Chapter 15

Discussion and Future Directions
Lung Cancer Mortality: Slow Progress over Decades

Lung cancer remains a devastating disease, responsible for over 200,000 deaths annually in Europe, with poor long-term survival outcomes.¹ Nearly half of lung cancer patients have metastatic disease at presentation, and median survival for stage IV patients is 6-7 months, even with chemotherapy.²,³ Only 15-20% of NSCLC patients have stage I disease at presentation, and this is the only subset of patients with projected five year survival of greater than 50%.⁴,⁵ For patients with pathologically-staged disease, 5-year survival is 73% and 54% for stage IA and IB disease, respectively.⁵

In the Netherlands, lung cancer is responsible for 6800 male deaths and 3000 female deaths annually. The absolute number of annual lung cancer deaths in the Netherlands has been declining in males over the past 15 years but rising in females,⁶ a pattern similar to trends in other developed countries.⁷ These disparate trends are due to differences in smoking rates: per capita daily cigarette consumption has been falling in men but rising in women.⁶

Overall survival improvements in lung cancer have been scarce over the past 30 years. In the United States, 5-year survival for NSCLC patients was 14% in 1975-77, and increased only marginally to 18% in 1999-2005. Compared to other tumor sites, progress in lung cancer has been slow: 5-year survival for women with breast cancer has increased from 75% to 90% respectively in those time periods, and for men with prostate cancer survival has increased from 69% to 99%. Even if modest gains in lung cancer survival can be achieved, the public health implications would be large: if it is assumed that 5-year survivors are cured of their lung cancer, an improvement in 5-year survival to 30% would save over 20,000 lives annually in Europe.¹ Clearly, advances in outcomes for lung cancer have the potential for a large public health benefit.

SBRT: Current Status and Future Directions

SBRT is a step along the path of improved outcomes for stage I NSCLC. SBRT has generated widespread enthusiasm and research interest as a result of dramatic improvements in local control: the number of publications in PubMed containing the terms “stereotactic”, “radiation”, “lung” and “cancer” has increased rapidly: in 1995, 4 such publications appeared; in 2000, 13 articles were published; in 2005, 29 articles, and in 2010, 139 articles. SBRT is now recognized as a key treatment for inoperable patients with stage I NSCLC: the U.S. National
Comprehensive Cancer Network treatment guidelines confirm that SBRT “results in higher local control and possibly better long-term survival than 3DCRT in stage I NSCLC”.8

This thesis addresses several aspects of SBRT delivery and treatment efficacy. It provides a comparison of outcomes using population-based studies both before and after the advent of SBRT, and contrasts SBRT with surgery in the treatment of high-risk subgroups of patients. It reviews methods of delivering SBRT, and measures radiation-induced lung injury after SBRT delivery. These studies help to define the role of SBRT in the treatment of stage I NSCLC, and to refine treatment techniques to minimize toxicity.

Despite ongoing research, SBRT is still a relatively new technique and several major unanswered questions remain. Comparisons of efficacy between surgery, SBRT, and 3D-conformal RT have now been addressed by a large body of literature, including cohort studies, and population studies, systematic reviews, and meta-analyses.9-12 Although such studies will continue to be presented and published in the coming years, definitive comparisons will likely only come from randomized studies, which are currently open but results are at least several years away.

The optimal SBRT dose has not yet been defined. A phase I trial established the maximum safe doses to be delivered in 3 fractions: for T1 tumors, 60 Gy in 3 fractions was the maximum dose studied and was safe; for T2 tumors, dose-limiting toxicity was found at 72 Gy, with 3/5 patients at that dose level experiencing grade 3 or higher toxicity, and the maximum tolerated dose was set at 66 Gy for T2 tumors.13 It is clear that patients who are treated with doses in excess of a biologically effective dose (BED) of 100 Gy have better local control,10,11 but there is considerable uncertainty around that estimate for several reasons: first, the linear-quadratic formula used to calculate BED has been criticized as inaccurate for SBRT;14 secondly, whether an absolute threshold exists at 100 Gy, as opposed to a linear or logistic dose-response curve, is unclear; and thirdly, considerable variation in prescribing practices makes comparisons of dosing very difficult. Some centers prescribe to the isocenter (center of the tumor), while most do not, resulting in substantial variation in doses delivered to the entire target volume (Figure 1).11,15,16
Figure 1. Variation in treatment plans after a prescription of 60 Gy, depending on the prescription point. The plan on the left delivers the lowest equivalent dose, and the plan on the right delivers the highest equivalent dose.

Toxicity from SBRT depends on tumor size, location, and dose fractionation.\textsuperscript{17,18} In 2003, the VUmc adopted a ‘risk-adapted’ strategy, where the prescription dose is selected based on the risk of complications. In situations with the lowest risk of normal tissue toxicity (small tumors surrounded by lung parenchyma), 60 Gy was delivered in 3 fractions. As risk of toxicity increased, due to larger tumor size or proximity to the chest wall, more fractions were used (60 Gy in 5 fractions). In cases with the highest risk of toxicity, with tumors in close proximity to mediastinal structures or brachial plexus, 60 Gy in 8 fractions was used.\textsuperscript{19} Doses were prescribed to an isodose line encompassing the target (center panel in Figure 1). Results have been excellent with long-term follow-up, with a 3-year local control rate of 89%, a favourable toxicity profile, and no clinically significant adverse effect on health-related quality of life scores.\textsuperscript{20}
The question of optimal SBRT dosing is being addressed in two multicenter randomized trials, both organized by the Radiation Therapy Oncology Group. RTOG 0915 is a randomized trial comparing two different fractionation schemes: 34 Gy in a single fraction vs. 48 Gy in 4 fractions. It is expected that subsequent to RTOG 0915, a follow-up trial will compare the preferred arm from RTOG 0915 study with a dose of 60 Gy in 3 fractions. RTOG 0813 is a phase I trial assessing the optimal dose for treatment of central tumors in 5 fractions. The study began at a dose level of 50 Gy in 5 fractions and has now escalated to a dose of 55 Gy in 5 fractions. These studies will provide important data to improve our understanding of SBRT dosing and normal tissue toxicity.

SBRT has now been extended for use in larger tumors, in situations where patients are not candidates for surgery or chemo-radiation therapy. For such patients, no other radical-intent option is available, and a larger risk of toxicity may be acceptable in an attempt at cure. However, as tumor size increases, the risk of pneumonitis increases, in excess of 20%. For tumors <5 cm, the risk of treatment-related death is estimated at 0.7%, but with larger tumors this risk may be higher. Reliable normal tissue constraints are being increasingly reported to help guide treatment planning. However, with all hypofractionated radiation schedules, long-term follow-up is crucial to detect late side effects. Further studies are required to determine if large tumors are better treated with concurrent chemo-radiation at standard doses (e.g. 60-66 Gy in 2 Gy per fraction) or with SBRT. Furthermore, the feasibility of combining SBRT with systemic agents is largely untested.

Quality assurance is an integral aspect of radiation treatment and delivery, to ensure patient safety and confirm treatment precision. Image-guided radiotherapy is complex and challenging, and with large doses per fraction, even small errors can result in serious harm or death. Consensus guidelines for implementation of an SBRT program are available, and successful quality assurance programs can detect small differences between centers, allowing for correction of errors and standardization of protocols, ultimately to improve patient care.
Decision-Making in the Era of Evidence-Based Medicine

As the body of evidence for the efficacy of SBRT grows larger, physicians and administrators must decide how to incorporate new data into clinical practice. Physicians tend to over-interpret anecdotal experiences from individual patients while under-applying evidence from high-quality studies.\textsuperscript{31}

Evidence-based medicine (EBM) has been defined as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients”.\textsuperscript{32} For each individual clinical decision, EBM attempts to combine two factors: clinical expertise and the best available evidence from research, in order to arrive at an optimal treatment recommendation. Either of these two factors alone is insufficient for optimal decision making. Relying on clinical expertise alone results in risks of out-of-date practices and decision-making driven by anecdotes; conversely, relying on research evidence alone can paralyze medical decision making if evidence is not applicable to an individual patient.\textsuperscript{32,33}

Although randomized trials are considered the gold-standard of evidence, EBM is not limited to randomized controlled trials (RCTs) and meta-analyses.\textsuperscript{32} For several reasons, clinicians cannot rely on RCTs alone: some questions are not amenable to RCTs, randomization may be unethical, RCTs may not be feasible or funded, patient decisions cannot be deferred for years until RCTs are complete, and RCTs may not be generalizable due to strict patient enrolment criteria. When RCT data is available, it should be incorporated into clinical practice, but when it is not available, clinicians must turn to other sources of evidence.\textsuperscript{32,33}

In order to assist physicians in decision-making and study design, the U.S. National Cancer Institute provides a hierarchy of evidence strength based on two factors: study design and endpoint (Figure 3).\textsuperscript{34} The strongest type of study design is the RCT, preferably double-blinded, or meta-analyses of RCTs. Although meta-analyses increase statistical power, they are limited by the heterogeneity and flaws of individual studies. Meta-analyses do not always agree with large RCTs that are subsequently done, and two separate meta-analyses on the same topic may lead to contradictory results.\textsuperscript{35} The second-strongest type of study design is a controlled trial allocating patients to treatment based on non-randomized factors, such as birth date or chart number, but such studies are rare.
In the absence of such controlled trials, physicians must look to other sources of evidence, and population-based consecutive series are the next-strongest study design. Population-based studies usually include an entire population within a geographically defined region, and have several advantages: they report real-world outcomes, and they have the best external validity (i.e. they are the most generalizable type of study).³⁶

The role of SBRT in the treatment of stage I NSCLC is currently being investigated in several RCTs, some comparing SBRT against surgery (including the ROSEL study in the Netherlands ³⁷), and others answering dose-related questions.¹⁵ These RCTs, if completed, will answer some key questions about SBRT, but answers are several years away, and not all questions can be asked in an RCT setting. In the absence of level 1 evidence, physicians will rely on population based data and other well-designed cohort data to define the role and applicability of SBRT, and to develop SBRT technology while reducing toxicity. The lack of evidence from
randomized studies must be noted, but does not preclude informed evidence-based decision making.

Conclusions

SBRT has changed the treatment paradigm for stage I NSCLC. Based on advances in treatment planning and delivery, SBRT safely delivers doses that would have once been considered excessive, and achieves outcomes that would have been considered unattainable for radiotherapy. In the process, some previously held theories underlying radiation fractionation, cell killing, normal tissue tolerance, and radiotherapy delivery have been challenged and subsequently redefined.

SBRT results in excellent rates of tumor control. In some situations, SBRT appears to be preferable to surgery, especially in patients with high risk disease, based on non-randomized data. At the population level, the introduction of SBRT leads to increased treatment utilization and improved survival. At the individual patient level, SBRT results in low rates of complications and a favourable toxicity profile. A detailed understanding of normal CT changes after SBRT is important, since these changes evolve over time, even years after treatment. Ongoing research will continue to refine and expand the use of SBRT, with the ultimate goal of further improving outcomes for patients with lung cancer.

References


30. Hurkmans CW, van Lieshout M, Schuring D, et al: Quality Assurance of 4D-CT Scan Techniques in Multicenter Phase III Trial of Surgery Versus Stereotactic Radiotherapy (Radiosurgery Or Surgery for operable Early stage (Stage 1A) non-small-cell Lung cancer


