Dr. Herbst reviewed the 10-year journey of lung cancer treatment from Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) to immunotherapy. The BATTLE trials were the first completed prospective, adaptively randomized studies in heavily pretreated non-small cell lung cancer (NSCLC) patients. It mandated tumour profiling with ‘real-time’ biopsies, taking a substantial step toward realizing personalized lung cancer therapy by integrating molecular findings into the delineation of specific patient populations for individualized treatment.

Dr. Herbst highlighted one of the most significant recent developments in the management of advanced NSCLC: immunotherapy. In cancer, the programmed death 1 (PD-1) receptor expressed on activated T cells is engaged by the tumour-expressed PD-1 ligand, PD-L1, to downregulate T-cell activation and promote tumour immune escape. The PD-1 immune checkpoint inhibitor antibodies, nivolumab and pembrolizumab, disrupt PD-1 mediated signaling, restoring antitumour immunity. Dr. Herbst traced the growing evidence around the effectiveness of these therapies.

In the phase III study, CheckMate 057, PD-L1 unselected patients with advanced nonsquamous NSCLC failing platinum-doublet chemotherapy were randomized to nivolumab or standard of care, docetaxel. The primary endpoint of the study, overall survival (OS), was positive for nivolumab, 12.2 months compared to 9.4 months with docetaxel (p=0.0015). The safety profile proved favourable for nivolumab, with fewer grade 3–4 drug events compared to docetaxel. Similarly, in the CheckMate 017 study, which evaluated nivolumab in an unselected advanced squamous cell carcinoma population, nivolumab had a survival benefit compared to docetaxel: 9.2 vs 6 months (p=0.00025).

Pembrolizumab has also demonstrated superior outcomes compared to docetaxel after platinum-based chemotherapy in advanced PD-L1-positive NSCLC. In Keynote 010, 2 different doses of pembrolizumab, 2 mg/kg and 10 mg/kg were compared to docetaxel. Again, a survival benefit was seen, with a median OS of 10.4 months, 12.7 months and 8.5 months respectively (p<0.0001). An analysis looking at the patient subgroups by PD-L1 status suggests that the magnitude of benefit may be more pronounced in patients with ≥50% expression.

From a Canadian perspective, Dr. Ellis cautioned us to pay close attention to the overall impact of drugs like nivolumab and pembrolizumab in advanced lung cancer care. Challenges in implementation include decisions regarding patient selection, determining appropriate biomarker expression and treatment cost.

Dr. Ellis noted that there is contention surrounding the importance of PD-L1 positivity and the methodology used for assessing PD-L1 status, as different screening antibodies are available. While pembrolizumab confirmed the benefit of immunotherapy in PD-L1-positive patients, the CheckMate studies suggest that it is effective in an unselected population, making it challenging to determine which patients are the best candidates for treatment.

The controversy over which patient population would derive the most benefit is heightened by the cost of the drug (e.g. calculated cost of nivolumab for a 70-kg patient: is $4110 per cycle). At $106,800 per year per patient, this has a large impact on Canadian health care.

In summary, immune checkpoint inhibition has shown overwhelmingly positive outcomes, but comes with equally significant healthcare costs. While it is an exciting addition to advanced lung cancer treatment, it is yet to be determined how this therapy will be incorporated into patient care in Canada.
outcome, increased radiotherapy dose delivered in a conventional manner did not improve outcomes, with a median OS of 19.5 months with 74 Gy compared to 28.7 months with 60 Gy. There was much speculation as to the reason for this outcome, but it suggested that more was not necessarily better. Dr. Yom pointed out that the dose-response question is not entirely answered, however, as dose-intensive, highly localized stereotactic body radiotherapy (SBRT) has demonstrated efficacy with respect to local control, as well as OS. The appropriate dose may relate to the radiotherapy technology and therapeutic ratio associated with the mode of delivery.

Dr. Yom also highlighted that in the US, with the rise of the machines, IMRT has been rapidly and widely adopted. The benefits of IMRT over conventional radiotherapy, however, have not been clearly established.

Canadian perspective: George Rodrigues, MD, FRCPC, Radiation Oncologist, University of Western University, London, Ontario

Dr. Rodrigues discussed his role in the recent American Society for Radiation Oncology (ASTRO) guidelines from a Canadian perspective. ASTRO, a panel of leading American and Canadian radiation oncologists, has issued multiple guidelines for best practice management in lung cancer. The most recent endeavor, “Definitive and adjuvant radiotherapy in locally advanced non-small cell lung cancer: ASTRO evidence-based clinical practice guideline,” summarizes treatment recommendations based on the evidence, incorporating data from the trials discussed by Dr. Yom. The guidelines indicate that, for locally advanced NSCLC managed by RT alone, the minimum dose should be 60 Gy. Dose escalation beyond 60 Gy in the context of combined modality with chemotherapy is not recommended. Finally, in combined-modality therapy, chemotherapy and radiation should ideally be given concurrently to maximize benefit. The role of ASTRO is pivotal in continued improvements in the radiotherapeutic approach to lung cancer treatment.

References

Presentation Summary: Innovation “Curve” in lung cancer surgery

Dr. Thomas D’Amico, MD, Chief, Section of General Thoracic Surgery, Vice Chair of Surgery, and Chief Medical Officer, Duke Cancer Institute

Dr. D’Amico presented the integration of innovative practices in lung cancer over a span of 2 decades. Innovations in surgical practices such as the adoption of minimally invasive thoracic surgery, video-assisted thoracoscopic surgery (VATS), robotics and nonintubated surgeries provide a range of possible surgical options. However, innovative practice has a long lag time to adoption and implementation in general practice. Dr. D’Amico proposes that, to some degree, surgeons overestimate the benefit of current or old procedures; some lack belief in the need for innovation, while others fear the difficulty of learning new skill sets and embracing them in their practice.

To illustrate his point, he used the Rogers Adoption of Innovation Curve, where adoption of newer practices ranges among innovators, early adopters, early majority, late majority and laggards. Innovators typically represent only a small fraction of the population and are responsible for driving the adoption of innovation against the status quo.

To illustrate his point, he uses VATS lobectomy as an example of innovation and compares it to open thoracotomy. He reports the advantages over thoracotomy: less postoperative pain, shorter chest tube duration, shorter hospital stay, faster return to full activity, preservation of pulmonary function, lower inflammatory cytokine response and lower cost. Yan et al published a review on the safety and efficacy of VATS lobectomy compared to open lobectomy and found there was no significant difference in locoregional recurrence (P=0.24) and improved 5-year mortality rate (P=0.04). While the adoption of VATS lobectomy has been slow, the proportion of patients continues to increase with time, and it has become part of the accepted standard of care.

Dr. D’Amico suggests that the mechanism of advancement rests in the hands of the surgeons where innovations in practice, such as incorporation of VATS lobectomy, have forever changed the landscape of surgical oncology and continue to push the boundaries.