Thesis Summary
THESIS SUMMARY

The work performed for this thesis examined issues related to the use of SABR in treatment of patients with ES-NSCLC.

Chapter 2 is a Markov model that compares best supportive care versus SABR for ES-NSCLC. Using data from a variety of sources, SABR was found to be beneficial for all modeled cohorts, including those with the most advanced age and COPD.

Chapter 3 addresses a common clinical dilemma, which is determining when a biopsy is required for a solitary pulmonary nodule suspicious for ES-NSCLC that is to be treated with SABR. For patients with suspected ES-NSCLC being considered for surgery, a likelihood of malignancy threshold of 65% is commonly accepted, and was arrived upon based on modeling data. We employed a similar methodology, which found that a threshold of approximately 85% was indicated for SABR patients, a finding that was robust over a wide range of assumptions.

With the advent of CT screening, it is foreseeable that the incidence of small pulmonary nodules will be on the rise. Chapter 4 addresses clinical, dosimetric, and image-guidance considerations for such sub-centimeter lesions that may be treated with SABR, as an alternate to surgery. A key finding in this study was that in small peripheral ground glass lesions surrounded by emphysematous (extremely low density) lung treated with SABR, underdosage as high as 20-25% can occur, if modern dose calculation algorithms are not employed.

Chapters 5 and 6 explore survivorship considerations in patients previously treated for head and neck squamous cell cancer (HNSCC) who develop second primary, ES-NSCLC. While there is a possibility of misclassification bias between ES-NSCLC and solitary metastatic HNSCC to the lung in both studies, we found that radical treatment with surgery or SABR may be warranted in either scenario.
In the population-based cohort studied using the Netherlands Cancer Registry, a key finding was that radiotherapy (presumed to be SABR) may achieve similar survival outcomes as surgery in this setting.

**Chapter 7** represents the first published lung cancer application of the Canadian Research Management Model (CRMM), a microsimulation tool designed to estimate the impact of novel cancer therapies in the Canadian population. We found that the use of SABR for ES-NSCLC is projected to result in significant cost savings and survival gains. Although SABR was cost-effective when compared to sublobar resection, conventional radiotherapy and best supportive care, lobectomy was the most cost-effective option overall for operable patients.

In **Chapter 8**, we created a Markov model to simulate the clinical history of various cohort of ES-NSCLC patients (stratified by smoking history, age and sex) treated with either surgery or SABR. The model was built at a time when the STARs and ROSEL RCTs were actively accruing, using the best available evidence over a range of sensitivity analyses. We found that surgery (lobectomy) was preferred over SABR, however this finding was highly sensitive to differences in utility (0.18) and treatment-related death (~3%) estimates. The latter finding is particularly noteworthy, as several studies have since demonstrated that a rate of treatment-related death may be a key reason for why long-term survival differences between surgery and SABR may be small, a phenomenon known as the head-start effect.

While most studies comparing surgery and SABR for ES-NSCLC have focused on survival outcomes, **Chapters 9 and 10** examine quality of life (QoL) considerations. First, in a systematic review of the literature, 9 SABR QoL studies were identified, with the majority of studies finding no clinically significant changes in QoL following SABR. Two studies demonstrated significant deteriorations in fatigue and dyspnea, and a single study noted significant improvements in emotional functioning. Secondly, we performed an exploratory analysis of QoL and indirect costs from the ROSEL RCT comparing surgery and SABR for ES-NSCLC. Recognizing the limitations of a small sample size of 22 patients, we found that SABR was favored for the endpoints of global QoL and indirect costs.
In Chapter 11, we created, then internally and externally validated an overall survival nomogram for ES-NSCLC patients treated with SABR. The nomogram, which is available for clinical use online at www.predictcancer.org, incorporates tumor diameter age, WHO performance status, smoking history and charlson comorbidity index in its prognostication.

Chapter 12 is a pooled analysis of the STARs and ROSEL RCTs comparing SABR and surgery for ES-NSCLC. Although both trials closed due to poor accrual, a combined 58 patients were randomized. Although overall survival at 3 years favored SABR (95% vs. 79%, log rank p =0.037), although on cox proportional hazards modeling this did not retain significance (HR 0.14, 95% CI 0.017-1.190). Regardless, the findings of this pooled analysis support equipoise for newer ongoing RCTs comparing the two treatment modalities.

Chapter 13 is an editorial on a SEER population based analysis, evaluating the merits of SABR as an alternative gold-standard treatment option to surgery for Stage I NSCLC.

Chapter 14 is a review article discussing new developments, current controversies and future priority areas of research in ES-NSCLC.

Chapter 15 is, to our knowledge, the first manuscript that systematically reviews the radiation oncology cost-effectiveness and cost-utility literature. 102 studies were identified and appraised using the Consolidate Health Economic Evaluation Reporting Standards (CHEERS) guideline, which is a checklist of key metrics that should be included in any health economic study. We found that study quality has improved over time; however, it remains to be seen whether such improvements will translate to more efficient usage and funding of radiation cancer care.

Chapters 16 to 20 comprise letters to the editor related to i) the Markov model in chapter 8, ii) the debate of surgery vs. SABR, iii) the utility of CT surveillance following radical treatment of lung cancer, iv) the role of sublobar resection vs. SABR in ES-NSCLC and v) the role of RFA vs. SABR in ES-NSCLC.
The thesis concludes with **Chapter 21**, which highlights new RCTs comparing surgery and SABR in ES-NSCLC, as well as additional priority areas for research in ES-NSCLC.