Diagnosis and treatment of early and locally advanced non-small-cell lung cancer: The 2019 AIOM (Italian Association of Medical Oncology) clinical practice guidelines

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\textbf{A B S T R A C T}

The Italian Association of Medical Oncology (AIOM) has developed clinical practice guidelines for the diagnosis and treatment of patients with early and locally advanced non-small cell lung cancer. In the current paper a panel of AIOM experts in the field of thoracic malignancies discussed these topics, analyzing available scientific evidences, with the final aim of providing a summary of clinical recommendations, which may guide physicians in their current practice.

1. Epidemiology

Over the last century, lung cancer switched from a rare disease to one of the most common malignant neoplasm as well as the first cause of cancer death in most countries, including Italy. The Italian Association for Medical Oncology (AIOM) and the Italian Association of Tumor Registries (AIRTUM) estimated about 42,500 new cases and 33,800 deaths from lung cancer in Italy in 2019, with a 5-year survival of 16 % and 10-year survival of 12 % (11 % men, 15 % women) (The Numbers of Cancer in Italy, 2019). Currently, lung cancer represents the third most common neoplasm in the overall Italian population, while it is the first cause of cancer death in male and the third in women, with both incidence and mortality increasing in people who are 50 years or older (The Numbers of Cancer in Italy, 2019).

In the last few decades we have witnessed a small and steady decrease of lung cancer incidence and mortality in men (-1.6 %/year; -1.9 %/year), along with a significant increase among women (+2.2 %/year; +0.7 %/year).

The patterns of lung cancer incidence are mainly dependent on tobacco consumption, being smoking habit the main cause of lung cancer, accounting for 85–90 % of cases in Italy, with other factors as genetic susceptibility, diet, asbestos, radon, and indoor air pollution less contributing to the descriptive epidemiology of this disease (The Numbers of Cancer in Italy, 2019). A 2019 survey on smoking behavior in our country revealed a slight decrease in the percentage of smokers, representing now about 22 % of overall Italian population (28 % men, 16.5 % women) as compared to 23.3 % (27.7 % men, 19.2 % women) in 2018 (National Health Institute, 2019). Of major concern is the diffuse attitude to smoke among Italian teenagers (14–17 years old), with 11 % of “baby smokers” reported in 2018, representing one of the highest

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percentage in Europe. The 2017 World Health Organization (WHO) report on the global tobacco epidemic revealed that Italy adequately addressed the majority of MPower measures, ultimately making cigarettes less affordable since 2008 (World Health Organization, 2017). Several anti-smoking campaigns and educational meetings have been promoted by the Health Ministry, scientific societies, like AIOm, and Advocacy groups, like Women Against Lung Cancer Europe (WALCE). However, more efforts are required in terms of cessation programs and advertising bans, since it became clear that a significant reduction in tobacco consumption would result in the prevention of a large fraction of lung cancers, making lung cancer a paradigm of the superiority of prevention over treatment.

2. Screening

Lung cancer is usually diagnosed in advanced stages with the majority of patients already presenting metastatic disease. Therefore, early detection by screening could be a meaningful approach to detect the disease earlier, when still asymptomatic and potentially curable.

The National Lung Cancer Screening Trial (NLST) (National Lung Screening Trial Research Team et al., 2011) showed a 20% reduction in lung cancer-related death in over 53,000 current or former heavy smokers (30 pack-years or no more than 15 years since smoking cessation) who received a low-dose computed tomography (LDCT) as compared to chest X-ray, leading to the introduction of lung cancer screening by LDCT in the United States. However, because of concerns about high rate of over-diagnosis of indolent cancers and uncertain risk/benefit ratio, screening with computed tomography (CT)-scan has not been endorsed yet in Italy as well as in the majority of European Countries.

Afterwards NLST, several European studies (MILD, ITALUNG, DanTE, DLCT, COSMOS, NELSON, LUSI, and UKLS) (Pastorino et al., 2019; Paci et al., 2017; Infante et al., 2015; Rasmussen et al., 2015; Veronesi et al., 2013; Youssaf Khan et al., 2017; Becker et al., 2019; Field et al., 2016) investigated the role of LDCT in the early detection of lung cancer. Among these, the NELSON trial (De Koning et al., 2018) has recently shown a significant 26% and 39% reduction in lung cancer deaths at 10 years in men and women, respectively. Similarly, the MILD trial (Pastorino et al., 2019) revealed as a prolonged LDCT screening beyond five years significantly reduced lung cancer mortality of 39% at ten years, compared to clinical observation. Based on these evidences and according to the 2018 International Association for the Study of Lung Cancer (IASLC) Statement on Lung Cancer Screening, AIOm, along with other scientific societies and the National Health Service, has recently promoted an interactive discussion on this topic, with the aim of implementing the national screening services in our country.

3. Diagnosis and staging

The diagnostic evaluation should initially focus on careful physical examination and patient's history, to identify new symptoms or a significant change in the common respiratory symptoms. For all patients with suspected lung cancer, an urgent referral to non-invasive chest imaging is recommended, including X-rays, CT-scan, and positron emission tomography (PET) with fluorodeoxyglucose (FDG) (Ost et al., 2013). Conventional contrast-enhanced chest CT-scan is considered the best exam to detect lung cancer, as it provides detailed information on anatomic location, margins, invasion of surrounding structures or chest wall, and mediastinal lymph nodes involvement (Patel et al., 2013). FDG-PET is very accurate for differentiating benign from malignant lesions, as it plays a crucial role in the diagnostic algorithm of solitary nodules as well as in the mediastinal and extra-thoracic staging, since it has shown to have both higher sensitivity and specificity than CT (Voigt, 2017). Because of the high frequency of false positive imaging tests, all patients with abnormal mediastinal lymph nodes on CT and/or PET-scan should undergo invasive tissue sampling by endobronchial ultrasound (EBUS)/endoscopic ultrasound (EUS)-guided needle aspiration (TBNB), to confirm nodal involvement and, if results are negative, surgical staging by mediastinoscopy is recommended (Rivera et al., 2013a; Czarnecka-Kujawa and Yasufuku, 2017; Sehgal et al., 2016; Silvestri et al., 2013) (Table 1). Invasive staging in case of negative radiological mediastinal involvement, is currently recommended only for centrally-located tumours, T > 3 cm, and abnormal hilar-nodes at PET/CT scan, since this subgroup of patients seems to be at higher risk of nodes occult metastasis (ranging from 8% to 30%) (Silvestri et al., 2013; Vilmann et al., 2015).

The overall diagnostic information emerging from non-invasive imaging (CT, PET, or combined PET-CT), including size and location of the tumor, presence of mediastinal or distant metastasis, and patient’s clinical status, will guide the most appropriate strategy to achieve final diagnosis and staging of lung cancer. Bronchoscopy, EBUS-TBNB or EUS(B)-FNA are the most common procedures used to obtain a pathological diagnosis of NSCLC, especially in presence of centrally-located lesions (Rivera et al., 2013b; Adams et al., 2009; Gu et al., 2009). The diagnostic approach to peripheral lesions may be variable. The presence of “bronchus sign” on CT-scan, T > 2 cm, and solid pattern predict high rate of success by bronchoscopic approach, with a diagnostic accuracy of 70%, but it is feasible at centers with availability of appropriate guidance tools (at least fluoroscopy and/or radial EBUS) (Wang Memoli et al., 2012). CT-guided needle aspiration biopsy, most commonly performed by interventional radiologists is, by far, the preferred option in centers lacking bronchoscopic guidance tools or expertise, as well as in presence of peculiar features (small lesions, ground glass pattern, subpleural location), which make bronchoscopy less likely to succeed.
4. Pathological features

Pathological diagnosis is recommended prior to any curative treatment and should be made according to the 2015 World Health Organization (WHO) classification (Travis et al., 2011; Rossi et al., 2013).

Non-small cell lung cancer (NSCLC) accounts for 80%-95% of lung cancers in Italy, including 50% of adenocarcinoma (34% men, 50% women), and 21% of squamous cell carcinoma (25% men, 12% women).

Changes in composition and patterns of tobacco consumption have led to a significant change in the distribution of lung cancer histological subtypes, with squamous cell carcinoma now decreasing in men (-2.6%/year) and adenocarcinoma increasing in both genders (+ 4.5%/year in men; +7%/year in woman) (The Numbers of Cancer in Italy, 2019).

Immunohistochemistry (IHC), including p40 for squamous cell carcinoma and Thyroid Transcription Factor-1 (TTF1) or napsin A for adenocarcinoma, is generally required to increase the specificity of diagnosis in the small sample setting and reduce the NSCLC-NOS (not otherwise specified) rate below 10% (Yatabe et al., 2019; Lozano et al., 2018; Walia et al., 2017; Pelosi et al., 2015; Inamura, 2018; Pelosi et al., 2017; Gurdan et al., 2015).

IHC analysis should be preferably performed on tissue samples obtained by surgery or tumor biopsy. However, cell-block is considered as a valid alternative option when tumor tissue is sampled on effusion and/or FNA. Paraffin-embedded biocassettes obtained from cell-blocks should be considered as micro-biopsies when enrolling patients into clinical trials, requiring further centralized analyses (Saqi, 2016; Thunnissen et al., 2012; Dong et al., 2017; van der Heijden et al., 2014; Lindeman et al., 2018).

The last 2015 pathologic classification highlighted the concept that personalized medicine for patients with advanced lung cancer is determined by histology and genetics and that tissue/cells management of small biopsy/cytology samples is critical for pathologic and molecular diagnosis in order to prevent the loss of tissue in less important analysis.

5. Treatment of early disease

5.1. Surgery

Although recent advances in diagnostic procedures, only 20% of NSCLC patients have early stage disease at the time of diagnosis, thus being potentially resectable.

The recommended treatment of patients with stage I–II NSCLC who are considered clinically “operable” is curative-intent surgical resection (Rosen et al., 2016), with a 5-year survival rate reported to be 60–90% for stage I and 40–60% for stage II. The current gold standard is lobectomy with hilar and mediastinal lymph-node sampling or dissection (Ginsberg et al., 1995; Rami-Porta et al., 2005). Systematic nodal dissection of a minimum six nodes/stations, three of which should be mediastinal, including the sub-carinal station, should be guaranteed to ensure “R0 resection.” Surgical treatment should be performed at reference centers for thoracic surgery, characterized by major experience, high volume, and case mix, since has been largely demonstrated how these factors significantly impact on patients’ survival (Flum and Varghese, 2009). Either open thoracotomy or minimally invasive surgery (VATS or robotic surgery) are recommended as appropriate surgical approaches to the expertise of the surgeon, even if minimally invasive surgery should be preferred in stage I tumors, because associated with lower postoperative morbidity/mortality, thus resulting in
Table 2
The 8th Edition of the TNM Clinical Classification of Lung Cancer.

<table>
<thead>
<tr>
<th>TNM Clinical Classification</th>
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<tbody>
<tr>
<td>Primary Tumor</td>
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<td>TX</td>
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<tr>
<td>T0</td>
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<td>Tis</td>
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<td>T3</td>
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<td>T4</td>
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</tbody>
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Regional Lymph Nodes
- N0: Regional lymph nodes cannot be assessed
- N1: Metastasis in ipsilateral hilar lymph nodes and ipsilateral mediastinal nodes, including involvement by direct extension
- N2: Metastasis in bilateral mediastinal nodes
- N3: Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes

Distant Metastasis
- M0: No distant metastasis
- M1: Distant metastasis present
  - M1a: Separate tumor nodules in a contralateral lobe; tumor with pleural or pericardial effusion
  - M1b: Single extrathoracic metastasis
  - M1c: Multiple extrathoracic metastases in one or more organs

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>5-year OS</th>
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<tbody>
<tr>
<td>Occult carcinoma</td>
<td>Tx</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td></td>
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<tr>
<td>Stage IA1</td>
<td>T1a, T1a(mi)</td>
<td>N0</td>
<td>M0</td>
<td>92%</td>
</tr>
<tr>
<td>Stage IA2</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>83%</td>
</tr>
<tr>
<td>Stage IA3</td>
<td>T1c</td>
<td>N0</td>
<td>M0</td>
<td>77%</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>68%</td>
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<tr>
<td>Stage IIA</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>60%</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T1a, T1b, T1c</td>
<td>N1</td>
<td>M0</td>
<td>53%</td>
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<tr>
<td></td>
<td>T2a, T2b</td>
<td>N1</td>
<td>M0</td>
<td></td>
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<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1a, T1b, T1c</td>
<td>N2</td>
<td>M0</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>T2a, T2b</td>
<td>N2</td>
<td>M0</td>
<td></td>
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<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
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<tr>
<td></td>
<td>T4</td>
<td>N1</td>
<td>M0</td>
<td></td>
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<tr>
<td>Stage IIIB</td>
<td>T1a, T1h, T1c</td>
<td>N3</td>
<td>M0</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>T2a, T2b</td>
<td>N3</td>
<td>M0</td>
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<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
<td></td>
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<tr>
<td></td>
<td>T4</td>
<td>N2</td>
<td>M0</td>
<td></td>
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<tr>
<td>Stage IIC</td>
<td>T3</td>
<td>N3</td>
<td>M0</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N3</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage IVA</td>
<td>Any T</td>
<td>Any N</td>
<td>M1a</td>
<td>10%</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1b</td>
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<td>M1c</td>
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Improved quality of life (Petrella and Spaggiari, 2016; Bendixen et al., 2016) (Table 1). Interestingly, Italian VATS group data enlightens the higher penetration of VATS lobectomy application in Italy, as compared to other European Countries (European Society of Thoracic Surgeons, 2019). Furthermore Italy stands as one of the countries with a greater concentration of Thoracic Surgery Units with the availability of robotic systems.

Alternative approaches, as segmentectomy, could be reserved to patients with limited cardiopulmonary function (Linden et al., 2005; Veluswamy et al., 2015). The same outcomes of segmentectomy and lobectomy were reported in patients with radiologically pure solid cT1a adenocarcinomas (Koike et al., 2016). Therefore, limited resection may be considered a valid option also in case of Tis, T1a, or ground glass opacities (GGO), which often are associated to multifocal presentation and “in-situ” adenocarcinomas.

5.2. Radiotherapy

Curative stereotactic body radiotherapy (SABR) should be offered to patients with stage I NSCLC who have clinical comorbidities or are at very high surgery-related risk, and those who refuse to undergo surgical procedure (Baumann et al., 2009; Ricardi et al., 2010; Timmerman et al., 2010). The introduction of SABR was associated to an increased survival, likely due to a reduction in the number of untreated patients.
among elderly population (Haasbeek et al., 2012). Even if 58% of the Italian radiotherapy centers claim to offer a curative SABR, the availability of this special technique varies across the geographical region, as reported by the Italian Association of Radiotherapy and Clinical Oncology (AIRO) (AIRO Survey, 2019). Acute, severe toxicities with SABR are uncommon, but a careful evaluation of risk/benefit ratio at single patient level is recommended within a multidisciplinary tumor board. A recent meta-analysis (Chen et al., 2018) including 16 trials 19,882 patients showed a significant longer OS in favor of surgery compared with SABR [hazard ratio, HR 1.48 95% confidence interval, 95% CI, 1.26–1.72; I = 80.5%], without any differences in tumor-related survival [HR 1.17 (95% CI 0.92–1.50); I = 18.6%]. Prospective data from ongoing randomized studies will be crucial to define the best strategy in this setting. For patients with multifocal NSCLC or multiple primaries, who are not good candidates to radical surgery, SABR represent also a valid alternative treatment option, after discussion within a multidisciplinary team.

5.3. Adjuvant treatments

Post-operative platinum-based chemotherapy is recommended for all patients with stage II and III surgically resected disease, with performance status (ECOG PS) of 0-1 and without significant comorbidities (Table 1). Two meta-analysis demonstrated that post-operative platinum-based chemotherapy led to more than 10% reduction in the risk of death, resulting in about 5% absolute 5-years OS and disease-free survival (DFS) improvement. Incidence of severe toxicities was about 65%, with grade 3-4 neutropenia reported in 37% of cases (Pignon et al., 2008; Burdett et al., 2015). Although the optimal interval between surgery and adjuvant treatment, emerging from randomized studies, is actually considered 6–8 weeks, a recent analysis of the National Cancer Database showed a comparable outcome in patients treated after a longer interval (Salazar et al., 2017).

Data coming from the LACE meta-analysis suggested that adjuvant chemotherapy efficacy and tolerability are the same in the small subgroup of >70 years old patients, while prospective data on patients >75 years old are lacking (Pignon et al., 2008). The majority of studies investigating carboplatin-based adjuvant regimens failed to show any survival benefit (Strauss et al., 2008; Ou et al., 2010; Felip et al., 2010), while direct comparison with cisplatin-based regimens is currently lacking. Based on the results of the JBR.10 and ANITA trials (Douillard et al., 2006; Butts et al., 2010), cisplatin-vinorelbine is currently considered as the best regimen for adjuvant setting. Third-generation agents, with at least comparable efficacy, such as gemcitabine, may be considered as an alternative valid option. Even if platinum-pemetrexed showed equal efficacy and better tolerability profile in phase II-III studies (Kreuter et al., 2016; Kenmotsu et al., 2019), it is not currently reimbursed and recommended as adjuvant therapy in Italy. In the decision process for adjuvant chemotherapy, several factors, including age, pre- and post-operative morbidities, should be considered and discussed within a multidisciplinary team (Fig. 2).

Several studies investigated the role of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in the adjuvant setting showing conflicting results, with a potential benefit likely limited to EGFR-mutated NSCLC (Kelly et al., 2015; Goss et al., 2013; Yue et al., 2018; Zhong et al., 2018; Li et al., 2014). The high heterogeneity of included populations, comparator arms, and treatment regimens, among these studies, along with the absence of OS data, do not allow to draw any definitive conclusion about the efficacy of these agents. Waiting for the ongoing prospective randomized trials investigating the efficacy of third-generation TKIs in biomarker-selected NSCLC patients, the use of EGFR-TKIs is not currently recommended in the adjuvant setting (Table 2).

Several studies and meta-analyses clearly demonstrated that post-operative radiotherapy (PORT) in patients with stage I-II NSCLC, is associated with higher risk of death (HR 1.18 [95% CI 1.07–1.31]), disease recurrence (HR 1.10 [IC 95% 0.99–1.21]), and local recurrence (HR 1.12 [IC 95% 1.01–1.24]), with absolute 5% decrease in survival rate at 2 years (PORT Meta-analysis Trialists Group, 1998; Burdett et al., 2016). Therefore, it cannot be recommended as part of adjuvant strategies (Table 1).

6. Treatment of locally advanced disease

Stage III account for 25–30% of NSCLC, including a heterogeneous group of tumors: IIA (T3-T4, N1; T1-T2, N2); IIIB (T3-T4, N2; T1-T2, N3); IIEC (T3-T4, N3) with different prognosis and controversial treatment. A careful evaluation and discussion of clinical management of these patients within a multidisciplinary team of experts is advised.

6.1. Resectable disease

6.1.1. Surgery

Patients with locally advanced stage IIA-IIIB NSCLC may be candidate to surgical therapy if they have N1 disease or single station N2 involvement (T1-T3), with pre-operative mediastinal nodal staging performed by invasive methods. In these cases, different options are recommended:

- Surgery followed by adjuvant chemotherapy
- Neoadjuvant chemotherapy followed by surgery
- Neoadjuvant chemo-radiation followed by surgery

Eligibility for pre-operative or post-operative platinum-docetaxel with or without radiotherapy should be evaluated in the context of an experienced multidisciplinary team. Selected patients with non-bulky, multi-station N2 involvement, who achieved a nodal down-staging (assessed by invasive methods) by induction treatments may be suitable for surgery, after discussion in the context of an experienced multidisciplinary team.

Two randomized studies compared surgical treatment to definitive radiotherapy in patients with stage III, N2 NSCLC who obtained partial response after induction chemotherapy, showing no significant differences in terms of 5-years PFS and OS between the two treatment arms (van Meerbeeck et al., 2007; Eberhardt et al., 2015). Even if the high heterogeneity of populations included in both these studies do not
allow to draw any definitive conclusions in specific subgroups, right pneumonectomy was associated to higher morbidity and mortality. Therefore, for patients who may not be candidate to a lobectomy after induction therapies, definitive radiotherapy is recommended.

6.1.2. Neoadjuvant treatment

Several studies and meta-analyses (Jim et al., 2009; NSCLC Meta-analysis Collaborative Group, 2014) suggested that the estimated benefit from neoadjuvant chemotherapy is comparable to that expected with adjuvant chemotherapy (5 % absolute 5 years OS increase), thus it may be considered as a feasible and ethical approach for patients with stage IIIA-IIIB (N2) NSCLC, and should be always evaluated in the context of multidisciplinary teams.

The phase III, randomized, Lung Intergroup trial 0139 (Albain et al., 2009) compared concurrent definitive chemoradiation versus concurrent induction chemoradiation followed by surgery in stage III (N2) NSCLC patients, showing no survival differences between the two treatment arms. A significant increase of median OS in favor of trimodal strategy has been observed in the subgroup of patients undergoing lobectomy (OS: 34 months versus 22 months), while median OS was significantly lower (19 months) with pneumonectomy. Another study compared sequential chemoradiation versus chemotherapy alone as induction treatment in stage III (N2) NSCLC, showing no significant OS differences between the two arms (Pless et al., 2014). These data suggest that concurrent chemoradiation may be an effective induction strategy in selected patients with stage IIIA-IIIB (N2) NSCLC, and should be evaluated in the context of an experienced multidisciplinary team.

An Italian 2019 survey revealed as in patients with stage III, nonbulky, multi-station N2 disease, 66 % of thoracic specialists declare to prefer a neoadjuvant approach (with chemo or chemoradiation), rather than a definitive concomitant chemoradiation treatment (Bruni et al., 2018).

6.1.3. Adjuvant treatments

Several studies included in the LACE meta-analysis (Pignon et al., 2008) demonstrated a 4.2 % absolute 5 years survival rate improvement for the subgroup of patients with stage IIIA-IIIB (N1 or single station N2) NSCLC who received adjuvant chemotherapy after surgical resection, suggesting cisplatin–doublets as the best regimen.

Although the results of the PORT meta-analysis (PORT Meta-analysis Trialists Group, 2000) showed a not clear survival benefit in patients with stage III, N2 pathological disease undergoing radiotherapy after radical surgery, more recent meta-analyses demonstrated that PORT is associated to a reduction in risk of loco-regional and systemic recurrences (Billiet et al., 2014; Li et al., 2016; Liu et al., 2019), with a significant increase in OS in the subgroup of patients with extensive pN2 involvement (HR = 0.85; 95 % CI: 0.79-0.92) (Liu et al., 2019). Waiting for the final results of the prospective LungArt trial, PORT may be considered as an effective treatment for surgically resected patients with extensive N2 pathological involvement or R1 disease, and should be evaluated in the context of an experienced multidisciplinary team.

6.2. Unresectable disease

6.2.1. Chemo-Radiotherapy

For patients with unresectable stage III NSCLC, definitive concurrent chemoradiation is currently recommended as treatment of choice (Table 1), with historical 5-year survival rate reported to be around 10 %. An individual patient data meta-analysis (Aupérin et al., 2010) including six randomized studies demonstrated 4.5 % absolute 5-years OS increase with concurrent versus sequential treatment, even if at cost of increased severe esophagitis (4 %-18 %). Nevertheless, sequential chemotherapy followed by definitive radiotherapy may be considered an alternative valid option for elderly or frail patients with clinical comorbidities and ECOG PS 2 and is still largely adopted in real-world practice. Another meta-analysis showed that the use of cisplatin significantly increase response rate (RR) and patients’ survival as compared to carboplatin (Hotte et al., 2004). Furthermore, third-generations agents (taxane or gemcitabine) were more effective and better tolerated than second-generation compounds (irinotecan, vindesine, mitomycin) (Yamamoto et al., 2010; Segawa et al., 2010). A prospective randomized study (Jiang et al., 2017) compared cisplatin-etoposide versus carboplatin-paclitaxel in patients with unresectable, stage III NSCLC receiving concurrent chemoradiation. The results of this trial showed a not significant increase in both RR (73.7 % versus 64.5 % (p = 0.21)) and OS [median 23.3 versus 20.7 months (HR 0.76, 95 % CI 0.55–1.05; p = 0.095)] in favor of the cisplatin-etoposide regimen, along with a significant 15 % absolute 3-years survival improvement and similar toxicity, compared to carboplatin-paclitaxel. Conversely several other trials revealed a comparable efficacy between these two treatment regimes, whit safety profile favouring carboplatin-paclitaxel (Steuer et al., 2017). The phase III PROCLAIM study (Senan et al., 2016) compared cisplatin-pemetrexed versus cisplatin-etoposide in non-squamous histology, failing to show any difference, except for lower incidence of severe hematological toxicities in the pemetrexed arm. Based on these evidences a cisplatin-based combination is currently recommended as concurrent regimen in association to definitive radiotherapy (Table 1). For patients with stage IIIB (N3)-IIIA NSCLC, tumor molecular profiling including at least EGFR mutations, ALK and ROSI rearrangements assessment should be performed in order to identify actionable alterations, which may be suitable for targeted treatments.

6.2.2. Immunotherapy

Recently the prospective, randomized, phase III PACIFIC study compared the anti-PD-L1 monoclonal antibody durvalumab versus placebo, as consolidation therapy in patients with stage III unresectable NSCLC, after definitive concurrent chemoradiation, showing a significant PFS (HR 0.51, 95 % CI 0.41 – 0.63; p = 0.001) and OS (HR 0.68, 95 % CI 0.53 – 0.87; p = 0.005) improvement in patients treated with durvalumab. OS benefit was regardless of tumor PD-L1 expression levels at pre-specified cut-off of 25 % (PD-L1 ≥ 25 % HR 0.46; PD-L1 < 25 %: HR 0.92) (Antonia et al., 2018). A subsequent, unforeseen, post hoc explorative analysis, required by the European Medicines Agency (EMA), revealed that patients without PD-L1 expression did not gain any survival benefit from consolidation immunotherapy (cut-off < 1 %: HR 1.36), thus leading to the subsequent approval of durvalumab in NSCLC patients with tumor PD-L1 ≥ 1 %. Conversely, patients with tumor PD-L1 negative or unknown are currently excluded from access to this curative-intent therapy. A survival update of this study has been recently presented at the 2019 American Association of Medical Oncology (ASCO) meeting (Gray et al., 2019), confirming a significant median OS benefit in favor of durvalumab (not reached versus 29.1 months, HR 0.69, 95 % CI 0.55 – 0.86) with about 15 % absolute 3-years survival improvement in the overall included population. However, the OS improvement continued to be limited only to patients with tumor PD-L1 expression ≥ 1 %, while no OS improvement has been observed in the subgroup with PD-L1 < 1 % (PD-L1 ≥ 1 %: HR 0.59; PD-L1 < 1 %: HR 1.14). Based on these data, for patients with unresectable stage III NSCLC who had partial response or stable disease (RECIST v1.1) after concurrent or sequential chemoradiation, and tumor PD-L1 ≥ 1 %, treatment consolidation with durvalumab for 12 months should be considered as treatment of choice (Fig. 3 and Table 1).

7. Follow-up

For patients with early stage NSCLC undergoing local treatments with curative intent, large follow-up studies revealed a risk of relapse ranging from 6 % to 10 % per-person per-year within the first four years, significantly decreasing to 2 % thereafter (Lou et al., 2013). The
most common patterns of relapse included loco-regional recurrence within the first two years, and distant metastasis between the second and the fourth year. The risk of relapse is virtually absent after the fifth year, however other series suggest a permanent risk between 3.5 and 15 % also beyond the fifth year from surgery (Demicheli et al., 2012; Verstegen et al.). The risk of second primary tumors ranges from 1 to 6 % per-person per-year and it is almost stable over time (Lou et al., 2013). There are not prospective studies showing the best follow-up strategy for these patients. Clinical visit every three-six months along with a contrast enhanced thorax CT-scan every six months are currently recommended during the first two years from treatment, and annually thereafter. Bronchoscopy at one year is recommended only in case of centrally-located tumors that were visible at diagnostic bronchoscopy and were associated to dysplasia/carcinoma in situ or suboptimal surgical margins (< 1 cm) (Peled et al., 2009; Postmus et al., 2017b). Smoking cessation should be always encouraged and adequately supported during the follow-up period (Colt et al., 2013).

8. Methodology

The AIOM Clinical Practice Guidelines were developed in accordance to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method.

8.1. Literature search

The literature search was conducted using Medline (PubMed), Embase-databases and Cochrane-Library, up to September 2019. The clinical questions were formulated according to the P.I.C.O (P: Population; I: Intervention; C: Comparison; O: Outcome) process, and P.I.C.O keywords were used as literature search terms. The literature search was limited to human studies in English language, and relevant studies were selected by expert members of the AIOM Lung Cancer Working Group. Relevant abstracts from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), International Society for the study of Lung Cancer and other international or national meetings were also included as scientific support to published evidences. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was used to describe literature search and trials selection processes for each clinical question.

8.2. Quality of evidence

The expert members of the AIOM Lung Cancer Working Group evaluated the following features in order to define the quality of available, selected studies: risk of bias, precision, directness, consistency, and publication bias.

The global quality of evidence was defined as follow:

- High (high grade of confidence in the study results): high probability that the estimated effect is similar to the true effect.
- Moderate (moderate grade of confidence in the study results): moderate probability that the estimated effect is similar to the true effect, but limited possibility that it is substantially different.
- Low (low grade of confidence in the study results): limited probability that the estimated effect is similar to the true effect, with high possibility that it is substantially different.
- Very low (very low grade of confidence in the study results): very limited probability that the estimated effect is similar to the true effect, with very high possibility that it is substantially different.

8.3. Strength of recommendation

The strength of clinical recommendations is graduated on four levels according to their clinical relevance, taking into account the benefit/risk outcomes ratio, the quality of evidence and other additional variables (equity, acceptability, feasibility, and patients’ preference):

- Strong for: The intervention should be considered as the treatment of choice (benefits are higher than risks).
- Conditional for: The intervention may be considered as treatment of choice (not sure that benefits are higher than risks).
- Conditional against: The intervention should not be considered as treatment of choice, except for selected cases after discussion with the patient (not sure that benefits are higher than risks).
- Strong against: The intervention must be never considered as a treatment option (risks are higher than benefits).

8.4. Clinical recommendation

Clinical recommendations were assessed reflecting the clinical relevance of a medical intervention, formulated according to the P.I.C.O (P: Population; I: Intervention; C: Comparison; O: Outcome) process. All clinical recommendations include both strengths levels and global quality of evidence grading, according to the GRADE method.

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Declaration of Competing Interest

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