines future directions for research to ultimately further improve cure rates for early-stage non-small cell lung cancer.