Stage III Non-Small Cell Lung Cancer

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Stage III Non-Small Cell Lung Cancer (NSCLC) is a challenge for clinicians, patients, and their families. By contrast most patients comprehend stage IV disease is incurable, as it has metastasised to another organ with usually no curative role for surgery. Stage III or locally advanced NSCLC is a heterogenous disease which includes local occurrence confined to a single lung and may also include mediastinal (regional) lymph node metastasis. In Ireland, 26% of male and 23% of all female NSCLC are diagnosed at stage III[1]. No single treatment paradigm exists for stage III NSCLC owing to its heterogenous nature. Therefore, all treatments are possible including surgery, radiotherapy, systemic anticancer therapy (SACT) and immunotherapy,[2] most often as a hybrid of up to three modalities.

Stage III NSCLC is further sub-classified into stage IIIA, stage IIIB & stage IIIC with a 5-year overall survival (OS) of 36%, 26% and 13% respectively[3]. International guidelines recommend evaluation of each case through a multidisciplinary team (MDT)[4, 5]. The MDT comprises of expertise from respiratory medicine, medical oncology, radiation oncology, thoracic surgery, and pathology departments. This forum utilises staging as outlined in the eight edition of the NSCLC tumour, node, and metastasis (TNM) classification[3] to optimise each patient treatment plan.

Is there a role for surgery?

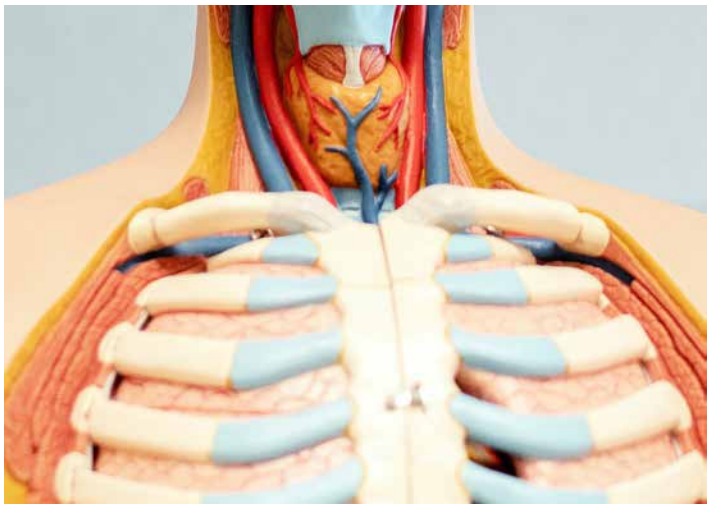
Yes, surgery is an option for some patients diagnosed with stage IIIA NSCLC and a good performance status (PS, Eastern Cooperative Oncology Group PS 0-1) where a clear resection is potentially achievable. Resectability generally refers to the following situations (i) tumour exceeding 5cm with no nodal metastasis (N0) or ipsilateral hilar or pulmonary lymphadenopathy (N1), (ii) tumour size less than 5cm with involvement of single ipsilateral mediastinal or subcarinal lymph node(N2).

As treatment is directed largely by lymph node status a positron emission tomography (PET-CT) scan is imperative to direct the site of lymph node sampling. This is typically completed by endobronchial ultrasound (EBUS), however occasionally invasive mediastinoscopy is required. A computerised tomography (CT) or ideally magnetic resonance imaging (MRI) brain scan must out rule brain metastases, prior to surgery. Patients are also counselled on the intra- and post-operative complications.

Adjuvant chemotherapy is recommended to reduce the risk of distant metastasis. The Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group was a meta-analysis of five randomised clinical trials, including 4,584 early lung cancer patients (Stage I to III) and identified a 5.4% absolute survival benefit (38% to 43.4%) in the 5-year OS following adjuvant cisplatin doublet[6]. A sub-group analysis[7] examined the benefit specifically of adjuvant cisplatin and vinorelbine (n=1,888) when compared with surgery alone and identified an improved 5-year absolute survival benefit of 8.9% (55.1% vs. 46.2%) with the greatest benefit in stage III at 14.7% (39.9% vs 25.2%)[7]. Cisplatin doublet chemotherapy is standard of care and is most frequently partnered with vinorelbine.

The Japanese multi-institutional phase III trial[8] compared adjuvant cisplatin pemetrexed with SOC, cisplatin and vinorelbine. This included 402 patients in the cisplatin-vinorelbine and cisplatin-pemetrexed cohorts, (stage II & IIIA non-squamous NSCLC). At a median follow-up time of 45.2 months there was a non-significant higher recurrence-free survival with cisplatin-pemetrexed when compared with SOC (38.9 vs 37.3 months). The investigational platinum doublet had fewer grade 3+ toxicities, including febrile neutropaenia (11.6 vs 0.3%) and anaemia (9.3 vs 2.8%), therefore is an acceptable adjuvant regimen in non-squamous cell histology.

Incomplete surgical recovery and significant comorbidities are a challenge to completion of planned adjuvant chemotherapy, and this prompted consideration of neoadjuvant chemotherapy. In addition to improved tolerability prior to surgery, neoadjuvant SACT could potentially eliminate micrometastases earlier. High completion rates of neoadjuvant chemotherapy in the NSCLC Meta-analysis Collaborative Group study were identified and included 15 randomised control trials with 2,385 patients. This identified an improvement in the 5-year OS to 45% (from 40% in the observational arm)[9]. As this is comparable with the LACE meta-analysis outcome, neo- and adjuvant SACT are acceptable options. There is no OS benefit with post-operative RT (PORT) in completely resected NSCLC and meta-analysis (albeit old studies) identified a detrimental impact based on sub-group analysis of patients with resected N0 and N1 nodal metastasis[10]. The recent Lung ART phase 3 trial concluded a similar outcome in the 3-year OS (66.5% PORT vs. 68.5% with no PORT) for stage IIIA-N2 metastasis. The PORT patients were more likely to experience grade 3–4 early toxicities than controls (11.6% vs 7.7%) and



at least one late toxicity at this severity (14.6% vs 8.9%). There was also an increased rate of late cardiopulmonary toxicity at grade 3–4 (10.8% vs 4.9%) or a second primary tumour (11.1% vs 7.2%), including second lung cancers (39.3 vs 22.2%). Therefore, the role of PORT is usually reserved for incomplete surgical resections[11].

Trimodality therapy has been explored in Stage IIIA-N2 patients, deemed initially as unresectable with the aim of converting to potentially resectable with improved OS. In the Intergroup 0139 trial[12], both cohorts received pre-operative induction chemoradiation therapy (CRT) with cisplatin & etoposide and 45Gy of thoracic RT. This was followed by either surgery (n=202) or completing RT to 61 Gy (n=194). Both cohorts received two further cycles of consolidation cisplatin and etoposide. The improved progression free survival (PFS) in the surgical group did not translate to a significantly improved median OS (23.6 months vs. 22.2 months, non-surgical). There was significantly more grade 3+ haematological and oesophageal toxicities reported in the in the non-surgical cohort.

Definitive chemoradiation

The standard of care treatment for non-resectable stage III NSCLC (including inoperable IIIA-N2, IIIB & IIIC) is concurrent chemoradiation therapy (cCRT). Stage IIIB includes (i) tumours up to 5cm and N3 lymph node metastasis (contralateral hilar and / or mediastinal lymphadenopathy, ipsilateral/ contralateral scalene and /or supraclavicular lymphadenopathy), (ii) tumours have spread to the main bronchus or visceral pleura, of any size and N2 lymph node metastasis. Stage IIIC is new in the TNM eight edition and previously was part of the stage IIIB (seventh edition) and includes tumours exceeding 5cm with N3 lymph node metastasis. The NSCLC Collaborative Group NSCLC confirmed cCRT is more efficacious than sequential chemotherapy followed by radiation confirmed therapy (sCRT). This meta-analysis[13] included 1205 patients from six trials identified an absolute 5-year OS benefit from cCRT over sCRT of 4.5% (15.1% vs 10.6%). There was almost a five-fold increase in grade 3+ oesophagitis with cCRT when compared with sCRT with no significant difference in grade 3+ pulmonary toxicities. Accordingly, sCRT is recommended for frailer patient (ECOG-PS 2) or those with significant comorbidities.

The two commonly used chemotherapy regimens for all histologies include (i) weekly carboplatin (AUC = 2) and paclitaxel (40 to 50mg/m2) for six cycles with two cycles of consolidation chemotherapy or (ii) cisplatin (50mg/m2 day 1 & 8) and etoposide (50mg/m2 day 1 to 5) for two cycles every 28-days. Both regimens included 60 – 66Gy (2Gy per fraction) of thoracic RT. A head-to-head comparison[14] of these regimens with 95 and 96 patients randomised to cisplatin & etoposide (EP) and carboplatin & paclitaxel (PC), respectively with no significant difference in the mean OS (23.3 vs 20.7 months). However, the 3-year OS was higher for EP (41%) than PC (26%), though this study was limited by small sample size and the PC arm did not include the standard two cycles of consolidation PC chemotherapy. EP was associated with significantly more grade 3+ oesophagitis (20.0% vs. 6.3%) than PC, with PC associated with significantly more grade 2+ radiation pneumonitis (33.3% vs 18.9%) than EP.

Use of platinum doublet with pemetrexed was assessed in the PROCLAIM phase III trial and included almost 600 patients (non-squamous histology). Each cCRT arms was randomised to 60 to 66Gy thoracic RT and received EP for two cycles followed by two cycles of consolidation platinum doublet or cisplatin with pemetrexed for three cycles followed by consolidation pemetrexed for four cycles[15]. The median OS for the pemetrexed regimen was not significantly higher at 26.8 months when compared with 25 months for EP. This was associated with significantly less grade 3 & 4 adverse events (64.0% vs. 76.8%) when compared with EP including less neutropenia (24.4% vs 44.5%) and represents an alternative less toxic CRT regimen for inoperable stage III NSCLC (non-squamous).

Immunotherapy

Pre-clinical data suggested (chemo)radiotherapy may up regulate programmed death ligand 1 (PD-L1) expression on tumour cells. Durvalumab is a selective, high affinity, engineered, human IgG1 monoclonal antibody which binds to PD-L1 and prevents binding with PD-1 and CD-80 enabling activated T-cells to kill cancer cell[16]. The premise of the PACIFIC trial was durvalumab could promote a long term and durable immune response in Stage III non-resectable patients following cCRT. This randomised, placebo-controlled phase 3 trial was conducted at 235 centres in 26 countries (n=709) with a 2:1 randomisation to durvalumab / placebo at 10mg/kg intravenous (iv) every two weeks in patients with any PD-L1 level. This study met its co-primary endpoints[2] with significantly prolonged PFS when compared with placebo (16.8 months vs. 5.6 months) & OS benefit with a 32% risk reduction in mortality[17]. The recent 4-year OS demonstrates a sustained and significant benefit at 49.6% when compared with placebo, 36.3%[18].

There was a comparable level of grade 3+ toxicities associated with durvalumab (29.9%) and placebo (26.1%) with pneumonia the most common toxicity in each cohort. The potential for acute and delayed immune related adverse events (irAE's) needs special consideration. Accordingly, pre- treatment measurements of biochemical end organ function, including thyroid function and glucose are mandatory. These irAE's can also occur after immunotherapy cessation. The differential diagnosis of acute shortness of breath should also include immune mediated pneumonitis and radiation pneumonitis (depending on timing after cCRT) and the differentiation between these two is critical (especially during the first two months) as durvalumab must be permanently stopped in grade 3+ immune mediated pneumonitis.

This study did not mandate pre-specified tumour biomarkers; however, the sub-group analysis did not identify a survival benefit in tumours with EGFR (Epidermal Growth Factor Receptor) variants and with PD-L1 < 1%. Maintenance durvalumab represents a new standard of care for patients with unresectable NSCLC (with PD-L1 $\geq$ 1%) and have not progressed during cCRT. The use of maintenance durvalumab was approved in Ireland on February 1st, 2021 at either 10mg/kg every two weeks or a fixed dose of 1500mg every four-weeks for a maximum of 12 months.

The role of neoadjuvant immunotherapy in early lung cancer was explored in a feasibility study by Dr Patrick Forde[19]. There was a potential greater expansion and activation of tumour-specific T cells and improved surveillance of micrometastases with the primary tumour in-situ. This novel approach aimed to improve on the modest perioperative SACT OS benefit accompanied by at

least 50% grade 3+ toxicities. Neoadjuvant nivolumab was administered two-weekly at 3mg/kg for two cycles. A major pathological response (defined as not more than 10% viable tumour cells) was identified in nine of the 20 resected tumours (45%). Tumour mutation burden was predictive of the pathological response to PD-1 blockage. The rate of recurrence-free survival at 18 months was 73%. Any grade treatment related events were 23% and there was 5% grade 3+ toxicity. Neoadjuvant combination immunotherapy with chemotherapy (two cycles of atezolizumab with nab-paclitaxel and carboplatin) also demonstrated an impressive major pathological response[20] in 17 of 30 patients (57%) in a recent phase 2 trial. While these approaches are not standard of care, it does offer a future glimpse of how OS can be potentially improved with neoadjuvant therapies in stage III resectable lung cancers.

Stage III NSCLC is a challenging diagnosis owing to its heterogeneity and therefore has a wide ranging 5-year OS from 13-36%. The role of the MDT is essential to optimise best patient outcomes and for any surgical planning. Platinum based doublet SACT is recommended in the adjuvant or neoadjuvant setting. Currently there is no role for PORT in completely resected tumours. The role of immunotherapy is now a new standard with maintenance durvalumab in (PD-L1 positive, defined as $\geq$ 1%) unresectable stage III NSCLC following cCRT with a 4-year survival of almost 50%. Phase 3 clinical trials are required to determine if this benefit is achievable with neoadjuvant immunotherapy or chemo-immunotherapy.

References

1. Ireland NCR. Lung Cancer Factsheet May 2018, accessed 5th April 2021.
2. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(20):1919-29.
3. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(1):39-51.
4. Kris MG, Gaspar LE, Chaft JE, Kennedy EB, Azzoli CG, Ellis PM, et al. Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non-Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update. J Clin Oncol. 2017;35(25):2960-74.
5. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv1-iv21.
6. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26(21):3552-9.
7. Douillard JY, Tribodet H, Aubert D, Shepherd FA, Rosell R, Ding K, et al. Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: subgroup analysis of the Lung Adjuvant Cisplatin Evaluation. J Thorac Oncol. 2010;5(2):220-8.
8. Kenmotsu H, Yamamoto N, Yamanaka T, Yoshiya K, Takahashi T, Ueno T, et al. Randomized Phase III Study of Pemetrexed Plus Cisplatin Versus Vinorelbine Plus Cisplatin for Completely Resected Stage II to IIIA Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2020;38(19):2187-96.
9. Group NM-aC. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet. 2014;383(9928):1561-71.
10. Group PM-aT. Postoperative radiotherapy for non-small cell lung cancer. Cochrane Database Syst Rev. 2005(2):CD002142.
11. Abstract LBA3_PR 'An international randomized trial cp-ocrPtnP, in patients with completely resected non-small cell lung cancer (NSCLC) and mediastinal N2 involvement. Primary end-point analysis of Lung ART (IFCT-0503, UK NCRI, SAKK) NCT00410683.' Annals of Oncology, Volume 31 Supplement 4, September 2020.
12. Albain KS, Swann RS, Rusch VW, Turrisi AT, 3rd, Shepherd FA, Smith C, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374(9687):379-86.
13. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(13):2181-90.
14. Liang J, Bi N, Wu S, Chen M, Lv C, Zhao L, et al. Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. Ann Oncol. 2017;28(4):777-83.
15. Senan S, Brade A, Wang LH, Vansteenkiste J, Dakhil S, Biesma B, et al. PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2016;34(9):953-62.
16. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest. 2014;124(2):687-95.
17. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018;379(24):2342-50.
18. Faivre-Finn C, Vicente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste JF, et al. Four-Year Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC-an Update From the PACIFIC Trial. J Thorac Oncol. 2021.
19. Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. N Engl J Med. 2018;378(21):1976-86.
20. Shu CA, Gainor JF, Awad MM, Chiuzan C, Grigg CM, Pabani A, et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020;21(6):786-95.