Management and Treatment of Lung Cancer

While lung cancer was a rare disease at the start of the 20th century, today it represents one of the most common cancers worldwide. Lung cancer is the second most commonly diagnosed cancer in Ireland, with over 2,300 cases per year. It is also our leading cause of cancer mortality, accounting for 20% of all cancer deaths.

Encouragingly however, notable achievements have been made in lung cancer care in the last number of years. Firstly rapid access services have achieved efficiencies and improvements in lung cancer detection and staging. Lung cancer has rapidly become a leading model for personalised cancer medicine with a detailed understanding of its molecular pathogenesis and consequently the development of precise, targeted molecular and immuno-therapies improving survival, with 5 new drugs approved by the FDA in the last year alone.

Improvements in the delivery of lung cancer care have been achieved through earlier diagnosis, with online referrals, rapid access to diagnostic and minimally invasive staging procedures, such as Endobronchial Ultrasound (EBUS) for accurate assessment of mediastinal lymph nodes, and the provision of coordinated care by a multidisciplinary team (MDT) of specialists who care for a significant number of patients with lung cancer on a regular basis.

The standard therapy for patients with early stage lung cancer is surgical resection, which offers the best chance of cure. Many patients presenting with small tumours have significant co-morbidities however, particularly co-existing COPD that may have previously deemed them inoperable.

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While the high incidence and mortality of this disease has thankfully declined somewhat in recent years in men, they are worryingly increasing in women. This new trend is attributable to societal changes in cigarette smoking over the past 30 years and underlines the importance of providing concerted action to address smoking cessation and prevention efforts to women in particular. Other risk factors for lung cancer include exposure to radon gas (particularly relevant in Ireland), asbestos, diesel exhaust and air pollution, COPD, pulmonary fibrosis, and immune suppression. These risk factors are common in patients seen in a respiratory practice, and so respiratory physicians have a unique opportunity in recognising and facilitating the early diagnosis of this disease.

While lung cancer kills more Irish people every year than breast and colon cancer combined it rather perversely receives far less attention, possibly due to its strong association with high deprivation indices and social stigma. Slow improvements in 5-year survival figures for patients with lung cancer in Ireland have been achieved over the last decade according to the most recent data from the National Cancer Registry but still remain only just above 13%. By comparison, the survival for bowel cancer in Ireland, a disease that affects patients with a similar age profile is almost 60%.

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Lung cancer screening using low-dose CT has shown to be effective in reducing lung
cancer mortality with ongoing efforts worldwide to improve its affordability. Academically, thoracic oncology is now a distinct assembly of the European Respiratory & the American Thoracic Society, with high quality research regularly published in major peer review journals. Closer to home, attendance rates and output at the British Thoracic Oncology Group (BTOG) annual meeting in Dublin increase year on year. Lung cancer therefore is a rapidly evolving, increasingly specialized area and there are reasons for optimism for lung cancer specialists and patients alike.

**ORGANISATION OF CARE**

Improvements in the delivery of lung cancer care have been achieved through earlier diagnosis, with online referrals, rapid access to diagnostic and minimally invasive staging procedures, such as Endobronchial Ultrasound (EBUS) for accurate assessment of mediastinal lymph nodes, and the provision of coordinated care by a multidisciplinary team (MDT) of specialists who care for a significant number of patients with lung cancer on a regular basis. Modern multidisciplinary management leads to more efficient use of scarce resources, better quality of life and improved survival.

Respiratory physicians have an important role in this team leadership, as they are most frequently involved with patients from their initial diagnosis and staging through treatment and restaging. They are subsequently often involved with complications, the palliation of symptoms and end-of-life care. There are also societal efforts for a greater involvement of respiratory physicians in lung cancer research, given the rapid advances in the understanding of its tumour biology.

The National Cancer Control Programme (NCCP) was established in 2007 to manage, organise and deliver cancer services in Ireland. Lung cancer has been a key area of focus of the NCCP, which supports Rapid Access Diagnostic Clinics in each of the eight designated cancer centres. These clinics are run by Respiratory physicians who are referred patients with abnormal chest imaging or haemoptysis. The Rapid Access clinic serves as a conduit to the lung cancer MDT and the four designated surgical lung cancer centres in Cork University Hospital, Galway University Hospital, and St James’s and the Mater hospitals in Dublin. The work of lung cancer specialist nurse coordinators in each centre has facilitated this integration and enhanced the patient’s journey through the service. In 2015 over 3,000 new patients were seen at Rapid Access Lung Cancer Clinics in Ireland with a case find rate of almost 30%.

The NCCP role also includes collection and reporting of Key Performance Indicators (KPIs) across a number of areas including: Access to care, Multidisciplinary working, Time to Diagnosis and Time to treatment. An annual Irish National Lung Cancer Quality and Audit meeting has been held since 2013 and provides a forum for the purpose of clinical audit, sharing of good practice and problem solving into the future. A key challenge will be continuing to provide prompt access to cancer services and diagnostics and advocacy for more resources for service improvement and research.

**EARLY STAGE LUNG CANCER**

The standard therapy for patients with early stage lung cancer is surgical resection, which offers the best chance of
cure. Many patients presenting with small tumours have significant co-morbidities however, particularly co-existing COPD that may have previously deemed them inoperable. Advances in surgical techniques including less invasive procedures e.g. Video-assisted thoracoscopic (VATS)-lobectomy and sub-anatomic resection for smaller tumours, together with the increasing evidence for efficacy of stereotactic radiotherapy (SBRT) have broadened the therapeutic options available to the MDT when planning treatment.

ADVANCED LUNG CANCER - TARGETED THERAPIES:

Up until recently the role of the pathologist in lung cancer management was only to differentiate small cell from non-small cell lung cancer (NSCLC). Platinum-doublet based chemotherapy was the standard of care for advanced disease and the treatment for all forms of NSCLC was the same. However with the advent of newer therapies, more accurate histological classification was necessary via immuno-histochemical staining. This diagnostic landscape changed markedly in 2004 with the discovery of the sensitizing mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) domain. This was the first driver mutation identified in lung cancer for which a targeted therapeutic drug, gefitinib (a first generation TK inhibitor) was available. Driver mutations are mutations in genes that encode signalling proteins crucial for cell proliferation and drive tumour formation. Subsequently, these somatic mutations were identified as occurring predominantly in adenocarcinomas of the lung and more frequently in non-smokers. Tyrosine kinase inhibition has been shown to improve survival in lung cancer patients harbouring an EGFR mutation compared to conventional chemotherapy and newer generation TKI’s can now also target evolving resistance patterns providing patients with prolonged disease control.

Rarer driver mutations have also been identified; a transforming echinoderm microtubule-associated protein like (EML) 4-anaplastic lymphoma kinase (ALK) gene fusion and more recently ROS-1 rearrangements. The ALK rearrangements constitute about 5% of all non-small cell lung cancers and have also been shown to occur predominantly in lung adenocarcinomas. Crizotinib, the first in class oral inhibitor of ALK and ROS-1 is associated with superior response rates and significant improvements in quality of life compared to chemotherapy in patients harbouring these re-arrangements.

The understanding of the impact of the molecular classification of lung cancer and the advent of targeted therapies has further enhanced the role of the pathologist in lung cancer management. As a result of a more precise classification of a patient’s lung cancer, there have been significant improvements in outcomes in selected patients, and mutational analysis of lung tumours prior to consideration of systemic therapy has now become standard in clinical practice.

Immunotherapy has also recently emerged as an exciting avenue for targeted lung cancer treatment after many years of failure. Antibodies directed against negative immunologic regulators (checkpoints) have been developed. Blocking programmed cell death protein 1 (PD-1) and its ligand (PD-L1) restores anti-tumour T-cell activity. Phase II & Phase III studies of previously treated patients randomised to Nivolumab or Pembrolizumab have shown improved survival and more favourable toxicity profiles. Further studies investigating their use in earlier stages of NSCLC and extending their use to other thoracic malignancies such as mesothelioma and thymic carcinoma are in the pipeline.

SCREENING

The majority of new lung cancer diagnoses present later in the course of disease leading to poor outcomes. In 2011, the National Lung Screening Trial in the U.S. demonstrated a significant reduction in lung cancer mortality of 20% among a high risk group undergoing screening with low-dose CT scan of the thorax annually for 3 years compared to chest x-ray. Lung cancer screening with low-dose CT in high-risk individuals now has a grade B recommendation by the U.S. Preventative Services Task Force. Many questions remain regarding widespread implementation of lung cancer screening programs; while there will likely be a big impact on stage at detection – so called ‘stage shift’, significant concerns exist regarding health care costs (modeled recently across the Medicare population in the United States at $9.3 billion over the first 5 years) as well as the high rates of false positive findings once nodules were detected. The NELSON study the largest European lung cancer screening trial used volume doubling time (VDT) of nodules as a management strategy. This resulted in a higher positive predictive value (40.6% vs 3.6%) and a substantially lower false positive result (59.4% vs 98.4%) than in NLST, with final cost analysis eagerly awaited.
TOBACCO CONTROL

Over 90% of lung cancer in Ireland may be attributed to smoking tobacco and thus is theoretically preventable. The prevalence of smoking in Ireland remains around 19.5%, with peak prevalence of 27.3% in the 25-34 year old age group. In Ireland the incidence of lung cancer in women has been rising steadily over past three decades and is projected to increase by 141% in this group between 2010 and 2030. There is no doubt that continued efforts to curb tobacco dependence will have the largest impact in improving outcomes and should remain a priority in any multidisciplinary approach to management of lung cancer.

CONCLUSION

Lung Cancer continues to result in high mortality with profound effects on the quality of life of patients and their families. Modern multidisciplinary care, advances in diagnostics and therapies, together with targeted treatments for advanced lung cancer are evolving rapidly. Screening of high-risk individuals with low-dose CT scan will emerge further in the coming years and will become more cost-effective. So there is cause for optimism for this disease and greater advocacy and research on our part will only help to further advance our drive for better outcomes.

Over a third of Irish adults who are currently experiencing three or more symptoms of lung cancer are unconcerned about being diagnosed with the disease, according to the Irish Cancer Society who launched new research around the Irish public at the start of the year. According to this research, the disease with just over a half of Irish adults unable to identify lung cancer as the leading cancer killer and a third of the public with three or more symptoms unconcerned about being diagnosed with lung cancer.

Despite this ambivalence to lung cancer, the disease continues to increase with 2,312 people diagnosed in Ireland in 2012. While the incidence in men is decreasing every year by one per cent, lung cancer in women continues to increase at a significant rate of two per cent each year.

For the first time, lung cancer has now moved from 3rd place to 2nd place ahead of colorectal cancer when it comes to the most common cancers in Irish women*. The majority of lung cancer patients are also diagnosed at a later stage when there may be fewer treatment options available. Between 2004 to 2008, 64 per cent of lung cancer patients were diagnosed at an advanced stage (stage three or stage four lung cancer)**.

Lung cancer is also the leading cause of cancer death in both men and women comprising 18% of cancer deaths in women and 23% of cancer deaths in men during the period 2011-2012*. Kevin O’Hagan, Cancer Prevention Manager at the Irish Cancer Society said, “Lung health needs to be taken seriously – we need Irish people to start talking about it and to consider it important enough to take action. Lung cancer can be treated once it is diagnosed at an early stage but unfortunately too many people don’t go to their doctor at a time when it would be most beneficial for them. We need doctors and pharmacists to keep lung cancer front of mind and to encourage their patients to maintain good lung health.

When it comes to lung cancer, awareness and early detection are the key to survival.” The Irish Cancer Society, developed an Online Lung Health Checker to help the public find out if their lungs are in a healthy condition. The Online Lung Health Checker also provides users with a printable letter which they can bring along to their doctor to help explain any symptoms. O’Hagan continued: “We are inviting members of the public to take our Online Lung Health Checker which is available on our website and to encourage friends and family to do the same.

“This will help you consider your lung health and to examine symptoms you may be experiencing. We want Irish people to take action and this is a simple way to do so.”

The Irish Cancer Society is reminding the public to get to know the signs and symptoms of lung cancer and to act quickly. With early detection, patients can have more effective treatment options and potential cures available to them. All patients can now be fast tracked through to early diagnosis and treatment through the Lung Cancer Rapid Access Clinics which are in operation in all eight of the designated cancer centres. This has resulted in a steady improvement in lung cancer survival from 10 per cent to 15 per cent over the last 15 years.