

Thoracic surgery multidisciplinary team; Thoracic Symposium

Kastelik JA MD¹, Brown V², Tentzeris V³, Gooseman M³, Lind M², Hatcliffe S², Barton R², Hearne H¹, Tariq K¹, Qadri S³

1. Department of Respiratory Medicine, Hull University Teaching Hospitals NHS Trust, University of Hull and Hull York Medical School, Castle Hill Hospital, Castle Road, Cottingham, East Yorkshire HU16 5JQ, UK
2. Department of Oncology, Castle Hill Hospital, Hull University Teaching Hospitals NHS Trust, University of Hull and Hull York Medical School, UK
3. Department of Cardiothoracic Surgery, Castle Hill Hospital, Hull University Teaching Hospitals NHS Trust, University of Hull and Hull York Medical School, UK

Corresponding Author:

Professor Jack Kastelik: jack.kastelik@nhs.net

Thoracic surgery has evolved over the recent years. A significant part of thoracic surgeons work involves working as part of multidisciplinary team, which includes respiratory physicians, radiologists, pathologists, specialist nurses and oncologists. A proportion of surgical work involves thoracic oncological work for patients with pulmonary or pleural malignancy. However, there has always been a need for non-malignant thoracic surgery. One such example is thoracic surgery to advance emphysema services. Chronic Obstructive Pulmonary Disease (COPD) or emphysema is a very common respiratory disorder ⁽¹⁾. Globally, we are observing a significant rise in Emphysema suffering patients ^(1,2). In addition, there is evidence that there is a shift of the disease from the 6-7th decade of life towards much younger patients in their 30s. This may reflect the trends related to increased popularity of vaping and cannabis abuse ⁽²⁾. There is a proportion of patients with COPD that have a pattern of hyperinflation that may benefit from lung volume reduction. The selection of patients for lung volume reduction requires a careful assessment. Firstly, they would require to have optimisation of the therapeutic interventions including smoking cessation and pharmacological therapies, as well as non-pharmacological interventions, such as pulmonary

rehabilitation. The patients are managed through a comprehensive emphysema service ⁽³⁾. A designated advanced COPD multidisciplinary team meeting forms an important aspect of the services. The advanced COPD multidisciplinary team is composed of respiratory physicians, thoracic surgeons, radiologists, physiotherapists and specialist respiratory COPD nurses. The patients undergo physiological assessment including detailed lung function, which allows to assess the hyperinflation as well as transfer factor and 6 minute walk. Lung volume reduction could be undertaken using bronchoscopy approach as well as surgical approach ⁽⁵⁻⁷⁾. In 2018, the Thoracic Surgery Department in our institution established a comprehensive treatment for Emphysema, thorough a dedicated Emphysema service and a Multi Disciplinary Team (MDT) meeting. The catchment area of our services is not limited to Hull, but also extends from Scarborough, York and Goole to Scunthorpe, Lincoln and Grimsby covering a population of around 1.2 million. Our centre also accepts referrals from outside our catchment area. The respiratory and thoracic surgery department invested in this service and apart from transplantation are offering a comprehensive array of procedures including minimally invasive video assisted surgery, robotic surgery and endobronchial implantation of valves. Our advanced experience is recognised nationally. We are the 5th largest centre in UK, out of a total of 24 centres. Our centre is involved in the national trials that will shape the evolution of Surgical emphysema treatment. The patients without interlobar collateral ventilation and mainly upper lobe distribution of emphysema, could be considered for bronchoscopic lung volume reduction, which utilises endobronchial valves ^(5, 6). The studies showed that that these procedures can result in improvement lung function, breathless and exercise tolerance ^(5, 6). In patients with collateral interlobar ventilation there is an option of

lung volume surgery, which again was shown to improve physiological parameters, dyspnoea and walking distance ⁽⁷⁾.

Pulmonary and pleural malignancies are common. In the UK there are approximately 39,000 people diagnosed with lung cancer every year ^(8 9). The mortality rates for malignant mesothelioma are still significant with reports suggesting mortality of 4.9 per million ⁽¹⁰⁾. Data suggests that 10% of lung cancers are of small cell subtype and approximately 90% are non-small cell subtype, which can be further subdivided into adenocarcinoma (36%), squamous carcinoma (22%), not pathologically confirmed (31%) and others, including large cell carcinoma (11%) and carcinoid (1.5%) ⁽¹⁰⁾. There are four histological types of mesothelioma including epithelioid (60%), sarcomatoid (10-15%), biphasic (25-30%) and the rare desmoplastic ⁽¹¹⁾.

The treatment of non-small cell lung cancer (NSCLC) depends upon cancer stage, and patient-specific factors (pulmonary function, comorbidities and performance status). The usual recommended treatment in fit patients with early-stage NSCLC is surgical resection ⁽¹⁰⁾. For patients who are unwilling to undergo surgery and those who are considered high risk for operative complications, curative radiotherapy (RT) using radical RT or stereotactic body RT (SABR) are alternatives, with the latter suitable for peripherally smaller cancers ^(10 12). Multimodality treatment is considered optimal treatment for stage II to III NSCLC with surgery or radiotherapy targeting the visible disease to reduce local recurrence and systemic anticancer treatment (SACT) treating occult micro-metastatic disease with the aim to prevent distant recurrence ⁽¹³⁾. Even despite aiming for curative intent most patients with NSCLC will

experience recurrence with a 5-year survival of around 65% for localized disease and reducing to 6.9% in advanced stage [\(14\)](#). In recent years there have been significant advances in new SACT treatments including targeted therapies and immune checkpoint inhibitors (ICI) in both the curative and non-curative settings [\(15\)](#). Currently in the curative operative setting SACT is administered as neoadjuvant (preoperative), adjuvant (post-surgery) or as perioperative (neoadjuvant and adjuvant) treatment. It can be given concurrently alongside radiotherapy or after completion of radiotherapy treatment (adjuvant). Where cure is not possible such as in advanced disease, SACT can be used to try and extend survival and improve cancer related symptoms. SACT requires careful consideration of the risks versus benefit for each patient.

International guidelines such as ESMO (European Society for Medical Oncology) recommend broad molecular profiling in patients with NSCLC to identify driver alterations to guide SACT treatment decision [\(16\)](#). Around 50% of patients with advanced NSCLC are found to have an actionable oncogenic driver mutation [\(17\)](#). Profiling has traditionally been carried out on cancer biopsy tissue but can now be carried out as a liquid biopsy on plasma samples (circulating tumour DNA) [\(18\)](#). The specific molecular aberrations where National Institute for Health and Excellence (NICE) has approved drugs include EGFR, ALK, KRAS, BRAF, ROS 1, NTRK1/2, METex14 skipping, and RET [\(19\)](#). Future biomarkers include human epidermal growth factor 2 (HER 2) and neuregulin 1 (NRG1) [\(20\)](#).

Alterations in the gene encoding epidermal growth factor receptor (EGFR) are among the most frequent activating mutations in NSCLC [\(21\)](#). Mutations of EGFR are detected in about 15

-20% of NSCLC, mostly of adenocarcinoma histology, and predominantly in non-smokers, women and those of Asian ethnicity [\(21\)](#). The most common alterations are deletions in exon 19 and point mutation in exon 21 (L858R) which make up around 90% of the EGFR alterations in NSCLC leading to activation of the tyrosine kinase domain [\(21\)](#). Osimertinib is a third-generation oral tyrosine kinase inhibitor (TKI) and recommended by NICE in patients with advanced NSCLC with common mutations based on the data from the Flaura trials [\(19 22 23\)](#). Flaura, a phase 3 trial compared Osimertinib to 1st generation TKI's and showed a median overall survival (OS) benefit with Osimertinib (38.6 vs 31.8 months) and with a favourable toxicity profile [\(22\)](#). Flaura 2 compared Osimertinib with Osimertinib plus chemotherapy and showed the addition of chemotherapy prolonged OS (47.5 months versus 37.6 months with Osimertinib alone) [\(23\)](#). The addition of chemotherapy led to increased grade 3 reported side effects. Amivantamab is an EGFR mesenchymal - epithelial transition factor (MET) bispecific antibody and Lazertinib is a selective third-generation EGFR-TKI. MARIPOSA, a phase 3 trial in advanced NSCLC randomised patients to receive Amivantamab - Lazertinib combination, or Osimertinib alone [\(24\)](#). The results showed a significantly longer median progression-free survival (PFS) in the Amivantamab - Lazertinib combination group compared to Osimertinib alone (23.7 vs. 16.6 months), however median OS has not yet been reached. Adverse events of grade 3 or higher were more common with combination treatment (skin - related events, venous thromboembolism, and infusion-related events). The combination of Amivantamab - Lazertinib is currently being reviewed by NICE [\(19\)](#). Osimertinib as a single agent is still a reasonable choice for many patients with common EGFR mutations due to its favourable

toxicity profile. Osimertinib is NICE approved in patients with resected stage 1b to 3a NSCLC after complete tumour resection (with or without prior adjuvant chemotherapy) [\(19, 25\)](#).

Fusions (rearrangements) involving ALK, ROS1, NTRK1-3 and RET genes are important oncogenic drivers in lung adenocarcinomas. Anaplastic lymphoma kinase (ALK) gene rearrangements are found in approximately 3% to 5% of NSCLC cancers [\(26\)](#). Cancers that contain ALK fusion oncogenes or its variants are associated with never - or light-smoking history and younger age [\(26\)](#). Initial studies showed that ALK inhibitors Crizotinib and Ceritinib were more effective than chemotherapy in advanced disease [\(27\)](#). Alecitinib and very recently Lorlatinib are both recommended options as a first line treatment by NICE based on superior 5-year survival benefits and compared to Crizotinib [\(19, 28\)](#). Alectinib is NICE approved for use in the adjuvant setting post-surgical resection in stage 1B to 3A [\(19, 29\)](#).

Cancer cells frequently reduce the expression of immune surveillance-related proteins, shielding them from the host's protective immune responses. Activated T cells carry a receptor called the programmed cell death-1 (PD-1) protein which helps to regulate immune responses [\(30\)](#). Its counterpart, PD-L1, is found in both immune and cancer cells and the interplay between the PD-1/PD-L1 pathways plays a critical role in enabling cancers to evade the immune system. When this interaction is blocked, there is reactivation of T cell-mediated anticancer immunity [\(31\)](#). Immune checkpoint inhibitors (ICIs) have transformed the therapeutic landscape of advanced NSCLC and has significantly improved clinical outcomes. Immunotherapy drugs currently approved by NICE in NSCLC include Atezolizumab,

Pembrolizumab and Nivolumab ⁽¹⁹⁾. The benefit of ICI in NSCLC was first seen in several clinical trials in advanced NSCLC in the second line setting after progression on first line platinum chemotherapy where Nivolumab, Atezolizumab and Pembrolizumab were each compared to chemotherapy ^(32 33). Subsequently phase III clinical trials in the first line setting showed an improvement in OS with ICI or ICI plus platinum-based chemotherapy compared to chemotherapy in advanced NSCLC ^(34 35). ICI has led to durable survival benefits for example, KEYNOTE-024 trial comparing Pembrolizumab with chemotherapy as first-line treatment harbouring PD-L1 expression of $\geq 50\%$ demonstrated 5-year OS of 32% ⁽³⁶⁾.

The choice of treatment (ICI alone or with chemotherapy) in clinical practice is largely determined by PD-L1 expression and burden of disease ⁽³⁷⁾. Commonly used expression thresholds to identify patients who may benefit from immune checkpoint inhibitors include 1% and 50% of tumour cells. However, PD-L1 expression is considered an "imperfect" biomarker as patients with high expression do not always benefit from immunotherapy and patients with low expression occasionally benefit. Nevertheless, PD-L1 is currently the only robust predictor of immunotherapy response and remains a useful guide in clinical decision making. International and National Guidelines recommend ICI plus chemotherapy as the preferred first - line option in patients with PD-L1 $< 50\%$ in both squamous and non-squamous lung cancers ^(16 19). Based on ICI - chemotherapy combinations consistently providing the most robust clinical benefit across OS and progression free survival endpoints in clinical trials in the absence of high PD-L1 expression. ICI monotherapy is effective primarily in patients with PD-L1 $\geq 50\%$ cancers ^(16 19). The role of ICI's in oncogene-driven NSCLC

remains unclear, as most trials excluded patients with established oncogenic mutations. In addition, mutations of EGFR, ALK, KRAS, MET exon 14 skipping mutation, and RET have been shown to confer a poor benefit from immunotherapy ⁽³⁸⁾.

The first trial demonstrating a survival benefit from immunotherapy in non-metastatic NSCLC was the PACIFIC trial, which randomly assigned patients with unresectable stage III NSCLC (AJCC v 7), including those who had completed chemoradiotherapy with neither progression nor decline in performance status to Durvalumab vs. placebo ⁽³⁹⁾. Durvalumab showed superior median OS (44.6 months versus 21.3 months). In patients who received Durvalumab, there was a significantly longer survival in patients with PD-L1 $\geq 50\%$ vs PDL1 $< 1\%$ (hazard ratio = 0.24; $p < 0.001$). Recently ICI has established a role as multimodality treatment for resectable NSCLC. Pembrolizumab and Atezolizumab are both NICE approved in the adjuvant setting post-surgical resection and after completion of adjuvant chemotherapy ⁽¹⁹⁾. Adjuvant Atezolizumab in stage II and III NSCLC after adjuvant platinum chemotherapy, led to a 5-year OS rate which was similar to best supportive care at a median follow up of 65 months (70% versus 69%) ⁽⁴⁰⁾. However, in prespecified subgroups, OS was improved with ICI in patients with PD-L1 $\geq 50\%$ (83% versus 65%), and there was a nonsignificant trend towards improvement in those with PDL1 $\geq 1\%$ (75% versus 66%) however OS results remain immature. In the PEARLS/KEYNOTE-091 trial (stage IB to IIIA) Pembrolizumab showed a non-significant trend towards improvement in Disease Free Survival (DFS) in those with PD-L1 $\geq 50\%$ ⁽⁴¹⁾.

ICI's is also utilised in the neoadjuvant and perioperative settings with more evidence of benefit emerging [\(42\)](#). In surgically resectable NSCLC, NICE has approved neoadjuvant chemotherapy-ICI combination and also a perioperative approach with neoadjuvant chemotherapy-ICI followed by adjuvant ICI post op [\(43, 44\)](#). There can be challenges in the selection of the optimal perioperative treatment with the range of choices including preoperative, perioperative or a postoperative approach [\(45\)](#). Surgery alone is curative in some patients, therefore any significant toxicity from anticancer agents which prevent surgery being performed is a major concern. CheckMate 816 trial showed that neoadjuvant Nivolumab plus chemotherapy significantly improved OS in patients with resectable NSCLC compared with chemotherapy alone (5-year OS 65.4% versus 55.0%) [\(46\)](#). Survival was greatest in those with a pathological complete response (95.3% versus 55.7%) compared to those without such a response. KEYNOTE-671 trial compared neoadjuvant Pembrolizumab plus chemotherapy followed by resection and adjuvant Pembrolizumab to neoadjuvant chemotherapy alone [\(47\)](#). The trial showed the former led to a significantly improved Event-Free Survival (EFS), major pathological response (30.2% versus 11.0%) and pathological complete response (18.1% versus 4.0%) [\(47\)](#). Several meta-analyses have shown that neoadjuvant immunotherapy is safe and effective in advanced resectable NSCLC, and data from trials such as NADIM, NEOSTAR, and SAKK 16/14 have been analysed. These meta-analyses included only RCTs or retrospective studies up to 2021, and only pCR, MPR, resection rates, and complications were discussed. There were large studies such as KEYNOTE-671, CheckMate816, CheckMate-77T [\(42, 48-55\)](#).

Immunotherapy is an option for the management in unresectable malignant pleural mesothelioma (MPM) and is NICE approved [\(56\)](#). Checkmate 743, a phase 3 randomised clinical trial assessed immunotherapy (Nivolumab/Ipilimumab) compared to chemotherapy (Platinum/Pemetrexed) and showed an improved OS with the use of immunotherapy (18.1 versus 14.1 months), with those with epithelioid MPM (18.7 vs 16.5 months) and non-epithelioid MPM (18.1 vs 8.8 months) (57,58). Chemotherapy (Platinum/Pemetrexed) can be considered as a 2nd line therapy [\(59\)](#). Surgery can be considered in patients with malignant mesothelioma [\(60\)](#). In selected cases, mainly those with epithelioid malignant mesothelioma, surgery may have benefits [\(60\)](#). Those patients should undergo a very careful assessment and systematic investigations, together with the decision of the multidisciplinary team, composed of respiratory physicians, histopathologists, radiologists, thoracic surgeons and oncologists. Extra-pleural pneumonectomy used to be performed in a small number of carefully selected patients due to potential issues of morbidity and impact on quality of life [\(61\)](#). For this reason, there has been change in practice towards undertaking more lung sparing procedures such as pleurectomy/decortication [\(61\)](#). A small feasibility study called MARS evaluated survival and quality of life in patients with mesothelioma randomising to extra-pleural pneumonectomy with postoperative hemithorax irradiation versus no surgery following induction chemotherapy [\(62\)](#). The study reported high morbidity associated with extra-pleural pneumonectomy and reported that 16 patients who had surgery had a median survival of 14.4 months compared with 19.5 months for those that did not undergo surgery [\(62\)](#). There are recognised limitations of this study mainly related to the small number of participants, however, the results suggested that the radical approach with extra-pleural pneumonectomy

did not offer additional benefits. For this reason, in the context of malignant mesothelioma the surgical approach is guided towards pleurectomy/decortication ⁽⁶⁰⁾. In addition, there is evidence from MesoVATS that showed no difference in survival between video-assisted thoracoscopic partial pleurectomy VAT-PP and talc pleurodesis in patient with malignant mesothelioma ^(63, 64). In order to provide best prognostic outcomes lung cancer should be diagnosed at early stages, which allows for radical options of treatment, but epidemiological data reveals that around 17% of cases are diagnosed at stage I or II ⁽⁶⁵⁾. In resectable MPM platinum/pemetrexed chemotherapy may be used as part of multimodality treatment (neoadjuvant and adjuvant setting) but the role of ICI is unclear and under exploration ⁽⁶⁶⁾.

The importance of detecting lung cancer at an early stage relates to the treatment options. The extrapolation of the data from the national audit in the UK revealed that radical radiotherapy was undertaken in 8% of lung cancer cases and surgery in around 8% of case ⁽⁶⁷⁾. The selected cancer screening has been shown to benefit early diagnosis of lung cancer. For example, The NLST trial studied a large number of high-risk group of patients and showed that low-dose CT scanning was more sensitive to compared to the chest radiography with 320 CT scans required to detect one lung cancer ⁽⁶⁸⁾. Another study: Dutch Belgian Lung Cancer Screening Trial NELSON, showed lung cancer detection rates of 0.9% with low dose CT screening and 26% reduction in lung cancer death over the 10-year period ⁽⁶⁹⁾. Similar 39% reduction in lung cancer mortality was reported in the Multicentric Italian Lung Detection (MILD) study ⁽⁷⁰⁾. The Manchester community-based Lung Health Check also showed that lung cancer screening with low dose CT detected 3% of lung cancer cases with majority being

of early stage [\(71 72\)](#). For this reason, many centres have now introduced lung cancer screening.

As the patients undergoing lung cancer screening are diagnosed with an early stages of lung cancer the role of surgical intervention remains of great importance. The most important aspect of thoracic surgery is assessment for fitness. One such tool for assessing fitness for surgery is the Thoracic Revised Cardiac Risk score (ThRCRI), that helps to stratify risks of cardiac complications and helps to estimate risks of major cardiac complications [\(73 74\)](#). From pulmonary physiology aspects with regards to fitness for lung surgery and associated mortality or morbidity are forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), which estimate the airflow and the diffusing capacity for carbon monoxide (DLCO) to measure alveolar capillary transfer [\(75 76\)](#). The calculated post-operative FEV1 of less than 40% is associate with a high risk post lung resection surgery [\(75 76\)](#). In addition, cardiopulmonary exercise testing (CPET) can be undertaken, especially in patients who may be deemed to be borderline from fitness for surgery [\(75 76\)](#). The CPET allows to perform exercise capacity and physiological parameters such as VO2 max, which is maximum oxygen consumption or maximal anaerobic capacity measures the maximum rate of oxygen consumption attainable during the exercise [\(76\)](#). The calculation of VO2 max allows to stratify the risks for patients undergoing thoracic surgery. The value of VO2 max of more than 20 ml/kg/min or more than 75% of predicted is associated with low risk even for pneumonectomy, however, VO2 max of 10 to 12 ml/kg/min or less is associated with higher

risk and should be considered other forms of treatment including stereotactic radiotherapy [\(75, 76\)](#).

It is now over 20 years since the first cases of robotic lung resection were reported and robotic assisted thoracic surgery (RATS) has become increasingly established in a complex surgical landscape. As robotic surgery adoption has increased there has been a steady collection of evidence demonstrating its benefits, including when compared to VATs in respect of decreased mortality and reduced length of hospital stay [\(77\)](#). Robotic surgery with the current technology available is able to present a number of potential technical benefits. This includes fully articulating instruments that can be manoeuvred in a similar manner to the wrist and decreased fulcrum pivoting. Combined with this is a magnified binocular high resolution vision. The advantages this provides are seen when undertaking complex and delicate dissection such as in segmentectomy, an operation considered technically more challenging than lobectomy especially when undertaken through closed chest surgery [\(78\)](#). Robotic surgery or a robot-assisted surgery is a form of minimally invasive surgery; a technique that involves the use of specialized robotic platforms during surgical procedures to improve the precision of surgery [\(77-79\)](#). The robotic surgery allows for three-dimensional views for anatomical localisation within the thorax and mediastinum with the use of instruments of easy control. In the context of thoracic surgery robotic surgery can be undertaken for robotic airway resection and sleeve resection [\(80\)](#). In addition, robotic surgery allows complex sub-lobar resection including segmentectomy, which is of particular relevance of early stage lung cancer [\(80\)](#). Robotic surgery has advantages compared with video assisted thoracic surgery or

open thoracic surgery. The main benefits of robotic surgery include better pain control, faster recovery and better anatomical access with the main disadvantages being related to the costs ⁽⁸⁰⁾. As the recovery from thoracic surgery may be complex, the application of early physiotherapy input is of importance. The application of an early physiotherapy technique may lead to faster recovery and shorter hospital stay ⁽⁷⁾. The techniques used may be related to post-operative pain control, wound support, positioning including gravity positioning to improve ventilation and clearance of bronchial secretions as well as early mobilisation ⁽⁸¹⁾.

For the patients not fit to undergo thoracic surgery for lung cancer, resection stereotactic radiotherapy remains an alternative. Stereotactic radiotherapy compared to conventional radiotherapy delivers with a high precision fewer fractions of high dose radiation per fraction ⁽⁸²⁾. As a result, there is sparing of the surrounding tissue, which minimises toxicity and local control ⁽⁸²⁾. Overall surgery offers better outcomes compared to stereotactic radiotherapy but this may be related to the characteristics of the patients as the patients undergoing stereotactic radiotherapy are less fit with a number of co-morbidities, which would preclude surgery ^(81, 82). Another role for radiotherapy is in the context of concurrent chemoradiation and Immunotherapy ⁽⁸³⁻⁸⁶⁾. Concurrent chemotherapy has been shown to improve outcomes in advanced stage III lung cancer ^(84, 85). In addition, there is evidence of the use of immunotherapy such as durvalumab as an adjuvant treatment after chemoradiotherapy ⁽⁸⁷⁾. In addition, palliative radiotherapy which uses radiation to manage symptoms is of importance in managing patients with advanced lung cancer ⁽⁸⁸⁾.

In conclusion the work of thoracic surgeon relies on the support of the multidisciplinary team.

As the management of lung cancer has become more complex, the close interactions between thoracic surgeons, chest physicians, oncologists, radiologists and specialist nurses form an integral aspect of care for patients with this disease.

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