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Contents

Lung Cancer Screening

Geena X. Wu and Dan J. Raz

Abstract

Lung cancer is the leading cause of cancer mortality in the United States and worldwide. Since lung cancer outcomes are dependent on stage at diagnosis with early disease resulting in longer survival, the goal of screening is to capture lung cancer in its early stages when it can be treated and cured. Multiple studies have evaluated the use of chest X-ray (CXR) with or without sputum cytologic examination for lung cancer screening, but none has demonstrated a mortality benefit. In contrast, the multicenter National Lung Screening Trial (NLST) from the United States found a 20 % reduction in lung cancer mortality following three consecutive screenings with low-dose computed tomography (LDCT) in high-risk current and former smokers. Data from European trials are not yet available. In addition to a mortality benefit, lung cancer screening with LDCT also offers a unique opportunity to promote smoking cessation and abstinence and may lead to the diagnoses of treatable chronic diseases, thus decreasing the overall disease burden. The risks of lung cancer screening include overdiagnosis, radiation exposure, and false-positive results leading to unnecessary testing and possible patient anxiety and distress. However, the reduction in lung cancer mortality is a benefit that outweighs the risks and major health organizations currently recommend lung cancer screening using age, smoking history, and quit time criteria derived from the NLST. Although more research is needed to

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clearly define and understand the application and utility of lung cancer screening in the general population, current data support that lung cancer screening is effective and should be offered to eligible beneficiaries.

Keywords
Lung cancer · Screening · Computed tomography · Cancer prevention

Contents

1 Why Screen for Lung Cancer?

As the most common cause of cancer-related deaths in the United States and worldwide, lung cancer is a public health problem of global magnitude. In 2015, an estimated 221,200 new cases of lung cancer will be diagnosed in the United States and 158,040 deaths will occur as a result of lung cancer [1]. Worldwide, 1.6 million lung cancer-associated deaths were estimated in 2012 [1].

Five-year relative survival rate for lung cancer is only 17.4 % due to more than half of patients being diagnosed with distant disease by the time-associated symptoms manifest. Lung cancer outcomes are highly dependent on stage at diagnosis. Patients with stage I non-small-cell lung cancer (NSCLC) have five-year overall survival of at least 60 %, whereas those with stage IV disease have survival of less than 5 % [2]. Tumor size in early lung cancer (stage I) has also been identified as a predictor of nodal status and thus stage [3]. Incidentally detected NSCLC in asymptomatic patients tends to be smaller, earlier stage, and have similar stage-specific overall survival as symptomatic disease [4, 5]. Data on screen-detected lung cancer report stage I disease in 85 % of participants and estimate 10-year overall survival to be 88 % [6].

In addition to having high morbidity and mortality, a long preclinical phase, and improved survival with early-stage diagnosis, lung cancer also has identifiable risk factors such as age and smoking history, which can be used for screening criteria. All these characteristics suggest that screening may be effective in improving lung cancer outcomes as it has for other malignancies including colon, breast, and cervical. For screening to be considered beneficial, it must lead to the reduction in

disease-specific and overall mortality. Effective screening ideally involves an inexpensive, low-risk, and easily accessible test that is sensitive and specific for detecting cancer in its early stages before symptoms manifest as advanced disease. Chest X-ray (CXR) with or without sputum cytologic analysis and low-dose computed tomography (LDCT) have been studied as lung cancer screening tools, and the evidence is presented in this chapter.

2 Screening with Chest X-Ray and Sputum Cytologic Studies

Six randomized controlled trials (RCTs) from the 1960s and 1970s have evaluated the use of CXR in lung cancer screening (Table 1). None of these studies clearly demonstrated a benefit in lung cancer mortality, although most studies had limitations due to methodological flaws [7]. The Northwest London Mass Radiography Service Study began in 1960 and was a prospective trial of 55,023 male factory workers of variable smoking status (19 % former smokers, 67 % current smokers) who were 40 years or older. Of these, 29,723 were randomized to receive CXR every 6 months and 25,300 were randomized to a control group that received screening at baseline and at 3 years. After 3 years of screening, lung cancer patients in the screening group had a higher proportion of resectable lung cancer than those from the control group (44 % versus 29 %, $p = 0.03$). Five-year survival rate was also better in lung cancer cases identified by the intervention than in those identified in the control group (23 % versus 6 %, $p < 0.01$). However, the annual mortality rates from all lung cancers were not significantly different between the groups (0.7 versus 0.8 deaths per 1000 person-years). Only 65 % of lung cancers in the intervention group were identified by 6-monthly CXR [8, 9].

In 1964, the Kaiser Permanente Study randomized 5156 Kaiser Foundation Health Plan men and women aged 35–54 years to be encouraged to undergo annual multiphasic health checkups (including CXR), while a comparable group of 5557 members were not encouraged to do so. Patients were followed for 16 years, and those in the intervention group had 6.8 mean checkups and a mortality of 8.6 per 1000 person-years compared to mean 2.8 checkups and a mortality of 7.6 per 1000 person-years in the participants from the control group. The difference did not meet statistical significance [10, 11].

In the 1970s, 4 RCTs studied lung cancer detection in male smokers using CXR and sputum cytology. The Mayo Lung Project was the first study to evaluate the intense use of these dual-screening tools in lung cancer screening; 10,933 participants aged 45 years or older underwent baseline (prevalence screening) CXR and sputum cytologic examination from 3-day pooled samples, and 91 (0.83 %) lung cancer cases were detected [12]. Following the prevalence round, 4618 men were randomized into the intervention group (CXR and sputum cytologic examination every 4 months for 6 years) and 4593 were assigned to the control group (annual CXR and sputum testing advised as usual care). Over the 6-year study period, 206 and 160 new lung cancer cases were diagnosed in the screening and control groups,

Table 1 Controlled trials of lung cancer screening with chest radiography (CXR) with or without sputum cytologic examination

Study (year)	Population	Intervention, n Control, n	Screening frequency and length	Baseline results, n (%)	Incidence results, n	F/u (years)	Mortality rate (per 1000 person-years)	Other/Limitations
Northwest London Mass Radiography Service Study [8, 9] (1960)	Sex: 100 % men Age: >40 years Smokers: 67 % current, 19 % former	29,723 received CXR 25,300 received CXR at baseline and at 3 years	Baseline, then every 6 months for 3 years	CXR: 31 (0.1) Control: 20 (0.08)	CXR: 101 Control: 76	3	CXR: 0.7 Control: 0.8	99 % follow-up 63 % adherence
Kaiser Permanente Study [10, 11] (1964)	Sex: 46.7 % men Age: 35–54 years Smokers: 17 %	5156 recommended MHC[a] (CXR) 5557 not recommended MHC (CXR)	Annual	NR	NR	16	MHC (CXR): 8.6 Control: 7.6	Poor follow-up 64 % of controls got MHC
Mayo Lung Project [12–14, 16] (1971)	Sex: 100 % men Age: $\geq$45 years Smokers: 100 % current	4618 received CXR/3-day pooled sputum 4593 received baseline CXR and usual care (recommended annual CXR and sputum)	Baseline, then every 4 months for 6 years	91 (0.8)	CXR/sputum: 206 Control: 160	20	CXR/sputum: 4.4 Control: 3.9	88 % follow-up 75 % adherence for intervention group 73 % controls had CXR Overdiagnosis

(continued)

Table 1 (continued)

Study (year)	Population	Intervention, n Control, n	Screening frequency and length	Baseline results, n (%)	Incidence results, n	F/u (years)	Mortality rate (per 1000 person-years)	Other/Limitations
Wilde et al. [25] (1972)	Sex: 100 % men Age: 40–65 years Smokers: NR	41,532 received CXR 102,348 received CXR every 18 months (control)	Baseline, then every 6 months	CXR: 54 Control 68	CXR: 320 Control: 599	10	CXR: 0.8 Control: 0.6	Nonrandomized More dropouts in control group
Johns Hopkins Study [17, 19] (1973)	Sex: 100 % men Age: $\geq$45 years Smokers: 100 %	5266 received CXR/sputum examination 5161 received CXR only (control)	Baseline, then annual for 5–8 years	CXR/sputum: 39 (0.75) CXR only: 40 (0.78)	CXR/sputum: 194 CXR only: 202	5–8	CXR/sputum: 3.4 CXR only: 3.8	98.7 % follow-up 19 % withdrew from screening
Memorial Sloan-Kettering Study [18, 20, 21] (1974)	Sex: 100 % men Age: $\geq$45 years Smokers: 100 %	4968 received CXR/sputum examination 5072 received CXR only (control)	Baseline, then annual for 5–8 years	CXR/sputum: 30 (0.6) CXR only: 23 (0.5)	CXR/sputum: 146 CXR only: 155	5–8	CXR/sputum: 2.7 CXR only: 2.7	99 % follow-up 63–65 % adherence

(continued)

Table 1 (continued)

Study (year)	Population	Intervention, n Control, n	Screening frequency and length	Baseline results, n (%)	Incidence results, n	F/u (years)	Mortality rate (per 1000 person-years)	Other/Limitations
Czech study [23, 24, 84] (1975)	Sex: 100 % men Age: 40–64 years Smokers: 100 % current	3171 received CXR/sputum examination 3174 received baseline CXR, usual care for 4–6 years, then CXR thereafter	Baseline, then every 6 months for 3 years, then annually	19 (0.3)	CXR/sputum: 108 Control: 82	15	CXR/sputum: 7.8 Control: 6.8	92.5 % adherence Poor randomization
Prostate, Lung, Colorectal, and Ovarian [30, 31] (1993)	Sex: 50 % men Age: 55–74 years Smokers: 10 % current, 42 % former	77,445 received CXR 77,456 received usual care (no CXR)	Baseline, then annual for 4 years	CXR: 126 (0.2)	CXR: 1695 Control: 1620	13	CXR: 14.0 Control: 14.2	84–91 % adherence Overdiagnosis

[a]Multiphasic health checkup

respectively. Although lung cancers detected in the screening group were earlier staged, more resectable, and resulted in improved survivorship than those detected in the control group, there was no difference in late-stage cancers or lung cancer mortality between the two groups [13]. Mortality rates after 20 years of follow-up were significantly higher in the screening group (4.4 deaths per 1000 person-years) compared to the control group (3.9 deaths per 1000 person-years) [14]. Limitations of the study included the exclusion of the 91 prevalent cases from the analysis, the absence of a true control group (since nearly half of the controls received annual CXR as part of "usual care"), and low adherence in the screening group (75 %). In addition, lung cancer incidence was 22 % higher in the intervention group than in the control group, which may represent selection bias due to the incomplete randomization or overdiagnosis [15, 16].

The Johns Hopkins and Memorial Sloan-Kettering studies evaluated the addition of frequent sputum cytologic examination to annual CXR as a supplemental screening tool. Both studies combined recruited 20,427 male smokers of 20 or more pack-years who were at least 45 years of age and randomized 10,234 (5266 Hopkins and 4968 Memorial participants) to the screening arm and 10,233 (5161 Hopkins and 5072 Memorial participants) to the control arm. All participants underwent baseline radiographic and sputum cytologic testing and were followed for 5–8 years. The screening group underwent annual dual testing every 4 months, while the control group underwent annual CXR only [17, 18]. The Johns Hopkins Study yielded 39 and 40 prevalent malignancies in the screening and control groups, respectively [17]. Additionally, 194 and 202 incident cases of lung malignancy were diagnosed in the screening and control groups, respectively, during the 8-year follow-up period. Mortality rates were comparable at 3.4 deaths per 1000 person-years in the screening group and 3.8 per 1000 person-years in the control group [19]. In the Memorial Sloan-Kettering Study, baseline screening in the intervention and control groups identified 30 and 23 lung cancers, respectively [20]. Additionally, 114 and 121 incident lung cancers were later detected in the intervention and control groups, totaling 144 cases of lung cancer detected in each arm. Moreover, mortality rates were identical in the dual-screen and CXR-alone groups (2.7 deaths per 1000 person-years) [21, 22].

The fourth RCT evaluating dual screening for lung cancer was from Czechoslovakia where 6364 high-risk male smokers aged 40–64 years were randomized to receive initial baseline and then semiannual CXR and sputum cytologic evaluation for 3 years (n = 3172), or only baseline and final screening after 3 years of no intervention (n = 3174). Initially, 18 lung cancer cases were diagnosed at baseline, and after 3 years of dual screening, there were 39 and 27 incident lung cancer cases in the groups with and without biannual intervention [23]. Mortality rates at 15-year follow-up were comparable with 7.8 deaths per 1000 person-years in the intervention group and 6.8 deaths per 1000 person-years in the control group [24]. These results supported the previous findings of the three American studies that screening using CXR with or without sputum cytologic examination did not reduce lung cancer mortality and should not be recommended.

In addition to the six RCTs, a large nonrandomized controlled trial that took place in Germany (1972–1977) also did not find significant differences in overall or lung cancer-specific mortality between the screening group (n = 41,532) that underwent CXR every 6 months and the control group (n = 102,348) that underwent CXR every 18 months [25]. In contrast to the previous data, several case-controlled trials from recent years (1987–2001) endorse a significant mortality benefit with the use of CXR screening with or without cytologic sputum examination [26–29]. However, the risk of selection bias in these nonrandomized studies is high, and these results must be interpreted with caution.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was a phase III RCT that included lung cancer screening with annual CXR for 3 years in 154,942 participants aged 55–74 years regardless of the risk related to smoking history (51.6 % were ever smokers). The study included women and analyzed the prevalence screening results (126 lung cancers diagnosed from 5991 suspicious CXR) with incidence screening results [30]. Follow-up through 13 years in participants with and without screening found no difference in lung cancer incidence (20.1 versus 19.2 per 10000 person-years in intervention group vs. control group, respectively) or mortality rates (14.0 versus 14.2 per 10000 person-years in intervention group versus control group, respectively). However, lung cancer incidence was higher in current and former smokers (83 and 23 per 10000 person-years, respectively) than in never smokers (3.1 per 10000 person-years), but there was no significant difference in incidence rates, mortality rates, or stages of lung cancer between smokers in the intervention and control groups [31].

The failure of CXR and sputum cytology to impact lung cancer survival in clinical trials may have been due to the inability to identify lung cancers at a small enough size that they could be treated before metastasis occurred. This led to efforts to investigate new screening tools, including low-dose computed tomography (LDCT).

3 Screening with Low-Dose CT of the Chest

The advent of multidetector LDCT as a screening tool that is more sensitive than CXR and capable of generating high-resolution images in a single breath-hold has led several large cohort studies as well as RCTs to evaluate its utility in lung cancer screening [32].

The Early Lung Cancer Action Project (ELCAP) was a single-arm cohort study that evaluated the utility of LDCT in the early diagnosis of lung cancer. In the initial cohort of 1000 asymptomatic smokers aged 60 years or older, all patients underwent both CXR and LDCT baseline screening with 233 (23 %) suspicious lesions found by LDCT and 68 (7 %) lesions by CXR. After appropriately selective diagnostic investigations, 27 (2.7 %) and 7 (0.7 %) malignancies were discovered by LDCT and CXR, respectively [33]. Results of 1184 subsequent screenings every 6–18 months over 2 incidence rounds among 841 participants yielded 30 positive

findings (2.5 %), of which 8 continued to receive invasive biopsy and 7 were diagnosed with malignancy. Other key findings were that false positives were less common in incidence screening than during prevalence screening. In addition, greater than 80 % of malignancies diagnosed were stage I disease for both prevalence and incidence screenings.

ELCAP was expanded internationally (I-ELCAP) to include 31,567 asymptomatic patients from several countries across the world that were considered high risk for lung cancer and received baseline LDCT. These patients were 40 years or older and 83 % were current or former smokers, while the remaining patients had reported exposure to either second-hand smoke or occupational hazards such as asbestos, beryllium, uranium, or radon. There were 4186 positive findings (13.3 %) and 405 lung cancers (1.3 %) diagnosed from baseline scanning. Cumulatively, 27,456 annual screenings were performed over a period of 11 years, and of these, 1460 positive findings were identified, which resulted in 74 lung cancer diagnoses. Altogether, 484 lung cancers were detected during the study, 412 of which were clinically stage I disease (85 %). Ten-year survival rate was estimated to be 88 % in these patients. In the subgroup that had undergone surgery, the estimated 10-year survival rate was 92 % [6].

Table 2 summarizes the findings from the major RCTs that evaluate lung cancer screening with LDCT. Sponsored by the National Cancer Institute, the National Lung Screening Trial (NLST) was the largest RCT that compared annual screening with LDCT (intervention) and with CXR (control) for 3 consecutive years. It included 53,454 high-risk patients from multiple medical centers in the United States (26,722 randomized to intervention group and 26,732 to control group). Selection criteria included current and former smokers who were 55–74 years of age with at least a 30 pack-year smoking history and if a former smoker, cessation within the last 15 years since enrollment [34].

Patients randomized to LDCT underwent a baseline scan followed by two-yearly scans, and then were followed clinically. The study was terminated early due to the significant mortality benefit observed. During baseline screening, there were 7191 (27.3 %) and 2387 (9.2 %) positive findings in the LDCT and CXR arms, respectively. The majority of positive results identified by LDCT (90.4 %) and CXR (92.7 %) underwent diagnostic follow-up including repeat LDCT (81.5 %) or CXR (85.6 %) as well as surgery (4.2 % for LDCT findings and 5.2 % for CXR findings). There were 292 lung cancers (1.1 %) diagnosed in the LDCT group, and 190 lung cancers (0.7 %) were diagnosed in the CXR group [35].

The NLST defined a positive scan as a lung nodule 4 mm in size or larger. The study did not specify how to manage nodules or when to perform invasive procedure, leaving this up to the discretion of the study site. Among all LDCT scans from baseline and incidence screenings, 24.2 % were positive and 72.1 % of these underwent diagnostic follow-up (mostly imaging) with the identification of 96.4 % false-positive results. In the control arm, 6.9 % of CXR were considered positive and 85 % underwent further diagnostic follow-up with the identification of 94.5 % false-positive results. In addition to positive lung findings, there were also other incidental clinically significant findings from both the LDCT (7.5 %) and CXR

Table 2 Randomized controlled trials of lung cancer screening with low-dose computed tomography (LDCT)

Study (year)	Population/Screening criteria	Intervention/Control	Screening frequency and length	Baseline results, n (%)	Lung cancer incidence results, n	F/u (years)	Lung cancer (LC) mortality	Other
NLST [35, 36, 75] (2002)	Sex: 59 % men Smokers: all (48 % current) Age: 55–74 years Pack-year: ≥ 30 Quit time: ≤ 15 years	26,723 received LDCT 26,733 received CXR[a]	Baseline, then annual for 3 years (terminated early)	LDCT: 292 (1.1) of 7191 (27.3) positive results Control: 190 (0.7) of 2387 (9.2) positive results	LDCT: 1060 Control: 941	6.5	LDCT: 247 deaths per 100,000 person-years Control: 309 deaths per 100,000 person-years RR 0.8 ($p = 0.04$)	70 % screen-detected LC were stages I–II 20 % reduction in lung cancer mortality >90 % White
NELSON [39] (2009)	Sex: 84 % men Smokers: all (55 % current) Age: 50–75 years Pack-year: 15 cig/d for >25 years or 10 cig/day for >30 years Quit time: ≤ 10 years	7515 received LDCT 7907 received no LDCT	Baseline and at 1, 2, 2.5 years intervals since previous screen	62 (0.9) of 184 positive results (3.0)	LDCT: 187 of 463 positive results Control: NR	8.16	unavailable	66 % screen-detected LC were stage I 35 interval cancers detected between screenings
DLCST [40, 41] (2004)	Sex: 55 % men Smokers: all (76 % current) Age: 50–70 years Pack-year: ≥ 20 Quit time: after age 50 and ≤ 10 years	2052 received LDCT 2052 received no LDCT	Baseline, then annual for 5 years	17 (0.8) of 179 positive results (8.7)	LDCT: 52 of 469 lung nodules Control: 24	5	LDCT: 15 LC deaths (0.73 %) Control: 11 LC deaths (0.54 %) Log-rank test $p = 0.43$	68 % screen-detected LC were stage I

(continued)

Table 2 (continued)

Study (year)	Population/Screening criteria	Intervention/Control	Screening frequency and length	Baseline results, n (%)	Lung cancer incidence results, n	F/u (years)	Lung cancer (LC) mortality	Other
DANTE [42, 43] (2001)	Sex: 100 % men Smokers: all (55 % current) Age: 60–74 years Pack-year: ≥ 20 Quit time: ≤ 10 years	1276 received LDCT 1196 received no LDCT (all had baseline CXR, and 68 % had sputum examination)	Baseline, then annual for 5 years	LDCT: 28 (2.2) of 199 positive results (15.6) CXR with sputum: 8 (0.7) of 37 positive results (3.1)	LDCT: 60 (4.7 %) Control: 34 (4.7 %) $p = 0.016$	2.8	LDCT: 20 (1.6 %) LC deaths Control: 20 (1.7 %) Log-rank test $p = 0.84$	65 % screen-detected LC were stage I
MILD [44] (2005)	Sex: 66 % men Smokers: all (77 % current) Age: >49 years Pack-year: ≥ 20 Quit time: ≤ 10 years	2376 received LDCT 1723 received no LDCT	1186 biennial 1190 annual	LDCT: 17 (0.7) Biennial: 6 (0.5) Annual: 11 (0.9)	LDCT: 32 Biennial: 14 Annual: 18 Control: NR	6	LDCT: 108.5 deaths per 100,000 person-years (biennial: 108.8, annual: 216) Control: 108.5 deaths per 100,000 person-years	65 % screen-detected LC were stage I

(continued)

Table 2 (continued)

Study (year)	Population/Screening criteria	Intervention/Control	Screening frequency and length	Baseline results, n (%)	Lung cancer incidence results, n	F/u (years)	Lung cancer (LC) mortality	Other
LUSI [85, 86] (2007)	Sex: 65 % men Smokers: all (62 % current Age: 50–69 years Pack-year: 15 cig/d for 25 years or 10 cig/d for 10 years Quit time: 10 years	2029 received LDCT 2023 received no LDCT	Baseline, then annual for 4 years	LDCT: 23 (1.1) of 540 positive results (26.6 %) Control: NR	LDCT: 35 (674 cases per 100,000 person-years) Control: 363 cases per 100,000 person-years	3–6.5	NR Overall mortality: LDCT: 43 Control: 54 $p = 0.26$	72 % of screen-detected LC were stage I 4 interval cancers detected Ongoing last incidence screening and follow-up for last 3 incidence rounds
ITALUNG [87]	Sex: 65 % men Smokers: all (65 % current) Age: 55–69 years Pack-year: ≥ 20 Quit time: ≤ 10 years	1406 received LDCT 1593 received no LDCT	Baseline, then annual for 4 years	LDCT: 21 (1.5) from 639 nodules in 426 patients (30 %)	unavailable	NR	Unavailable	52 % of screen-detected LC were stage I

[a]*CXR* Chest X-ray, *cig* cigarette, *LC* lung cancer

(2.1 %) groups that were not suggestive of lung cancer. Positive and incidental findings and their need for diagnostic follow-up were significantly reduced by the second incidence round since most abnormal or clinically significant findings that remained unchanged on repeated screenings were considered negative.

There were 1060 lung cancers diagnosed in the intervention group, of which 649 (61.2 %) were identified by positive LDCT; this was compared to 941 lung cancers diagnosed in the control group, of which 279 (29.6 %) were identified by positive CXR [36]. Lung cancer detection rates were consistent across screening years. Stage I and II lung cancers made up 70 and 56.7 % of malignancies diagnosed by LDCT and CXR, respectively. In addition, 92.5 % of stage I cancers diagnosed by LDCT and 87.5 % diagnosed by CXR were treated with surgery with or without adjuvant chemoradiotherapy. Metastatic disease was less common in the LDCT group than in the CXR group in later screenings. Lung cancers detected by LDCT were mostly adenocarcinoma (40 %) and only a small proportion were small-cell histology (7.6 %) although the majority of these (87.2 %) were diagnosed at stages IIIa-IV [37].

There were 247 deaths per 100,000 person-years in the intervention group versus 309 deaths per 100,000 person-years in the control group. This corresponded to a 20 % relative reduction in death rate from lung cancer when using LDCT instead of CXR for screening ($p = 0.004$). In addition, LDCT conferred a 6.7 % reduction in overall mortality ($p = 0.02$), although this benefit was reduced to 3.2 %, which was no longer significant ($p = 0.28$) when lung cancer deaths were excluded [36].

The NLST is the only RCT that has demonstrated a reduction in lung cancer mortality using LDCT screening. Currently, several European RCTs are ongoing although none appear to be individually large enough to demonstrate a mortality benefit. Pooled data for combined analysis will be reported in the next few years [38]. Among the European studies, the NELSON Trial from the Netherlands and Belgium was the largest with 15,822 current and former smoking participants aged 50–75 years that were randomized to LDCT or no screening. Preliminary results over 3 screenings reported 196 screen-detected lung cancers among 187 (3 %) of 7155 screened participants. There were 276 (4 %) false positives and 35 interval lung cancers. Screen-detected lung cancers were more often adenocarcinoma (52 %) and early stage (77 % stages I–II). Data were not reported for the control group [39].

The Danish Randomized Lung Cancer CT Screening Trial (DLCST) was the second largest European RCT featuring 4104 past or present smokers (≥ 20 pack-years) aged 50–70 years randomized to receive LDCT or no screening. Baseline screening detected only 17 cases of lung cancer (0.83 %) among 2052 screened participants, of which 9 had stage I disease (53 %) and 11 underwent surgery (65 %). The false-positive rate was 7.9 % [40]. After 5 incidence screening rounds, 69 total lung cancers were diagnosed in the screening group (0.67 % mean annual detection rate) compared to 24 in the control group ($p < 0.001$). Stage I disease made up 70 % of diagnosed lung cancers ($n = 48$) in the screening group compared to 33 % in the control group ($n = 8$). Lung cancer-specific mortality and

overall mortality were not significantly different between the two groups ($p = 0.428$ and 0.059, respectively) [41].

The DANTE (Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays) Trial was a randomized study from Italy that included 2472 male current and former smokers (≥ 20 pack-years) aged 60–74 years. All participants underwent baseline CXR and sputum cytologic examination. The intervention group then underwent baseline and annual LDCT for 5 years. Baseline lung cancer detection rate was 2.2 % ($n = 28$) in the intervention group and 0.67 % ($n = 8$) in the control group [42]. After a median of 33-month follow-up, there were 60 lung cancers (4.7 %) in participants receiving LDCT and 34 (2.8 %) in those from the control arm ($p = 0.016$). Stage I disease was detected in 54 % of lung cancers identified by LDCT and 34 % of lung cancers diagnosed in the control group. Lung cancer mortality was comparable in the LDCT group ($n = 20$, 1.6 %) and the control group ($n = 20$, 1.7 %) [43].

Finally, the prospective, randomized Multicentric Italian Lung Detection (MILD) Trial recruited 4099 smokers aged 49 years or older who had smoked at least 20 pack-years and if a former smoker, had quit within 10 years of recruitment. The intervention group received biennial LDCT ($n = 1186$) or annual LDCT ($n = 1190$), while the control group did not undergo screening ($n = 1723$). There were 17 lung cancers identified from baseline LDCT which increased to 49 after 5 years of screening (20 in biennial and 29 in annual arm), of which 63 % were stage I. Twenty lung cancers were diagnosed in the control group, but stage distribution was not reported. Lung cancer incidence was higher in the screening groups than in the control group ($p = 0.025$), but was similar between the two screening groups ($p = 0.24$). When comparing lung cancer-specific and total mortality among the two screening groups and the control group, no significant differences were reported by the authors [44]. However, a meta-analysis comparing mortality between the annual LDCT and control groups found an increased risk of lung cancer mortality (RR 1.98, 95 % CI 1.57–2.50) as well as all-cause mortality (RR 1.80, 95 % CI 1.03–3.13) in the annual LDCT groups. These results were difficult to interpret as the study was judged to be of low quality due to poor randomization and follow-up [45].

4 Benefits and Risks of LDCT Screening

The NLST provided unequivocal evidence that screening with three annual LDCT reduced lung cancer mortality. Although the study was prematurely terminated due to the mortality benefit, lung cancer detection rates were constant over screening years, which suggested that ongoing screening beyond three years may provide additional benefit [36]. While the European trials have yet to demonstrate a mortality benefit from lung cancer screening, they have reported a significant preponderance of early-stage screen-detected cancers (48–81 % stage I) [38] compared to conventional clinically diagnosed lung cancers, of which a minority were detected early (15 % stage I) [2].

The diagnosis and treatment of lung cancer in the preclinical stage have the potential to reduce the symptom burden of lung cancer manifesting at a later stage. However, this has not been reported and a controlled analysis of the difference in lung cancer symptoms in patients diagnosed by screening or by clinical presentation is necessary to make any conclusions about whether screening decreases the burden of disease-related symptoms.

Furthermore, the diagnosis of lung cancer at an earlier stage has important implications when considering treatment options. Since curative resection with adequate lymph node examination remains the standard for curative therapy, it is important to minimize the morbidity and mortality of surgery. Early-stage screen-detected lung cancers are less likely to require pneumonectomy [46] and more likely to be amenable to minimally invasive video-assisted thoracoscopic surgery (VATS), which has been shown in institutional series and population studies to have reduced postoperative complications but similar oncologic outcomes as open thoracotomy [47–51]. In addition, small peripheral screen-detected lung tumors may be treated definitively with stereotactic body radiation therapy (SBRT) [52]. With VATS and SBRT as treatment options, even elderly and high-risk patients may benefit from and should be considered for lung cancer screening.

The NLST reported that 7.5 % of all LDCT scans were positive for abnormalities that were clinically significant, but not suspicious for lung cancer. These findings include chronic obstructive pulmonary disease (COPD), cardiovascular disease (as predicted by coronary calcium scoring), and osteoporosis [53–55]. Treatment for these asymptomatic but clinically significant conditions could potentially prevent chronic exacerbations or acute events such as myocardial infarction or debilitating fracture. Prospective studies are needed to critically analyze whether discovering and treating these incidental findings provide any benefit in morbidity or mortality.

Lung cancer screening offers a unique opportunity to promote smoking cessation [56]. Some studies have reported that participants of screening were more likely to be abstinent from smoking if they had abnormalities on LDCT; however, after long-term follow-up, participants with positive, noncancerous findings were found to have similar quit rates as those with consistently negative findings [57]. Furthermore, smoking behavior was not appreciably different between the intervention and control groups in lung cancer screening studies [58, 59]. Nevertheless, current smokers who present for screening should be advised to quit and former smokers should be encouraged to continue abstinence from smoking. In fact, adding smoking cessation counseling to a lung cancer screening program may increase its cost-effectiveness [60].

In addition to the benefits of lung cancer screening with LDCT, there are also risks and limitations to be considered. First, although LDCT is highly sensitive for detecting lung abnormalities, it is not very specific for malignancy as demonstrated by the high rates of false-positive results in lung cancer screening studies. The rate of false-positive findings is directly related to the nodule size threshold used to define a positive screen. While NLST used a 4-mm threshold, data from the

IELCAP group demonstrated that raising the size threshold to 6 mm leads to a marked decrease in positive tests and false-positive tests, but lung cancers are not missed by increasing this size threshold [61]. These data and others led to the development and implementation of the American College of Radiology (ACR) Lung Reporting and Data System (Lung-RADS) to standardize reporting of LDCT screening and management of screen-detected nodules [62].

Most positive findings from LDCT screening were followed up with imaging, and only a small minority required invasive biopsy or surgery [63]. In NLST, approximately 1 % of patients who did not have a malignancy underwent needle or transbronchial biopsy and less than 1 % had surgery. The 60-day mortality and complication rates following invasive diagnostic procedures for false positives were also very low, estimated at 0.06 and 0.36 %, respectively. However, this was difficult to interpret since details regarding whether death or complication was attributed to the diagnostic procedure were not collected in the study [36].

The imaging required to follow up all positive findings from lung cancer screening with LDCT raises the concern of the risks of radiation exposure. Although LDCT was performed with as little as 1.5 mSv per examination, the additional use of diagnostic and positron emission tomography (PET) CT scans increased the radiation exposure to approximately 8 mSv per participant in the NLST over 3 years of screening. The effects of repeated exposure of the chest to radiation in individuals already at high risk for lung cancer are unknown, but the mortality benefit from LDCT screening currently outweighs the risk of additional radiation-induced deaths. Furthermore, the lung cancer risk from radiation exposure is a delayed effect that is unlikely to impact participants until 10–20 years after the initiation of screening [63]. The cumulative risk of repeated radiation exposure from lung cancer screening may be greater for younger participants based on modeling studies, but additional research is needed to better characterize this risk, especially if LDCT screening is to continue beyond three years [63, 64].

Overdiagnosis, or the detection of clinically indolent disease, is another potential harm of lung cancer screening [65]. These patients with slow-growing tumors that would otherwise not impact their life spans may be subjected to unnecessary workup and treatment along with their associated risks. Randomized CXR and observational LDCT screening studies have estimated that overdiagnosis may occur 13–27 % of the time [16, 66, 67]; however, true estimates from the NLST will require longer follow-up. Nevertheless, the natural course of most NSCLC is progressive and most likely fatal within 5 years if left untreated [68]. As a result, the reduction in lung cancer mortality with LDCT screening is likely a benefit that outweighs the risk of overdiagnosis in the minority of detected indolent disease.

Two recent systematic reviews detailed the impact of lung cancer screening on patient anxiety, risk perception, and health-related quality of life (HRQoL). The findings were based on thirteen studies from three RCTs and three from cohort studies. In one analysis, nearly half of NELSON participants reported psychological distress while awaiting screening results. These patients as well as those who had high perceived risk of lung cancer reported increased distress with indeterminate results at the short-term follow-up, but not at the long-term follow-up. In contrast,

NLST participants who received true-positive results demonstrated worse anxiety and HRQoL at the short-term and long-term follow-up, while those with false-positive results did not show worse measures of anxiety or quality of life at any time point. The DLCST reported worse measures of psychological consequences in trial participants for years following lung cancer screening although these measures eventually normalized to baseline levels. Interestingly, the DLCST control group scored worse than the screening group at all time periods. This may be due to participation bias from inadequate randomization and disappointment in the control group at not receiving the intervention. Although lung cancer screening does not appear to cause significant lasting anxiety or adverse impact on HRQoL in trial participants, additional studies are necessary to assess the potential psychological harms of screening when applied to the general populations [69, 70].

5 Guidelines for LDCT Screening

Several major health organizations have put forth lung cancer screening guidelines based on criteria used by the NLST to select for eligible screenees. The United States Preventative Services Task Force (USPSTF) has published criteria recommending lung cancer screening in individuals aged 55–80 years who are current or former smokers with at least a 30 pack-year history and if a former smoker, have quit within the last 15 years. The specific age, smoking history, and quit time criteria are derived from various screening scenario models that weigh the benefit of lung cancer deaths averted against the potential harms of radiation-induced lung cancer deaths and overdiagnosis. The USPSTF also recommends that those who have limited life expectancy or refuse surgery should not undergo screening [71].

Similarly, the National Comprehensive Cancer Network (NCCN) has also published guidelines for lung cancer screening that parallel the USPSTF guidelines with the exception of a more restrictive age criterion of 55–74 years as used by the NLST. However, in addition to the primary lung cancer screening criteria (age 55–74 years, $\geq$30 pack-year smoking history, smoking cessation within 15 years), the NCCN also supplies secondary screening criteria that consist of lowered age (age $\geq$ 50 years) and smoking history criteria ($\geq$20 pack-years) with the addition of a lung cancer risk factor other than second-hand smoking. The additional risk factors include documented high radon exposure, occupational exposures (i.e., asbestos), cancer history (head and neck, lymphoma, lung, or other smoking-related cancers), and history of COPD or pulmonary fibrosis [72].

Other major health organizations and their lung cancer screening criteria are seen in Table 3. Notably, the American Association for Thoracic Surgeons (AATS) extends screening to individuals aged 55–79 years who have smoked at least 30 pack-years without a quit time maximum requirement for former smokers [73]. In early 2015, the Centers for Medicare and Medicaid Services (CMS) issued a decision memo detailing coverage for lung cancer screening with annual LDCT. Beneficiary eligibility criteria include asymptomatic current and former smokers aged 55–77-years with a minimum 30 pack-year history and if a former smoker,

Table 3 Lung cancer screening (LCS) criteria among major health organizations

LCS criteria for screening	USPSTF [71] (2013)	CMS [74] (2015)	NCCN [72] (2012)		AATS [73] (2012)		Other [23, 88, 89] using NLST derived criteria[a] (2012–2013)
			Primary	Secondary	Primary	Secondary	
Age (years)	55–80	55–77	55–74	50–79	55–79	≥ 50	55–74
Smoking history (pack-year)	≥ 30	≥ 30	≥ 30	≥ 20	≥ 30	≥ 20	≥ 30
Quit time (years)	15	15	15	none	none	none	15
Other criteria	–	–	–	Additional risk factor[b]	–	Additional risk factor[c] or Lung cancer survivors[d]	–

USPSTF US Preventative Services Task Force; *CMS* Center for Medicare and Medicaid Services; *NCCN* National Comprehensive Cancer Network; *NLST* National Lung Screening Trial; *AATS* American Association for Thoracic Surgery

[a]Organizations including the American Cancer Society (ACS), American College of Chest Physicians (ACCP), American Society of Clinical Oncology (ASCO), American Lung Association (ALA)

[b]History of cancer (especially head and neck, lymphoma, lung, and other smoking-related cancers), lung disease (COPD, pulmonary fibrosis), family member with lung cancer, radon exposure, occupational exposure

[c]Resulting in cumulative lung cancer risk ≥ 5 % in 5 years (i.e., COPD with FEV1 <70 %, environmental/occupational exposure, prior cancer/radiation therapy, genetic/family history)

[d]After 4 years of negative surveillance

maximum 15 years of cessation. The memo also stipulated requirements for facilities providing LDCT and for radiologists interpreting the imaging; this included data submission to a CMS-approved registry for each screening performed [74].

As lung cancer screening disseminates into the general population, there are still many questions to be addressed. The first question is whether the criteria used by the NLST are applicable outside of the trial population, which was reported as >90 % White, more educated, and younger than national smokers [75]. A study applying existing USPSTF lung cancer screening criteria to a population cohort of NSCLC patients found that the proportion of patients qualifying for lung cancer screening has been declining due to reduced smoking prevalence [76]. When lung cancer screening criteria were applied to an institutional cohort of NSCLC patients, only a third met all USPSTF criteria and current smokers were more likely to be screening-eligible than former smokers, since only half of former smokers had quit smoking within 15 years [77].

Furthermore, there is considerable variability in the age criterion and use of secondary screening criteria among various major health organizations. The upper age limit remains controversial, and while some studies report increased morbidity and mortality in elderly patients who undergo lung surgery, others contend that elderly patients, when treated surgically for their lung cancer, have better outcomes [78–80]. As mentioned previously, advances in minimally invasive surgery and SBRT permit elderly and other high-risk patients with early-stage screen-detected tumors to benefit from treatment. In addition, although the NLST stopped screening at 3 annual LDCTs, there is no evidence to suggest that the mortality benefit of lung cancer screening is limited to three years. However, when to start and when to stop screening remain important questions to be addressed as screening becomes prolific in the general population.

Additional evidence-based research is needed to validate existing lung cancer screening criteria. Indeed, models that consider various age and smoking history criteria and those that incorporate risk factors from secondary screening criteria as well as race, education level, and body mass index (BMI) suggest that better selection criteria for lung cancer screening are possible [81, 82]. Indeed, any revisions of screening guidelines need to take into consideration the benefits and risks of screening and arrive at criteria that allow maximum mortality benefit with minimal harm to the patient and low cost to the healthcare system. Cost-effectiveness analysis performed for the NLST study has found that LDCT for lung screening is cost-effective [83]. True cost-benefit analysis for lung cancer screening remains to be realized as more follow-up is required before the true potential benefit of lung cancer screening can be quantified.

6 Conclusions

Lung cancer screening with LDCT is safe and effective in reducing lung cancer mortality and is recommended by the USPSTF for high-risk current and former smokers. In addition, LDCT is cost-effective. Screening for lung cancer with chest X-ray is not recommended. Additional research is needed on which populations benefit most from screening, based on age, tobacco exposure history, and sex. Current recommendations are based on data from NLST, but a minority of patients with lung cancer would be detected on LDCT using existing guidelines. Data from ongoing lung cancer screening studies including IELCAP and several European studies may improve the selection of patients for screening. Finally, additional research is needed to improve the identification of smokers and improve the integration of LCS with tobacco cessation counseling. Moreover, a better understanding of the impact of LCS on tobacco use and psychosocial well-being in diverse populations is needed.

References

1. Torre LA et al (2015) Global cancer statistics, 2012. CA Cancer J Clin 65(2):87–108
2. Howlader N et al (2014) SEER cancer statistics review, 1975–2012, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015
3. Flieder DB et al (2005) Tumor size is a determinant of stage distribution in T1 non-small cell lung cancer. Chest 128(4):2304–2308
4. Raz DJ et al (2007) Clinical characteristics and survival of patients with surgically resected, incidentally detected lung cancer. J Thorac Oncol 2(2):125–130
5. Quadrelli S et al (2015) Clinical characteristics and prognosis of incidentally detected lung cancers. Int J Surg Oncol 2015:287604
6. International Early Lung Cancer Action Program I et al (2006) Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 355(17):1763–1771
7. Humphrey LL et al (2004) Lung cancer screening with sputum cytologic examination, chest radiography, and computed tomography: an update for the U.S. preventive services task force. Ann Intern Med 140(9):740–753
8. Brett GZ (1968) The value of lung cancer detection by six-monthly chest radiographs. Thorax 23(4):414–420
9. Brett GZ (1969) Earlier diagnosis and survival in lung cancer. Br Med J 4(5678):260–262
10. Dales LG, Friedman GD, Collen MF (1979) Evaluating periodic multiphasic health checkups: a controlled trial. J Chronic Dis 32(5):385–404
11. Friedman GD, Collen MF, Fireman BH (1986) Multiphasic health checkup evaluation: a 16-year follow-up. J Chronic Dis 39(6):453–463
12. Fontana RS et al (1984) Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo clinic study. Am Rev Respir Dis 130(4): 561–565
13. Fontana RS et al (1986) Lung cancer screening: the Mayo program. J Occup Med 28(8): 746–750
14. Marcus PM et al (2000) Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. J Natl Cancer Inst 92(16):1308–1316
15. Fontana RS et al (1991) Screening for lung cancer. A critique of the Mayo Lung Project. Cancer. 67(4 Supp):1155–1164
16. Marcus PM et al (2006) Extended lung cancer incidence follow-up in the Mayo Lung Project and overdiagnosis. J Natl Cancer Inst 98(11):748–756
17. Frost JK et al (1984) Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. Am Rev Respir Dis 130(4):549–554
18. Melamed MR et al (1984) Screening for early lung cancer. Results of the memorial Sloan-Kettering study in New York. Chest 86(1):44–53
19. Tockman MS (1986) Survival and mortality from lung cancer in a screened population: the Johns Hopkins study. Chest 89(4 Supp):324S–325S
20. Flehinger BJ et al (1984) Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Memorial Sloan-Kettering study. Am Rev Respir Dis 130(4):555–560
21. Martini N (1986) Results of the Memorial Sloan-Kettering study in screening for early lung cancer. Chest 89(4Supp):325S–325S
22. Melamed MR (2000) Lung cancer screening results in the National Cancer Institute New York study. Cancer 89(11 Suppl):2356–2362
23. Kubik A, Polak J (1986) Lung cancer detection. Results of a randomized prospective study in Czechoslovakia. Cancer 57(12):2427–2437
24. Kubik AK, Parkin DM, Zatloukal P (2000) Czech study on lung cancer screening: post-trial follow-up of lung cancer deaths up to year 15 since enrollment. Cancer 89(11 Suppl): 2363–2368

25. Wilde J (1989) A 10 year follow-up of semi-annual screening for early detection of lung cancer in the Erfurt County, GDR. Eur Respir J 2(7):656–662
26. Okamoto N et al (1999) Evaluation of a clinic-based screening program for lung cancer with a case-control design in Kanagawa, Japan. Lung Cancer 25(2):77–85
27. Nishii K et al (2001) A case-control study of lung cancer screening in Okayama Prefecture, Japan. Lung Cancer 34(3):325–332
28. Sagawa M et al (2001) A case-control study for evaluating the efficacy of mass screening program for lung cancer in Miyagi Prefecture, Japan. Cancer 92(3):588–594
29. Tsukada H et al (2001) An evaluation of screening for lung cancer in Niigata Prefecture, Japan: a population-based case-control study. Br J Cancer 85(9):1326–1331
30. Oken MM et al (2005) Baseline chest radiograph for lung cancer detection in the randomized prostate, lung, colorectal and ovarian cancer screening trial. J Natl Cancer Inst 97(24): 1832–1839
31. Oken MM et al (2011) Screening by chest radiograph and lung cancer mortality: the prostate, lung, colorectal, and ovarian (PLCO) randomized trial. JAMA 306(17):1865–1873
32. Black WC (2007) Computed tomography screening for lung cancer: review of screening principles and update on current status. Cancer 110(11):2370–2384
33. Henschke CI et al (1999) Early lung cancer action project: overall design and findings from baseline screening. Lancet 354(9173):99–105
34. National Lung Screening Trial Research T et al (2011) The national lung screening trial: overview and study design. Radiology 258(1):243–253
35. National Lung Screening Trial Research T et al (2013) Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med 368(21):1980–1991
36. National Lung Screening Trial Research T et al (2011) Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 365(5):395–409
37. Aberle DR et al (2013) Results of the two incidence screenings in the national lung screening trial. N Engl J Med 369(10):920–931
38. Field JK et al (2013) European randomized lung cancer screening trials: post NLST. J Surg Oncol 108(5):280–286
39. Horeweg N et al (2014) Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. Lancet Oncol 15 (12):1342–1350
40. Pedersen JH et al (2009) The Danish randomized lung cancer CT screening trial–overall design and results of the prevalence round. J Thorac Oncol 4(5):608–614
41. Saghir Z et al (2012) CT screening for lung cancer brings forward early disease. The randomised danish lung cancer screening trial: status after five annual screening rounds with low-dose CT. Thorax 67(4):296–301
42. Infante M et al (2008) Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. Lung Cancer 59(3):355–363
43. Infante M et al (2009) A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med 180 (5):445–453
44. Pastorino U et al (2012) Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. Eur J Cancer Prev 21(3):308–315
45. Humphrey LL et al (2013) Screening for lung cancer with low-dose computed tomography: a systematic review to update the US preventive services task force recommendation. Ann Intern Med 159(6):411–420
46. Grannis FW (2004) Can we avert the need for pneumonectomy by screening for lung cancer? Eur J Cardiothorac Surg 25(2):296
47. Flores RM et al (2009) Lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy for lung cancer. J Thorac Cardiovasc Surg 138(1):11–18

48. Paul S et al (2010) Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. J Thorac Cardiovasc Surg 139(2):366–378
49. Paul S et al (2013) Outcomes after lobectomy using thoracoscopy vs thoracotomy: a comparative effectiveness analysis utilizing the nationwide inpatient sample database. Eur J Cardiothorac Surg 43(4):813–817
50. Higuchi M et al (2014) Long-term outcomes after video-assisted thoracic surgery (VATS) lobectomy versus lobectomy via open thoracotomy for clinical stage IA non-small cell lung cancer. J Cardiothorac Surg 9:88
51. Lee PC et al (2013) Long-term survival after lobectomy for non-small cell lung cancer by video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg 96(3):951–60 (discussion 960-1)
52. Timmerman R et al (2010) Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 303(11):1070–1076
53. Mets OM, de Jong PA, Prokop M (2012) Computed tomographic screening for lung cancer: an opportunity to evaluate other diseases. JAMA 308(14):1433–1434
54. Mets OM et al (2011) Identification of chronic obstructive pulmonary disease in lung cancer screening computed tomographic scans. JAMA 306(16):1775–1781
55. Jacobs PC et al (2011) Unrequested information from routine diagnostic chest CT predicts future cardiovascular events. Eur Radiol 21(8):1577–1585
56. Taylor KL et al (2007) Lung cancer screening as a teachable moment for smoking cessation. Lung Cancer 56(1):125–134
57. Anderson CM et al (2009) Smoking cessation and relapse during a lung cancer screening program. Cancer Epidemiol Biomarkers Prev 18(12):3476–3483
58. Ashraf H et al (2009) Effect of CT screening on smoking habits at 1-year follow-up in the danish lung cancer screening trial (DLCST). Thorax 64(5):388–392
59. Townsend CO et al (2005) Relation between smoking cessation and receiving results from three annual spiral chest computed tomography scans for lung carcinoma screening. Cancer 103(10):2154–2162
60. Villanti AC et al (2013) A cost-utility analysis of lung cancer screening and the additional benefits of incorporating smoking cessation interventions. PLoS ONE 8(8):e71379
61. Henschke CI et al (2013) Definition of a positive test result in computed tomography screening for lung cancer: a cohort study. Ann Intern Med 158(4):246–252
62. Pinsky PF et al (2015) Performance of Lung-RADS in the national lung screening trial: a retrospective assessment. Ann Intern Med 162(7):485–491
63. Bach PB et al (2012) Benefits and harms of CT screening for lung cancer: a systematic review. JAMA 307(22):2418–2429
64. Berrington de Gonzalez A, Kim KP, Berg CD (2008) Low-dose lung computed tomography screening before age 55: estimates of the mortality reduction required to outweigh the radiation-induced cancer risk. J Med Screen 15(3):153–158
65. Reich JM (2008) A critical appraisal of overdiagnosis: estimates of its magnitude and implications for lung cancer screening. Thorax 63(4):377–383
66. Lindell RM et al (2007) Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. Radiology 242(2):555–562
67. Sone S et al (2007) Long-term follow-up study of a population-based 1996–1998 mass screening programme for lung cancer using mobile low-dose spiral computed tomography. Lung Cancer 58(3):329–341
68. Raz DJ et al (2007) Natural history of stage I non-small cell lung cancer: implications for early detection. Chest 132(1):193–199
69. Slatore CG et al (2014) Patient-centered outcomes among lung cancer screening recipients with computed tomography: a systematic review. J Thorac Oncol 9(7):927–934
70. Wu GX et al (2015) Psychological harm associated with lung cancer screening: a systematic review, in Submitted to Psychooncology

71. Moyer VA, U.S.P.S.T. Force (2014) Screening for lung cancer: U.S. preventive services task force recommendation statement. Ann Intern Med 160(5):330–338
72. Wood DE et al (2012) Lung cancer screening. J Natl Compr Canc Netw 10(2):240–265
73. Jaklitsch MT et al (2012) The American association for thoracic surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg 144(1):33–38
74. Jensen T et al (2015) Final national coverage determination on screening for lung cancer with low dose computed tomography (LDCT). The Centers for Medicare & Medicaid Services (CMS)
75. National Lung Screening Trial Research T et al (2010) Baseline characteristics of participants in the randomized national lung screening trial. J Natl Cancer Inst 102(23):1771–1779
76. Wang Y et al (2015) Trends in the proportion of patients with lung cancer meeting screening criteria. JAMA 313(8):853–855
77. Wu GX et al (2015) The proportion of newly diagnosed non-small cell lung cancer patients that would have been eligible for lung cancer screening. Submitted to JTCVS
78. Gray SW et al (2012) Improved outcomes associated with higher surgery rates for older patients with early stage nonsmall cell lung cancer. Cancer 118(5):1404–1411
79. Mery CM et al (2005) Similar long-term survival of elderly patients with non-small cell lung cancer treated with lobectomy or wedge resection within the surveillance, epidemiology, and end results database. Chest 128(1):237–245
80. Rueth NM et al (2012) Surgical treatment of lung cancer: predicting postoperative morbidity in the elderly population. J Thorac Cardiovasc Surg 143(6):1314–1323
81. McMahon PM et al (2014) Comparing benefits from many possible computed tomography lung cancer screening programs: extrapolating from the national lung screening trial using comparative modeling. PLoS ONE 9(6):e99978
82. Tammemagi MC et al (2013) Selection criteria for lung-cancer screening. N Engl J Med 368 (8):728–736
83. Black WC et al (2014) Cost-effectiveness of CT screening in the national lung screening trial. N Engl J Med 371(19):1793–1802
84. Kubik A et al (1990) Lack of benefit from semi-annual screening for cancer of the lung: follow-up report of a randomized controlled trial on a population of high-risk males in Czechoslovakia. Int J Cancer 45(1):26–33
85. Becker N et al (2012) Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. J Cancer Res Clin Oncol 138 (9):1475–1486
86. Becker N et al (2015) Randomised study on early detection of lung cancer with MSCT in Germany: results of the first 3 years of follow-up after randomisation. J Thorac Oncol 10: 890–896
87. Lopes Pegna A et al (2009) Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. Lung Cancer 64(1):34–40
88. Smith RA et al (2014) Cancer screening in the United States, 2014: a review of current American cancer society guidelines and current issues in cancer screening. CA Cancer J Clin 64(1):30–51
89. Detterbeck FC et al (2013) Screening for lung cancer: diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 143(5 Suppl):e78S–e92S

Diagnosis and Molecular Classification of Lung Cancer

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Abstract

Lung cancer is a complex disease composed of diverse histological and molecular types with clinical relevance. The advent of large-scale molecular profiling has been helpful to identify novel molecular targets that can be applied to the treatment of particular lung cancer patients and has helped to reshape the pathological classification of lung cancer. Novel directions include the immunotherapy revolution, which has opened the door for new opportunities for cancer therapy and is also redefining the classification of multiple tumors, including lung cancer. In the present chapter, we will review the main current basis of the pathological diagnosis and classification of lung cancer incorporating the histopathological and molecular dimensions of the disease.

Keywords

Lung cancer · Pathology classification · Molecular targets

Contents

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1 Introduction

Despite a recent decline in the incidence and death rate, lung cancer still remains as the leading cause of death by cancer in the United States, with 158,040 deaths expected to occur in 2015, which represent about 27 % of all cancer deaths [1]. Among the reasons for its high mortality is the fact that 57 % of the cases are diagnosed at a distant stage in which the 1- and 5-year survivals are 26 and 4 %, respectively [1, 2]. Lung cancer is a heterogeneous disease, which comprises several subtypes with pathological and clinical relevance [3–5]. All lung cancer subtypes are strongly associated with exposure to tobacco smoking; however, adenocarcinoma is the most common type in never-smoker patients [1, 2, 6–9]. Based on main histotype, prognostic, and therapeutic implications, lung cancers are divided in two main groups: small-cell carcinoma (SCLC, 13 % of the cases) and non-small-cell carcinoma (NSCLC, 83 % of the cases) [1, 5]. In this chapter, we will focus on the NSCLC group, with special emphasis on the main subtypes of NSCLC and its clinical and molecular importance, while SCLC will be discussed in Chap. XV [5].

2 Histological Classification of NSCLC

To the present day, the gold standard procedure for the diagnosis of lung cancer remains the microscopic evaluation of histological or cytological specimens under the microscope by a pathologist [10]. The biopsy or cytology specimen provides initial key information of clinical relevance including the confirmation of the presence of a tumor and its histotype based on morphological and immunohistochemical (IHC) features [11–13]. In the past, the major focus of the clinical diagnosis was to make the distinction between SCLC and NSCLC, without major therapeutic indications to further classify NSCLC tumors. However, the advent of molecular profiling and targeted therapy renewed interest to the further classify NSCLC into adenocarcinoma (ADC) and its variants, squamous cell carcinoma (SqCC), and large-cell lung carcinoma (LCLC) [2, 4, 6, 14]. Other types, including salivary gland-type tumors, sarcomatoid carcinomas, and others, represent a very minor part of the total NSCLC cases. The first step in the diagnosis of NSCLC is the histological classification based on the evaluation of the tumor morphological features followed by ancillary IHC methodologies. In small biopsies, when the histological features and IHC phenotype are not conclusive to subtype NSCLC, the term "not otherwise specified" (NSCLC-NOS) is used.

2.1 Adenocarcinoma (ADC)

ADC represents the majority of NSCLC, accounting for the 38.5 % of all lung cancer cases [15]. ADC is defined as a malignant epithelial tumor with glandular differentiation, which can show mucin production detectable by mucin staining like mucicarmin, or pneumocyte marker expression like napsin A or thyroid transcription factor 1 (TTF1) [6]. In general, ADC is located at the periphery of the lung [16–18]. ADC can present diverse histological patterns, which can be intermixed in the same tumor including lepidic, acinar, papillary, micropapillary, and solid patterns. While lepidic pattern is associated with a favorable prognosis, micropapillary and solid patterns are associated with a more aggressive behavior [3, 6]. Solid ADC can be confused with SqCC or LCLC; the mucin production and IHC expression of TTF-1 or napsin A can help in the diagnosis of solid ADC in challenging cases [6].

2.2 Squamous Cell Carcinoma (SqCC)

SqCC accounts for nearly 20 % of all lung cancers [15]. SqCC usually presents in a central location, arising in a main or lobar bronchus [6]. Histologically, SqCC is defined by the World Health Organization (WHO) as a malignant epithelial tumor that either shows keratinization and/or intercellular bridges or expresses IHC markers of squamous cell differentiation [6]. Although keratinization is the hallmark of SqCC, many SqCC may not show morphological features of keratinization.

Also, poorly differentiated SqCC can show pseudoglandular appearance, as well as poorly differentiated adenocarcinomas can show pseudosquamous features, making the interpretation of small biopsies or cytological specimens particularly challenging [3, 6, 12]. IHC tests including markers of squamous cell differentiation such as p40 or p63 and cytokeratins 5/6 represent helpful tools in the identification of SqCC in difficult cases. A distinct entity is the basaloid squamous cell carcinoma, a poorly differentiated malignant tumor without morphological features of squamous cell differentiation which can be confused with small-cell lung carcinoma, but it is characteristically positive for immunomarkers of squamous cell differentiation including p40, p63, and cytokeratins 5/6, while TTF-1 is negative [6].

2.3 Large-Cell Lung Carcinoma (LCLC)

LCLC accounts for the 2.9 % of all lung cancers [15]. LCLC is defined as an undifferentiated NSCLC carcinoma, which does not show histological or IHC evidence of squamous cell, glandular, or small-cell differentiation [6]. The diagnosis of LCLC requires extensive sampling of a surgical resected specimen after ruling out SqCC, ADC, or SCLC, and therefore, it cannot be made on core needle biopsies or cytology samples [6]. Mucin production detected by mucin staining such as mucicarmine is absent. Immunohistochemically, LCLC may be positive for cytokeratins but they are negative for TTF-1 and p40 [6]. LCLC is to be distinguished from large-cell neuroendocrine (usually expressing TTF-1 and neuroendocrine markers), solid pattern of ADC (TTF-1 positive), non-keratinizing SqCC (p40 positive), and rarely adenosquamous carcinoma (showing both ADC and SqCC differentiation) [6]. As stated, in small biopsies, tumors with NSCLC features and null IHC phenotype are named NSCLC-NOS.

3 Molecular Alterations of NSCLC

In the last years, there has been an increasing amount of new molecular alterations identified in NSCLC including oncogenes and tumor suppressor genes, many of them represent novel predictive biomarkers or targets for cancer therapy [5]. A representation of the relative frequencies of molecular targets in NSCLC is shown in Fig. 1. The following molecular alterations represent those which may have clinical relevance as molecular targets for NSCLC.

3.1 Epidermal Growth Factor Receptor (EGFR)

The *EGFR* gene is located on the short arm of chromosome 7 at position 12 [19]. The protein encoded by this gene is a transmembrane glycoprotein that is a member of the protein kinase superfamily [19]. EGFR is overexpressed in 40–80 % percent of NSCLC and many other epithelial cancers. Approximately 10 % of patients with

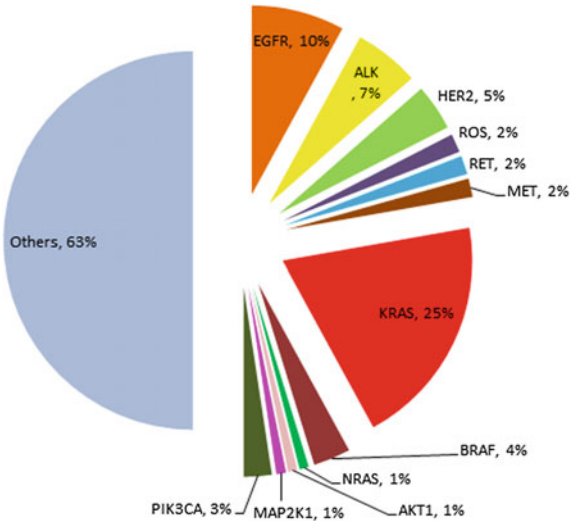

Fig. 1 Representation of the relative frequency of the main molecular targets in NSCLC. Still, the number of novel molecular targets may increase as further research will continue to discover and validate them

NSCLC in the United States and 35 % in East Asia have lung tumors associated with *EGFR* mutations [20–22]. These mutations occur within exons 18–21, which encodes a portion of the EGFR kinase domain. *EGFR* mutations are usually heterozygous, with the mutant allele also showing gene amplification [23]. Approximately 90 % of these mutations are in exon 19, deletions CTG to CGG or exon 21 at nucleotide 2573, that results in substitution of leucine by arginine at codon 858 (L858R) [24]. These mutations increase the kinase activity of EGFR, leading to hyperactivation of downstream prosurvival signaling pathways [25]. *EGFR* mutations are more often found in tumors from female never smokers, defined as less than 100 cigarettes in a patient's lifetime, with adenocarcinoma histology [20–22]. However, *EGFR* mutations can also be found in patients with other clinicopathologic features, including former and current smokers as well as in other histological types. Tumors with *EGFR* mutations are susceptible to be treated highly responsive to treatment with EGFR tyrosine kinase inhibitors (EGFR TKIs) such as gefitinib, erlotinib, and afatinib; however, most patients relapse and develop resistance, most commonly associated with a second mutation in exon 20 (*T790M*, 60 *%0*), *MET* amplification, and *PI3KCA* mutations [5]. Interestingly, "transformation" to SCLC has been described in a subset of lung adenocarcinomas exhibiting resistance to EGFR TKIs [5].

3.2 Anaplastic Lymphoma Kinase (ALK)

Anaplastic lymphoma kinase (*ALK*) was originally discovered from chromosomal translocations leading to the production of fusion proteins consisting of the COOH-terminal kinase domain of *ALK* and the NH_2-terminal portions of different genes [26]. The *ALK* gene is located on the short arm of chromosome 2 at position

23 [27]. Translocation of *ALK* has been identified in approximately 3 to 7 % of lung tumors [28–30]. Nucleophosmin (NPM) is the most common fusion partner of *ALK* accounting for 80 % of *ALK* translocations, but at least six other fusion partners have been identified [30–35]. In NSCLC, the more common *ALK* fusion variants are comprised of portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the *ALK* gene. *EML4-ALK* is an aberrant fusion gene that encodes a cytoplasmic chimeric protein with constitutive kinase activity [36]. *EML4-ALK* fusions are more commonly found in younger patients who have never smoked or who have a history of light smoking (<10 pack years) [30, 35] and in patients with adenocarcinomas with acinar histology and with signet-ring cells [28, 34, 37]. Other less common fusion partners for *ALK*, such as *KIF5B* and *TFG,* have also been described in NSCLC [32, 38]. In most cases, *ALK* rearrangements are non-overlapping with other oncogenic mutations found in NSCLC, such as *EGFR* and *KRAS* mutations [28–30, 39]. The most common methods to detect *ALK* fusion genes include break-apart fluorescence in situ hybridization (FISH), IHC, and reverse transcription polymerase chain reaction (RT-PCR). Break-apart FISH has been the standard method for confirmation of *ALK* status in clinical trials [40]. In preclinical analyses, a selective ALK inhibitor (Crizotinib, PF-02341066, Pfizer) reduced the proliferation of cells carrying genetic alterations in *ALK*, supporting the role of ALK in malignant proliferation and crizotinib as a valid therapeutic target [41]. As with all targeted therapies, resistance to crizotinib is a significant issue for therapy, and most patients experience crizotinib resistance as described in a young patient with *EML4–ALK*-positive NSCLC [42]. Two independent mutations were identified cases that developed resistance: a substitution of adenine for guanine at position 4374 of *EML4–ALK*, resulting in replacement of cysteine with tyrosine at position 1156 of *ALK* (C1156Y), and a substitution of adenine for cytosine at *ALK* position 4493, resulting in replacement of leucine with methionine at position 1196 of *ALK* (L1196M) [42]. A third mutation (F1174L) has been identified in a patient with *RANBP2–ALK*-positive inflammatory myofibroblastic tumor, and it was associated with decreased sensitivity of Ba/F3 cells to crizotinib, although this mutation was unlikely to directly prevent binding of crizotinib to ALK [43]. Further investigations to understand the resistance mechanisms to crizotinib are necessary as well as study of potential combination therapies with different intracellular signaling inhibitors to target proliferation and resistance pathways.

3.3 Human Epidermal Growth Factor Receptor 2 (HER2)

HER2, also known as *ERBB2*, *NEU*, or *EGFR2*, is one of the members of the EGFR family and plays an important role in cell growth, differentiation, and survival. *HER2* encodes a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases and is a proto-oncogene located on chromosome 17 at position 12 [44]. The HER2 protein has no ligand-binding domain of its own and therefore cannot bind growth factors. However, HER2 does bind tightly to other ligand-bound EGF receptor family members to form a heterodimer, stabilizing

ligand binding and enhancing kinase-mediated activation of downstream signaling pathways, such as those involving mitogen-activated protein kinase and phosphatidylinositol-3 kinase. Activating mutations in the tyrosine kinase domain of HER2 have recently been reported in less than 5 % of NSCLC [45–47]. Studies of *HER2* mutations in lung cancer showed association with Asian ethnicity, female gender, and non-smokers and with adenocarcinoma histology, particularly lepidic pattern [45–47]. However, *HER2* mutations can also be found in other patient subsets of NSCLC, including in former and current smokers [45, 46]. The vast majority of *HER2* mutations are represented by a 12-base pairs duplication/insertion of the amino acid sequence YVMA in exon 20 at codon 776 [48, 49]. The exon 20 insertion results in increased HER2 kinase activity and enhanced signaling through downstream pathways, resulting in increased survival, invasiveness, and tumorigenicity [50].

3.4 ROS Proto-Oncogene 1, Receptor Tyrosine Kinase (ROS)

The *ROS1* proto-oncogene is located on the long arm of chromosome 6 at position 22, and it is part of tyrosine kinase insulin receptor gene family, and is a type I integral membrane protein with tyrosine kinase activity that may function as a growth or differentiation factor receptor. *ROS1* rearrangements lead to constitutively active fusion proteins and are detected in approximately 1–2 % of NSCLC [51, 52]. In NSCLC, *ROS1* gene rearrangements are associated with adenocarcinoma, and more commonly found in light and never smokers and young patients (<50 years) [51], and are most often mutually exclusive from *EGFR* mutations, *KRAS* mutations, and *ALK* rearrangements [53]. Several different *ROS1* rearrangements have been described in NSCLC as *SLC34A2-ROS1*, *CD74-ROS1*, *EZR-ROS1*, *TPM3-ROS1*, and *SDC4-ROS1* [38, 52, 53]. In preclinical studies, patients with advanced NSCLC harboring *ROS1* rearrangements derived great benefit from crizotinib treatment that targets ROS1 in addition to ALK and MET [51, 52]. Furthermore, in a clinical trial published by Shaw et al. [54] on 50 patients with advanced NSCLC who tested positive for *ROS1* rearrangement, crizotinib showed marked antitumor activity with 33 partial responses and 3 complete responses. Interestingly, no correlation between the type of *ROS1* rearrangement and the clinical response to crizonitib was found [54].

3.5 Ret Proto-Oncogene (RET)

The *RET* gene is located on the long arm of chromosome 10 at position 11.2, and it encodes for a tyrosine kinase that is involved in cell proliferation, migration, and differentiation [55]. Although *RET* point mutations and fusions have long been recognized in medullary and papillary thyroid carcinomas, respectively, *RET*

rearrangements in NSCLC were only recently discovered and involve the kinesin family member 5B (*KIF5B*) among other partners [53, 56–58]. Alternative *RET* fusion partners, such as *CCDC6-RET*, *NCOA4-RET,* and *TRIM33-RET* have since been also described [59]. In early studies, *RET* rearrangements were identified in approximately 1–2 % of NSCLC [53, 57, 58]. Like other rearrangements such as *ALK* and *ROS1*, *RET* fusions are associated with specific clinicopathologic features, such as smoking history, younger patients (age $\leq$ 60 years), and adenocarcinoma histology, especially in those with more poorly differentiated tumors [59]. *RET* rearrangements are usually mutually exclusive with genetic alterations in other oncogenic drivers, such as *EGFR*, *KRAS*, *ALK*, and *ROS1*, [53, 57–59] suggesting that *RET* rearrangements define a new, distinct molecular subset of NSCLC. *RET* fusions have been shown to be oncogenic in models, and some in vitro studies have showed evidence that small molecule inhibitors such as vandetanib, sorafenib, and sunitinib can be used as inhibitors of *RET* fusion products [57, 58]. A recent study showed that cabozantinib, a RET inhibitor, represents a promising targeted therapy for *RET* fusion-positive lung adenocarcinoma cases [60].

3.6 NTRK1 (TrkA) Fusions

Neurotrophic tyrosine kinase, receptor, type 1 (NTRK1), also called tropomyosin receptor kinase A (TrkA) or high-affinity nerve growth factor receptor, is a protein encoded by the gene *NTRK1*, which is located on chromosome 1q21-22 [61, 62]. NTRK1 is a receptor tyrosine kinase, which is part of the tropomyosin-related kinases (TRK) superfamily of receptor tyrosine kinases [61, 62]. NTRK1 acts to control of cell growth and differentiation via the MAPK, phosphatidylinositol 3-kinase (PI3K), and PLC-γ pathways when activated by the nerve growth factor (NGF) ligand [63]. *NTRK1* fusions have been reported in colon cancer, thyroid cancer, and glioblastoma multiforme [64–66]. In a study in lung cancer, *NTRK1* fusions have been found in 3.3 % of the cases (3 out of 91 patients) corresponding to ADC histological type [67]. The same study identified two *NTRK1* fusions, *MPRIP-NTRK1* and *CD74-NTRK1*, which can be detected by fluorescence in situ hybridization (FISH) with an *NTRK1* break-apart probe, although the FISH alone cannot discriminate between the two types of fusions [67]. The *NTRK1* fusions trigger constitutive NTRK1 kinase activity via autophosphorilation leading to the oncogenic process [67]. The importance of the *NTRK1* fusions is that they represent a new potential target for therapy, as preclinical tests in cell lines showed evidence of response to *NTRK1* inhibitors [67]. For instance, promising results have been recently reported on case of a patient with metastatic sarcoma harboring LMNA-NTRK1 fusion after treatment with LOXO-101, a highly selective inhibitor for the TRK family of receptors that can be orally administrated [68]. Nevertheless, further studies are still needed to confirm the value of this new target in human patients with tumors harboring *NTRK1* fusions.

3.7 MET

This gene encodes a receptor with tyrosine kinase activity. The primary single-chain precursor protein is post-translationally cleaved to produce the alpha and beta subunits, which are disulfide linked to form the mature receptor [69]. MET transduces signals from the extracellular matrix into the cytoplasm by binding to hepatocyte growth factor/HGF ligand and regulates many physiological processes including proliferation, motility, invasion, and survival [69]. The *MET* gene is located on the long arm of chromosome 7 at position 31 [70] and can have activating mutations, especially in the semaphorin (sema) domain and juxtamembrane (JM) domain, or it can be amplified [71, 72]. In lung cancer, *MET* gene mutations are found both in extracellular and JM domains [73, 74]. The extracellular sema domain, encoded by exon 2, is required for receptor dimerization and activation [75]. The presence of these mutations has been clearly defined in lung cancer; however, because of certain histologic and ethnic variation, their biologic relevance still needs to be further clarified. In NSCLC, overexpression of MET and HGF protein in tumor tissue and in cells lines have been associated with higher pathologic tumor stage and worse prognosis [76–79] and multiple studies have reported primary *MET* amplification in NSCLC adenocarcinoma ranging from 2 to 20 %, particularly in EGFR TKI-naive patients [80–82]. A recent study unveiled a mechanism of activation of MET via diverse exon 14 splicing alterations (METex14) that occurs in multiple tumor types including lung [83]. The same study showed that METex14 mutations are detected most frequently in lung adenocarcinomas (3 %) [83]. Importantly, in vitro tests showed sensitivity to MET inhibitors in cells harboring METex14 alterations and patients whose tumors harbored these alterations derived meaningful clinical benefit from MET inhibitors [83]. Currently, there are a number of clinical trials for MET and HGF that have shown that MET and HGF can be targeted in patients with NSCLC.

3.8 Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS)

KRAS is an oncogene located on the short arm of chromosome 12 at position 12.1, and it encodes the KRAS protein which is involved primarily in regulating cell division [84]. KRAS is part of a signaling pathway known as the RAS/MAPK pathway, and it relays signals from outside the cell to the cell's nucleus [85]. Activating *KRAS* gene point mutations have been detected in approximately 15 to 25 % of patients with lung adenocarcinoma. *KRAS* mutations are uncommon in lung squamous cell carcinoma [86]. Mutations in the *KRAS* gene have important effects on the process of carcinogenesis, which depend on the cells and tissues involved [87]. The mutations found most frequently in the *KRAS* gene of cancer cells are located at positions 12 and 13 in exon 1, and less frequently in codons 61, 63, 117, 119, and 146 [88]. *KRAS* mutations are associated with tumors from both former/current smokers and never smokers [89]. However, they are less common in never smokers and in East Asian than Western patients [90, 91]. *KRAS* is also one of the most frequently

mutated oncogenes in many cancers, and it is a predictor of resistance to targeted therapy using EGFR TKIs in patients with NSCLC [86, 92, 93]. Molecular analysis revealed that patients who have activating mutations involving exon 1, codons 12, 13, or 61 in the *KRAS* gene with or without increase in *EGFR* copy numbers did not derive benefit from EGFR TKI therapy and had about a 96 % chance of disease progression [94]. Also, *KRAS* mutations may be negative predictors of radiographic response to the EGFR TKIs erlotinib and gefitinib [92, 95].

3.9 B-Raf Proto-Oncogene, Serine/Threonine Kinase (BRAF)

The *BRAF* gene belongs to a class of genes known as oncogenes. The *BRAF* gene is located on the long arm of chromosome 7 at position 34 [96]. This gene encodes BRAF, a serine/threonine kinase that helps to transmit chemical signals from outside the cell to the cell's nucleus [96]. BRAF is part of a signaling pathway known as the RAS/MAPK pathway, a key molecular cascade that regulates important cell functions such as proliferation, differentiation, migration, and apoptosis. Mutations in *BRAF* are more commonly seen in melanoma (50–70 %) than in lung cancer, where they have been found in 1–4 % [97–103]. In contrast to melanoma, where the majority of *BRAF* mutations occur at valine 600 (V600) within exon 15 of the kinase domain, *BRAF* mutations in lung cancer occur at other positions in exons 11 and 15, within the kinase domain as G469A and D594G, and they are mutually exclusive of *EGFR* and *KRAS* mutations [101]. *BRAF* mutations in NSCLC are most frequently in adenocarcinomas and there are more likely to be found in former and current smokers [101, 102]. Clinically, *BRAF* inhibitors, such as vemurafenib and dabrafenib, have potent and selective activity against the V600-mutant *BRAF* kinases [104, 105]. Agents targeting the BRAF pathway have demonstrated efficacy in NSCLC. For instance, Gautschi et al. [106] have recently documented promising results with BRAF-targeted therapy on BRAF-mutated lung adenocarcinomas. Furthermore, a recent study on multiple non-melanoma tumors BRAF V600-mutated, vemurafenib activity was observed in non-small-cell lung cancer, confirming the potential of BRAF inhibitors for therapy of BRAF-mutated lung cancer [107]. The combination of trametinib and dabrafenib has also demonstrated clinical benefit.

3.10 Neuroblastoma RAS Viral (V-Ras) Oncogene Homolog (NRAS)

The *NRAS* gene is located on the short arm of chromosome at position 13.2, and it encodes a protein called NRAS that is involved primarily in regulating cell division [108]. Although *NRAS* gene mutation might be one of the mechanisms of oncogenesis of lung cancer, this is a very rare event it has been found in $\sim$1 % of all NSCLC [97, 109–111]. *NRAS* mutations are more frequently found in lung cancers

with adenocarcinoma histology and in patients with a history of smoking [81, 112]. In the majority of cases, these mutations are reported at codon 61 and mutations at position 12 have also been described [81]. The result of these mutations is constitutive activation of NRAS signaling pathways. Currently, there are no direct anti-NRAS therapies available, but preclinical models suggest that MEK inhibitors may be effective [81, 113].

3.11 v-AKT Murine Thymoma Viral Oncogene Homolog 1 (AKT1)

The *AKT1* gene is located on the long arm of chromosome 14 at position 14q32.32. *AKT1* gene encodes AKT1 serine/threonine protein kinase found in various cell types, which plays a critical role in many signaling pathways helping in cellular proliferation, differentiation, and cell survival [114]. AKT1 is a downstream mediator of the PI 3K pathway, and it helps to control apoptosis [114]. Somatic mutations in *AKT1* are rare in lung cancer and they have been found in approximately 1 % of all NSCLC including ADC and SqCC [115, 116]. Mutations in the regulatory domain of *AKT1* lead to structural alteration of the ligand-binding site resulting in cellular transformation in vitro and in vivo [117]. AKT1 is predominantly detected in lung epithelium by IHC, while it is absent in stromal cells. In normal lung tissue, AKT1 is exclusively cytoplasmic but in the tumor tissue, the anti-AKT1 antibodies' stain also reinforces the membrane of those cells [116]. Although *AKT1* mutation is a relatively rare event in NSCLC, it may represent a potential molecular target in a subset of NSCLC.

3.12 Mitogen-Activated Protein Kinase 1 (MAP2K1)

The *MAP2K1* gene provides instructions for making a protein known as MEK1 protein kinase. MEK1 is part of a signaling pathway called the RAS/MAPK pathway, which transmits chemical signals from outside the cell to the cell's nucleus [118]. RAS/MAPK signaling helps control the proliferation, differentiation, and apoptosis of cells. The *MAP2K1* gene is located on the long arm of chromosome 15 between positions 22.1 and 22.33. Somatic mutations in *MAP2K1* have been found in less than 1 % of all NSCLC and are more common in adenocarcinoma than squamous cell carcinoma [119, 120]. In a retrospective study of lung adenocarcinoma cases with *MEK1* gene mutation, these mutations were more strongly associated with former smoking status, and there were no other associations with age, sex, race, or stage [119]. The most frequent mutations of *MAP2K1* were K57N (64 %) and Q56P (19 %), and *MEK1* mutations were mutually exclusive of mutations in *EGFR*, *KRAS*, *BRAF,* and other driver mutations [119].

3.13 Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha (PIK3CA)

The *PIK3CA* gene is located on the long arm of chromosome 3 at position 26.3 [121]. The *PIK3CA* gene encodes p110 alpha protein, which is one piece, a subunit, of an enzyme called PI3K [122]. The p110α protein is called the catalytic subunit because it performs the action of PI3K, while the other subunit regulates the enzyme's activity [121]. PI3K signaling is important for many cell activities, including cell proliferation, migration, and cell survival. Mutations of *PIK3CA* occur in many human epithelial cancers, resulting in *PIK3CA* being one of the two most commonly mutated oncogenes, along with *KRAS*, identified in human cancers [121, 123]. However, individual types of epithelial cancers show great variability in their mutational rates, and the rates described in NSCLC are relatively low, 1–3 % [124, 125], and usually affecting the helical binding domain (exon 9, E545K, or E542K) or the catalytic subunit (exon 20, H1047R, or H1047L) [126]. *PIK3CA* mutations appear to be more common in squamous cell histology than in adenocarcinoma [124] and can occur in never and ever smokers. *PIK3CA* mutations can co-occur with *KRAS* and *EGFR* mutations, and it is more frequently seen with *KRAS* than with *EGFR* [91, 127]. *PIK3CA-KRAS* co-mutation is more prevalent in Western countries [128], while *PIK3CA-EGFR* is more prevalent in lung cancer patients from Eastern countries [91, 129].

4 Diagnostic and Molecular Testing of NSCLC

Today the diagnosis of NSCLC usually starts with a small biopsy like a core needle biopsy (CNB) or a cytological like a fine needle aspiration (FNA), in which the pathologist has to make the best effort to not only provide a diagnosis of NSCLC and to further classify it as an ADC or SqCC [5, 6]. The advent of targeted therapy introduced a new challenge to the pathologist in order to maximize the efficiency in the use of small samples for clinical diagnosis and molecular testing. Overall, the diagnostic and molecular testing of NSCLC samples involves the following steps.

4.1 Pathological Diagnosis of NSCLC

As stated before, the pathology classification starts with a hematoxylin–eosin-stained tissue section evaluated under the microscope for morphological changes to identify the presence of a NSCLC and then try to classify it as any of the major subtypes such as ADC, SqCC, LCLC, or special subtypes. However, sometimes, the histology evaluation can be limited, particularly in small biopsies or tumors with poor differentiation, which can make challenging the classification of the neoplasm. In these cases, ancillary diagnostic techniques will help in the pathology classification. Some of the main ancillary diagnostic markers are TTF-1, p40, and mucicarmin.

4.1.1 Thyroid Transcription Factor 1 (TTF-1)

Also called NK2 homeobox 1 (NKX2-1), this is a protein encoded by the gene *NKX2-1*. TTF-1 regulates the transcription of genes specific for the thyroid, lung, and diencephalon differentiation. In diagnostic pathology, the IHC detection of TTF-1 in the nucleus of cells is a tool for the identification of thyroid or lung differentiation. In normal lung, TTF-1 labels some of the bronchial epithelial cells, type II pneumocytes, and club cells (Clara cells). In tumors, TTF-1 is expressed on 60–74 % of ADC and between 6 and 32 % of SCC, depending on the study and the antibody used [130]. In diagnostic pathology, TTF-1 expression is considered a marker that favors the diagnosis of ADC [12]. Interestingly, TTF-1 expression has been found to correlate with a better prognosis in ADC [130, 131].

4.1.2 p40

This is an isoform of p63 protein also called ΔNp63-a, encoded by the gene *TP63*. ΔNp63 is involved in multiple functions during skin development and in adult

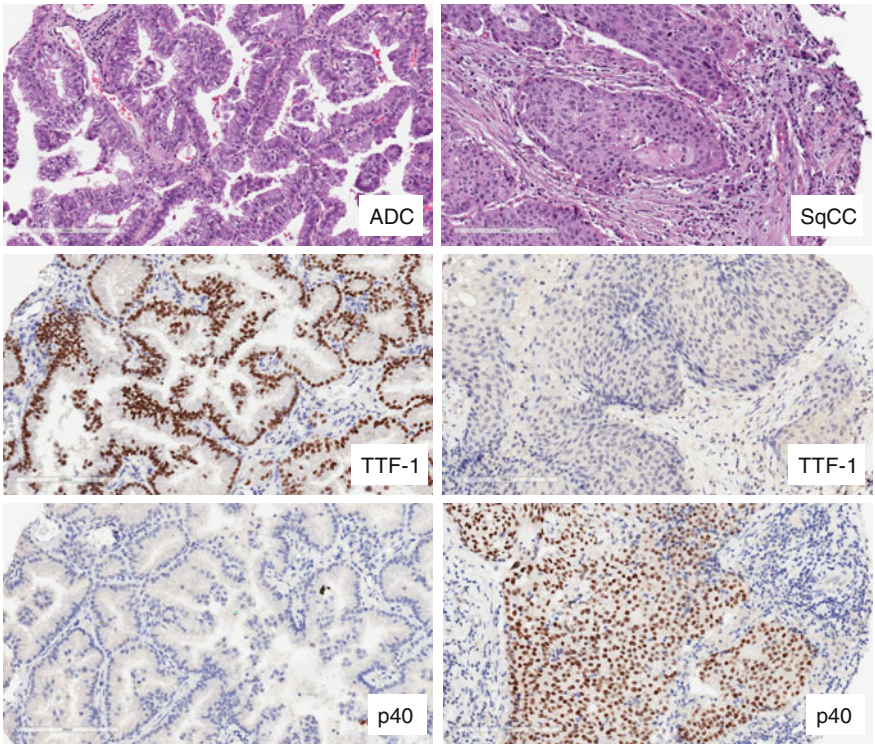

Fig. 2 Example of an adenocarcinoma (*ADC*) and squamous cell carcinoma (*SqCC*). ADC is a tumor showing epithelial cells arranged in glandular like structures, which is usually positive for TTF-1 and negative for p40. Instead, SqCC is composed by tumor epithelial cells arranged in a solid fashion, sometimes showing signs of squamous cell differentiation such as keratinization, which is usually negative for TTF-1 and positive for p40. (Microphotographs taken from Aperio scanned slides using a 20× objective lens)

stem/progenitor cell regulation [132]. In pathology, p40 is expressed in the nucleus of many basal cells (prostate, breast epithelia) and in squamous cells. In diagnostic pathology, p40 is used as a marker for squamous cell differentiation as it labels near 100 % of SCC and up to 3 % of ADC [12]. In general, p40 and TTF-1 are used in combination (Fig. 2) [12].

4.1.3 Mucicarmin

This is an old histochemical stain employed for the detection of mucins, which are high-molecular-weight glycoproteins that are found dispersed throughout several glandular epithelia, including respiratory epithelium. Mucicarmin can also be employed for the differential diagnosis of ADC, particularly in the identification of solid variants, being considered positive when five or more tumor cells are found to show mucin staining in the cytoplasm in two microscopic high-power fields (×400) [6, 14, 133].

4.2 Molecular Testing of NSCLC

The advent of targeted therapy has opened a new door for the discovery and validation of novel biomarkers with prognostic and therapeutic value [5]. Today, the pathologist has to further classify a NSCLC as ADC or SqCC employing the previously mentioned analysis techniques on small samples such as CNB or FNA [5, 6]. The importance of this diagnostic effort is based on the novel therapeutic approaches for ADC. For instance, a tumor classified as ADC or NSCLC favor ADC will undergo routine molecular testing for the currently most important molecular alterations described before, including *EGFR* mutations and *ALK* and *ROS* rearrangement analyses, offering the option of a targeted therapy for these molecular alterations to the cancer patient. Currently, novel multiplexing technologies such as multiplex-PCR platforms and next-generation sequencing (NGS) techniques allow for specific and high-throughput molecular profile of individual tumors, which is necessary for a precision medicine approach for the cancer patient [5].

5 Future Directions: Immunotherapy Revolution and Its Integration with Lung Cancer Diagnostics and Therapy

The development and application of high-throughput molecular profiling techniques for the cancer patient allows for further identification and validation of novel biomarkers of cancer, which can help to define a precision medicine approach for cancer therapy [134]. For instance, precision medicine requires a detailed molecular profile of the tumor for an individual patient that will allow the design of a specific targeted therapy strategy for the particular tumor.

A novel area of cancer therapy is represented by the development of immunotherapy for cancer. The specific blocking of immune checkpoints such as programmed death ligand 1 (PD-L1, also known as B7-H1 or CD274) and programmed cell death protein 1 (PD1, or CD279) can unleash the immunological system, particularly T-cell lymphocytes, to attack the cancer cells [135, 136]. Immunotherapy has shown promising results in several solid tumors, including melanoma, kidney cancer, and lung cancer, however, in lung cancer, further studies and clinical trials are needed [137–139]. Currently, IHC markers for the expression of key immune checkpoints such as PD-L1, and also others like PD-L2, VISTA, B7-H3, and B7-H3, are being added to the pathological analysis of NSCLC [140]. Also, particular attention is being paid to the amount and composition of the inflammatory cells present in the tumor region, which includes different subpopulations of tumor-infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs) [141]. For instance, a novel immunological classification of tumors has been proposed based on the T-cell infiltration and the PD-L1 expression, classifying them into four categories: type I or adaptive immune resistance (TIL+/PDL1+), type II or immunological ignorance (TIL−/PDL1−), type III or immunological tolerance (TIL+/PDL1−), and type IV or intrinsic induction (TIL−/PDL1+) [142]. The demonstration of the clinical value of such immunological classification of cancer for immunotherapy will enforce pathologists to incorporate immunological markers into their clinical practice.

One of the challenges for the pathologists is the evaluation of PD-L1 expression in IHC assays on biopsies. Currently, there are several antibodies and clones available, employing property staining platforms and particular scoring systems, and some of them are not fully validated [143]. One of the validated and FDA approved PD-L1 antibodies is clone 22C3 (Dako); its cell membrane expression on at least 50 % of tumor cells has a positive correlation with improved efficacy of pembrolizumab, a monoclonal therapeutic antibody targeting PD1 [144]. Another FDA approved assay for PD-L1 IHC is antibody clone 28-8 (Dako and Abcam), a complimentary test for nivolumab, a human IgG4 PD-1 inhibitor. Interestingly, a recent study comparing nivolumab and docetaxel in patients with advanced, previously treated lung squamous cell carcinomas, the overall survival, response rate, and progression-free survival were significantly better with nivolumab than with docetaxel, regardless of PD-L1 expression level evaluated with the PD-L1 antibody clone 28-8 [145]. A similar study in advanced non-squamous cell carcinomas of the lung comparing nivolumab and docetaxel also showed longer overall survival with nivolumab than with docetaxel in patients with tumors expressing PD-L1 [146]. In this study, there was a trend toward a greater response rate as the PD-L1 expression level increased (>1, 5, and 10 % of membranous positive tumor cells); however, a meaningful separation of the overall survival curves was observed across all expression levels [146]. Interestingly, both studies seem to suggest that nivolumab is a reasonable therapy for advanced NSCLC regardless of the PD-L1 IHC expression level [145, 146]. Another challenge in the evaluation of PD-L1 is the fact that PD-L1 is expressed not only in the tumor cells but also in the tumor inflammatory infiltrate component, including macrophages,

dendritic cells, and T cells [147]. For instance, PD-L1-positive tumor-infiltrating inflammatory cells have been found to be more common than PD-L1-positive tumor epithelial cells [147]. A study by Herbst et al. [147] showed evidence that the evaluation of PD-L1 in both cell compartments, tumor cells and the inflammatory cell infiltrate, can have clinical relevance. Furthermore, as the tumor-infiltrating inflammatory cell component may have relevance for the clinical response to immunotherapy, also the mutation burden in tumors may be relevant. In a study by Rizvi et al. [148] on NSCLC, higher non-synonymous mutation burden in tumors was associated with improved objective response, durable clinical benefit, and progression-free survival. Taking this information together, it is likely that a new classification of lung cancer will include the immunoprofiling status integrated with the mutation status of key genes.

6 Conclusions

Lung cancer is a complex and heterogeneous group of diseases in which a multidisciplinary approach for diagnosis, classification, and therapy is needed. The advent of large-scale molecular profiling and targeted therapy represent the main future direction for personalized and efficient cancer therapy. In this regard, the ongoing cancer immunotherapy revolution is already redefining the classification and treatment of cancer, offering promising therapeutic windows to lung cancer patients. However, further research is still needed to integrate the complex information from genomics and immunology into a new classification of lung cancer with clinical relevance for therapy and improved outcomes.

References

1. American Cancer Society (2015) Cancer facts & figures 2015. American Cancer Society, Atlanta
2. Herbst RS, Heymach JV, Lippman SM (2008) Lung cancer. N Engl J Med 359(13): 1367–1380
3. Travis WD et al (2013) Diagnosis of lung adenocarcinoma in resected specimens: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Arch Pathol Lab Med 137 (5):685–705
4. Travis WD, Brambilla E, Riely GJ (2013) New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. J Clin Oncol 31(8):992–1001
5. Fujimoto J, Wistuba II (2014) Current concepts on the molecular pathology of non-small cell lung carcinoma. Semin Diagn Pathol 31(4):306–313
6. Travis WD, Bambrilla E, Burke AP, Marx A, Nicholson AG (2015) WHO classification of tumours of the lung, pleura, thymus and heart, 4th edn. IARC WHO Classification of Tumours 2015: World Health Organization
7. Biesalski HK et al (1998) European consensus statement on lung cancer: risk factors and prevention. Lung Cancer Panel. CA Cancer J Clin 48(3):167–76 (discussion 164–166)
8. Hecht SS (2012) Lung carcinogenesis by tobacco smoke. Int J Cancer 131(12):2724–2732

9. Khuder SA (2001) Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. Lung Cancer 31(2–3):139–148
10. Rosai J (2007) Why microscopy will remain a cornerstone of surgical pathology. Lab Invest 87(5):403–408
11. Kadota K et al (2015) Reevaluation and reclassification of resected lung carcinomas originally diagnosed as squamous cell carcinoma using immunohistochemical analysis. Am J Surg Pathol 9:1170–1180
12. Rekhtman N et al (2011) Immunohistochemical algorithm for differentiation of lung adenocarcinoma and squamous cell carcinoma based on large series of whole-tissue sections with validation in small specimens. Mod Pathol 24(10):1348–1359
13. Travis WD, Rekhtman N (2011) Pathological diagnosis and classification of lung cancer in small biopsies and cytology: strategic management of tissue for molecular testing. Semin Respir Crit Care Med 32(1):22–31
14. Travis WD et al (2011) International association for the study of lung cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 6(2):244–285
15. Dela Cruz CS, Tanoue LT, Matthay RA (2011) Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med 32(4):605–644
16. Shimosato Y et al (1980) Prognostic implications of fibrotic focus (scar) in small peripheral lung cancers. Am J Surg Pathol 4(4):365–373
17. Russell PA et al (2011) Does lung adenocarcinoma subtype predict patient survival? A clinicopathologic study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. J Thorac Oncol 6(9):1496–1504
18. Russell PA et al (2013) Correlation of mutation status and survival with predominant histologic subtype according to the new IASLC/ATS/ERS lung adenocarcinoma classification in stage III (N2) patients. J Thorac Oncol 8(4):461–468
19. Voldborg BR et al (1997) Epidermal growth factor receptor (EGFR) and EGFR mutations, function and possible role in clinical trials. Ann Oncol 8(12):1197–1206
20. Lynch TJ et al (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350 (21):2129–2139
21. Paez JG et al (2004) EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 304(5676):1497–1500
22. Pao W et al (2004) EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci US A 101(36):13306–13311
23. Soh J et al (2009) Oncogene mutations, copy number gains and mutant allele specific imbalance (MASI) frequently occur together in tumor cells. PLoS ONE 4(10):e7464
24. Ladanyi M, Pao W (2008) Lung adenocarcinoma: guiding EGFR-targeted therapy and beyond. Mod Pathol 21(Suppl 2):S16–S22
25. Sordella R et al (2004) Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. Science 305(5687):1163–1167
26. Morris SW et al (1994) Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science 263(5151):1281–1284
27. Roskoski R Jr (2013) Anaplastic lymphoma kinase (ALK): structure, oncogenic activation, and pharmacological inhibition. Pharmacol Res 68(1):68–94
28. Kwak EL et al (2010) Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 363(18):1693–1703
29. Shinmura K et al (2008) EML4-ALK fusion transcripts, but no NPM-, TPM3-, CLTC-, ATIC-, or TFG-ALK fusion transcripts, in non-small cell lung carcinomas. Lung Cancer 61 (2):163–169

30. Wong DW et al (2009) The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer 115(8): 1723–1733
31. Choi YL et al (2008) Identification of novel isoforms of the EML4-ALK transforming gene in non-small cell lung cancer. Cancer Res 68(13):4971–4976
32. Takeuchi K et al (2009) KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. Clin Cancer Res 15(9):3143–3149
33. Horn L, Pao W (2009) EML4-ALK: honing in on a new target in non-small-cell lung cancer. J Clin Oncol 27(26):4232–4235
34. Koivunen JP et al (2008) EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res 14(13):4275–4283
35. Soda M et al (2007) Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 448(7153):561–566
36. Shaw AT et al (2009) Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 27(26):4247–4253
37. Mano H (2008) Non-solid oncogenes in solid tumors: EML4-ALK fusion genes in lung cancer. Cancer Sci 99(12):2349–2355
38. Rikova K et al (2007) Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell 131(6):1190–1203
39. Inamura K et al (2009) EML4-ALK lung cancers are characterized by rare other mutations, a TTF-1 cell lineage, an acinar histology, and young onset. Mod Pathol 22(4):508–515
40. Yi ES et al (2011) Correlation of IHC and FISH for ALK gene rearrangement in non-small cell lung carcinoma: IHC score algorithm for FISH. J Thorac Oncol 6(3):459–465
41. Bang YJ (2011) The potential for crizotinib in non-small cell lung cancer: a perspective review. Ther Adv Med Oncol 3(6):279–291
42. Choi YL et al (2010) EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. N Engl J Med 363(18):1734–1739
43. Sasaki T et al (2010) The neuroblastoma-associated F1174L ALK mutation causes resistance to an ALK kinase inhibitor in ALK-translocated cancers. Cancer Res 70(24):10038–10043
44. Popescu NC, King CR, Kraus MH (1989) Localization of the human erbB-2 gene on normal and rearranged chromosomes 17 to bands q12-21.32. Genomics 4(3):362–366
45. Buttitta F et al (2006) Mutational analysis of the HER2 gene in lung tumors from Caucasian patients: mutations are mainly present in adenocarcinomas with bronchioloalveolar features. Int J Cancer 119(11):2586–2591
46. Shigematsu H et al (2005) Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. Cancer Res 65(5):1642–1646
47. Stephens P et al (2004) Lung cancer: intragenic ERBB2 kinase mutations in tumours. Nature 431(7008):525–526
48. Serizawa M et al (2014) Assessment of mutational profile of Japanese lung adenocarcinoma patients by multitarget assays: a prospective, single-institute study. Cancer 120(10): 1471–1481
49. Li C et al (2014) Prognostic value analysis of mutational and clinicopathological factors in non-small cell lung cancer. PLoS ONE 9(9):e107276
50. Wang SE et al (2006) HER2 kinase domain mutation results in constitutive phosphorylation and activation of HER2 and EGFR and resistance to EGFR tyrosine kinase inhibitors. Cancer Cell 10(1):25–38
51. Bergethon K et al (2012) ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 30(8):863–870
52. Davies KD et al (2012) Identifying and targeting ROS1 gene fusions in non-small cell lung cancer. Clin Cancer Res 18(17):4570–4579
53. Takeuchi K et al (2012) RET, ROS1 and ALK fusions in lung cancer. Nat Med 18(3): 378–381

54. Shaw AT et al (2014) Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 371(21):1963–1971
55. Knowles PP et al (2006) Structure and chemical inhibition of the RET tyrosine kinase domain. J Biol Chem 281(44):33577–33587
56. Ju YS et al (2012) A transforming KIF5B and RET gene fusion in lung adenocarcinoma revealed from whole-genome and transcriptome sequencing. Genome Res 22(3):436–445
57. Kohno T et al (2012) KIF5B-RET fusions in lung adenocarcinoma. Nat Med 18(3):375–377
58. Lipson D et al (2012) Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. Nat Med 18(3):382–384
59. Wang R et al (2012) RET fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. J Clin Oncol 30(35):4352–4359
60. Drilon A et al (2013) Response to Cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov 3(6):630–635
61. Sossin WS (2006) Tracing the evolution and function of the Trk superfamily of receptor tyrosine kinases. Brain Behav Evol 68(3):145–156
62. Nakagawara A (2001) Trk receptor tyrosine kinases: a bridge between cancer and neural development. Cancer Lett 169(2):107–114
63. Alberti L et al (2003) RET and NTRK1 proto-oncogenes in human diseases. J Cell Physiol 195(2):168–186
64. Martin-Zanca D, Hughes SH, Barbacid M (1986) A human oncogene formed by the fusion of truncated tropomyosin and protein tyrosine kinase sequences. Nature 319(6056):743–748
65. Greco A, Miranda C, Pierotti MA (2010) Rearrangements of NTRK1 gene in papillary thyroid carcinoma. Mol Cell Endocrinol 321(1):44–49
66. Kim J et al (2014) NTRK1 fusion in glioblastoma multiforme. PLoS ONE 9(3):e91940
67. Vaishnavi A et al (2013) Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. Nat Med 19(11):1469–1472
68. Doebele RC et al (2015) An oncogenic NTRK fusion in a patient with soft-tissue sarcoma with response to the tropomyosin-related kinase inhibitor LOXO-101. Cancer Discov 5 (10):1049–1057
69. Trusolino L, Bertotti A, Comoglio PM (2010) MET signalling: principles and functions in development, organ regeneration and cancer. Nat Rev Mol Cell Biol 11(12):834–848
70. Zhen Z et al (1994) Structural and functional domains critical for constitutive activation of the HGF-receptor (Met). Oncogene 9(6):1691–1697
71. Yi S, Tsao MS (2000) Activation of hepatocyte growth factor-met autocrine loop enhances tumorigenicity in a human lung adenocarcinoma cell line. Neoplasia 2(3):226–234
72. Cooper CS et al (1984) Molecular cloning of a new transforming gene from a chemically transformed human cell line. Nature 311(5981):29–33
73. Kong-Beltran M et al (2006) Somatic mutations lead to an oncogenic deletion of met in lung cancer. Cancer Res 66(1):283–289
74. Ma PC et al (2003) c-MET mutational analysis in small cell lung cancer: novel juxtamembrane domain mutations regulating cytoskeletal functions. Cancer Res 63 (19):6272–6281
75. Kong-Beltran M, Stamos J, Wickramasinghe D (2004) The sema domain of met is necessary for receptor dimerization and activation. Cancer Cell 6(1):75–84
76. Ichimura E et al (1996) Expression of c-met/HGF receptor in human non-small cell lung carcinomas in vitro and in vivo and its prognostic significance. Jpn J Cancer Res 87 (10):1063–1069
77. Olivero M et al (1996) Overexpression and activation of hepatocyte growth factor/scatter factor in human non-small-cell lung carcinomas. Br J Cancer 74(12):1862–1868
78. Benedettini E et al (2010) Met activation in non-small cell lung cancer is associated with de novo resistance to EGFR inhibitors and the development of brain metastasis. Am J Pathol 177(1):415–423

79. Nakamura Y et al (2007) c-Met activation in lung adenocarcinoma tissues: an immunohistochemical analysis. Cancer Sci 98(7):1006–1013
80. Onozato R et al (2009) Activation of MET by gene amplification or by splice mutations deleting the juxtamembrane domain in primary resected lung cancers. J Thorac Oncol 4 (1):5–11
81. Onitsuka T et al (2010) Comprehensive molecular analyses of lung adenocarcinoma with regard to the epidermal growth factor receptor, K-ras, MET, and hepatocyte growth factor status. J Thorac Oncol 5(5):591–596
82. Beau-Faller M et al (2008) MET gene copy number in non-small cell lung cancer: molecular analysis in a targeted tyrosine kinase inhibitor naive cohort. J Thorac Oncol 3(4):331–339
83. Frampton GM et al (2015) Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov 5 (8):850–859
84. McBride OW et al (1983) Regional chromosomal localization of N-ras, K-ras-1, K-ras-2 and myb oncogenes in human cells. Nucleic Acids Res 11(23):8221–8236
85. Jancik S et al (2010) Clinical relevance of KRAS in human cancers. J Biomed Biotechnol 2010:150960
86. Tam IY et al (2006) Distinct epidermal growth factor receptor and KRAS mutation patterns in non-small cell lung cancer patients with different tobacco exposure and clinicopathologic features. Clin Cancer Res 12(5):1647–1653
87. Guerra C et al (2003) Tumor induction by an endogenous K-ras oncogene is highly dependent on cellular context. Cancer Cell 4(2):111–120
88. Popescu NC et al (1985) Chromosomal localization of three human ras genes by in situ molecular hybridization. Somat Cell Mol Genet 11(2):149–155
89. Soung YH et al (2005) Mutational analysis of EGFR and K-RAS genes in lung adenocarcinomas. Virchows Arch 446(5):483–488
90. Riely GJ et al (2008) Frequency and distinctive spectrum of KRAS mutations in never smokers with lung adenocarcinoma. Clin Cancer Res 14(18):5731–5734
91. Sun Y et al (2010) Lung adenocarcinoma from East Asian never-smokers is a disease largely defined by targetable oncogenic mutant kinases. J Clin Oncol 28(30):4616–4620
92. Pao W et al (2005) KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. PLoS Med 2(1):e17
93. Eberhard DA et al (2005) Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol 23(25):5900–5909
94. Massarelli E et al (2007) KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. Clin Cancer Res 13(10):2890–2896
95. Riely GJ, Ladanyi M (2008) KRAS mutations: an old oncogene becomes a new predictive biomarker. J Mol Diagn 10(6):493–495
96. Wan PT et al (2004) Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell 116(6):855–867
97. Brose MS et al (2002) BRAF and RAS mutations in human lung cancer and melanoma. Cancer Res 62(23):6997–7000
98. Cardarella S et al (2013) Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. Clin Cancer Res 19(16):4532–4540
99. Davies H et al (2002) Mutations of the BRAF gene in human cancer. Nature 417(6892): 949–954
100. Naoki K et al (2002) Missense mutations of the BRAF gene in human lung adenocarcinoma. Cancer Res 62(23):7001–7003
101. Paik PK et al (2011) Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. J Clin Oncol 29(15):2046–2051

102. Pratilas CA et al (2008) Genetic predictors of MEK dependence in non-small cell lung cancer. Cancer Res 68(22):9375–9383
103. Fang M et al (2014) A comparison of consistency of detecting BRAF gene mutations in peripheral blood and tumor tissue of nonsmall-cell lung cancer patients. J Cancer Res Ther 10(Suppl):C150–C154
104. Gautschi O et al (2012) A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. J Thorac Oncol 7(10):e23–e24
105. Falchook GS et al (2012) Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet 379(9829):1893–1901
106. Gautschi O et al (2015) Targeted therapy for patients with BRAF-mutant lung cancer: results from the European EURAF cohort. J Thorac Oncol 10(10):1451–1457
107. Hyman DM et al (2015) Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med 373(8):726–736
108. McCormick F (1995) Ras-related proteins in signal transduction and growth control. Mol Reprod Dev 42(4):500–506
109. Ding L et al (2008) Somatic mutations affect key pathways in lung adenocarcinoma. Nature 455(7216):1069–1075
110. Ohashi K et al (2013) Characteristics of lung cancers harboring NRAS mutations. Clin Cancer Res 19(9):2584–2591
111. Sasaki H et al (2007) Nras and Kras mutation in Japanese lung cancer patients: genotyping analysis using lightcycler. Oncol Rep 18(3):623–628
112. Reynolds SH et al (1991) Activated protooncogenes in human lung tumors from smokers. Proc Natl Acad Sci USA 88(4):1085–1089
113. Huang MH et al (2013) MEK inhibitors reverse resistance in epidermal growth factor receptor mutation lung cancer cells with acquired resistance to gefitinib. Mol Oncol 7 (1):112–120
114. Franke TF (2008) PI3K/Akt: getting it right matters. Oncogene 27(50):6473–6488
115. Bleeker FE et al (2008) AKT1 (E17K) in human solid tumours. Oncogene 27(42):5648–5650
116. Malanga D et al (2008) Activating E17K mutation in the gene encoding the protein kinase AKT1 in a subset of squamous cell carcinoma of the lung. Cell Cycle 7(5):665–669
117. Carpten JD et al (2007) A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. Nature 448(7152):439–444
118. Derijard B et al (1995) Independent human MAP-kinase signal transduction pathways defined by MEK and MKK isoforms. Science 267(5198):682–685
119. Arcila ME et al (2015) MAP2K1 (MEK1) mutations define a distinct subset of lung adenocarcinoma associated with smoking. Clin Cancer Res 21(8):1935–1943
120. Marks JL et al (2008) Novel MEK1 mutation identified by mutational analysis of epidermal growth factor receptor signaling pathway genes in lung adenocarcinoma. Cancer Res 68 (14):5524–5528
121. Karakas B, Bachman KE, Park BH (2006) Mutation of the PIK3CA oncogene in human cancers. Br J Cancer 94(4):455–459
122. Hiles ID et al (1992) Phosphatidylinositol 3-kinase: structure and expression of the 110 kd catalytic subunit. Cell 70(3):419–429
123. Samuels Y, Ericson K (2006) Oncogenic PI3K and its role in cancer. Curr Opin Oncol 18 (1):77–82
124. Kawano O et al (2006) PIK3CA mutation status in Japanese lung cancer patients. Lung Cancer 54(2):209–215
125. Lee JW et al (2005) PIK3CA gene is frequently mutated in breast carcinomas and hepatocellular carcinomas. Oncogene 24(8):1477–1480
126. Oxnard GR, Binder A, Janne PA (2013) New targetable oncogenes in non-small-cell lung cancer. J Clin Oncol 31(8):1097–1104
127. Sequist LV et al (2011) Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 3(75):75ra26

128. Chaft JE et al (2012) Coexistence of PIK3CA and other oncogene mutations in lung adenocarcinoma-rationale for comprehensive mutation profiling. Mol Cancer Ther 11 (2):485–491
129. Xu J et al (2011) Somatic mutation analysis of EGFR, KRAS, BRAF and PIK3CA in 861 patients with non-small cell lung cancer. Cancer Biomark 10(2):63–69
130. Anagnostou VK et al (2009) Thyroid transcription factor 1 is an independent prognostic factor for patients with stage I lung adenocarcinoma. J Clin Oncol 27(2):271–278
131. Berghmans T et al (2006) Thyroid transcription factor 1–a new prognostic factor in lung cancer: a meta-analysis. Ann Oncol 17(11):1673–1676
132. Crum CP, McKeon FD (2010) p63 in epithelial survival, germ cell surveillance, and neoplasia. Annu Rev Pathol 5:349–371
133. Travis WD et al (2013) Diagnosis of lung cancer in small biopsies and cytology: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Arch Pathol Lab Med 137(5):668–684
134. Collins FS, Varmus H (2015) A new initiative on precision medicine. N Engl J Med 372 (9):793–795
135. Topalian SL et al (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366(26):2443–2454
136. Brahmer JR et al (2012) Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 366(26):2455–2465
137. Massarelli E et al (2014) Immunotherapy in lung cancer. Transl Lung Cancer Res 3(1):53–63
138. Anagnostou VK, Brahmer JR (2015) Cancer immunotherapy: a future paradigm shift in the treatment of non-small cell lung cancer. Clin Cancer Res 21(5):976–984
139. Brahmer JR (2014) Immune checkpoint blockade: the hope for immunotherapy as a treatment of lung cancer? Semin Oncol 41(1):126–132
140. Velcheti V et al (2014) Programmed death ligand-1 expression in non-small cell lung cancer. Lab Invest 94(1):107–116
141. Schalper KA et al (2015) Objective measurement and clinical significance of TILs in non-small cell lung cancer. J Natl Cancer Inst 107(3):dju435
142. Teng MW et al (2015) Classifying cancers based on T-cell Infiltration and PD-L1. Cancer Res 75(11):2139–2145
143. Kerr KM et al (2015) Programmed death-ligand 1 immunohistochemistry in lung cancer: in what state is this art? J Thorac Oncol 10(7):985–989
144. Garon EB et al (2015) Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 372(21):2018–2028
145. Brahmer J et al (2015) Nivolumab versus Docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373(2):123–135
146. Borghaei H et al (2015) Nivolumab versus Docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373(17):1627–1639
147. Herbst RS et al (2014) Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 515(7528):563–567
148. Rizvi NA et al (2015) Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 348(6230):124–128

Lung Cancer Staging and Prognosis

Gavitt A. Woodard, Kirk D. Jones and David M. Jablons

Abstract

The seventh edition of the non-small cell lung cancer (NSCLC) TNM staging system was developed by the International Association for the Staging of Lung Cancer (IASLC) Lung Cancer Staging Project by a coordinated international effort to develop data-derived TNM classifications with significant survival differences. Based on these TNM groupings, current 5-year survival estimates in NSLCC range from 73 % in stage IA disease to 13 % in stage IV disease. TNM stage remains the most important prognostic factor in predicting recurrence rates and survival times, followed by tumor histologic grade, and patient sex, age, and performance status. Molecular prognostication in lung cancer is an exploding area of research where interest has moved beyond TNM stage and into individualized genetic tumor analysis with immunohistochemistry, microarray, and mutation profiles. However, despite intense research efforts and countless publications, no molecular prognostic marker has been adopted into clinical use since most fail in subsequent cross-validation with few exceptions. The recent interest in immunotherapy for NSCLC has identified new biomarkers with early evidence that suggests that PD-L1 is a predictive marker of a good response to new immunotherapy drugs but a poor prognostic indicator of overall survival.

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Future prognostication of outcomes in NSCLC will likely be based on a combination of TNM stage and molecular tumor profiling and yield more precise, individualized survival estimates and treatment algorithms.

Keywords
International association for the study of lung cancer (IASLC) lung cancer staging project · NSCLC seventh edition TNM staging system · Prognostic clinical variables · Prognostic biomarkers · Immunotherapy

Contents

1 Lung Cancer Overview

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality in men and women with an overall 5-year survival rate of 19.3 % [1]. Tumor TNM staging using tumor size, local invasion, and the presence of nodal and distant metastases remains the prevailing method to predict patient survival with 5-year stage-specific survival rates ranging from 73 % in stage IA disease to 13 % in stage IV disease [2]. In addition to these long-established clinical methods of predicting survival, newer prognostic tools based on individual tumor mutations and protein expression show great promise in providing additional personalized genetic information with the potential to revolutionize treatment algorithms and tumors classifications.

2 Lung Cancer Staging

Cancer staging systems provide a standardized framework to define a tumor's spread so homogenous patient groups can be studied and discussed by different sources. The lung cancer staging system provides useful prognostic information for patients and structures treatment plans for providers. The current staging system developed by the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project is the seventh widely used NSCLC staging system and is the first in NSCLC to be developed from an international patient database and to be internally and externally validated to significantly stratify patients based on survival outcomes.

2.1 History of Lung Cancer Staging

In the 1950s, the Veterans' Affairs Lung Study Group introduced a two-stage system to classify lung cancer for use in clinical trials, which described patients as having either limited or extensive disease. The first TNM classification of lung cancer was introduced by the Union Internationale Contre le Cancer (UICC) now known as the International Union Against Cancer in 1966 as part of a series of brochures that proposed TNM descriptions for a variety of different organ sites. In 1968, lung TNM definitions were published under the section "other sites" in the UICC "TNM Classification of Malignant Tumors." No stage groupings were suggested, and the TNM descriptors were used to simply convey the anatomic extent of the tumor: T1 for a tumor localized to one lung segment, T2 for a tumor confined to one lobe, T3 for a tumor involving the main bronchus or more than one lobe, T4 for tumors extending beyond the lung, and N1 to describe any involvement of intrathoracic lymph nodes [3].

Soon after the initial UICC proposal in 1973, the American Joint Committee for Cancer Staging and End Results Reporting (AJC), now the American Joint Committee on Cancer (AJCC) Task Force on Lung Cancer, proposed new data-driven TNM definitions and introduced stage groupings. The AJCC system, published by Clifton Mountain, David Carr, and W.A. Anderson, was based on 2155 surgical lung cancer specimens mainly from MD Anderson Cancer Center in Houston, Texas from patients with at least 4 years of follow-up data. This first AJCC system outlined the majority of the T descriptors still used today, including size cutoff of 3 cm, invasion of visceral and parietal pleura, chest wall, diaphragm, and mediastinum and an N2 lymph node category was added to describe mediastinal lymph node involvement. Different TNM permutations were grouped into stages I, II, and III to allow for the maximum separation in survival outcomes between the groups [4]. While some TNM groupings had too few cases for analysis and there was no validation of the proposed stages, this data-driven publication represented a major step forward in NSCLC staging and laid the framework for the current staging system.

Based mainly on a growing number of patients in Dr. Mountain's MD Anderson database and some from the National Cancer Institute (NCI), newer updated editions of the lung cancer staging system were published through 1997. These newer editions divided the T classification into subdivisions such as T1a and T1b, added N3 to accommodate contralateral or distant nodal metastases, further stratified TNM stage groupings into A and B, and added stage IV to describe metastatic disease. In addition, the descriptors "c," "p," "y," and "r" were introduced to identified tumors staged clinically, pathologically, following treatment, and following recurrence, respectively. TNM groups were assigned to stages I to IV based on survival data, with statistically significant survival differences seen between different stage groups [5].

All of the AJCC staging system revisions continued to be based on Dr. Mountain's database, which at the time of the last revision consisted of 5319 specimens. At the time, this was the largest collection of patient pathologic and survival information available, but using Dr. Mountain's database was flawed in that the samples were mainly drawn from a single institution in USA, some survival data that were more than twenty years old, and none of the staging cutoffs were externally validated. In addition, the patient population reflected historic lung cancer demographics. Dr. Mountain's original staging study patients were mostly male and the database contained 1712 cases of NSCLC of which 30 % were adenocarcinoma and 58 % were squamous cell carcinoma [4]. Since that time, the histologic prevalence of lung cancer had shifted, major advances in imaging dramatically changed the way lung cancer was diagnosed and staged, and new chemotherapy regimens and radiation treatments had evolved.

The IASLC Lung Cancer Staging Project was an unprecedented international effort to revise the staging system to reflect a global patient population, all treatment modalities of care, and current survival outcomes. The IASLC Staging Project lead to the 2010 adoption of the seventh and current edition of the TNM staging in lung cancer which is based on 81,015 international lung cancer cases including 67,725 NSCLC, 13,290 small cell lung cancer (SCLC), and 513 carcinoid tumors. The IASLC staging system represents a milestone in accurate and scientifically based lung cancer staging as it underwent extensive internal and external validation and resulted in modified T and M categories and updated stage groupings to reflect the most current survival data.

2.2 Non-small Cell Lung Cancer Staging

NSCLC is the broad grouping of primary lung tumors including adenocarcinoma, squamous cell carcinoma, and large cell neuroendocrine carcinoma which combined comprise 85–90 % of all newly diagnosed lung and bronchus tumors [1]. Adenocarcinoma is the most common form of NSCLC and lung cancer overall, and accounts for about 50 % of NSCLC and 38 % of newly diagnosed lung cancers. Squamous cell carcinoma has slowly been decreasing in incidence and is currently the second most common NSCLC. Recent Surveillance, Epidemiology, and End

Result (SEER) cancer registry data indicate that it accounts for 30 % of nearly diagnosed NSCLC in men and 20 % of new diagnoses in woman [6, 7].

2.2.1 IALSC NSCLC TNM Descriptors

The result of the IASLC Staging Project was the seventh edition of the UICC/AJCC TNM system for NSCLC. The TNM system is used to stage most cancers and describes the anatomic spread of a tumor. In it, the T descriptor describes the extent of the primary tumor, the N descriptor reflects the extent of lymph node involvement, and the M descriptor defines spread to distant sites.

The T descriptor in most cases is determined by tumor size as measured by the greatest dimension on computerized tomography (CT) imaging with T1a $\leq$ 2 cm, T1b > 2 but $\leq$ 3 cm, T2a > 3 but $\leq$ 5 cm, T2b > 5 but $\leq$ 7 cm, and T3 > 7 cm [8]. There is debate and no official consensus regarding how to measure semisolid lesions or ground glass opacities with a solid component as the measurable tumor dimensions change when viewed on a lung or a mediastinal window [9]. In our practice, both measures are reported, but we base our clinical T stage off the measured solid component. For the pathologic T stage, tumors should be measured prior to fixation to determine the greatest diameter as fixation in formalin can cause up to 20 % shrinkage in tumor size [10]. Beyond size criteria alone, direct invasion of nearby structures can increase a tumor's T stage. T2 is used to describe tumors that invade the visceral pleural, involve the main bronchus but remain $\geq$2 cm away from the carina, or tumors which cause atelectasis or obstructive pneumonia that does not involve the entire lung. T3 tumors directly invade the chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium, and T3 also describes a tumor in the main bronchus <2 cm from the carina, a tumor causing atelectasis or obstructive pneumonia of the entire lung, or a separate tumor nodule (s) in the same lobe. T4 describes a tumor of any size with invasion of the heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina, or a separate tumor nodule(s) in a different ipsilateral lobe [8]. Pancoast tumors which invade thoracic nerve roots would be classified as T3, and T4 if the tumor invades C8 or higher cervical nerve roots, the brachial plexus, subclavian vessels, vertebral bodies, lamina, or the spinal canal [9] (Table 1).

Pleural invasion, particularly the presence of tumor at the surface of the visceral pleura, has been an indicator of a poor prognosis since the early systems for lung cancer staging were established [4]. In subsequent years, the definition of what constitutes invasion has been interpreted differently by different clinicians and varied from gross pleural puckering to histologic confirmation of tumor on the visceral pleural surface. Several studies showed that there was a significant survival difference in patients when tumor crossed the visceral pleural elastica [11, 12]. Additionally, cases with invasion across the visceral pleural elastica showed similar prognoses as those with tumor at the visceral pleural surface. Pleural invasion can be classified using histologic criteria put forth by Hammar [13]. Using these criteria, a tumor can be classified as PL0 (no invasion), PL1 (invasion through visceral pleural elastica), PL2 (tumor present at surface of visceral pleura), and PL3 (tumor invades into parietal pleura) (Fig. 1). Tumors with visceral pleural invasion (PL1 and PL2)

Table 1 Seventh edition TNM staging system for NSCLC

Primary tumor (T)	
Tis	Focus of in situ cancer
T0	No primary tumor identified
T1	Size $\leq$ 3 cm surrounded by visceral pleura
T1a	Size $\leq$ 2 cm
T1b	Size $\leq$ 2 but $\leq$ 3 cm
T2	Size > 3 but $\leq$ 5 cm Tumor of any size with invasion of the visceral pleural Tumor involving the main bronchus $\geq$2 cm distal to the carina Tumors causing atelectasis or obstructive pneumonia extending to the hilum but not involving the entire lung
T2a	Size > 3 but $\leq$ 5 cm
T2b	Size > 5 but $\leq$ 7 cm
T3	Size > 7 cm Tumor of any size with invasion of the chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium Tumor involving the main bronchus <2 cm distal to the carina Tumor causing atelectasis or obstructive pneumonia of the entire lung Separate tumor nodule(s) in the same lobe
T4	Tumor of any size with invasion of the heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina Separate tumor nodule(s) in a different ipsilateral lobe
TX	T status not able to be assessed
Regional lymph nodes (N)	
N0	No regional lymph node metastasis
N1	Metastasis or direct extension into ipsilateral peribronchial or perihilar lymph nodes and intrapulmonary lymph nodes
N2	Metastasis or direct extension into ipsilateral mediastinal or subcarinal lymph nodes
N3	Metastasis into contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular nodes
NX	N status not able to be assessed
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion
M1b	Distant metastasis (in extrathoracic organs)
MX	M status not able to be assessed

are classified as T2a unless other factors result in a higher designation. Tumors with parietal pleural invasion (PL3) are classified as T3 unless other factors result in a higher designation [14].

Nodal involvement is characterized by the N descriptor with N0 indicating no nodal involvement. N1 is defined by tumor metastasis or direct extension into ipsilateral peribronchial or perihilar lymph nodes and intrapulmonary nodes,

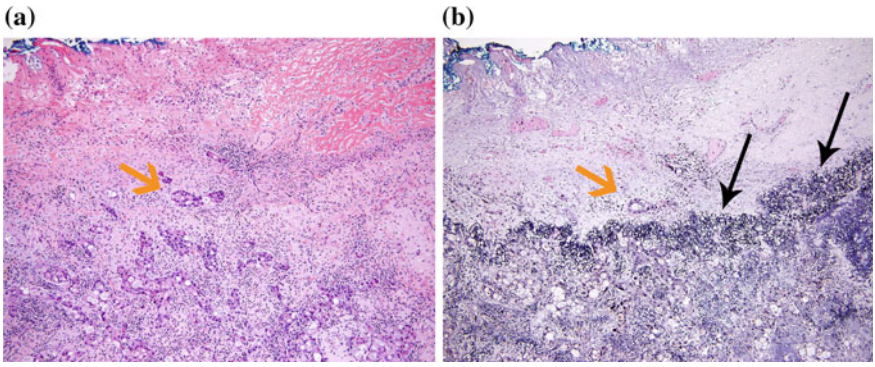

Fig. 1 Pleural invasion. Hematoxylin and eosin (H&E) stain 100x (**a**) and Verhoeff-van Gieson (VVG) stain 100x (**b**) of a lung adenocarcinoma invading the visceral pleura. The visceral pleural surface is seen in the *top left corner inked blue* with the tumor invading from the bottom of the image. Multiple tumor deposits (*orange arrow*) can be seen approaching the visceral pleural surface on the H&E stain. The VVG stain allows visualization of the visceral pleural elastica layer (*black arrows*). The presence of the tumor deposit (*orange arrow*) superficial to the visceral pleural elastica layer stages this tumor as PL1 pleural invasion

representing lymph node stations 10–14. N2 describes tumor metastasis or direct extension into ipsilateral mediastinal or subcarinal lymph nodes, representing lymph node stations 2–9. N3 status reflects metastasis into contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene or station 1 supraclavicular nodes. Extrathoracic nodal involvement, such as a positive axillary lymph node, is classified as M1b [8] (Table 1). The lymph node stations and radiographic borders defined by IASLC are shown in Fig. 2.

Micrometastases as defined by UICC and AJCC contain cancerous cells with mitoses and invasion and can be seen on standard hematoxylin and eosin staining. Micrometastases in lymph nodes should be considered a positive node and described as N2 (mi). However, isolated tumor cells, which are differentiated as being small clusters of tumor cells without mitosis, vascular invasion, or lymphatic invasion, should not be counted as a positive metastasis [9].

The M descriptor relates to distant metastatic disease and is divided into M1a and M1b. M1a describes tumors with a separate tumor nodule in a contralateral lobe, pleural nodules, or malignant pleural dissemination. M1b describes metastases to distant sites and extrathoracic organs (Table 1). The same rules regarding nodal micrometastases and isolated tumor cells apply to M staging [8].

The TNM stage grouping scheme was adjusted in the seventh edition of the staging guidelines to best separate survival outcomes between stages [2]. Stage IA includes tumors up to 3 cm with no lymphatic spread. These early-stage tumors are managed with surgical resection alone. Adjuvant treatments are not indicated in stage IA NSCLC, and patients are followed with surveillance CT scans. Stage IB tumors measure between 3 and 5 cm or have other criteria to make them T2 such as invasion of the visceral pleura or involvement of the main bronchus without any

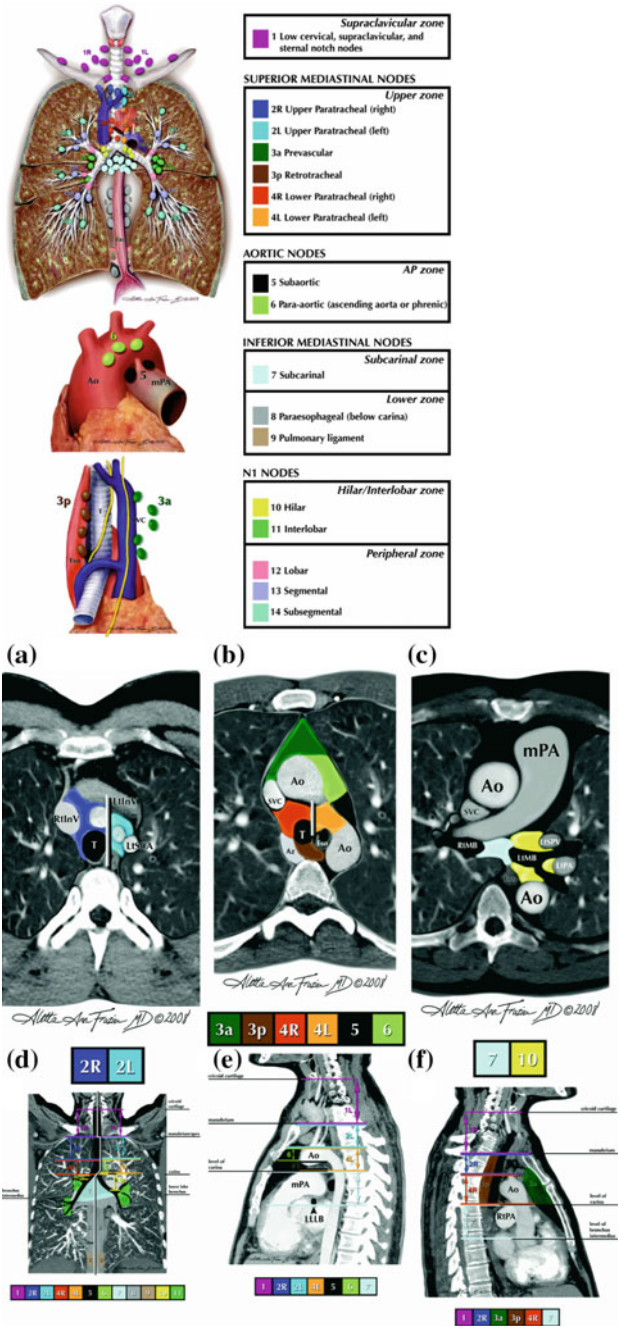

Fig. 2 Non-small cell lung cancer lymph node stations. **a** International Association for the Study of Lung Cancer (IASLC) lymph node station map, stations, and CT scan. **b** Application of the IASLC lymph node stations and borders to CT scans. Reproduced from Rusch et al. [101] with permission

lymphatic spread. Stage IIA tumors are any T1 or T2 tumor with N1 nodal involvement or a tumor between 5 and 7 cm in size without nodal involvement. Positive N1 nodal involvement and a 5- to 7-cm tumor becomes Stage IIB. Stage IIB also includes T3 tumors without nodal involvement such as tumors greater than 7 cm, tumors that invade the chest well, diaphragm, or mediastinal pleura, tumors that involve the main bronchus, or a separate tumor nodule in the same lobe [2]. Stage IB-IIB tumors without nodal involvement amenable to complete surgical resection can be managed with upfront surgery followed by adjuvant therapy. Tumors that are locally invasive or have suspect N1 should undergo neoadjuvant chemotherapy to attempt to reduce and downstage tumors prior to surgical resection.

Stage IIIA tumors are the most heterogeneous group with a wide range of presentations from smaller tumors with mediastinal nodal involvement to large and locally invasive tumors. This stage grouping includes any T1, T2, and T3 tumor with N2 nodal involvement and T3 tumors with N1 nodal involvement. Stage IIIA also includes stage T4 tumors with invasion of the great vessels or heart or with a separate ipsilateral tumor nodule with N0 or N1 lymph nodes [2]. It is challenging to develop rigid treatment algorithms for stage IIIA patients due to the diversity of tumors, and as a result, treatment plans for IIIA patients should be discussed by a multidisciplinary tumor board. Survival outcomes can vary widely within this complex group depending on the presence of mediastinal nodal disease, the tumor's response to neoadjuvant chemotherapy and or radiation, and the pulmonary operation required to achieve a complete resection [15].

Advanced-stage lung cancers, where a surgical resection for local control no longer offers a survival advantage, include stage IIIB and IV tumors. Stage IIIB tumors are T4 tumors which invade the heart, great vessels, trachea, or other major nearby structures or T4 tumors with a separate ipsilateral tumor nodule with N2 lymph node involvement, or any tumor with N3 lymph node involvement of contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular nodes. Stage IV disease comprises tumors with any M1 distant metastasizes including separate tumor nodules in a contralateral lobe, pleural nodules, malignant effusion, or metastasis to an extrathoracic organ [2] (Table 2).

Table 2 Seventh edition NSCLC staging definitions

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	IA	IIA	IIIA	IIIB
	T1b	IA	IIA	IIIA	IIIB
T2	T2a	IB	IIA	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	IIIB
M1	M1a/1b	IV	IV	IV	IV

Table 3 Staging modifiers

Staging modifier prefixes	
c	Pretreatment stage based on information such as physical exam, imaging, biopsy, endoscopy, or surgery for staging purposes
p	Staging from pathology specimen after a definitive surgical resection
y	Stage following induction treatment, can be described as clinical "yc" or pathologic "yp"
r	Restaging done following a recurrence
a	Stage at the time of death based on information obtained via an autopsy

TNM staging can be assessed at multiple time points and tumors can be down-staged by treatment or upstaged as disease progresses. The type of staging classification is denoted by prefix with clinical stage and pathologic stage being the two most commonly used types. Clinical stage, denoted by a "c" prefix, refers to staging based on exam, imaging, biopsy, and surgical staging done prior to any treatment. Pathologic staging is the gold standard and is based on the surgical specimen and information obtained from a definitive surgical resection. The seventh edition of the NSCLC staging system allows clinical and pathologic classifications to be applied to T, N, and M individually when only partial information is available [16]. After induction treatment, staging or restaging is denoted with the prefix "y" which can be further described as "yc" or "yp." Staging done after a recurrence developed is denoted by the prefix "r," and staging done postmortem based on an autopsy is denoted by the prefix "a." [9] (Table 3).

The most recent NCI SEER data on 48,315 annual cases of lung cancer show the following NSCLC incidence by stage: stage IA 11.7 %, stage IB 6.1 %, stage IIA 3.6 %, stage IIB 3.7 %, stage IIIA 11.7 %, stage IIIB 5.6 %, stage IV 49.3 %, with 1.5 % being occult and 5.1 % of cases with stage unknown. SEER data indicate that over the past few years, there has been a steady rise in the incidence of smaller, early-stage tumors, and particularly stage IA lesions which has been attributed to the increasing use of chest CT scans and increasing detection of incidental lung lesions [17].

2.2.2 Synchronous Tumor Nodules

The most important distinction in approaching additional pulmonary nodules in the setting of a primary lung cancer is determining whether they represent a separate primary lung cancer, an isolated pulmonary metastasis, or multifocal lung cancer. IASLC guidelines give the pathologist primary responsibility for determining when nodules represent a synchronous primary lung cancer or a pulmonary metastasis [5]. This distinction was historically more difficult to make as most synchronous primary lung cancers have the same histologic type [18]. However, the current era of rapid tumor mutation profiling will likely simplify this process though mutation profiling for this exact purpose has yet to be validated.

The distinction between a metastatic single lung cancer and two separate early-stage cancers dramatically alters the clinical stage and patient management, so

this determination ideally needs to occur prior to a surgical resection. For this reason, others have recommended [9], and it is our practice to discuss these complex patients with an experienced multidisciplinary tumor board before defining lesions as synchronous primary lung cancers with separate TNM staging and treatment plans.

The most widely known criteria for histologic differentiation of synchronous primaries from intrapulmonary metastases are those proposed by Martini and Melamed [19]. According to these criteria, tumors of similar histology are categorized as synchronous primaries if they are in different segments, lobes, or lungs, showing a component of carcinoma in situ, and there is an absence of both intralymphatic tumor in shared lymphatics and extrapulmonary metastasis. At the time of the publication of the criteria of Martini and Melamed, the majority of the tumors evaluated were squamous cell carcinoma, and the diagnosis of adenocarcinoma in situ had not been accepted in lung tumors. More recently, Girard et al. [20] presented a method of comprehensive histologic assessment to compare separate nodules to determine whether they represent synchronous primaries or metastases. This method evaluates tumor histologic type (e.g., adenocarcinoma, squamous cell carcinoma), histologic pattern and percentage breakdown of pattern for adenocarcinomas (e.g., lepidic, acinar), and stromal and cytologic features (e.g., lymphoid hyperplasia, signet ring cells). Comprehensive histologic assessment correlated well with molecular profiling and showed prognostic accuracy when staging patients. Patients determined to have intrapulmonary metastases within the same lobe have survival outcomes similar to patients with solitary tumors designated as T3. Patients with ipsilateral metastases to a different lobe show survival outcomes similar to patients with solitary tumors designated as T4. Patients with contralateral metastases are designated as M1a [14].

2.3 Pulmonary Carcinoid Tumor Staging

As part of the IASLC Lung Cancer Staging project 513, carcinoids were submitted to the international lung cancer database used to define the NSCLC TNM stage groups. These tumors were excluded from the NSCLC analysis and were not used in creating the new TNM categories; however, subsequent review of the IASLC data as well as SEER data has demonstrated that the T, N, and M categories as well as the TNM groupings for NSCLC are also significant predictors of survival when applied to pulmonary carcinoid tumors [21].

SEER data on 1437 pulmonary carcinoid tumors indicate that carcinoids are diagnosed at an earlier stage than NSCLC with the following incidence: stage IA 57 %, stage IB 22 %, stage IIA 9 %, stage IIB 3 %, stage IIIA 6 %, stage IIIB <1 %, and stage IV 3 % [21]. Overall carcinoid tumors have a better prognosis stage-for-stage than NSCLC with 5-year survival rates of 93, 85 75, and 57 % in stage I, II, III, and IV tumors, respectively. As with NSCLC, older age and male sex are significantly associated with worse survival [21]. While SEER data analysis of the TNM staging system did not distinguish between typical and atypical carcinoid

tumors, typical carcinoids have a better prognosis than atypical carcinoids. Long-term survival data show 5-year and 10-year overall survival rates of 97 and 90 % for typical carcinoids and 71 and 62 % for atypical carcinoids, respectively [22].

2.4 Small Cell Lung Cancer Staging

Small cell lung cancer (SCLC) is characterized by rapid doubling time, early development of widespread metastases, and markedly worse survival outcomes than NSCLC [23]. SCLC has been decreasing in incidence with current NCI data indicating that SCLC currently comprises only 10 % of all new lung cancer diagnoses [1]. While most patients with SCLC will initially respond to chemotherapy and radiation, disease recurrence remains a major problem [24]. Outcomes have remained poor over the past several decades and only 4.6 % of all patients are still alive two years following diagnosis [25].

Over 60 % of SCLC patients present with overt metastatic disease and almost all of the remaining 35–40 % have locally advanced disease not amenable to surgical resection. Therefore, the classic TNM staging systems, based on pathologic confirmation from a surgical specimen, were historically considered neither practical nor clinically useful in these advanced-stage patients. Instead, a modification of the original VALSG two-stage lung cancer staging system was widely used with SCLC patients described as having "limited" or "extensive" disease which corresponded to TNM stages I-IIIB and stage IV, respectively.

Patients with "limited" disease were described as tumors confined to the ipsilateral hemithorax and regional nodes, which could be included in a single radiation treatment field. Such SCLC patients are generally treated with curative-intent chemoradiation and chemotherapy. In these favorable "limited" disease patients, there is still only a 10 % 5-year survival rate [25]. "Extensive" disease in SCLC is the stage IV equivalent and is defined as tumor beyond the boundaries of limited disease including distant metastasis, malignant pericardial or pleural effusion, or contralateral hilar or supraclavicular involvement. In this group, there are no long-term survivors.

While the two-stage system is still widely used in SCLC, the seventh edition of the TNM system that was developed for using in NSCLC successfully applies to SCLC. The IASLC staging project collected data on 12,620 cases of SCLC and had sufficient data to apply the new NSCLC TNM criteria to 8088 of them. SCLC clinical TNM stage data were used instead of pathologic TNM data as only 5 % of SCLC patients are eligible for surgery, and therefore, pathologic TNM stage cannot be obtained from the majority of patients. The TNM staging system predicted survival for SCLC patients with significantly worse outcomes among patients with increasing cT stage. There were no significant difference in survival between patients with cN0 versus cN1 nodal spread stage; however, cN2 and cN3 disease did correlate with progressively worse survival. Increased TNM stage groupings were associated with worse outcomes with shorter median survival times of 30 months in stage IA, 18 months in stage IB, 33 months in stage IIA, 18 months in stage IIB,

14 months in stage IIIA, 12 months in stage IIIB, and 7 months in stage IV patients. Five-year overall survival rates were as follows: stage IA 38 %, stage IB 21 %, stage IIA 38 %, stage IIB 18 %, stage IIIA 13 %, stage IIIB 9 %, and stage IV 1 %. Of note, outcomes in stage IIA patients were slightly off trend as N0 versus N1 nodal status was not shown to be an important distinction in SCLC [26].

3 Prognosis

The international database created for the IASLC lung cancer staging project lead to data-driven and extensively validated T, N, and M categories with significant differences in survival. TNM stage remains the most important factor in survival prognostication; however, heterogeneity in outcomes within the same TNM group suggests that other clinical or molecular prognostic markers should be developed and used to further refine risk stratification. Here, we present a review of the current evidence behind the major prognostic factors in NSCLC.

3.1 Stage-Based Survival Outcomes

The IASLC database of 81,015 eligible cases yielded prognostic information on T, N, M and overall stage medial survival times and overall 5-year survival rates from the largest collection of patient data ever available. Clinical and pathologic stage-based survival estimates are available and often provide different prognostic estimates. For example, tumors staged clinically as cT1a or cT1b have 5-year survival rates of 53 and 47 %, respectively, whereas pathologically staged pT1a and pT1b tumors have 5-year survival rates of 77 and 71 %, reflecting that early-stage tumors are often clinically under-staged. The presence of any nodal spread is a poor prognostic indicator. The clinical presence of cN1 nodal disease is associated with a 67 % 1-year survival rate and a 29 % 5-year survival rate. Pathological-staged pN1 nodal disease has a slightly better prognosis at 77 % 1-year survival and 38 % 5-year survival, reflecting how the inclusion of patients with micrometastatic nodal disease in the pathologically staged group will upstage the same patient, and therefore increase survival rates in the pathologically staged group. Any M1 categorization by malignant pleural effusion, contralateral nodule, or distant disease was associated with 5-year survival rates of less than 6 % [8]. Detailed information on survival by each T, N, and M descriptor from the IASLC database from the original Detterbeck et al. study is reproduced in Table 4.

TNM stage groupings currently provide the most accurate prognostic estimate of overall survival. Pathologically staged stage IA patients have a median survival time of 119 months or almost 10 years, and a 5-year overall survival rate of 73 %. This compares to a 46 % 5-year survival rate among stage IIA patients and a 24 % 5-year survival rate among IIIA patients (Table 5; Fig. 3) [2]. However, there is obvious heterogeneity within each stage group with some patients rapidly developing systemic disease and others surviving long term without recurrence. There is

Table 4 Staging modifiers

Survival rates by TNM stage				
	Clinical stage		Pathologic stage	
	MST	5-year (%)	MST	5-year (%)
T stage				
T1a	68	53	NR	77
T1b	52	47	113	71
T2a	43	43	81	58
T2b	30	36	56	49
T3, >7 cm	17	26	29	35
T3, invasion	19	27	24	31
T3, satellite nodules	25	29	21	28
T4, invasion	13	14	15	22
T4, ipsilateral nodules	15	25	18	22
M1a, plural dissemination	8	2	18	11
N stage				
N0	40	42	77	56
N1	23	29	34	38
N2	14	16	21	22
N3	9	7	12	6
M stage				
M1, pleural invasion	8	2	10	8
M1, contralateral nodule	10	3	10	3
M1, distant metastasis	6	1	6	1

Prognosis by T, N, M stage, modified from Detterbeck et al. [8]. *MST* median survival time in months. 5-year overall survival

Table 5 Prognosis by TNM stage group

Survival rates by TNM grouping				
	Clinical stage		Pathologic stage	
	MST	5-year (%)	MST	5-year (%)
IA	60	50	119	73
IB	43	43	81	58
IIA	34	36	49	46
IIB	18	25	31	36
IIIA	14	19	22	24
IIIB	10	7	13	9
VI	6	2	17	13

Prognosis by TNM stage grouping, modified from Goldstraw et al. [2]. *MST* median survival time in months. 5-year overall survival

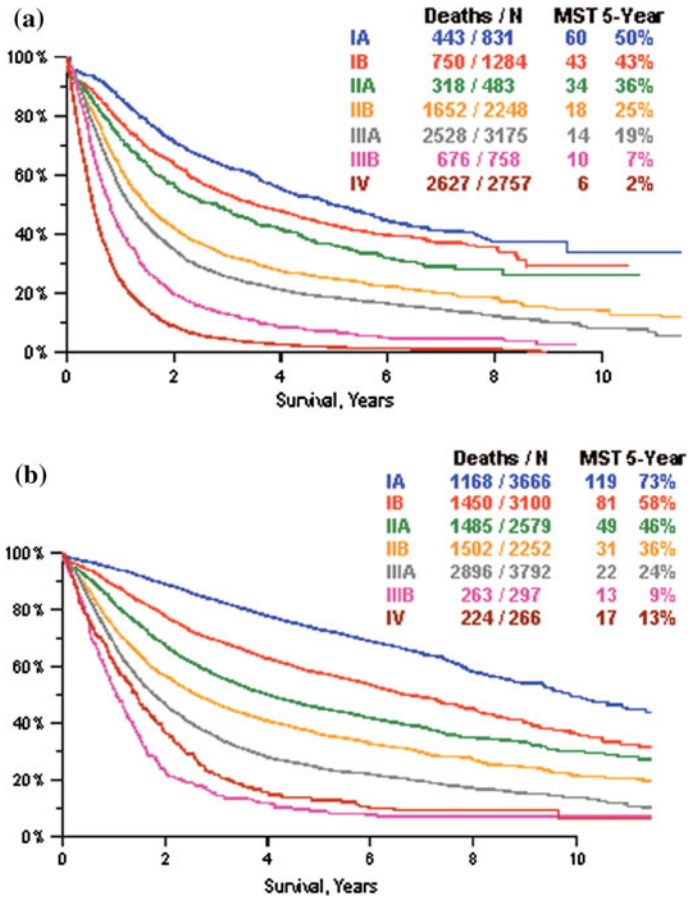

Fig. 3 NSCLC 5-year overall survival rates. **a** Overall 5-year survival by clinical stage. From Goldstraw et al. with permission. **b** Overall 5-year survival by pathologic stage. From Goldstraw et al. [2] with permission

great interest in identifying the clinical characteristics and tumor biologic markers that might be used to pinpoint more personalized and accurate survival outcomes within each TNM stage group.

3.2 Clinical and Demographic Prognostication

In addition to TNM stage, other factors that have been shown to have prognostic value include tumor grade, sex, age over 65 years, smoking status, performance status, comorbidities, type of pulmonary resection, and hospital case volume [27]. A Mayo clinic review of 5018 NSCLC patients found that following TNM stage, the most important prognostic factor was tumor grade with a 70 and 80 % higher

risk of death for poorly differentiated and undifferentiated carcinomas after controlling for age, sex, smoking history, tumor stage, histologic cell type, and treatment [28].

In addition to poorly differentiated tumor grade, prognostic factors shown in multiple studies to be independently associated with worse long-term survival include male gender, increased age, high pT stage, and patient's performance status [28–30]. Histologic subtype has often been cited as a prognostic factor in NSCLC with improved survival outcomes in patients with squamous cell histology [31]. However, repeated multivariate analyses have failed to identify histologic subtype as an independent prognostic marker [27]. Comorbid diseases at the time of diagnosis have been shown to independently decrease survival rates and a Charlson comorbidity score ≥ 3 is associated with an 80 % increased risk of death at 1-year [32]. Specifically, cardiovascular comorbidities have been shown to increase NSCLC risk of death by 30 %, diabetes increases mortality by 20 %, cerebrovascular disease increases mortality by 20 % [33], and a history of chronic obstructive pulmonary disease (COPD) decreased 5-year survival by 20 % [34]. In a recently published study of 394 patients with advanced NSCLC, the median survival was only 7.8 months, and on multivariate analysis, only performance status was a significant prognostic factor that influenced survival [35]. Smoking cessation following diagnosis with early-stage NSCLC has also been shown in meta-analysis to improve prognosis. Patients who continued to smoke following NSCLC diagnosis had increased mortality (HR 2.94, 95 % CI 1.15–7.54) compared with patients who stopped smoking after diagnosis [36].

A review of 19,702 stage I NSCLC cases from the California Cancer registry found that advanced age, male sex, low socioeconomic status, non-surgical treatment, and poor histologic grade were associated with increased mortality, whereas bronchoalveolar carcinoma histology and Asian ethnicity were associated with decreased mortality [37]. Unmarried patients and patients with lower socioeconomic status with early-stage NSCLC are less likely to undergo surgery. Lower socioeconomic status is associated with other potential prognostic factors including male sex, unmarried status, squamous cell histology, poorly differentiated tumors, fewer surgical resections, and less treatments overall in NSCLC. When these other factors are controlled for on multivariate analysis, low socioeconomic status remains an independent poor prognostic factor [38].

Long-term NSCLC survival data beyond 5 years from the SEER database demonstrate that patients still alive at 5 years can expect long-term overall survival rates of 55.4, 33.1, and 24.3 % at 10, 15, and 18 years, respectively, and disease-specific survival rates of 76.6, 65.4, and 59.4 % at 10, 15, and 18 years, respectively. Significant predictors of improved long-term disease-specific survival after 5 years include tumor size < 3 cm, age < 60 years, female gender, right-sided tumor, non-squamous histology, having undergone lobectomy or pneumonectomy. Poor predictors of long-term survival beyond 5 years include squamous cell histology and having a pulmonary wedge resection or no surgery at all [39].

For patients that undergo a surgical resection, hospital case volume has been shown repeatedly to impact prognosis. A study of 119,146 NSCLC patients from

the National Cancer Database found that among patients that underwent surgical resection, 30-day mortality was highest among patients who require a pneumonectomy (8.5 %), and among older patients (age > 85, 7.1 %), male patients (4.4 %), and patients with increasing comorbidities (Charlson score $\geq$ 2, 5.0 %). Hospital case volume was also a significant independent predictor of 30-day mortality with an overall 3.6 % 30-day mortality in low volume hospitals who perform less than 47 pulmonary resections a year and a 0.7 % 30-day mortality in high-volume hospitals that perform more than 190 pulmonary resections a year ($p < 0.0001$) [40]. In addition to the expected impact of case volume on 30-day mortality, SEER data indicate that 5-year survival is also impacted by hospital case volume. In the SEER database, patient's operated on at high volume centers have 5-year survival rates of 44 % compared with 33 % at low volume centers [41].

3.3 Biomarkers and Genetic Prognostic Indicators

Only 53 % of stage I and II NSCLC patients are alive 5 years after a complete surgical resection, with most deaths being directly related to cancer recurrence [42]. While the TNM staging system remains the strongest predictor of survival, tumor biology and survival outcomes vary widely within each stage. In the modern era of molecular biomarkers and rapid genetic sequencing, increasing amounts of tumor-specific information can refine prognostic estimates beyond crude anatomic TNM stage alone.

Over a thousand studies have been published that identify prognostic biomarker proteins, mRNA, miRNA, and oncogenes in NSCLC; however, no dominant single biomarker has withstood sufficient validation to be incorporated into clinical use. Immunohistochemistry (IHC) staining of tumors to identify overexpressed proteins is the most typical method used to identify and evaluate potential prognostic biomarkers, but IHC methods are not standardized using different antibodies and "positive" cutoff definitions, and as a result, data are inconsistent between studies. Single protein markers which initially seemed promising such as insulin-like growth factor-1 receptor (IGF1R), hepatocyte growth factor (MET), cyclin D1, Excision Repair Cross-Complementation group (ERCC1) [43, 44], and many others have later failed to be prognostic in subsequent cross-validation studies [45–50]. The most promising proteins which have shown more consistent support or been backed by meta-analysis include epidermal growth factor receptor (EGFR) [51, 52] and B cell lymphoma 2 (Bcl-2) [53, 54] as favorable prognostic markers and human epidermal growth factor receptor 2 (HER-2) [55], vascular endothelial growth factor (VEGF) [56, 57], Kirsten rat sarcoma (KRAS) [31, 51, 52], tumor protein p53 (TP53) [31, 52], and Ki-67 [58] as poor prognostic markers.

EGFR mutations are found at much higher rates among certain patient populations, most notably in over 60 % of never-smoking Asian women with lung adenocarcinoma [59] and in 20 % of NSCLC patients under the age of 50 [60]. In the TRIBUTE study, *EGFR* mutations were detected in 13 % of tumors in previously untreated NSCLC patients. These patients with *EGFR* mutations had longer overall

survival times regardless of treatment and improved responses to the EGFR tyrosine kinase inhibitor erlotinib [51]. A study in 397 Japanese patients found *EGFR* mutations in 49 % of patients and showed that *EGFR* mutations were a favorable prognostic indicator of improved overall survival times. However, multivariate analysis accounting for smoking history and tumor stage did not find *EGFR* mutations to be an independent prognostic indicator when controlling for other prognostic factors ($p = 0.03225$) [52].

There is mixed data regarding Bcl-2 and prognosis in lung cancer. One study found Bcl-2 to be highly expressed in 63 % of lung adenocarcinomas and 45 % of lung squamous cell carcinomas and patients with high Bcl-2 expressing tumors had longer survival times. Bcl-2 was found to be independently associated with survival on multivariate analysis [53]. Other studies have found no correlation between Bcl-2 expression and survival [31] but a recent meta-analysis over 7765 patients demonstrated that high expression of Bcl-2 protein was a favorable prognostic indicator [54].

In stages IB and IIA, NSCLC HER-2 expression is associated with poor prognosis [55]. Vascular endothelial growth factor (VEGF) overexpression has also been associated with poor survival [56]. A recent meta-analysis of the prognostic impact of VEGF expression found that increased expression of VEGFA and VEGFR was independently associated with poor survival outcomes in NSCLC and particularly in lung adenocarcinoma [57].

KRAS mutations have been repeatedly identified as a poor prognostic indicator [31]; however, this may be due to its known association with other prognostic factors including smoking history and tumor stage so the validity of *KRAS* as an independent prognostic marker is still under debate. In the TRIBUTE study, *KRAS* mutations were present in 21 % of tumors and were associated with shorter time to progression and worse survival in patients treated with erlotinib [51]. The association between *KRAS* mutation and poorer survival outcomes has also been shown in Japanese patients with shorter survival times among patients with a *KRAS* or *TP53* mutation on univariate analyses. Interestingly, *KRAS* and *TP53* mutations seem to correlate with other clinical prognostic factors such as smoking history and tumor stage. While smoking history ($p = 0.0310$) and tumor stage ($p < 0.0001$) remained significant poor prognostic indicators on multivariate analysis, neither *KRAS* ($p = 0.8500$)nor *TP53* ($p = 0.3191$) was independent prognostic factors [52]. In IHC studies, TP53 overexpression has been shown to correlate with worse survival outcomes [31].

Tumor cell proliferation measured by Ki-67 staining on IHC has produced conflicting results as a biomarker in NSCLC. However, a large study of 1065 patients demonstrated that perhaps some of these differences occurred from grouping lung adenocarcinoma and squamous cell carcinoma together in the analysis. The mean Ki-67 index in squamous cell carcinoma was twice as high as in lung adenocarcinoma, and data from this study indicated that high Ki-67 was a stage-independent negative prognostic factor in lung adenocarcinoma, whereas a high Ki-67 was a favorable prognostic factor in squamous cell cancer [58].

There has been much interest in developing liquid biopsy technology that detects either circulating tumor cells (CTCs) or circulating free DNA (cfDNA) in blood samples from patients with solid tumors. The detectable presence of circulating tumor cells itself has been suggested as a poor prognostic indicator in many types of malignancy. In NSCLC, serial analysis of CTC has demonstrated that a decreasing number of captured cells correlate with disease regression in response to treatment and increase in the number of circulating tumor cells is associated with tumor progression [61]. A recent meta-analysis of a total of 1576 patients found that CTCs were associated with lymph node metastasis, tumor stage, shorter overall survival, and progression-free survival [62]. Many of the studies in this area have examined the use of CTC or cfDNA to characterize well-known mutations such as *EGFR* mutations and secondary mutations along multiple time points of a patient's treatment. Patient who responded by RECIST criteria to treatment with pertuzumab and erlotinib had decreased CTC counts, and the patients with decreasing CTC counts had significantly longer progression-free survival times ($p = 0.05$) [63]. The relative amount of circulating cfDNA has also been shown to be of prognostic value in early studies. In a study of advanced NSCLC patients, levels of cfDNA increased as their disease progressed and overall survival and progression-free survival were both significantly shorter in patients with higher levels of cfDNA [64].

A large number of studies have used microarray technology to generate validated gene expression signatures from thousands of markers using high throughput sequencing and improving computational tools. Multiple assays have shown some prognostic value; however, there is disappointingly little overlap between different gene sets [65, 66]. Much of the problem in creating these prognostic algorithms lies in over-fitting of the prognostic signatures to the thousands of microarray data elements from a relatively small number of patients. Efforts lead by major scientific journals that require authors to make raw microarray data available in places such as the Broad Institute, Gene Expression Omnibus, or ArrayExpress may improve this computational process by sharing data and allowing more independent validation [45].

It has been shown in NSCLC that global DNA hypermethylation is associated with a worse prognosis [67]. However, it has been challenging to identify specific gene hypermethylation signatures that have consistent prognostic value. A study of 237 stage I NSCLC patients identified that hypermethylation of five genes (*HIST1H4F*, *PCDHGB6*, *NPBWR1*, *ALX1*, and *HOXA*9) was significantly associated with shorter recurrence-free survival in stage I NSCLC. The accompanying DNA methylation signature assay was able to divide patients into high- and low-risk groups with significant differences in recurrence [68]. Other studies have created other DNA methylation signatures which correlate with survival [69] or identify select genes which have prognostic significance within the dataset [67], but none have passed external validation. Like microarray signatures, the problem with these prognostic assays lies in over-fitting of the data and little overlap between DNA hypermethylation is seen between studies.

Given the complexity of tumor biology, a panel of genes to reflect the multiple mutations acquired by a tumor is likely to be more accurate and widely applicable than a single prognostic biomarker. A handful of assays has been developed and

validated to show prognostic value. Of these, the most widely tested and validated is a 14-gene expression assay on formalin-fixed paraffin-embedded tumors specimens developed at our institution. This gene expression assay uses QT-PCR and a computational algorithm on a panel of 14 genes to stratify non-squamous NSCLC patients into low-, intermediate-, or high-risk categories. It has proven to have prognostic value in over 2000 patients from multiple international validation cohorts [70–72]. In the initial validation study among 433 stage I, non-squamous NSCLC patients with an R0 surgical resection from the Kaiser Permanente Division of Research 5-year overall survival rates were 71.4, 58.3, 49.9 % among low-, intermediate-, and high-risk patients, respectively ($p = 0.0003$) [70]. Rigorously validated prognostic assays such as this one have clinical utility in identifying early-stage patients at higher risk of recurrence who may benefit from adjuvant chemotherapy and separating out the high-risk patients from those with a low risk of recurrence who might spare the toxicity of unnecessary adjuvant treatments.

Other notable multi-gene prognostic signatures include a 160-gene signature developed from 332 stages I to III NSCLC patients from the Directors' Challenge Consortium and validated on 264 patients from combined test series. Patients identified as "high-risk, poor prognosis" by this gene prognostic signature had 2.8 times greater risk of 5-year lung cancer-related mortality than "low-risk, poor prognosis" patients ($p < 0.0001$) [73]. The University of Texas Southwestern 12-gene signature was also developed from Directors' Challenge Consortium non-squamous NSCLC data on 422 patients and validated in two data sets consisting of a total of 266 validation patients. This gene signature predicts which patients are likely to benefit from adjuvant chemotherapy with improved survival (HR 0.34, $p = 0.017$) seen among patients predicted to benefit from adjuvant therapy and no improvement in survival (HR 0.80, $p = 0.070$) among the predicted the group without benefit [74]. Another signature, a 15-gene signature based on microarray of 133 Canadian patients from the Joint British Recommendations-10 trial has been validated in 5 microarray cohorts of fully resected, stages I to II NSCLC patients with worse survival (HR ranges 1.92–3.57) among patients with "high-risk" gene signatures [75, 76]. A cell cycle proliferation (CCP) score based off of 31-genes that was originally developed from RT-qPCR of fresh frozen paraffin-embedded prostate cancer samples has been validated in lung adenocarcinoma cohorts such as the Directors' Consortium Cohort to predictor cancer-specific survival (HR = 2.08, $p = 0.00014$) with significant prognostic value in both univariate and multivariate analyses [77].

In early-stage lung cancer, these prognostic assays can serve a valuable role in selecting which patients are more likely to recur following surgery, and therefore who may benefit from a more aggressive treatment approach or increased monitoring. Adjuvant chemotherapy has been shown repeatedly to add a survival benefit in fully resected, early-stage NSCLC [78, 79] and is recommended by National Comprehensive Cancer Network (NCCN) guidelines for patients with stage IIB and greater NSCLC and stages IB and IIA patients with certain "high-risk" clinicopathologic features [80]. Use of tumor molecular profiles to further risk-stratify

early-stage NSCLC patients has been demonstrated to better predict patients' recurrence risk following surgery than NCCN "high-risk" features [72].

3.4 Predictive Biomarkers

In addition to the aforementioned prognostic markers which provide survival outcomes information, many separate predictive markers have been identified that can be used to predict response to treatment. Studies of these predictive biomarkers are plagued by the same difficulties of over-fitting datasets and failure in cross-validation that make prognostic biomarkers challenging to identify. VeriStrat is a proteomic signature based on mass spectrometry that was developed to predict which advanced NSCLC patients would respond best to the EGFR tyrosine kinase inhibitors gefitinib and erlotinib. While initial data in validation cohorts seemed encouraging [81], testing on later patient cohorts showed that VeriStrat did not significantly predict erlotinib response. Though VeriStrat did not prove to be useful as a predictive marker, it did have some support as a prognostic marker in the subset of patients who did not receive erlotinib treatment where a VeriStrat "poor" stratification was predictive of worse survival overall [82].

A meta-analysis of BRCA1 as a predictive biomarker of outcome of NSCLC treated with platinum-based and paclitaxel-based chemotherapy showed that overall lower levels of BRCA1 were associated with greater responses to chemotherapy and better overall survival [83]. Another predictive biomarker in NSCLC is ribonucleotide reductase M1 (RRM1) that may have some use predicting response to gemcitabine. Meta-analysis of data on 1243 patients has shown that low RRM1 is associated with a better response to gemcitabine-based regimens and improved survival [84].

3.5 Immunotherapy and Prognosis

The recent FDA approval of the programmed death-1 (PD-1) inhibitor nivolumab as a second-line treatment for squamous non-small cell lung cancer marks the beginning of a new era of treatment options for advanced NSCLC with the potential for durable responses and prolonged survival in some patients. The major immune checkpoint modulators PD-1, PD-L1, and cytotoxic T lymphocyte antigen-4 (CTLA-4) are targets of new drugs in various stages of clinical trials and along with these expanding treatment options come new prognostic and predictive immunotherapy biomarkers.

The PD-1 receptor or CD279 is an immune checkpoint modulator that is expressed on the surface of CD4 and CD8 lymphocytes, B lymphocytes, and natural killer (NK) cells and plays a key role in blunting T cell immune function. PD-1 is also preferentially expressed on regulatory T cells, which generate the immunosuppressive tumor microenvironment. The ligand of PD-1, PD-L1, is upregulated in many solid tumors including NSCLC where it binds to regulatory T

cells and exploits the PD-1/PD-L1 pathway to evade recognition by the host's anti-tumor immune system [85].

A recent meta-analysis of 1157 NSCLC patients showed that PD-L1 expression was significantly associated with poorly differentiated tumor histology (OR 1.91, $p = 0.001$), and high PD-L1 expression was correlated with shorter overall survival times (HR 1.75, $p < 0.001$) [86]. Another study of 164 NSCLC surgical specimens found higher PD-L1 expression in tumors from female patients, never smokers, and higher expression in adenocarcinoma versus squamous cell carcinoma with *EGFR* mutations and adenocarcinoma histology independently associated with increased PD-L1 expression. This study also showed that higher levels of PD-L1 in resected tumors were associated with significantly shorter overall survival times and were a poor prognostic indicator [87].

PD-L1 has also been linked to the EGFR pathway. Activation of the EGFR pathway in NSCLC leads to overexpression of PD-L1, Il-6, and TGFβ all of which contribute to immunosuppression. In a xenograft model of EGFR-driven tumors PD-1 inhibition has been shown to cause tumor regression and improved survival [88]. PD-L1 overexpression has been correlated with *EGFR* mutations and is a poor prognostic indicator in *EGFR* wild-type patients; however, it has not been shown to correlate with survival in *EGFR* mutant patients [89].

Some data have suggested that PD-L1 expression might be a useful predictive biomarker for response to immune therapy; however, this has not been supported by more recent clinical trial data. Nivolumab is a PD-L1 monoclonal antibody that works by blocking PD-1 T cell tolerance and thereby activating the immune system against cancer cells. Phase 1 clinical trials of nivolumab demonstrated a 17 % objective response rate in patients with heavily pre-treated NSCLC [91]. PD-L1 is expressed by 50–95 % of all NSCLC [90] but trial data suggest that there is no clear association between PD-L1 expression and response to nivolumab or survival [91]. Pembrolizumab (MK-3475, Merck) is another anti-PD-1 immunotherapy that is FDA approved for ipilimumab-refractory melanoma is currently in clinical trials for NSCLC. Phase 1 trial data of pembrolizumab in advanced NSCLC showed an overall response rate of 19.4 %. NSCLC patients with elevated levels of PD-L1 on IHC had a 45.2 % pembrolizumab response rate versus 16.5 % response rate in patients with low levels of PD-L1 and 10.7 % response rate in patients with no PD-L1 expression, suggesting that PD-L1 is a predictive biomarker of pembrolizumab response [92].

Selecting patients most likely to respond to immune therapy remains a critical question in order to avoid the risks of autoimmune toxicity and pneumonitis in patients unlikely to respond to treatment. In the nivolumab phase I clinical trial, only 17 % of patients responded to treatment and only 2 patients had a response last longer than one year. Squamous cell tumors were more likely to respond than non-squamous tumors with response rates of 33 and 12 %, respectively [93]. In the 3 mg/kg dosing cohort with the best response rates, the median OS was 14.9 months, 1-year OS was 56 %, and 2-year OS was 45 % [94]. Squamous cell histology may be a useful predictive marker of nivolumab response, but current data suggest that PD-L1 on IHC is not. Using PD-L1 as a predictive marker is also

complicated by the fact that studies have used different IHC detection antibodies and different expression thresholds to define tumors as PD-L1 positive or negative [90]. More importantly, robust responses have also been observed in patients with low PD-L1 expression and use of PD-L1 as a predictive marker remains in early stages of development. Data from 135 patients that received nivolumab in the phase 3 clinical trial in squamous cell NSCLC showed that PD-L1 expression was neither prognostic nor predictive of benefit from nivolumab [95].

Ipilimumab is a human monoclonal antibody to CTLA-4 that has shown promise in early clinical trials of advanced NSCLC [96]. CD4 and CD8 T cells are activated when antigen presentation by a major histocompatibility complex is accompanied by binding of B7 molecules on the antigen presenting cell to CD28 receptors on the T cell. CTLA-4 acts competitively with CD28 for B7 binding, and when bound to B7 CTLA-4 inhibits T cell activation [97]. CTLA-4 is expressed in 51–87 % of NSCLC tumors, and its expression is associated with adenocarcinoma histology, older patient age, and poor tumor differentiation; however, none of the current studies have found it to be independently prognostic of overall survival nor has CTLA-4 expression been shown to be predictive of treatment response [98, 99].

3.6 The Future of NSCLC Prognostication

An updated IASLC database of 94,708 new patients diagnosed with lung cancer between 1999 and 2010 is currently being analyzed to inform recommendations for the eight edition of TNM NSCLC guidelines which are projected out in 2016 [100]. This dataset is expected to yield updated survival estimates and clarify minor issues with the seventh staging system but dramatic changes in the TNM classifications are not anticipated. Major shifts in the future of lung cancer prognostication are likely to come from widespread use of molecular testing and clinical application of our increasing knowledge of biomarkers in lung cancer. Further understanding of tumor biology and rapid genetic analysis will improve risk stratification within each TNM stage and lead to more individualized treatment plans and precise survival prognostication.

References

1. Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) (2013) SEER cancer statistics review, 1975–2010. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, April 2013
2. Goldstraw P, Crowley J, Chansky K et al (2007) The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thoracic Oncol Official Publ Int Assoc Study Lung Cancer 2(8):706–714
3. UICC (1968) TNM classification of malignant tumours. UICC, Geneva

4. Mountain CF, Carr DT, Anderson WA (1974) A system for the clinical staging of lung cancer. Am J Roentgenol Radium Ther Nucl Med 120(1):130–138
5. Goldstraw P (2009) Staging manual in thoracic oncology. FL Editorial Rx Press, Orange Park
6. Travis WD (2011) Pathology of lung cancer. Clin Chest Med 32(4):669–692
7. Meza R, Meernik C, Jeon J, Cote ML (2015) Lung cancer incidence trends by gender, race and histology in the United States, 1973–2010. PLoS ONE 10(3):e0121323
8. Detterbeck FC, Boffa DJ, Tanoue LT (2009) The new lung cancer staging system. Chest 136 (1):260–271
9. Detterbeck FC, Boffa DJ, Tanoue LT, Wilson LD (2010) Details and difficulties regarding the new lung cancer staging system. Chest 137(5):1172–1180
10. Hsu PK, Huang HC, Hsieh CC et al (2007) Effect of formalin fixation on tumor size determination in stage I non-small cell lung cancer. Ann Thorac Surg 84(6):1825–1829
11. Shimizu K, Yoshida J, Nagai K et al (2004) Visceral pleural invasion classification in non-small cell lung cancer: a proposal on the basis of outcome assessment. J Thorac Cardiovasc Surg 127(6):1574–1578
12. Osaki T, Nagashima A, Yoshimatsu T, Yamada S, Yasumoto K (2004) Visceral pleural involvement in nonsmall cell lung cancer: prognostic significance. Ann Thorac Surg 77(5) (1769–1773, discussion 1773)
13. Dail D, Hammar S (1994) Pulmonary pathology, 2nd edn. Springer, New York
14. Rami-Porta R, Ball D, Crowley J et al (2007) The IASLC lung cancer staging project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol Official Publ Int Assoc Study Lung Cancer 2(7):593–602
15. Woodard GA, Jablons DM (2015) The latest in surgical management of stage IIIA non-small cell lung cancer. ASCO Educational Book (in press)
16. American Joint Committee on Cancer (2009) AJCC cancer staging manual, 7th edn. Springer, New York
17. Chen VW, Ruiz BA, Hsieh MC, Wu XC, Ries LA, Lewis DR (2014) Analysis of stage and clinical/prognostic factors for lung cancer from SEER registries: AJCC staging and collaborative stage data collection system. Cancer 120(Suppl 23):3781–3792
18. Shen KR, Meyers BF, Larner JM, Jones DR (2007) Special treatment issues in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 132(3 Suppl):290s–305s
19. Martini N, Melamed MR (1975) Multiple primary lung cancers. J Thorac Cardiovasc Surg 70 (4):606–612
20. Girard N, Deshpande C, Lau C et al (2009) Comprehensive histologic assessment helps to differentiate multiple lung primary nonsmall cell carcinomas from metastases. Am J Surg Pathol 33(12):1752–1764
21. Travis WD, Giroux DJ, Chansky K et al (2008) The IASLC lung cancer staging project: proposals for the inclusion of broncho-pulmonary carcinoid tumors in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol Official Publ Int Assoc Study Lung Cancer 3(11):1213–1223
22. Stolz A, Harustiak T, Simonek J et al (2015) Long-term outcomes and prognostic factors of patients with pulmonary carcinoid tumors. Neoplasma 13
23. Elias AD (1997) Small cell lung cancer: state-of-the-art therapy in 1996. Chest 112(4 Suppl):251s–258s
24. Stupp R, Monnerat C, Turrisi AT 3rd, Perry MC, Leyvraz S (2004) Small cell lung cancer: state of the art and future perspectives. Lung Cancer (Amsterdam, Neth) 45(1):105–117
25. Govindan R, Page N, Morgensztern D et al (2006) Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol Official J Am Soc Clin Oncol 24(28):4539–4544
26. Shepherd FA, Crowley J, Van Houtte P et al (2007) The international association for the study of lung cancer lung cancer staging project: proposals regarding the clinical staging of

small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. J Thorac Oncol Official Publ Int Assoc Study Lung Cancer 2 (12):1067–1077
27. Kuo SW, Chen JS, Huang PM, Hsu HH, Lai HS, Lee JM (2014) Prognostic significance of histologic differentiation, carcinoembryonic antigen value, and lymphovascular invasion in stage I non-small cell lung cancer. J Thorac Cardiovasc Surg148(4):1200–1207, e1203
28. Sun Z, Aubry MC, Deschamps C et al (2006) Histologic grade is an independent prognostic factor for survival in non-small cell lung cancer: an analysis of 5018 hospital- and 712 population-based cases. J Thorac Cardiovasc Surg 131(5):1014–1020
29. Shao W, Xiong X, Chen H et al (2014) Long-term survival outcomes of video-assisted thoracic surgery for patients with non-small cell lung cancer. Chin J Cancer (Res = Chung-Kuo Yen Cheng Yen Chiu) 26(4):391–398
30. Lee PC, Nasar A, Port JL et al (2013) Long-term survival after lobectomy for non-small cell lung cancer by video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg 96 (3):951–960 (discussion 960–951)
31. Grossi F, Loprevite M, Chiaramondia M et al (2003) Prognostic significance of K-ras, p53, bcl-2, PCNA, CD34 in radically resected non-small cell lung cancers. Eur J Cancer (Oxford, Engl 1990) 39(9):1242–1250
32. Luchtenborg M, Jakobsen E, Krasnik M, Linklater KM, Mellemgaard A, Moller H (2012) The effect of comorbidity on stage-specific survival in resected non-small cell lung cancer patients. Eur J Cancer (Oxford, Engl 1990) 48(18):3386–3395
33. Iachina M, Jakobsen E, Moller H et al (2015) The effect of different comorbidities on survival of non-small cells lung cancer patients. Lung 193(2):291–297
34. Zhai R, Yu X, Shafer A, Wain JC, Christiani DC (2014) The impact of coexisting COPD on survival of patients with early-stage non-small cell lung cancer undergoing surgical resection. Chest 145(2):346–353
35. Simmons CP, Koinis F, Fallon MT et al (2015) Prognosis in advanced lung cancer—a prospective study examining key clinicopathological factors. Lung Cancer (Amsterdam, Neth)
36. Parsons A, Daley A, Begh R, Aveyard P (2010) Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. BMJ (Clin Res ed.) 340:b5569
37. Ou SH, Zell JA, Ziogas A, Anton-Culver H (2007) Prognostic factors for survival of stage I nonsmall cell lung cancer patients: a population-based analysis of 19,702 stage I patients in the California Cancer Registry from 1989 to 2003. Cancer 110(7):1532–1541
38. Ou SH, Zell JA, Ziogas A, Anton-Culver H (2008) Low socioeconomic status is a poor prognostic factor for survival in stage I nonsmall cell lung cancer and is independent of surgical treatment, race, and marital status. Cancer 112(9):2011–2020
39. Hubbard MO, Fu P, Margevicius S, Dowlati A, Linden PA (2012) Five-year survival does not equal cure in non-small cell lung cancer: a surveillance, epidemiology, and end results-based analysis of variables affecting 10- to 18-year survival. J Thorac Cardiovasc Surg 143(6):1307–1313
40. Rosen JE, Hancock JG, Kim AW, Detterbeck FC, Boffa DJ (2014) Predictors of mortality after surgical management of lung cancer in the National Cancer Database. Ann Thorac Surg 98(6):1953–1960
41. Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB (2001) The influence of hospital volume on survival after resection for lung cancer. New Engl J Med 345(3):181–188
42. Groome PA, Bolejack V, Crowley JJ et al (2007) The IASLC lung cancer staging project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol Official Publ Int Assoc Study Lung Cancer 2(8):694–705
43. Olaussen KA, Dunant A, Fouret P et al (2006) DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. New Eng J Med 355(10):983–991

44. Friboulet L, Olaussen KA, Pignon JP et al (2013) ERCC1 isoform expression and DNA repair in non-small-cell lung cancer. New Engl J Med 368(12):1101–1110
45. Zhu CQ, Tsao MS (2014) Prognostic markers in lung cancer: is it ready for prime time? Transl Lung Cancer Res 3(3):149–158
46. Shepherd FA, Domerg C, Hainaut P et al (2013) Pooled analysis of the prognostic and predictive effects of KRAS mutation status and KRAS mutation subtype in early-stage resected non-small-cell lung cancer in four trials of adjuvant chemotherapy. J Clin Oncol Official J Am Soc Clin Oncol 31(17):2173–2181
47. Agullo-Ortuno MT, Diaz-Garcia CV, Agudo-Lopez A et al (2015) Relevance of insulin-like growth factor 1 receptor gene expression as a prognostic factor in non-small-cell lung cancer. J Cancer Res Clin Oncol 141(1):43–53
48. Tran TN, Selinger CI, Yu B et al (2014) Alterations of insulin-like growth factor-1 receptor gene copy number and protein expression are common in non-small cell lung cancer. J Clin Pathol 67(11):985–991
49. Dziadziuszko R, Merrick DT, Witta SE et al (2010) Insulin-like growth factor receptor 1 (IGF1R) gene copy number is associated with survival in operable non-small-cell lung cancer: a comparison between IGF1R fluorescent in situ hybridization, protein expression, and mRNA expression. J Clin Oncol Official J Am Soc Clin Oncol 28(13):2174–2180
50. Go H, Jeon YK, Park HJ, Sung SW, Seo JW, Chung DH (2010) High MET gene copy number leads to shorter survival in patients with non-small cell lung cancer. J Thorac Oncol Official Publ Int Assoc Study Lung Cancer 5(3):305–313
51. Eberhard DA, Johnson BE, Amler LC et al (2005) Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol Official J Am Soc Clin Oncol 23(25):5900–5909
52. Kosaka T, Yatabe Y, Onozato R, Kuwano H, Mitsudomi T (2009) Prognostic implication of EGFR, KRAS, and TP53 gene mutations in a large cohort of Japanese patients with surgically treated lung adenocarcinoma. J Thorac Oncol Official Publ Int Assoc Study Lung Cancer 4(1):22–29
53. Anagnostou VK, Lowery FJ, Zolota V et al (2010) High expression of BCL-2 predicts favorable outcome in non-small cell lung cancer patients with non squamous histology. BMC Cancer 10:186
54. Zhao XD, He YY, Gao J et al (2014) High expression of Bcl-2 protein predicts favorable outcome in non-small cell lung cancer: evidence from a systematic review and meta-analysis. Asian Pac J Cancer Prev APJCP 15(20):8861–8869
55. Xia Q, Zhu Z, Wang J, Situ D, Zhou N, Jang W (2012) Expression and association of HER2 with prognosis in early-stage (T1-T2N0M0) non-small cell lung cancer. Tumour Biol J Int Soc Oncodev Biol Med 33(5):1719–1725
56. Liao M, Wang H, Lin Z, Feng J, Zhu D (2001) Vascular endothelial growth factor and other biological predictors related to the postoperative survival rate on non-small cell lung cancer. Lung Cancer (Amsterdam, Neth) 33(2–3):125–132
57. Zheng CL, Qiu C, Shen MX et al (2015) Prognostic impact of elevation of vascular endothelial growth factor family expression in patients with non-small cell lung cancer: an updated meta-analysis. Asian Pac J Cancer Prev APJCP 16(5):1881–1895
58. Warth A, Cortis J, Soltermann A et al (2014) Tumour cell proliferation (Ki-67) in non-small cell lung cancer: a critical reappraisal of its prognostic role. Br J Cancer 111(6):1222–1229
59. Ha SY, Choi SJ, Cho JH et al (2015) Lung cancer in never-smoker Asian females is driven by oncogenic mutations, most often involving EGFR. Oncotarget 6(7):5465–5474
60. VandenBussche CJ, Illei PB, Lin MT, Ettinger DS, Maleki Z (2014) Molecular alterations in non-small cell lung carcinomas of the young. Hum Pathol 45(12):2379–2387
61. Maheswaran S, Sequist LV, Nagrath S et al (2008) Detection of mutations in EGFR in circulating lung-cancer cells. New Eng J Med 359(4):366–377

62. Wang J, Wang K, Xu J, Huang J, Zhang T (2013) Prognostic significance of circulating tumor cells in non-small-cell lung cancer patients: a meta-analysis. PLoS ONE 8(11):e78070
63. Punnoose EA, Atwal S, Liu W et al (2012) Evaluation of circulating tumor cells and circulating tumor DNA in non-small cell lung cancer: association with clinical endpoints in a phase II clinical trial of pertuzumab and erlotinib. Clin Cancer Res Official J Am Assoc Cancer Res 18(8):2391–2401
64. Dowler Nygaard A, Spindler KL, Pallisgaard N, Andersen RF, Jakobsen A (2014) Levels of cell-free DNA and plasma KRAS during treatment of advanced NSCLC. Oncol Rep 31 (2):969–974
65. Zhu CQ, Pintilie M, John T et al (2009) Understanding prognostic gene expression signatures in lung cancer. Clin Lung Cancer 10(5):331–340
66. Carnio S, Novello S, Papotti M, Loiacono M, Scagliotti GV (2013) Prognostic and predictive biomarkers in early stage non-small cell lung cancer: tumor based approaches including gene signatures. Transl Lung Cancer Res 2(5):372–381
67. Moran A, Fernandez-Marcelo T, Carro J et al (2012) Methylation profiling in non-small cell lung cancer: clinical implications. Int J Oncol 40(3):739–746
68. Sandoval J, Mendez-Gonzalez J, Nadal E et al (2013) A prognostic DNA methylation signature for stage I non-small-cell lung cancer. J Clin Oncol Off J Am Soc Clin Oncol 31 (32):4140–4147
69. Lokk K, Vooder T, Kolde R et al (2012) Methylation markers of early-stage non-small cell lung cancer. PLoS ONE 7(6):e39813
70. Kratz JR, He J, Van Den Eeden SK et al (2012) A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: development and international validation studies. Lancet 379(9818):823–832
71. Kratz JR, Tham PT, Mulvihill MS et al (2013) Analytical validation of a practical molecular assay prognostic of survival in nonsquamous non-small cell lung cancer. Diagn Mol Pathol Am J Surg Pathol Part B 22(2):65–69
72. Woodard GA, Gubens MA, Jahan TM et al (2014) Prognostic molecular assay might improve identification of patients at risk for recurrence in early-stage non-small-cell lung cancer. Clin Lung Cancer 15(6):426–432
73. Van Laar RK (2012) Genomic signatures for predicting survival and adjuvant chemotherapy benefit in patients with non-small-cell lung cancer. BMC Med Genomics 5:30
74. Tang H, Xiao G, Behrens C et al (2013) A 12-gene set predicts survival benefits from adjuvant chemotherapy in non-small cell lung cancer patients. Clin Cancer Res Official J Am Assoc Cancer Res 19(6):1577–1586
75. Zhu CQ, Ding K, Strumpf D et al (2010) Prognostic and predictive gene signature for adjuvant chemotherapy in resected non-small-cell lung cancer. J Clin Oncol Official J Am Soc Clin Oncol 28(29):4417–4424
76. Der SD, Sykes J, Pintilie M et al (2014) Validation of a histology-independent prognostic gene signature for early-stage, non-small-cell lung cancer including stage IA patients. J Thorac Oncol Official Publ Int Assoc Study Lung Cancer 9(1):59–64
77. Wistuba II, Behrens C, Lombardi F et al (2013) Validation of a proliferation-based expression signature as prognostic marker in early stage lung adenocarcinoma. Clin Cancer Res Official J Am Assoc Cancer Res 19(22):6261–6271
78. Winton T, Livingston R, Johnson D et al (2005) Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. New Eng J Med 352(25):2589–2597
79. Douillard JY, Rosell R, De Lena M et al (2006) Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 7(9):719–727
80. Network NCC (2014) NCCN non-small cell lung cancer clinical practice guidelines. Version 2. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 29 Dec 2013

81. Stinchcombe TE, Roder J, Peterman AH et al (2013) A retrospective analysis of VeriStrat status on outcome of a randomized phase II trial of first-line therapy with gemcitabine, erlotinib, or the combination in elderly patients (age 70 years or older) with stage IIIB/IV non-small-cell lung cancer. J Thorac Oncol Official Publ Int Assoc Study Lung Cancer 8 (4):443–451
82. Carbone DP, Ding K, Roder H et al (2012) Prognostic and predictive role of the VeriStrat plasma test in patients with advanced non-small-cell lung cancer treated with erlotinib or placebo in the NCIC Clinical Trials Group BR.21 trial. J Thorac Oncol Official Publ Int Assoc Study Lung Cancer 7(11):1653–1660
83. Yang Y, Xie Y, Xian L (2013) Breast cancer susceptibility gene 1 (BRCA1) predict clinical outcome in platinum- and toxal-based chemotherapy in non-small-cell lung cancer (NSCLC) patients: a system review and meta-analysis. J Exp Clin Cancer Res CR 32:15
84. Gong W, Zhang X, Wu J et al (2012) RRM1 expression and clinical outcome of gemcitabine-containing chemotherapy for advanced non-small-cell lung cancer: a meta-analysis. Lung Cancer (Amsterdam, Neth) 75(3):374–380
85. Pardoll DM (2012) The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 12(4):252–264
86. Wang A, Wang HY, Liu Y et al (2015) The prognostic value of PD-L1 expression for non-small cell lung cancer patients: A meta-analysis. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol 41(4):450–456
87. Azuma K, Ota K, Kawahara A et al (2014) Association of PD-L1 overexpression with activating EGFR mutations in surgically resected nonsmall-cell lung cancer. Ann Oncol Official J Eur Soc Med Oncol/ESMO 25(10):1935–1940
88. Akbay EA, Koyama S, Carretero J et al (2013) Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. Cancer Dis 3(12):1355–1363
89. Tang Y, Fang W, Zhang Y et al (2015) The association between PD-L1 and EGFR status and the prognostic value of PD-L1 in advanced non-small cell lung cancer patients treated with EGFR-TKIs. Oncotarget 6:14209
90. Patel SP, Kurzrock R (2015) PD-L1 expression as a predictive biomarker in cancer immunotherapy. Mol Cancer Ther 14(4):847–856
91. Gettinger SN, Horn L, Gandhi L et al (2015) Overall survival and long-term safety of Nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol Official J Am Soc Clin Oncol 33(18):2004–2012
92. Garon EB, Rizvi NA, Hui R et al (2015) Pembrolizumab for the treatment of non-small-cell lung cancer. New Eng J Med 372(21):2018–2028
93. Topalian SL, Hodi FS, Brahmer JR et al (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. New Eng J Med 366(26):2443–2454
94. Brahmer J, Horn L, Gandhi L et al (2014) Nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients (Pts) with advanced non-small-cell lung cancer (NSCLC): survival and clinical activity by subgroup analysis. ASCO Meet Abs 32(8112)
95. Brahmer J, Reckamp KL, Baas P et al (2015) Nivolumab versus Docetaxel in advanced squamous-cell non-small-cell lung cancer. New Eng J Med 373(2):123–135
96. Lynch TJ, Bondarenko I, Luft A et al (2012) Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol Official J Am Soc Clin Oncol 30(17):2046–2054
97. Sundar R, Soong R, Cho BC, Brahmer JR, Soo RA (2014) Immunotherapy in the treatment of non-small cell lung cancer. Lung Cancer (Amsterdam, Neth) 85(2):101–109
98. Salvi S, Fontana V, Boccardo S et al (2012) Evaluation of CTLA-4 expression and relevance as a novel prognostic factor in patients with non-small cell lung cancer. Cancer Immunol Immunother CII 61(9):1463–1472

99. Zheng H, Li Y, Wang X, Zhang X, Wang X (2010) Expression and significance of gp96 and immune-related gene CTLA-4, CD8 in lung cancer tissues. Zhongguo fei ai za zhi = Chin J Lung Cancer 13(8):790–794
100. Rami-Porta R, Bolejack V, Giroux DJ et al (2014) The IASLC lung cancer staging project: the new database to inform the eighth edition of the TNM classification of lung cancer. J Thorac Oncol Official Publ Int Assoc Study Lung Cancer 9(11):1618–1624
101. Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P (2009) The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol Official Publ Int Assoc Study Lung Cancer 4(5):568–577

Surgical Treatment of Lung Cancer

Osita I. Onugha and Jay M. Lee

Abstract

In this chapter, we discuss the preoperative evaluation that is necessary prior to surgical resection, stage-specific surgical management of lung cancer, and the procedural steps as well as the indications to a variety of surgical approaches to lung resection.

Keywords

Non-small-cell lung cancer · Mediastinal staging · Small-cell lung cancer · Synchronous lung cancer · Metachronous lung cancer · Oligometastatic disease · Surgery · Lung resection

Contents

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1 Introduction

Surgery, with curative intent, is the major treatment modality for early-stage non-small-cell lung cancer (NSCLC). The primary goal of surgical treatment is twofold: (1) the complete resection of the tumor along with its regional lymphatic drainage and (2) tumor staging which will determine perioperative treatment and prognosis. The principal goal of resection is to obtain an R0 resection with negative microscopic and gross margins. In general, incomplete resection with microscopic (R1) or macroscopic (R2) margin positivity does not confer an overall survival benefit. *En bloc* resection of any adjacent tissue should be performed when possible, and margins should be assessed intraoperatively to ensure negativity.

2 Preoperative Evaluation

2.1 Radiographic Staging

Clinical staging for patients suspected to have lung cancer requires radiologic assessment for extent of disease workup with chest, abdomen, and pelvic CT scanning or whole-body PET/CT scanning with intravenous contrast. The use of PET/CT for preoperative staging has been shown to reduce the total number of thoracotomies and the number of futile thoracotomies for NSCLC stage IIIA, IIIB, IV, or benign lung lesions [1]. Although there has been no clear evidence that the use of PET/CT affects overall mortality [1], there has been routine use of preoperative PET/CT at many centers. Brain MRI with intravenous gadolinium to assess for brain metastases is more sensitive than CT and is generally obtained only in symptomatic or clinical stage II or III patients. While earlier detection of distant metastases has not been shown to provide survival benefit, detection of multiple occult metastases would prevent unnecessary lung surgery. With the exception of the brain and certain bony metastases, pathologic confirmation of the suspected metastatic focus with tissue diagnosis should be obtained. Chest MRI with

intravenous gadolinium is helpful in patients with paravertebral or superior sulcus tumors to rule out neuroforaminal invasion and to assess for brachial plexus and subclavian vessel involvement. Although the National Comprehensive Cancer Network (NCCN) guidelines suggest consideration for obtaining somatostatin receptor scintigraphy (octreotide scan) preoperatively for patients with a neuroendocrine tumor (e.g., carcinoid tumor), the clinical utility of this scan is questionable [2]. Although the majority of bronchial neuroendocrine tumors express somatostatin receptors, octreotide scans have limited specificity due to positivity in other tumors, granulomas, and autoimmune diseases, and therefore, its use as a preoperative extent of disease workup is limited [3, 4].

2.2 Tissue Diagnosis

The diagnosis of lung cancer requires pathologic evaluation of biopsied tissue. While a pathologic diagnosis can be made based on cytology or tissue samples, in general a tissue biopsy (core needle or surgical specimen) is preferable to cytology samples (fluid, sputum, bronchoscopic washings or brushings, or fine needle aspirates) due to the higher likelihood for distinguishing histologic subtypes of lung cancer and also allowing genetic analysis of the cancer for driver mutations. However, depending on the size, location, and clinical suspicion for primary lung cancer, a tissue diagnosis is not always necessary prior to surgical intervention. In situations where there is high clinical suspicion for lung cancer and radiographic appearance highly suspicious for primary bronchogenic carcinoma, tissue diagnosis is not required prior to invasive staging and surgery. In these patients, surgery would provide a tissue diagnosis, staging, and definitive resection of the tumor. It is acceptable to obtain a transbronchial or transthoracic needle biopsy for tissue diagnosis. Endobronchial and centrally located lesions are preferably biopsied bronchoscopically with endobronchial or transbronchial technique. More peripheral lesions are generally biopsied by a CT-guided transthoracic needle approach. In limited situations, there is a role for endoscopic ultrasound (EUS) biopsy of the mediastinal lymph nodes with a transesophageal needle biopsy technique to obtain a diagnosis. However, any needle biopsy has an attendant false negativity and a negative or non-diagnostic pathologic finding should not deter the high clinical concern for underlying malignancy and need for surgery for diagnostic and therapeutic purposes.

2.3 Physiologic Pulmonary Evaluation

Physiologic workup for pulmonary and cardiac risk profile is required as part of the preoperative evaluation. To determine pulmonary reserve, complete pulmonary function testing that includes diffusing capacity for carbon monoxide (DLCO) is required. Forced expiratory volume in one second (FEV_1) and DLCO are the most commonly used parameters to predict operative suitability and perioperative morbidity and mortality. The British Thoracic Society (BTS) suggests that patients with a

preoperative FEV_1 in excess of 2L (or >80 % predicted) generally tolerate pneumonectomy [5]. Patients with FEV_1 and DLCO >60 % are suitable for lobectomy. Patients with a preoperative FEV_1 or DLCO <60 % of predicted are at increased risk of developing postoperative respiratory complications but are still considered surgical candidates [5]. With the advent of video-assisted thoracic surgery (VATS), it is unclear if this population is at higher risk of complications and mortality based on PFT results [6, 7]. Patients with compromised pulmonary function with FEV_1 or DLCO <60 % should undergo quantitative lung perfusion (QLP) scan to better estimate postoperative pulmonary function based on measurements of lung perfusion to upper, mid, and lower lung zones [7]. Patients with a predicted postoperative FEV_1 and DLCO >40 % are considered at acceptable risk for lobectomy [5]. High-risk subjects with <40 % should undergo cardiopulmonary exercise testing (CPET) that measures maximal oxygen consumption/uptake (VO2 max). CPET has been shown to be a better predictor of postoperative complications than resting cardiac and pulmonary function. A VO2 max of at least 15 mL/kg/min is suitable risk for a lobectomy [8].

If the estimated predicted postoperative FEV_1 is <35–40 %, performing lung resection is extremely high risk with some studies demonstrating postoperative mortality as high as 50 %, and the tumors are generally considered unresectable [9, 10]. However, based on National Emphysema Treatment Trial (NETT), a subgroup of patients was identified with FEV_1 or DLCO >20 % that were deemed to be of acceptable risk for lung volume reduction surgery [11]. On this basis, there are select patients where surgical resection may be offered with predicted postoperative FEV_1 or DLCO as low as 20 %. But this is considered controversial.

2.4 Cardiac Evaluation

As part of a cardiac evaluation, a transthoracic echo (TTE) should be performed to evaluate for right ventricular systolic pressures (RVSP) and pulmonary hypertension. If there is any evidence of pulmonary hypertension and the patient is being considered for a pneumonectomy, then a right heart catheterization should be performed. Pneumonectomy is contraindicated in the presence of pulmonary hypertension. Pulmonary hypertension can also be identified in patients with main pulmonary artery diameter of >3 cm [12]. These patients should also be considered for right heart catheterization. A stress test is done in patients with suspected or known CAD or based on age and functional status as per the ACC/AHA guidelines [13]. If there is evidence of coronary disease requiring intervention, the treatment proposed must be evaluated based on the tumor histologic type and aggressiveness and risk and benefits of delaying surgery versus other oncologic treatment options.

2.5 Mediastinal Staging

Staging of the mediastinal lymph nodes entails radiologic (PET/CT scan) and pathologic (tissue biopsy) approaches. It is our preference to biopsy the mediastinal lymph nodes almost universally except for:

(1) peripheral <1-cm invasive adenocarcinomas,
(2) low-grade neuroendocrine carcinomas (aka typical carcinoid tumor) with negative PET/CT imaging,
(3) small pure ground glass lesions which are suspected to be adenocarcinoma in situ or minimally invasive adenocarcinomas.

It is our practice that preoperative staging of the mediastinum can be omitted for patients with small (<1 cm) peripheral tumors and suspected stage 1A (T1N0M0) disease. These patients are usually staged intraoperatively with VATS mediastinal lymph node biopsies. Invasive mediastinal staging is required for most patients of suspected stage IB, II, and III NSCLC. NSCLCs include lymph nodes that are enlarged on CT (e.g., >1 cm), and PET-avid lymph nodes regardless of their size are suspected to be involved with cancer. We do not use PET/CT as our only modality for evaluating the mediastinum. PET/CT has higher sensitivity and specificity than CT for staging the mediastinum (71 vs. 43 %, respectively), but it commonly has false-negative results in the subcarinal lymph nodes (level 7) and the AP window lymph nodes (level 5 and 6). In addition, many false-positive results occur [14].

We typically submit all patients to mediastinal staging with cervical mediastinoscopy (CM) as this is the gold standard for mediastinal lymph node staging with a false-negative rate of 5.5 % and mortality and morbidity rates of 0.005 and 1.07 %, respectively [15]. Anterior mediastinotomy is typically reserved for patients with left upper lobe tumors as the drainage pattern usually involves the aortopulmonary window (APW) lymph nodes. Extended cervical mediastinoscopy (ECM) is another way to access and pathologically evaluate APW lymph nodes. A retrospective analysis of 55 patients with NSCLC is compared with PET/CT and ECM and found a higher sensitivity (69 vs. 53 %) and negative predictive value (89 vs. 83 %) with ECM [16]. The main advantage of ECM is that when accessing the APW, it avoids the surgical risk and morbidity associated with a left anterior mediastinoscopy in addition to a CM. However, there are a limited number of centers with the expertise to perform ECM.

Endobronchial ultrasound (EBUS) with transbronchial needle aspiration (EBUS-TBNA) has emerged as a less invasive, non-surgical approach to obtain tissue from lymph nodes in the mediastinum. EBUS has been shown to have similar sensitivity, negative predictive value, and diagnostic accuracy as CM, 81, 91, and 93 %, and 79, 90, and 93 %, respectively [17]. However, in a study looking specifically at patients suspected of having N2 disease, 28 % of patients with negative EBUS-TBNA had positive lymph nodes on CM [18]. Given the discrepancy in results, it is still unclear how EBUS-TBNA should be incorporated into current algorithms for mediastinal staging. At our institution, it is typically used as a primary diagnostic modality in patients with high clinical suspicion of N2 disease. It is otherwise used as an adjunct to the CM.

Some centers have added endoscopic ultrasound (EUS) to EBUS-TBNA to improve the diagnostic accuracy. In a study of 138 patients, the combination of EUS plus EBUS had higher sensitivity and negative predictive value 93 and 97 %,

respectively, compared with sensitivity and negative predictive value of EBUS-TBNA (76 and 91 %, respectively) and EUS-TBNA (79 and 91 %, respectively) [19]. EUS plus EBUS also had higher sensitivity and higher negative predictive value for detecting lymph nodes for patients without lymph node enlargement on chest CT [19].

3 Surgery and Small-Cell Lung Cancer (SCLC)

Surgical resection has a limited role in small-cell lung carcinoma (SCLC). SCLC comprises 15 % of lung cancers and is considered aggressive with early development of systemic disease. Local treatment alone has been associated with poor survival. In 1969, the British Medical Research Council study reported a 5-year follow-up study of 144 potentially operable patients with SCLC diagnosed preoperatively on bronchial biopsy. Of the 144 patients, 71 were allocated randomly to surgery and 73 to radiation. The survival rates for the surgery series and the radiotherapy series were 4 and 10 % at 24 months, 3 and 7 % at 48 months, and 1 and 4 % at 60 months, respectively [20]. The study demonstrated extremely poor survival for both treatment groups defining that local treatment alone was inadequate for SCLC.

However, surgical resection does have a role in multimodality treatment of early-stage SCLC with chemotherapy and/or radiation. The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database from 1988 to 2004 identified 205 patients who underwent lobectomy without radiation for stage I SCLC and reported 3- and 5-year overall survival was 58.1 and 50.3 %, respectively [21]. The benefit of surgery for early-stage SCLC was also demonstrated by the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Study Project. The IASLC database included 349 patients post-resection and staged pathologically with reported 5-year survival rates for patients with pathologic stage I, II, and III SCLC of 48, 39, and 15 %, respectively [22]. Based on this study, patients with SCLC with pathologic absence of mediastinal nodal involvement and distant metastasis should be considered for resection if they are low-surgical-risk candidates.

Given the poor long-term survival with surgery alone historically, adjuvant chemotherapy is given to patients who have undergone a complete resection of pathologically stage I, II, or IIIA SCLC [21]. Patients found to have unsuspected N2 metastasis following resection should receive adjuvant mediastinal radiation. While adjuvant mediastinal radiation is considered in N2 disease, patients with pathologically negative N1 and N2 lymph nodes are generally not given radiation. However, the data on adjuvant radiation following lobectomy for early-stage SCLC are limited and unreliable. The role of prophylactic cranial irradiation is unclear following surgical resection of early-stage SCLC. Based on established data for limited stage SCLC treated with definitive chemoradiation, prophylactic cranial irradiation (PCI) is considered in the adjuvant setting following resection. However, there are no reliable data that addressed the role of PCI after surgical resection for SCLC.

4 Non-Small-Cell Lung Cancer (NSCLC)

4.1 Stage IA

In patients with stage I and II NSCLC, surgical resection is the treatment of choice. Clinical staging based on radiographic findings is limited requiring restaging following pathologic results from invasive mediastinal staging and resection. Stage I and II patients comprise about 30 % of NSCLC patients [23]. Surgical resection alone is the standard of care for stage IA patients.

The location of the tumor dictates the anatomic resection and surgical approach. Intraparenchymal lesions are best treated with surgical lobectomy, while lesions that are central and abutting the bronchus may require sleeve resection or pneumonectomy. Sublobar resection (segmentectomy or wedge resection) is considered in patients with marginal lung function or high-risk surgical candidates. Sublobar resection should be limited to tumors less than 3 cm.

4.2 Stage IB

In patients with stage IB, it is controversial whether tumors should be treated with adjuvant chemotherapy. The CALGB trial demonstrated that adjuvant chemotherapy with carboplatin and paclitaxel provided improved disease-free survival in patients with stage IB tumors in initial reports [24]. However, at 74 months, the difference in survival was not statistically significant. This has been the only study that has showed a potential benefit of adjuvant chemotherapy in stage IB tumors, which may be limited to patients with tumors greater than 4 cm. The ANITA trial demonstrated a benefit of adjuvant therapy in stage II NSCLC tumors [25]. It is our practice that these patients receive adjuvant chemotherapy.

4.3 Stage IIB

In patients with chest wall invasion stage IIB (T3N0), en bloc chest wall resection with ribs should be performed. It is associated with a 40 % five-year survival. However, five-year survival decreases to 12 % if there is any mediastinal lymph node involvement [26]. For this reason, it is crucial to have adequate mediastinal staging prior to surgical resection. Multiple studies have demonstrated improved survival in stage IIB NSCLC and are discussed with most patients [27, 28].

4.4 Stage III NSCLC

4.4.1 Stage IIIA (e.g., T3N1/T4N1)

If the patient has stage IIIA disease based on the involvement of the chest wall or proximal airways or due to the presence of satellite nodules within the same lobe as the primary tumor, they are candidates for surgical resection followed by adjuvant chemotherapy. These patients have a better prognosis than patients with stage IIIA secondary to mediastinal N2 nodal involvement [29]. The primary exceptions to this treatment are superior sulcus (Pancoast) tumors with hilar lymph node involvement. Patients with Pancoast tumors are typically treated with neoadjuvant chemoradiation followed by surgery [30].

4.4.2 Stage IIIA with N2 Disease

Patients with clinically resectable stage IIIA (T3N2) disease have been the only group of patients found to benefit from neoadjuvant chemotherapy or chemoradiation. It is our practice that these patients are staged cervical mediastinoscopy first and reserve EBUS for mediastinal restaging after neoadjuvant therapy to evaluate for persistent N2 disease. If there is no evidence of mediastinal disease or the patient is downstaged to N1 (N2 negative), then the patient is considered a candidate for surgical resection with increased survival if lobectomy is performed versus pneumonectomy [29, 31]. While it is controversial whether the induction should be chemotherapy alone or chemoradiation, when pneumonectomy is technically required, preoperative radiation should be omitted due to the attendant high risk of perioperative mortality associated with pneumonectomy following chemoradiation. It is our preference to offer preoperative chemotherapy alone and then perform pneumonectomy should there be any clearance of N2 disease on mediastinal restaging for low-risk patients [31, 25]. Based on the ANITA trial, adjuvant radiation should be considered in these patients.

4.5 Stage IIIB and IV NSCLC

Patients with stage IIIB or stage IV NSCLC are typically not candidates for resection and should be treated with definitive chemotherapy or chemoradiation.

4.6 Special Situations

4.6.1 Extended Resections

Resectable T4N0-1 lesions are uncommon, and most T4 lesions (mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina) are generally treated with definitive chemoradiation therapy. Patient selection is of critical importance. Surgery for T4 disease is contraindicated in the presence of N2 involvement (stage IIIB) or if a complete resection is not possible.

When carefully staged and selected, some patients with T4 (N2 negative) tumors appear to benefit from resection as part of the treatment as opposed to chemoradiotherapy alone [31–33].

4.6.2 Synchronous NSCLC

Patients that present with synchronous multiple primary lung cancer (MPLC) pose a variety of clinically important diagnostic and therapeutic dilemmas. Patients presenting with more than one pulmonary nodule at the same time must fulfill strict criteria to be classified as having synchronous MPLC. Based on the American College of Chest Physicians guidelines, the following are the considerations that define synchronous lung cancers [34]:

1. Both lesions must be malignant and must arise independently in the lung.
2. The second lesion cannot be assumed to represent a second primary lung cancer. A benign nodule, infectious process, or metastasis from an extrapulmonary site must be excluded.
3. The second malignant lesion must not represent a metastasis from the first lung lesion. Accepted criteria for distinction include different histology or origin from separate focus of carcinoma in situ. It has same histology but anatomically distinct, without involvement of the mediastinum (N2, N3, negative) and without systemic metastases.
4. Absence of systemic disease.

Patients with MPLC with N1 involvement of NSCLC should be considered for surgical resection if feasible. Some patients may be candidates for surgical resection of the primary with N1 nodal involvement and non-operative local management of the other primary malignancy if surgical resection is not feasible. MPLC with the same histology and N2 nodal involvement are generally treated as stage IV disease since a single malignant process is likely responsible for all the lesions and clinical carries a poorer prognosis compared to absent mediastinal involvement.

Surgery is a standard approach for treatment in patients with synchronous MPLC. Surgical planning is based on sufficient pulmonary reserve after resection. However, limited pulmonary reserve may require a patient to undergo a sublobar resection (e.g., segmentectomy) of one or both lesions, or limited resection to one lesion and definitive non-operative local therapy such as radiation or ablation. Patients with a satellite lesion in the same lobe as the primary lung cancer have a good prognosis and should be managed as dictated by the primary tumor alone.

4.6.3 Oligometastatic Disease

Oligometastatic disease is relatively common in NSCLC and does not always lead to widespread metastatic disease. Mediastinal staging is extremely important in this patient group as any positive mediastinal lymph nodes are a contraindication to resection.

(a) ***Brain metastasis***

Limited brain metastases can be managed aggressively with surgical resection. The use and benefit of directed therapy toward brain metastases has coincided with improved neurosurgical and radiosurgical techniques. Surgery is reserved for patients with limited number (1–3) of metastases. These patients benefit from a combination of stereotactic radiosurgery (if less than 3 cm or in a surgical inaccessible location) and/or surgical resection in addition to whole-brain radiation. Patients whose treatment included surgery had significantly fewer local recurrences (20 vs. 52 %), significantly improved survival (40 vs. 15 weeks), and a better quality of life [35]. Whole-brain radiation is primarily used to decrease risk of recurrence. The patients with stable extracranial disease had increased survival (median 12 months) [36]. In patients with >3 brain metastases, whole-brain radiation is the standard approach. Our practice is the local treatment of solitary brain metastasis (either surgically or with radiation) and resection of the primary lung cancer in mediastinal lymph node-negative patients with chemotherapy, preferably preoperative to the lung resection. Although there have been reports of lung cancer resection with oligometastatic brain lesions, the existing information suggests poorer prognosis with oligometastatic disease.

(b) ***Isolated Adrenal metastasis***

The adrenal gland is a common site of metastasis in NSCLC. Diagnosis should not be based exclusively on imaging findings as one study found that 4 of 14 suspected adrenal metastases were cortical adenomas [37]. Histologic confirmation is absolutely necessary.

Surgical resection in isolated adrenal metastasis from lung cancer should be considered in selected patients. Patients with metachronous adrenal metastases survived longer than those with synchronous adrenal metastases [38]. Favorable prognostic characteristics are R0 resection, long disease-free interval, and no other metastasis. In a study from the Massachusetts General Hospital, among 37 patients with isolated adrenal metastases, the five-year survival was 34 % in the adrenalectomy group versus 0 % in the non-operative group [39], thus emphasizing the important survival benefit of surgical resection. Our practice is surgery of solitary adrenal metastasis and resection of the primary lung cancer in mediastinal lymph node-negative patients with chemotherapy, preferably preoperative to the lung resection. Usually, patients are given systemic therapy first, followed by lung resection and finally adrenalectomy.

(c) ***Metachronous NSCLC***

Although many patients are treated successfully for NSCLC, approximately one-third of recurrences will be isolated from the ipsilateral thorax [40]. A complete metastatic workup should guide further therapy. Selected patients with the same type of cancer in a different lobe of the lung may benefit from aggressive surgical

resection. According to the American College of Chest Physicians guidelines and recommendations, the survival results after resection for either a synchronous presentation or a metachronous presentation with an interval of <4 years between tumors are variable and generally poor, suggesting that many of these patients may have had a pulmonary metastasis rather than a second primary lung cancer [41]. Although a thorough and careful evaluation of these patients is warranted to differentiate between metastatic disease from a second primary lung cancer, distinguishing criteria have not been defined in the literature [41]. Surgical resection should be considered in appropriately selected patients as it can prolong survival [42]. A retrospective study of 161 patients at the Mayo Clinic with metachronous NSCLC revealed a 5-year overall survival rate of 61 % calculated from the time of the second resection with improved survival and freedom from recurrence with tumors less than 2 cm [43]. If recurrence is restaged clinically a stage I or II, then re-resection should be considered. If the patient is not a candidate for additional surgery, definitive radiation or ablation should be the primary modality of treatment particularly in patients with a long disease-free interval. If the recurrence is restaged clinically as stage III with nodal involvement, then definitive chemoradiation should be considered [44].

(d) ***Synchronous Squamous cell carcinoma (SCC) of the head and neck and the lung***

Synchronous SCC of the head and neck with solitary SCC of the lung presents a very difficult diagnostic and therapeutic dilemma. If the tumors are found metachronously, then the treatment is based on established clinical criteria. For synchronous tumors, pan endoscopy and cervical mediastinoscopy are necessary for adequate staging. If there is no evidence of mediastinal disease, then surgical resection is warranted as this prolongs survival. In a retrospective study of 2964 patients with SCC of the head and neck, 27 patients were found to have synchronous SCC of the lung. Of those who had surgery with curative intent, the 5-year disease-free survival was 51 % if the mediastinum was radiographically negative compared to 13 % in patients who were surgical candidates but elected to treat with palliative therapy [45].

The appropriate sequence of surgery is still unclear. If the head and neck tumor will be treated with radiation, then it is reasonable to proceed with the thoracic resection first. However, if both tumors require surgery, then proceeding with the resection of the head and neck tumor to ensure a patent airway is a reasonable approach.

5 Surgical Options and Approaches

5.1 Types of Incisions

Lung resection, such as a lobectomy, can be performed through a thoracotomy (most common) or a median sternotomy. A posterolateral thoracotomy (Fig. 1) is a

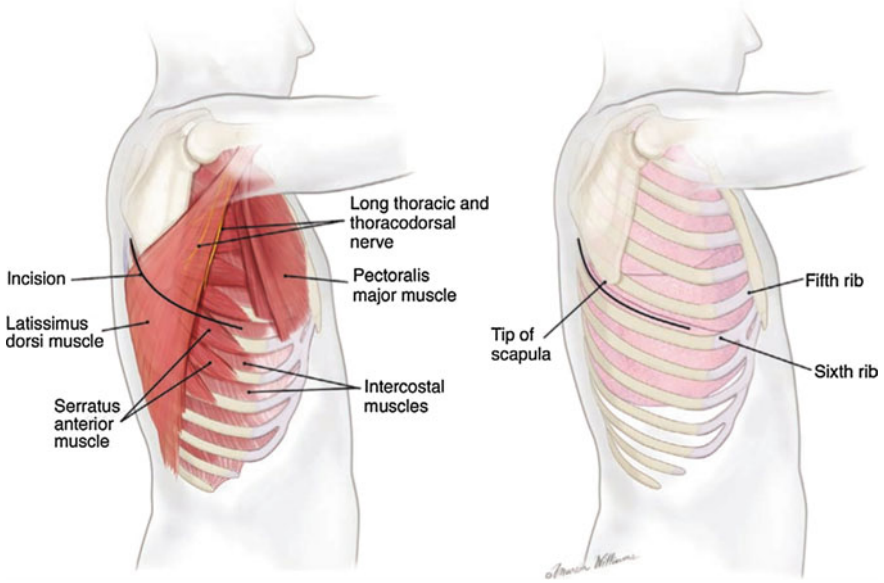


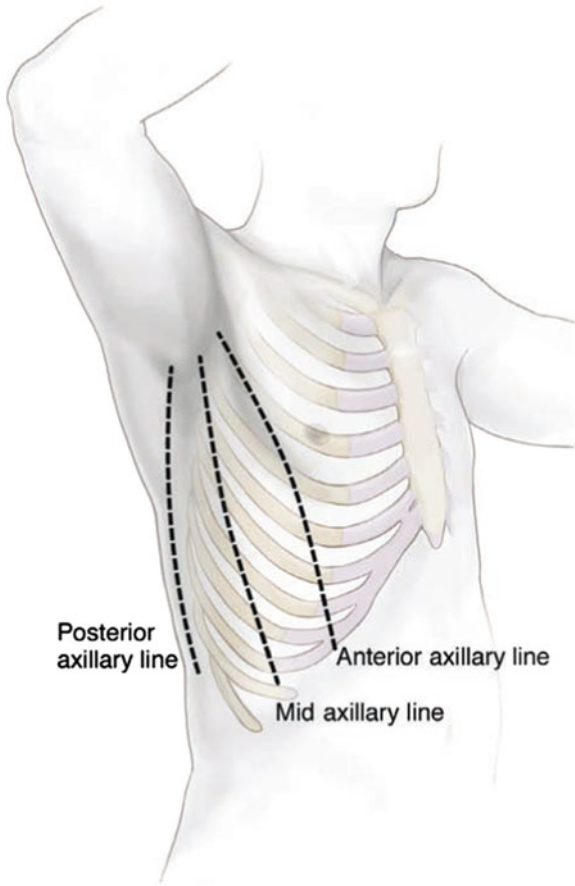
Fig. 1 Posterolateral thoracotomy

commonly used incision for lung resection. This incision is carried from the midpoint between the spine and the posterior border of the scapula to one fingerbreadth below the inferior tip of the scapula and then extended anteriorly the same distance toward the inframammary crease. The serratus anterior muscle is usually preserved and retracted anteriorly. For the standard pulmonary resection, the chest cavity is reached by entering through an intercostal space that provides the best access for the procedure to be performed (4th interspace for upper lobe lesions and 5th interspace for lower lobe lesions) [46]. The posterior muscle-sparing thoracotomy is preferred when possible as it spares all chest wall muscles by using the auscultatory triangle as the landmark. The initial skin incision is identical to the traditional thoracotomy. Subcutaneous skin flaps are created superiorly and inferiorly. The latissimus dorsi muscle is identified and mobilized from the underlying serratus muscle for its entire length. The serratus muscle is then elevated. A rib can be partially excised to facilitate spreading and to avoid rib fractures.

An axillary thoracotomy, or limited lateral thoracotomy (Fig. 2), can be used for upper or middle lobe resections or procedures confined to the anterior mediastinum or hilum. The incision is carried through the anterior aspect of the serratus muscle parallel to its fibers to the level of the 4th intercostal space. Care must be taken not to damage the long thoracic nerve posteriorly. With experience, this incision can be used for most situations. Since no muscle is divided, it can also be the least painful of the thoracotomy incisions.

The anterior thoracotomy (Fig. 3) is used to approach lesions in the anterior and middle thoracic cavity. An incision is made in the inframammary crease along the

Fig. 2 Axillary thoracotomy



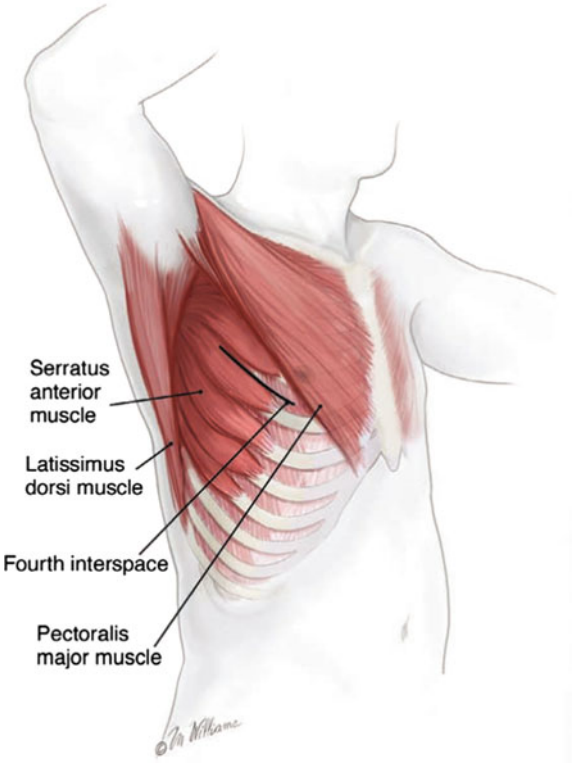
5th rib. The pectoralis major muscle is divided at its insertion into the medial chest wall. The serratus anterior muscles are then incised to expose the 4th and 5th ribs with the chest cavity entered at the 4th intercostal space. Lateral serratus fibers are spared to avoid long thoracic nerve injury [46].

5.2 Types of Surgical Resection

5.2.1 Wedge Resection

Several studies indicate that wedge resections for NSCLC are associated with higher local recurrence rates compared to lobectomy. Wedge resections are reserved for small peripheral lesions in patients with impaired cardiopulmonary reserve that are not candidates for lobectomy or segmentectomy [47–49]. Minimally invasive approaches such as VATS wedge resections are the standard of care that achieve shorter hospital stay and less patient morbidity than an open operation [50]. More

Fig. 3 Anterior thoracotomy



importantly, the 5-year survival rates are the same for patients with T1N0 lesions who underwent wedge resection whether by VATS or thoracotomy [51]. There is also no difference in disease-free survival when comparing wedge resection to anatomic lobectomy of stage IA patients [52]. Criteria for wedge resection that have been suggested include the following:

(1) Tumors less than 2 cm in diameter (T1a lesion);
(2) Tumors located in outer third of lung and approachable by wedge resection by staple, electrocautery, or laser;
(3) No endobronchial extension;
(4) Frozen section evidence of negative pathological resection margins; and
(5) Intraoperative mediastinal and hilar nodal staging [51].

Recurrences vary with tumor size and nodal involvement. For node-negative patients with T1 and T2 tumors, the long-term local recurrence occurs in 5–12 %, whereas distant metastasis occurs in 7–30 % of patients. Failure rates increase with the presence of hilar or mediastinal nodal disease. In N1 and N2 disease, several studies show the local failure rate ranges from 9–28 % to 13–17 %, respectively, while distant metastasis occurs in 22–61 % of patients [53–55]. Interestingly, if

recurrence occurs with initially clear margins, this is thought to reflect an aggressive, metastatic tumor phenotype rather than surgical failure leading to metastatic disease [51, 56–59].

A number of strategies have been shown to decrease local recurrence after wedge resections. External beam radiation has had promise, but in a prospective multi-institutional clinical trial of high-risk patients treated with post-wedge resection "postage stamp" radiotherapy, the results were less promising [47]. The phase III Alliance trial that enrolled 224 patients found no difference in local recurrence or survival between sublobar resection alone and sublobar resection combined with intraoperative placement of iodine-125 seeds. Local progression occurred in only 17 patients (8 %) overall, there was no significant difference between the two treatment arms, and the three-year overall survival rate was 71 % in each treatment arm. The median follow-up was 4.4 years [60].

5.2.2 Segmentectomy

Segmentectomy (Fig. 4) has been reserved for resection of selected NSCLC. These include stage I and II NSCLC in patients with impaired lung function, as a lung preservation operation in patients with synchronous or metachronous lung cancer, and for peripheral stage I lung cancer [61]. Retrospective studies have shown segmentectomies to confer equivalent survival rates to lobectomy in selected patients. Major complications include prolonged air leaks (5–16 %) and a higher rate of recurrence (11–16 vs. 5 % for lobectomy) [47, 62–65]. As expected, increased recurrence (22 %) was seen in segmentectomies with margins less than 1–2 cm as well as proximity to the hilum [66, 67]. With underlying pulmonary compromise, segmentectomies were associated with a 30-day mortality benefit of 1.1 versus 3.3 % for lobectomy [66]. This is supported by findings that segmentectomy results in better residual pulmonary function than lobectomy [68]. Thoracoscopic resection has been shown to result in shorter hospital stay as well as lower thirty-day mortality compared to the open approach [69]. Due to the improved tolerance of patients to adjuvant therapy, thoracoscopic segmentectomy may also yield better survival than the open technique [70]. Commonly performed segmentectomies include lingula-sparing left upper lobectomy, lingulectomy, superior segmentectomy, and basilar segmentectomy. Less commonly performed segmentectomies include anterior or posterior upper lobe segmentectomies [71].

5.2.3 Lobectomy

Open lobectomy has been the standard of care of early-stage NSCLC for many years. However, VATS lobectomy has emerged as an excellent alternative to open lobectomy and is now the standard of care for surgically amenable tumors. Comparable complication [72–74] and survival [73, 75, 76] rates between VATS and open lobectomies can be achieved. VATS lobectomies have several advantages over traditional open techniques. These include decreased postoperative pain [77, 78], lower chest tube output and duration [73], less blood loss [79], superior pulmonary function [80], shorter hospital stay, and earlier return to normal activities [72, 73]. Equivalent survival at 3 and 5 years has been reported for VATS

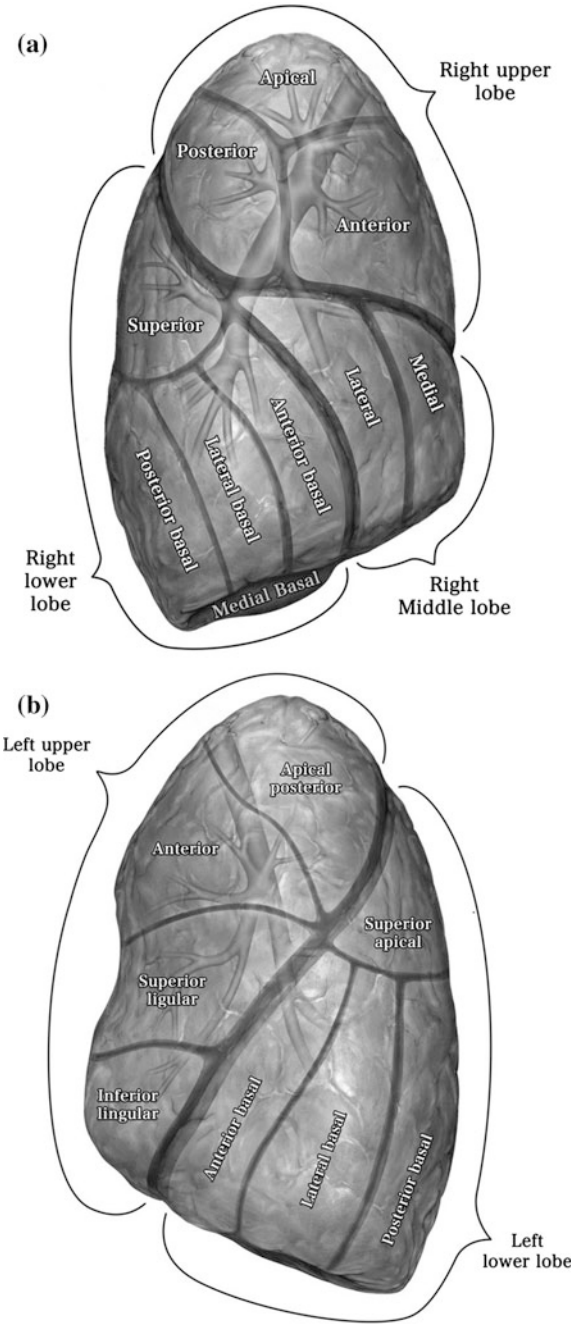


Fig. 4 Segments of the lung

lobectomy (90 and 90 %, respectively) and open lobectomy (93 and 85 %) for stage I NSCLC [81–83]. Importantly, patients who underwent VATS lobectomy were more tolerant of adjuvant therapy than their open lobectomy counterparts. Patients undergoing VATS lobectomy experienced fewer delays in chemotherapy and were more likely to tolerate and complete the entire adjuvant chemotherapy regimen. Furthermore, more VATS lobectomy patients received >75 % of their planned regimen without delayed or reduced doses. Long-term outcome differences remain unproven [84]. Although challenging, VATS lobectomy has also found to be feasible and safe after induction therapy [85].

5.2.4 Pneumonectomy

According to the Lung Cancer Study Group report, mortality in "pneumonectomies should carry a risk of less than 7 %, lobectomies less than 3 %, and lesser resections less than 2 %." Risk factors for mortality in pneumonectomies include right-sided pneumonectomies, older age (>70), and low-volume surgical centers. In addition, long-term sequelae of pneumonectomies include pulmonary hypertension, progression of emphysema, and increased right heart pressures during exercise [86, 87]. Pneumonectomies are considered when sleeve resections are considered technically not feasible [88]. Impaired function and shortened long-term survival due to cardiorespiratory compromise have been cited as risks against pneumonectomies in favor of sleeve resection [87, 89]. Patients treated with pneumonectomy have increased operative morbidity and mortality as well as reduced long-term survival compared with patients treated with lobectomy [90–92]. Late death may also be increased by the long-term cardiopulmonary morbidity of pneumonectomies [92]. Life-threatening complications following pneumonectomies are more likely when there is reduced preoperative diffusion capacity, preexisting compromising cardiopulmonary disease, excessive perioperative fluid administration, and a preoperative low hemoglobin [93]. Others have found that after performing a multivariate analysis, pneumonectomy was not an independent determinate of long-term survival [94]. Rather, it was the patient age, preoperative spirometry, and T and N status that determined long-term survival. It has also been argued that pneumonectomies are associated with a lower rate of second primaries compared with lobectomies, presumably because there is less remaining lung tissue at risk for malignancy.

The safety of chemoradiation therapy with pneumonectomy is an important issue for patients with more advanced NSCLC. Single-institution experiences report that chemoradiation induction therapy can be performed with acceptable 30- and 100-day mortality rates of 6 and 10 %, respectively, with good oncologic outcomes [95]. Long-term survival at 1 and 5 years for those receiving neoadjuvant therapy was 74 and 46 % and similar to the surgery-only group with the survival of 72 and 34 % [96]. However, definitive chemoradiation is recommended by some groups in NSCLC stage IIIA patients being considered for pneumonectomy as there is increased mortality in this select patient group, particularly with a right-sided pneumonectomy. Results from other similar reports were, however, less encouraging with 30- and 90-day mortality rates of 12 and 21 %. Survival at 3 and 5 years

was 35 and 25 %, respectively [97]. A consistent finding is that right pneumonectomies are associated with significantly greater morbidity and mortality and should be performed with great care [98]. Discrepant results are likely due to the retrospective nature of these studies that are subject to inherent biases. Differences in perioperative management can lead to variations in outcomes such as chest tube drainage, pain control, and fluid balance.

5.2.5 Sleeve Resections

Bronchial sleeve lobectomy was introduced by Sir Clement Price-Thomas in 1947 to allow parenchyma-sparing surgery. Allison subsequently performed the first sleeve lobectomy for bronchogenic carcinoma [99]. Bronchoplastic techniques are used in 3–13 % of resectable pulmonary tumors accompanied [99–101]. The purpose is to provide adequate tumor resection margins while conserving as much healthy lung parenchyma as possible [102]. Sleeve lobectomy has become an alternative to pneumonectomy for patients with marked impairment in pulmonary function, elderly patients, as well as those with serious comorbidities, and should be considered in all patients where technically feasible. In particular, it is the procedure of choice for cancer extending to the left or right upper lobe bronchial orifice and adjacent main stem bronchus or extending to the proximal left lower lobe bronchus. Compared to pneumonectomy, it provides an improved quality of life while achieving superior morbidity, mortality, and long-term survival [99, 103]. Interestingly, in addition to a better quality of life, the long-term cancer control appears to be no different than a pneumonectomy [104]. Sleeve resections have a reported mortality 4 % with survival at 1 and 5 years of 84 and 42 %, respectively. A sleeve lobectomy can reach the same functional result as a standard lobectomy. However, it takes 3–4 months for the reimplanted lobe to completely recover and contribute to residual postoperative pulmonary function [105]. Given that the lifelong risk of developing a second lung cancer is about 2 % per year after the resection, a subsequent lung resection can more safely be performed in patients who previously underwent a sleeve lobectomy versus those who had a prior pneumonectomy [103, 106]. The size of the tumor may limit the technical feasibility of sleeve lobectomy [107]. However, chemotherapy and radiation can downstage tumors in the presence of mediastinal disease to allow bronchoplastic techniques. Although chemotherapy has been associated with decreased mucosal blood flow and healing [108], clinical studies have shown that sleeve lobectomy is still safe after neoadjuvant chemotherapy [101, 109]. Operative mortality is high in patients with serious comorbidities (e.g., poor nutritional status, liver impairment, renal impairment, diabetes, cardiac compromise, peripheral vascular disease, stroke). Elderly patients must be very carefully selected as well [103].

Performance of sleeve resections involves a dissection of bronchus from its adjacent lung and pulmonary vessels at the lobar orifice level (Fig. 5). A bronchotomy is sometimes performed under bronchoscopic guidance to ensure adequate margins. After determining the extent of the tumor, resection is performed *en bloc* with a portion of the airway and sometimes the associated pulmonary artery perfusing the remaining lung. The specimen is then sent for frozen section to confirm

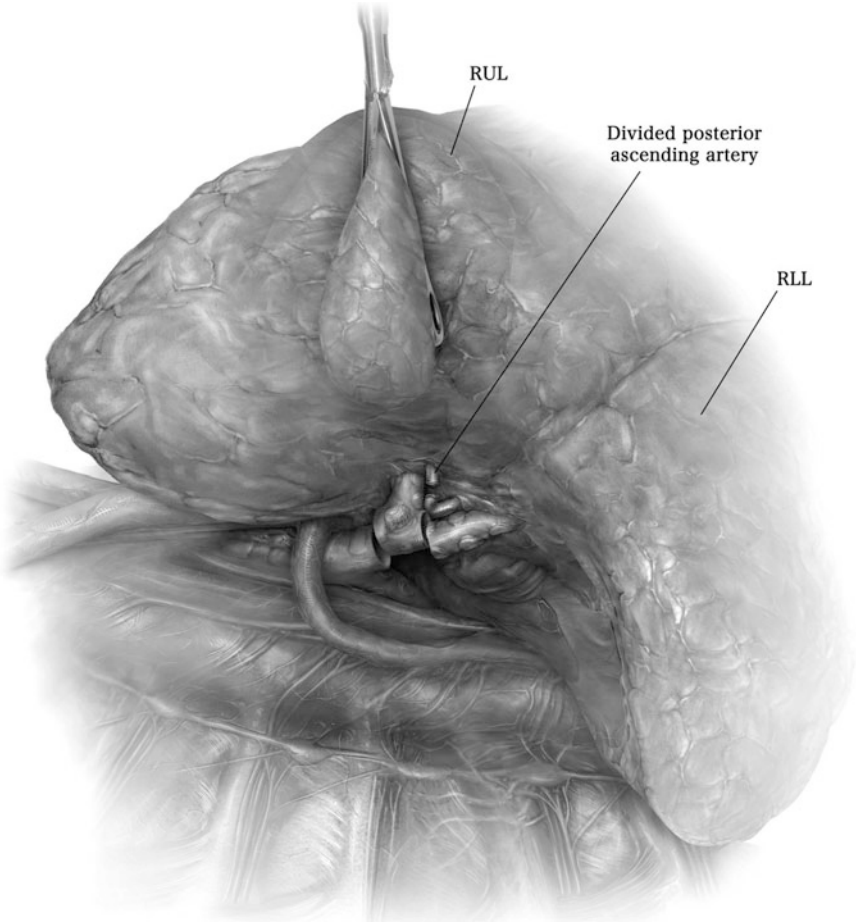


Fig. 5 Sleeve right upper lobectomy

negative margins. An end-to-end anastomosis (Fig. 6) is then performed and covered with a vascularized pleural or pericardial flap (Fig. 7) for protection and prevention of pulmonary vessel erosion by suture knots and to provide extra blood supply to the anastomosis [102, 110]. The most common site of sleeve resection is the right upper lobe [111–117].

Bronchoplastic procedures have more postoperative complications than standard lobectomies, thereby requiring intensive care monitoring in the immediate postoperative period. Early postoperative issues include partial atelectasis, lobar collapse, pneumonia, air leak, suture erosion of vessels, and transient vocal cord paralysis. Atelectasis commonly results from blood or mucus plugging. Routine postoperative flexible bronchoscopy and bronchial toilet are recommended for preemptive treatment prior to extubation. This also offers an opportunity for the surgeon to confirm the patency of the reconstructed bronchus. Pulmonary clearance

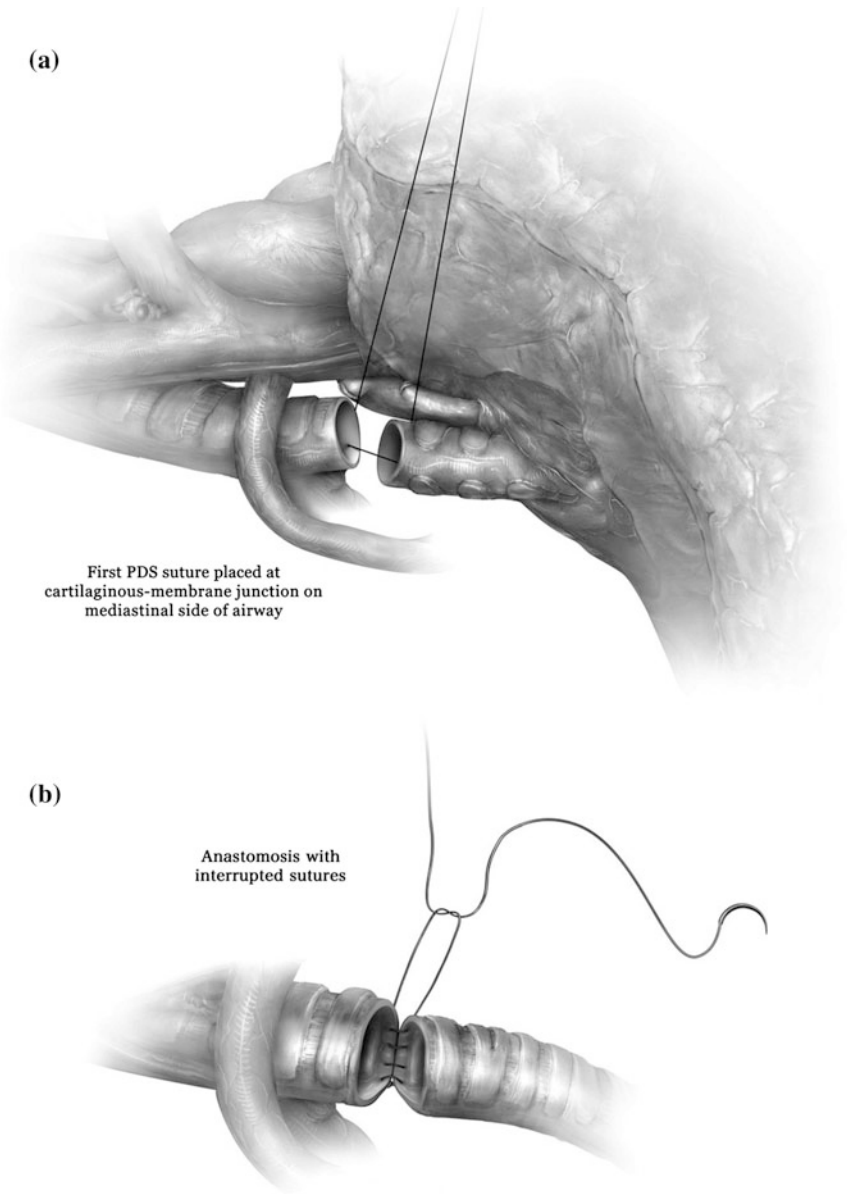


Fig. 6 Sleeve lobectomy anastomosis

mechanisms are compromised postoperatively, especially in elderly patients, so aggressive chest physiotherapy and steam inhalations may help prevent complications [102]. Transection of bronchial lymphatics increases pulmonary fluid and likely contributes to increased risk of infection [110]. Sleeve resection has a

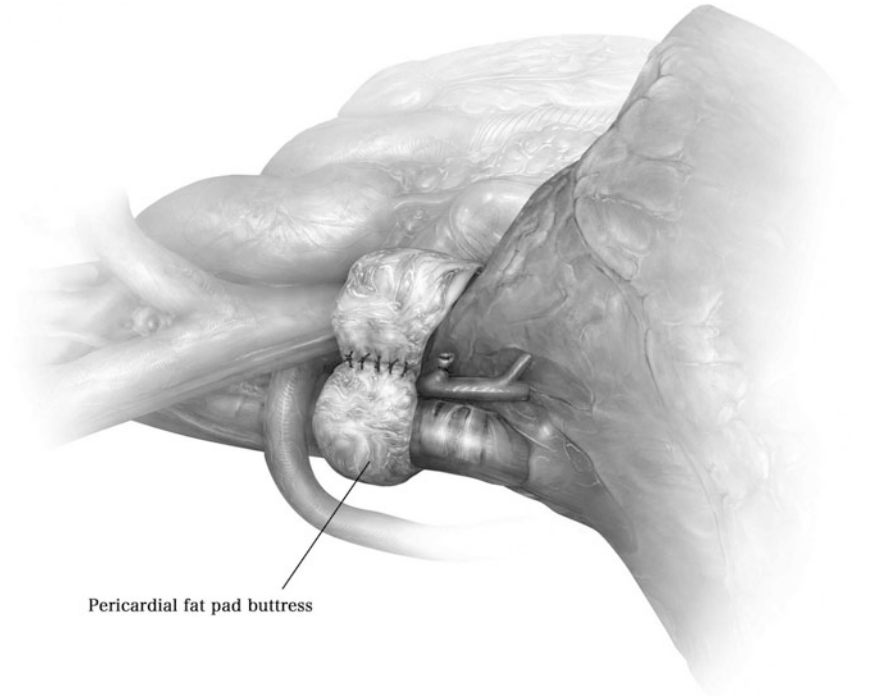


Fig. 7 Pericardial fat pad buttress

morbidity rate of 26.8 % and mortality rate of 5.5 % [101]. Other complications following sleeve resection are bronchoplasty site stenosis and dehiscence, bronchopleural fistulae, and bronchovascular fistulae [103, 104]. Late complications include bronchial stricture, bronchiectasis, bronchopleural fistula, and empyema [99]. The incidence of bronchial anastomotic complications is 6.4 % with a bronchopleural fistula rate of 3 % and a bronchovascular fistula rate of 2.5 %. There is also a 10 % rate of pneumonia following sleeve resection [99]. Predictive factors for postoperative complications include right-sided resections, smoking, and squamous cell carcinomas [118]. Technical points that can assist in minimizing complications include precise dissection and anastomotic technique, avoidance of anastomotic stenosis during initial surgery, preservation of blood supply, using a buttress for the anastomosis, and interpositing healthy tissue between the bronchial and vascular structures [118]. Anastomotic dehiscence or stenosis after sleeve lobectomy can require subsequent completion pneumonectomy [99]. This occurs more frequently in compromised patients [119], pathologic N2 status, as well as those with positive bronchial margins [119, 120]. The use of absorbable suture such as vicryl or PDS has decreased the incidence of bronchial anastomotic complications which can more readily allow postoperative dilatation [121]. Bronchoplastic procedures are technically demanding and have better outcomes by surgeons specializing in general thoracic surgery.

5.2.6 Carinal Resection

Lung cancers in close proximity to or involving the carina are often not amenable to resection. However, complete resection may be possible for a select patient group that does not have dissemination or invasion into vital structures [122, 123]. Utilization of bronchoplastic techniques in these patients can greatly improve outcomes and survival [124]. Several studies have shown that bronchoplastic operations for carinal involvement can be done with an acceptable mortality rate of approximately 16 % [124–130]. Tracheobronchial junction tumors are particularly challenging. While most of these tumors can be resected through the usual right posterolateral thoracotomy, Muscolino et al. used anterior thoracotomy through the fourth intercostal space to perform a right sleeve pneumonectomy. Good exposure, adequate anastomotic visualization, and nodal clearance from the paratracheal and subcarinal areas can be achieved through this incision [106]. Other exposures that have been described include bilateral thoracotomies or sternothoracotomy [128]. Lethal complications of this operation are acute respiratory distress syndrome (ARDS) and non-cardiogenic pulmonary edema. The etiology of post-lung-resection ARDS and is unknown, but this complication is associated with mortality rates as high as 90 % [123, 131]. Nitric oxide has been used to treat this devastating condition with modest success [132]. Anastomotic complications are major complications of bronchoplastic resection of carinal tumors. Most commonly, these result from excessive tension on the anastomosis either from an excessive airway resection or from inadequate mobilization of the remaining lung and trachea. Therefore, carinal resection should be limited to a maximum of 4 cm (measured from proposed tracheotomy to left main stem bronchotomy). Other key factors include preservation of airway vascularity, meticulous anastomotic technique, and careful tissue handling [125]. Prolonged postoperative mechanical ventilation increases mortality, so patients should be extubated immediately after surgery whenever possible [123].

6 Summary

Preoperative staging is very important and is considered to be one of the most important prognostic indicators in patients with lung cancer. Once adequately staged, a treatment regimen can be outlined for the patient. It is not uncommon for patients to be told they are unresectable without adequate staging only to be told later that they are surgical candidates. Cardiopulmonary testing is important to risk stratify patients and better estimate their risk of morbidity and mortality from surgery. There are several surgical approaches to surgical resection of a lung cancer. However, minimally invasive surgical approaches such as VATS and robot assistance are increasingly used for pulmonary resections for lung cancer. The T and N status of a surgically resected specimen determines whether it is beneficial to proceed with adjuvant chemotherapy or radiation. Genetic alterations in lung cancer may be able to predict sensitivity to chemotherapy agents and allow for more

targeted therapy. Due to the complexity of management, patients with lung cancer should be cared for by general thoracic surgeons and a multidisciplinary team to improve both disease-free survival and overall survival.

Bibliography

1. Fischer B et al (2009) Preoperative staging of lung cancer with combined PET-CT. N Engl J Med 361(1):32–39
2. Reidy-Lagunes DL, Gollub MJ, Saltz LB (2011) Addition of octreotide functional imaging to cross-sectional computed tomography or magnetic resonance imaging for the detection of neuroendocrine tumors: added value or an anachronism? J Clin Oncol 29(3):e74–e75
3. Granberg D et al (2003) Octreoscan in patients with bronchial carcinoid tumours. Clin Endocrinol (Oxf) 59(6):793–799
4. Gustafsson BI et al (2008) Bronchopulmonary neuroendocrine tumors. Cancer 113(1):5–21
5. British Thoracic S, Society of Cardiothoracic Surgeons of Great B, Ireland Working P (2001) BTS guidelines: guidelines on the selection of patients with lung cancer for surgery. Thorax, 56(2):89–108
6. Berry MF et al (2010) Pulmonary function tests do not predict pulmonary complications after thoracoscopic lobectomy. Ann Thorac Surg 89(4):1044–1051; discussion 1051–1052
7. Brunelli A et al (2013) Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 143 (5 Suppl):e166S–e190S
8. Datta D, Lahiri B (2003) Preoperative evaluation of patients undergoing lung resection surgery. Chest 123(6):2096–2103
9. Markos J et al (1989) Preoperative assessment as a predictor of mortality and morbidity after lung resection. Am Rev Respir Dis 139(4):902–910
10. Kearney DJ et al (1994) Assessment of operative risk in patients undergoing lung resection. Importance of predicted pulmonary function. Chest 105(3):753–759
11. Criner GJ, Sternberg AL (2008) National emphysema treatment trial: the major outcomes of lung volume reduction surgery in severe emphysema. Proc Am Thorac Soc 5(4):393–405
12. Karazincir S et al (2008) CT assessment of main pulmonary artery diameter. Diagn Interv Radiol 14(2):72–74
13. Gibbons RJ et al (1997) ACC/AHA guidelines for exercise testing: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Circulation 96(1):345–354
14. Cerfolio RJ et al (2003) The role of FDG-PET scan in staging patients with nonsmall cell carcinoma. Ann Thorac Surg 76(3):861–866
15. Lemaire A et al (2006) Nine-year single center experience with cervical mediastinoscopy: complications and false negative rate. Ann Thorac Surg 82(4):1185–1189; discussion 1189–1190
16. Metin M et al (2011) The role of extended cervical mediastinoscopy in staging of non-small cell lung cancer of the left lung and a comparison with integrated positron emission tomography and computed tomography: does integrated positron emission tomography and computed tomography reduce the need for invasive procedures? J Thorac Oncol 6(10):1713–1719
17. Yasufuku K et al (2011) A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. J Thorac Cardiovasc Surg 142(6):1393–400 e1
18. Defranchi SA et al (2010) Mediastinoscopy in patients with lung cancer and negative endobronchial ultrasound guided needle aspiration. Ann Thorac Surg 90(6):1753–1757

19. Wallace MB et al (2008) Minimally invasive endoscopic staging of suspected lung cancer. JAMA 299(5):540–546
20. Miller AB, Fox W, Tall R (1969) Five-year follow-up of the medical research council comparative trial of surgery and radiotherapy for the primary treatment of small-celled or oat-celled carcinoma of the bronchus. Lancet 2(7619):501–505
21. Yu JB et al (2010) Surveillance epidemiology and end results evaluation of the role of surgery for stage I small cell lung cancer. J Thorac Oncol 5(2):215–219
22. Vallieres E et al (2009) The IASLC lung cancer staging project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol 4(9):1049–1059
23. Groome PA et al (2007) The IASLC lung cancer staging project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2(8):694–705
24. Strauss GM et al (2008) Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the cancer and leukemia group B, radiation therapy oncology group, and north central cancer treatment group study groups. J Clin Oncol 26(31):5043–5051
25. Douillard JY et al (2006) Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (adjuvant navelbine international trialist association [ANITA]): a randomised controlled trial. Lancet Oncol 7 (9):719–727
26. Doddoli C et al (2005) Lung cancer invading the chest wall: a plea for en-bloc resection but the need for new treatment strategies. Ann Thorac Surg 80(6):2032–2040
27. Winton T et al (2005) Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 352(25):2589–2597
28. Arriagada R et al (2004) Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 350(4):351–360
29. Jaklitsch MT et al (2006) Nodal downstaging predicts survival following induction chemotherapy for stage IIIA (N2) non-small cell lung cancer in CALGB protocol #8935. J Surg Oncol 94(7):599–606
30. Detterbeck FC (1997) Pancoast (superior sulcus) tumors. Ann Thorac Surg 63(6):1810–1818
31. Albain KS et al (2009) Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 374 (9687):379–386
32. Detterbeck FC et al (2003) Lung cancer, special treatment issues. Chest 123(1 Suppl):244S–258S
33. DiPerna CA, Wood DE (2005) Surgical management of T3 and T4 lung cancer. Clin Cancer Res 11(13 Pt 2):5038s–5044s
34. Kozower BD et al (2013) Special treatment issues in non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 143(5 Suppl):e369S–e399S
35. Patchell RA et al (1990) A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322(8):494–500
36. Noordijk EM et al (1994) The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. Int J Radiat Oncol Biol Phys 29(4):711–717
37. Lucchi M et al (2005) Metachronous adrenal masses in resected non-small cell lung cancer patients: therapeutic implications of laparoscopic adrenalectomy. Eur J Cardiothorac Surg 27 (5):753–756
38. Porte H et al (2001) Resection of adrenal metastases from non-small cell lung cancer: a multicenter study. Ann Thorac Surg 71(3):981–985
39. Raz DJ et al (2011) Outcomes of patients with isolated adrenal metastasis from non-small cell lung carcinoma. Ann Thorac Surg 92(5):1788–1792; discussion 1793

40. Younes RN, Gross JL, Deheinzelin D (1999) Follow-up in lung cancer: how often and for what purpose? Chest 115(6):1494–1499
41. Shen KR et al (2007) Special treatment issues in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 132(3 Suppl):290S–305S
42. Hamaji M, Ali SO, Burt BM (2015) A meta-analysis of resected metachronous second non-small cell lung cancer. Ann Thorac Surg 99(4):1470–1478
43. Hamaji M et al (2013) Surgical treatment of metachronous second primary lung cancer after complete resection of non-small cell lung cancer. J Thorac Cardiovasc Surg 145(3):683–690; discussion 690–691
44. Harpole DH Jr et al (1995) Stage I nonsmall cell lung cancer. A multivariate analysis of treatment methods and patterns of recurrence. Cancer 76(5):787–796
45. Kuriakose MA et al (2002) Simultaneously presenting head and neck and lung cancer: a diagnostic and treatment dilemma. Laryngoscope 112(1):120–123
46. Nesbitt JC, Wind GG (2003) Thoracic surgical oncology: exposures and techniques. Lippincott Williams & Wilkins, Philadelphia
47. Miller JI, Hatcher CR Jr (1987) Limited resection of bronchogenic carcinoma in the patient with marked impairment of pulmonary function. Ann Thorac Surg 44(4):340–343
48. Pastorino U et al (1991) Limited resection for Stage I lung cancer. Eur J Surg Oncol 17 (1):42–46
49. Ginsberg RJ, Rubinstein LV (1995) Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 60 (3):615–622; discussion 622–623
50. Landreneau RJ et al (1993) Postoperative pain-related morbidity: video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg 56(6):1285–1289
51. Landreneau RJ et al (1997) Wedge resection versus lobectomy for stage I (T1 N0 M0) non-small-cell lung cancer. J Thorac Cardiovasc Surg 113(4):691–698; discussion 698–700
52. El-Sherif A et al (2006) Outcomes of sublobar resection versus lobectomy for stage I non-small cell lung cancer: a 13-year analysis. Ann Thorac Surg 82(2):408–415; discussion 415–416
53. Feld R, Rubinstein LV, Weisenberger TH (1984) Sites of recurrence in resected stage I non-small-cell lung cancer: a guide for future studies. J Clin Oncol 2(12):1352–1358
54. Thomas P, Rubinstein L (1990) Cancer recurrence after resection: T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 49(2):242–246; discussion 246–247
55. Pairolero PC et al (1984) Postsurgical stage I bronchogenic carcinoma: morbid implications of recurrent disease. Ann Thorac Surg 38(4):331–338
56. Siegfried JM et al (1994) Ability to culture resectable non-small cell lung carcinomas is correlated with recurrence. Ann Thorac Surg 58(3):662–666; discussion 667
57. Kessler R et al (1996) Blood vessel invasion is a major prognostic factor in resected non-small cell lung cancer. Ann Thorac Surg 62(5):1489–1493
58. Harpole DH Jr et al (1996) Angiogenesis and molecular biologic substaging in patients with stage I non-small cell lung cancer. Ann Thorac Surg 61(5):1470–1476
59. Johnson JR et al (1995) Successful xenotransplantation of human lung cancer correlates with the metastatic phenotype. Ann Thorac Surg 60(1):32–36; discussion 36–37
60. Fernando HC et al (2014) Impact of brachytherapy on local recurrence rates after sublobar resection: results from ACOSOG Z4032 (Alliance), a phase III randomized trial for high-risk operable non-small-cell lung cancer. J Clin Oncol 32(23):2456–2462
61. Deslauriers J et al (1989) Carcinoma of the lung. Evaluation of satellite nodules as a factor influencing prognosis after resection. J Thorac Cardiovasc Surg 97(4):504–512
62. Kutschera W (1984) Segment resection for lung cancer. Thorac Cardiovasc Surg 32(2):102–104
63. Bonfils-Roberts EA, Clagett OT (1972) Contemporary indications for pulmonary segmental resections. J Thorac Cardiovasc Surg 63(3):433–438

64. Jensik RJ, Faber LP, Kittle CF (1979) Segmental resection for bronchogenic carcinoma. Ann Thorac Surg 28(5):475–483
65. Bennett WF, Smith RA (1979) Segmental resection for bronchogenic carcinoma: a surgical alternative for the compromised patient. Ann Thorac Surg 27(2):169–172
66. Schuchert MJ et al (2007) Anatomic segmentectomy in the treatment of stage I non-small cell lung cancer. Ann Thorac Surg 84(3):926–932; discussion 932–933
67. Sienel W et al (2007) Frequency of local recurrence following segmentectomy of stage IA non-small cell lung cancer is influenced by segment localisation and width of resection margins—implications for patient selection for segmentectomy. Eur J Cardiothorac Surg 31 (3):522–527; discussion 527–528
68. Martin-Ucar AE et al (2005) A case-matched study of anatomical segmentectomy versus lobectomy for stage I lung cancer in high-risk patients. Eur J Cardiothorac Surg 27(4):675–679
69. Houck WV, Fuller CB, McKenna RJ Jr (2004) Video-assisted thoracic surgery upper lobe trisegmentectomy for early-stage left apical lung cancer. Ann Thorac Surg 78(5):1858–1860
70. Atkins BZ et al (2007) Pulmonary segmentectomy by thoracotomy or thoracoscopy: reduced hospital length of stay with a minimally-invasive approach. Ann Thorac Surg 84(4):1107–1112; discussion 1112–1113
71. D'Amico TA (2008) Thoracoscopic segmentectomy: technical considerations and outcomes. Ann Thorac Surg 85(2):S716–S718
72. Sugiura H et al (1999) Long-term benefits for the quality of life after video-assisted thoracoscopic lobectomy in patients with lung cancer. Surg Laparosc Endosc Percutan Tech 9(6):403–408
73. McKenna RJ Jr, Houck W, Fuller CB (2006) Video-assisted thoracic surgery lobectomy: experience with 1,100 cases. Ann Thorac Surg 81(2):421–425; discussion 425–426
74. Hoksch B et al (2003) Complication rate after thoracoscopic and conventional lobectomy. Zentralbl Chir 128(2):106–110
75. Sugi K et al (2003) Intrathoracic bleeding during video-assisted thoracoscopic lobectomy and segmentectomy. Kyobu Geka 56(11):928–931
76. Kaseda S, Aoki T (2002) Video-assisted thoracic surgical lobectomy in conjunction with lymphadenectomy for lung cancer. Nippon Geka Gakkai Zasshi 103(10):717–721
77. Walker WS (1998) Video-assisted thoracic surgery (VATS) lobectomy: the Edinburgh experience. Semin Thorac Cardiovasc Surg 10(4):291–299
78. Giudicelli R et al (1994) Major pulmonary resection by video assisted mini-thoracotomy. Initial experience in 35 patients. Eur J Cardiothorac Surg 8(5):254–258
79. Demmy TL, Curtis JJ (1999) Minimally invasive lobectomy directed toward frail and high-risk patients: a case-control study. Ann Thorac Surg 68(1):194–200
80. Nakata M et al (2000) Pulmonary function after lobectomy: video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg 70(3):938–941
81. Onaitis MW et al (2006) Thoracoscopic lobectomy is a safe and versatile procedure: experience with 500 consecutive patients. Ann Surg 244(3):420–425
82. Sugi K, Kaneda Y, Esato K (2000) Video-assisted thoracoscopic lobectomy achieves a satisfactory long-term prognosis in patients with clinical stage IA lung cancer. World J Surg 24(1):27–30; discussion 30–31
83. Walker WS et al (2003) Long-term outcomes following VATS lobectomy for non-small cell bronchogenic carcinoma. Eur J Cardiothorac Surg 23(3):397–402
84. Bonadonna G et al (1995) Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. N Engl J Med 332(14):901–906
85. Petersen RP et al (2006) Thoracoscopic lobectomy: a safe and effective strategy for patients receiving induction therapy for non-small cell lung cancer. Ann Thorac Surg 82(1):214–218; discussion 219
86. van Meerbeeck JP, Damhuis RA, Vos de Wael ML (2002) High postoperative risk after pneumonectomy in elderly patients with right-sided lung cancer. Eur Respir J 19(1):141–145

87. Burrows B et al (1960) The postpneumonectomy state: clinical and physiologic observations in thirty-six cases. Am J Med 28:281–297
88. Baumann M, Stamatis G, Thomas M (2001) Therapy of localized non-small cell lung cancer (take home messages). Lung Cancer 33(Suppl 1):S47–S49
89. Gaissert HA et al (1996) Survival and function after sleeve lobectomy for lung cancer. J Thorac Cardiovasc Surg 111(5):948–953
90. Ginsberg RJ et al (1983) Modern thirty-day operative mortality for surgical resections in lung cancer. J Thorac Cardiovasc Surg 86(5):654–658
91. Rocco PM et al (1996) Long-term outcome after pneumonectomy for nonsmall cell lung cancer. J Surg Oncol 61(4):278–280
92. Paulson DL, Reisch JS (1976) Long-term survival after resection for bronchogenic carcinoma. Ann Surg 184(3):324–332
93. Bernard A et al (2001) Pneumonectomy for malignant disease: factors affecting early morbidity and mortality. J Thorac Cardiovasc Surg 121(6):1076–1082
94. Kim DJ et al (2007) Long-term survival following pneumonectomy for non-small cell lung cancer: clinical implications for follow-up care. Chest 132(1):178–184
95. Allen AM et al (2008) Pneumonectomy after chemoradiation: the Dana-Farber Cancer Institute/Brigham and Women's Hospital experience. Cancer 112(5):1106–1113
96. Gudbjartsson T et al (2008) Early surgical results after pneumonectomy for non-small cell lung cancer are not affected by preoperative radiotherapy and chemotherapy. Ann Thorac Surg 86(2):376–382
97. Doddoli C et al (2005) One hundred consecutive pneumonectomies after induction therapy for non-small cell lung cancer: an uncertain balance between risks and benefits. J Thorac Cardiovasc Surg 130(2):416–425
98. Martin J et al (2001) Morbidity and mortality after neoadjuvant therapy for lung cancer: the risks of right pneumonectomy. Ann Thorac Surg 72(4):1149–1154
99. Tedder M et al (1992) Current morbidity, mortality, and survival after bronchoplastic procedures for malignancy. Ann Thorac Surg 54(2):387–391
100. Kim YT et al (2005) Local control of disease related to lymph node involvement in non-small cell lung cancer after sleeve lobectomy compared with pneumonectomy. Ann Thorac Surg 79(4):1153–1161; discussion 1153–1161
101. Burfeind WR Jr et al (2005) Low morbidity and mortality for bronchoplastic procedures with and without induction therapy. Ann Thorac Surg 80(2):418–421; discussion 422
102. Jalal A, Jeyasingham K (2000) Bronchoplasty for malignant and benign conditions: a retrospective study of 44 cases. Eur J Cardiothorac Surg 17(4):370–376
103. Terzi A et al (2002) Sleeve lobectomy for non-small cell lung cancer and carcinoids: results in 160 cases. Eur J Cardiothorac Surg 21(5):888–893
104. Ferguson MK, Karrison T (2000) Does pneumonectomy for lung cancer adversely influence long-term survival? J Thorac Cardiovasc Surg 119(3):440–448
105. Khargi K et al (1994) Pulmonary function after sleeve lobectomy. Ann Thorac Surg 57 (5):1302–1304
106. Van Schil PE et al (1992) Second primary lung cancer after bronchial sleeve resection. Treatment and results in eleven patients. J Thorac Cardiovasc Surg 104(5):1451–1455
107. Bagan P et al (2005) Sleeve lobectomy versus pneumonectomy: tumor characteristics and comparative analysis of feasibility and results. Ann Thorac Surg 80(6):2046–2050
108. Yamamoto R et al (2000) Effects of preoperative chemotherapy and radiation therapy on human bronchial blood flow. J Thorac Cardiovasc Surg 119(5):939–945
109. Rendina EA et al (1997) Safety and efficacy of bronchovascular reconstruction after induction chemotherapy for lung cancer. J Thorac Cardiovasc Surg 114(5):830–835; discussion 835–837
110. Mentzer SJ, Myers DW, Sugarbaker DJ (1993) Sleeve lobectomy, segmentectomy, and thoracoscopy in the management of carcinoma of the lung. Chest 103(4 Suppl):415S–417S

111. Faber LP, Jensik RJ, Kittle CF (1984) Results of sleeve lobectomy for bronchogenic carcinoma in 101 patients. Ann Thorac Surg 37(4):279–285
112. Weisel RD et al (1979) Sleeve lobectomy for carcinoma of the lung. J Thorac Cardiovasc Surg 78(6):839–849
113. Sartori F et al (1986) Sleeve lobectomy in the treatment of bronchogenic carcinoma. Int Surg 71(4):233–236
114. Brusasco V et al (1988) Lung function following upper sleeve lobectomy for bronchogenic carcinoma. Scand J Thorac Cardiovasc Surg 22(1):73–78
115. Jensik RJ et al (1972) Sleeve lobectomy for carcinoma. A ten-year experience. J Thorac Cardiovasc Surg 64(3):400–412
116. Van Schil PE et al (1991) TNM staging and long-term follow-up after sleeve resection for bronchogenic tumors. Ann Thorac Surg 52(5):1096–1101
117. Firmin RK et al (1983) Sleeve lobectomy (lobectomy and bronchoplasty) for bronchial carcinoma. Ann Thorac Surg 35(4):442–449
118. Grillo HC (2004) Surgery of the trachea and bronchi (vol xvi). BC Decker, Hamilton, 872 p
119. Hollaus PH et al (2003) Risk factors for the development of postoperative complications after bronchial sleeve resection for malignancy: a univariate and multivariate analysis. Ann Thorac Surg 75(3):966–972
120. Fadel E et al (2002) Sleeve lobectomy for bronchogenic cancers: factors affecting survival. Ann Thorac Surg 74(3):851–858; discussion 858–859
121. Tsang V, Goldstraw P (1989) Endobronchial stenting for anastomotic stenosis after sleeve resection. Ann Thorac Surg 48(4):568–571
122. Grillo HC (1982) Carinal reconstruction. Ann Thorac Surg 34(4):356–373
123. Mitchell JD et al (1999) Clinical experience with carinal resection. J Thorac Cardiovasc Surg 117(1):39–52; discussion 52–53
124. Wood DE, Vallieres E (1997) Tracheobronchial resection and reconstruction. Arch Surg 132 (8):850–854; discussion 854–856
125. Mitchell JD et al (2001) Resection for bronchogenic carcinoma involving the carina: long-term results and effect of nodal status on outcome. J Thorac Cardiovasc Surg 121 (3):465–471
126. Jensik RJ et al (1982) Survival in patients undergoing tracheal sleeve pneumonectomy for bronchogenic carcinoma. J Thorac Cardiovasc Surg 84(4):489–496
127. Tsuchiya R et al (1990) Resection of tracheal carina for lung cancer. Procedure, complications, and mortality. J Thorac Cardiovasc Surg 99(5):779–787
128. Maeda M et al (1993) Operative approaches for left-sided carinoplasty. Ann Thorac Surg 56 (3):441–445; discussion 445–446
129. Roviaro GC et al (1994) Tracheal sleeve pneumonectomy for bronchogenic carcinoma. J Thorac Cardiovasc Surg 107(1):13–18
130. Dartevelle P, Macchiarini P (1996) Carinal resection for bronchogenic cancer. Semin Thorac Cardiovasc Surg 8(4):414–425
131. Kutlu CA et al (2000) Acute lung injury and acute respiratory distress syndrome after pulmonary resection. Ann Thorac Surg 69(2):376–380
132. Mathisen DJ et al (1998) Inhaled nitric oxide for adult respiratory distress syndrome after pulmonary resection. Ann Thorac Surg 66(6):1894–1902

Treatment: Radiation Therapy

Sagus Sampath

Abstract

Radiation therapy (RT) is an integral part of treating all stages of lung cancer. Stereotactic ablative radiation therapy (SABR) has emerged as a standard treatment option for stage I–II patients with medically inoperable disease. Stage IIIA–IIIB disease is typically managed with definitive concurrent chemo-radiotherapy (CRT). Intensity modulated radiation therapy (IMRT) has enabled delivery of more potent RT dose while greatly limiting dose to surrounding normal organs, including lung, esophagus, and heart. SABR may have an expanding role in the treatment of stage IV patients, with new clinical trials exploring its combination with systemic immuotherapies.

Keywords

Radiation · Lung cancer · SABR · Stereotactic · Oligometastases · Chemoradiation

Contents

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1 Stage I–II Disease

1.1 Conventional Radiation Therapy

Prior to the advent of SABR, radiation therapy over 6–7 weeks to small tumors has yielded poor results, with local control rates in the range of 30–60 % [1, 2]. Patients were treated daily over 6–7 weeks. Doses greater than 65 Gy were associated with better local control. Possible explanations for these low local control rates include lack of soft tissue imaging for alignment during treatment, which may have resulted in under-dosing the target, as well as inadequate radiation dosing schedules.

1.2 Stereotactic Ablative Radiation Therapy

1.2.1 Technological Advancements

Advancements in radiation delivery and imaging technology have allowed for the development of stereotactic ablative radiation therapy (SABR) as an acceptable definitive treatment for early stage non-small cell lung cancer (NSCLC). The increased use of positron emission tomography/computed tomography (PET/CT) and bronchoscopy with endobronchial ultrasound for pathological nodal stage has increased the accuracy of tumor staging. This has helped select for a patient subgroup without regional nodal spread who are candidates for aggressive local therapy.

A major challenge in the treatment of lung tumors with SABR is accounting for lung tumor motion. Traditional three-dimensional CT scans capture only a limited phase of the respiratory cycle and do not provide information regarding the entire trajectory of a patient's tumor. Given this uncertainty, clinicians were obligated to add larger 'safety margins' around the gross tumor, in order to ensure that the tumor would not be missed. The introduction of four-dimensional CT (4DCT) scanners into the radiation clinic has revolutionized the treatment planning process, enabling the clinician to incorporate tumor motion data into designing the radiation field. Customized margins based on actual tumor motion data from the 4DCT are now used to generate the radiation field.

The next challenge is limiting the motion of the patient's tumor, especially in the superior–inferior dimension, in order to minimize the size of the radiation field. Tumor motion has been shown to be significantly higher when a patient is free-breathing as compared to using some form of abdominal compression device [3]. Another challenge is verifying the accuracy of patient setup during treatment. Cone-beam CT (CBCT) machines have now been integrated into the linear accelerator device as a single unit, which allows for imaging the patient's tumor prior to each delivered fraction. Once the image is obtained, software can fuse the image to the patient's original treatment planning CT to generate a set of table shifts needs to exactly align to the target. Suzuki et al. [4] have shown table shifts ranging from 3 to 12 mm were necessary to match the target when incorporating this CBCT data, which would have been missed if purely relying on bony anatomy alone. This process is known as image-guided radiation therapy or IGRT. Maintaining the same position during treatment delivery is also crucial, and therefore a tight vacuum cushion around the patient along with abdominal compression can address two sources of setup variability: the patient and the lung tumor.

1.2.2 Clinical Outcomes

Initial phase I/II SABR studies included medically inoperable patients. Patients were typically of poor performance status and had significant comorbidities. Table 1 displays recently published phase I/II trials of SABR. With approximately 3 years median follow-up, primary tumor control across studies is 80–100 % for T1 tumors.

The role of SABR in medically operable patients is an area of ongoing debate and active clinical investigation. Results from randomized trials in Japan (surgery vs. SABR) are maturing and are anticipated to be disclosed in the coming years.

Table 1 Recently published phase I/II trials of SABR

Trial	Years treated, patient number	Tumor stage (n)	Dose/fraction number	Median follow-up (months)	Local control	Overall survival
Timmerman et al. [36]	2000–2003, *N* = 37	T1: 19 T2: 18	24–60 Gy/3	15.2	87 %	1.5 yr: 64 %
Nagata et al. [37]	1998–2004, *N* = 45	T1: 32 T2 (<4 cm): 13	48 Gy/4	22–30	98 %	3 yr: T1: 83 % T2: 72 %
Lindberg et al. [38]	2003–2005, *N* = 57	T1:72 % T2:28 %	45 Gy/3	41.5	4 yr: 79 %	5 yr: 30 %
Koto et al. [39]	1998-2004, *N* = 31	T1: 19/31 T2: 12/31	45 Gy/3 for 20 patients, 60 Gy/8 for 11	32	3 yr: T1: 78 % T2: 40 %	3 yr: 72 %
Fakiris et al. [40]	2002-2004, *N* = 70	T1: 34 T2: 36	T1: 60 Gy/3 T2: 66 Gy/3 fxn	50.2	3 yr: 88 %	3 yr: 43 %

However, in the United States, it has been difficult to encourage patients to participate on a trial that randomizes them between two very different local therapies. Known as the StableMATE trial, it is now reopening with a pre-randomization schema in order to help increase accrual. As these studies reach completion, the role of SABR may be expanded to a more fit patient population.

1.3 Toxicities

Lung SABR is overall associated with very low rates of acute and late toxicity. Possible side effects include chest wall pain, rib fracture, and decline in pulmonary function tests. In the early experience with SABR, Timmerman reported an increased rate of grade 4–5 toxicities in centrally located tumors, defined as less than or equal to 2 cm from the proximal bronchial tree [5]. Lower doses per fraction were recommended as a way to lower risk for toxicities. In a large patient cohort with central tumors, overall grade 3 + toxicity was only 8 % [6]. The incidence Grade 1–2 chest wall pain was found to be associated with both moderate (30 Gy) and high (60 Gy) doses [7]. As reflected in the National Comprehensive Cancer Network (NCCN) guidelines, peripherally located tumors in close proximity to the chest wall are recommended to receive similar fractionation and doses as central tumors.

2 Stage III Disease

2.1 Technological Advancements

4DCT is now commonly used in the treatment planning phase for stage III patients. Motion data is acquired of both the primary lung tumor and mobile lymph node stations (e.g., hilar and subcarinal areas) to ensure that the entire trajectory is captured in the target. The increased certainty of tumor location has facilitated the use of tighter margins, allowing for increased sparing of normal tissues. IGRT is also incorporated in treatment in order to allow for smaller uncertainty margins.

Intensity modulated radiation therapy (IMRT) is commonly employed in the treatment of locally advanced disease, with the main benefit being lower doses to surrounding normal lung, compared to traditional three-dimensional conformal radiation therapy (3D-CRT). Clinical data show significantly lower rates of grade 3 + pneumonitis when using IMRT versus 3D-CRT, despite large tumor size in the patients treated with IMRT [8]. A population-based analysis of 7000 patients using the SEER-Medicare database demonstrated no difference in overall survival between 3D-CRT and IMRT [9]. Limitations of the study included the lack of information on total radiation dose and percentage of patients treated at higher volume academic centers. Besides sparing of regional lung, IMRT can also allow for sparing other critical organs, such as the heart and esophagus. Heart dose and esophageal toxicity were noted to be significant predictors for survival on the recently published RTOG 0617 trial [10]. Improved sparing of these structures is

only feasible with the advanced technologies like IMRT. Despite the lack of robust clinical outcome data supporting its use, the prevalence of IMRT will likely continue to increase in the treatment of NSCLC.

3 Clinical Results

3.1 Radiation Alone

In the past, conventional fractionation over 6–7 weeks with XRT alone was considered the standard treatment regimen in patients unable to tolerate surgery. Radiation Therapy Oncology Group (RTOG) 7301 compared 3 different radiation dose schedules: 40 Gy in 4 weeks, 60 Gy in 6 weeks, and a split-course regimen [11]. Two-year survival rates were 18 % in the 6-week group and 14 % in the 4-week group. At 5 years, all dose groups had uniformly poor overall survival (OS) less than 10 %. This established the standard dose of 60 Gy in 6 weeks, with local control approaching only 50 %.

To improve these outcomes, the RTOG 8311 trial was designed as a dose-escalation study, with the hypothesis that higher doses would result in improved LC and OS [12]. Patients were randomized to three groups using 1.2 Gy/fraction given twice daily: 60 total dose, 64.8, and 69.6 Gy. Two-year OS in the 69.6 Gy arm was 29 %, significantly higher than the 2 lower dose arms. This was demonstrated for the first time that more potent radiotherapy schedules can be given safely and lead to meaningful improvement in outcomes.

In addition to increasing the total radiation dose, another way to increase the potency is to the give the radiation over a shorter period of time. The European Organisation for Research and Treatment of Cancer (EORTC) conducted a phase III randomized trial comparing two different dose schedules: standard RT of 60 Gy in 6 weeks; or CHART, known as continuous hyperfractionated accelerated RT, which was 54 in 1.5 Gy given three times daily for 12 continuous days [13]. The CHART group demonstrated significantly improved local control and overall survival compared to standard RT (17% vs. 12% and 20% vs. 13 %, respectively). The survival benefit did come at a cost: approximately 50 % of the CHART group developed severe dysphagia, versus 19 % in the standard dose arm. The majority of patients on this study had squamous cell carcinoma histology.

Therefore, in poor performance status patients were unable to tolerate chemotherapy; RT alone-regimens usually consist of some form of altered fractionation, with the goal of maximizing potency while also allowing for time for normal tissue repair. Using the latest in radiation treatment technology, colleagues at MD Anderson reported on initial safety data from a proton beam dose-escalation trial starting at 45 up to 60 Gy in 3 weeks [14].

3.2 Sequential Chemotherapy Followed by Radiation

To improve outcomes in the radiation-alone patients with reasonable performance status, multiple cooperative groups embarked on studying the impact of the addition of chemotherapy to radiation in stage III disease. The Cancer and Leukemia Group B (CALGB) trial randomized 155 patients to induction chemotherapy with vinblastine/cisplatin followed by RT 60 Gy/6 weeks, versus RT alone 60 Gy/6 weeks [15]. The combined modality arm demonstrated significantly improved OS at 2 years, 26% versus 13 % ($p = 0.006$). Another phase III trial with similar design, conducted by LeChavalier et al. [16] showed a significant improvement in 3 year OS with combined modality treatment, 12% versus 4 % ($p = 0.02$). Local control at 1 year was very poor at 16 %. Finally, RTOG 8808 included 452 patients and had a three-arm randomization [17]. Arm 1 was sequential chemotherapy (cisplatin and vinblastine for 2 cycles) followed by RT 60 Gy; arm 2 was RT alone 60 Gy/6 weeks; and arm 3 was RT alone 69.6 Gy/6 weeks, given 1.2 Gy twice daily. There was a significantly improved 2-year OS in arm 1 of 32, versus 19 % in arm 2 ($p = 0.003$). Median survival was 13.2 versus 11.4 months, respectively. Patients in arm 3 had an intermediate outcome between arms 1 and 2, with a 2 year OS of 24 % ($p = 0.08$ when compared to arm 1).

Results from several meta-analyses have indicated an absolute OS benefit with the addition of chemotherapy to RT versus RT alone in locally advanced/non-metastatic patients. The non-small cell lung cancer collaborative group included 3033 patients from 22 trials using individual patient data [18]. Chemotherapy was associated with a 10 % reduction in mortality, translating to an absolute benefit of 2 % at 5 years. The most recent meta-analysis of 1764 patients conducted by Auperin et al. [19] demonstrated a 4 % absolute benefit with chemotherapy at 2 years. Only carboplatin or cisplatin-based chemotherapy studies were included. In summation, these large patient analyses clearly indicate the superiority of adding platinum-based therapy with radiation in locally advanced patients.

3.3 Sequential Versus Concurrent Chemotherapy and Radiation Therapy

With survival gains seen in patients receiving combined modality therapy, it was proposed that increasing the intensity of treatment by delivering chemotherapy concurrently with radiation may improve survival. Furuse et al. [20] from the West Japan Lung Cancer Group randomized 320 patients between sequential chemotherapy/radiation (SCR) and concurrent chemotherapy/radiation (CCR). CCR comprised of cisplatin, vindesine, and mitomycin. RT was given in a split-course fashion, with 28 Gy/14 fractions given daily with a 10 day break in between. SCR patients received the identical chemotherapy for 2 cycles, with RT starting after. Median survival was significantly improved in the CCR group, 16.5 versus 13.3 months ($p = 0.04$). Five-year survival in the CCR arm was 16%, versus 9 % in the SCR arm. There were no significant differences in the rates of pulmonary

or esophageal toxicity between the arms, although increased myelosuppression was noted in the CCR group.

In the randomized phase III trial published by Fournel et al. from the French Lung group, patients were randomized between SCR and CCR. SCR was cisplatin/vinorelbine followed by RT to 66 Gy. CCR patients received cisplatin/etoposide with RT 66 Gy. There was improved survival (16.3 vs. 14.5 months) in the CCR group, but this did not reach significance. In contrast to the Japanese trial, there was a marked increase in the rate of esophageal toxicity in the CCR arm (32 vs. 3 %).

Finally, the most recent phase III data come from the Radiation Therapy Oncology Group (RTOG) protocol 9410, which compared 3 arms. SCR to a dose of 63 Gy, CCR one fraction daily to 63 Gy, and CCR two fractions daily to 69.6 Gy. The first two groups received cisplatin/vinblastine, and third received cisplatin/vp16. The primary end point was overall survival. Median survival was the longest in the CCR once-daily arm (17 months), which was significantly higher than the SCR group (14.6 months), but not significantly different from the CCR twice-daily arm (15.6 months). Local failure was reduced in the CCR groups compared to SCR. (39 vs. 30 %). CCR patients had significantly higher incidence of acute grade 3 + esophagitis compared to SCR (only 4 %. $P < 0.001$). The rate in the twice-daily group was significantly higher than the once-daily patients (45% vs. 22 %, $P < 0.001$). However, late esophageal toxicity was similar among the arms. From the knowledge gained from RTOG 0617 regarding the impact of esophageal toxicity and survival (to be discussed), it is plausible that any potential survival advantage to be gained from more intense therapy in the twice-daily CCR group was outweighed by the increased rate of toxicity.

The above studies, in addition to several meta-analyses, have established CCR as the standard of care for locally advanced-stage IIIA/IIIB NSCLC with good performance status and <5 % weight loss. The Cochrane group showed a significant 14 % reduction in mortality risk with CCR versus SCR [21]. Finally, the NSCLC collaborative group (1,205 patients) reported an absolute survival benefit of 4.5 % at 5 years with CCR compared to SCR [22]. Local–regional failure was also significantly improved with CCR (HR 0.77, $p = 0.01$), accompanied by an increase in acute grade 3–4 esophagitis with CCR (RR 4.9, $p < 0.001$).

3.4 Radiation Dose Escalation with Concurrent Chemotherapy

The recently published RTOG 0617 trial was designed to answer two questions: (1) does higher radiation dose translate to improved survival? and (2) does the addition of concurrent cetuximab to chemotherapy improve survival? Approximately 500 analyzable patients were randomized in a 2 by 2 factorial design to 60 versus 74 Gy radiation to the lung primary and involved nodal disease. All patients received concurrent carboplatin/paclitaxel and a second randomization was chemotherapy alone or chemotherapy with cetuximab. Median overall survival in

the 74 Gy arm was 20 months, significantly inferior to the 60 Gy arm (29 months, HR 1.38, $p = 0.004$). Cetuximab-chemotherapy patients had a median OS of 25, versus 24 months in those receiving chemotherapy alone. There was a significantly higher rate of severe esophagitis in the 74 Gy arm (21% vs., 7 %, p <0.001). In fact, on multivariate analysis, only RT dose level and esophagitis grade reached significance for overall survival.

From this publication, significant controversy has arisen among lung radiation oncologists regarding the optimal dose for treatment. Post hoc analyses of radiation planning compliance and margins may help to elucidate why the higher dose arm did so poorly. Identifying the specific causes of death also would be beneficial. Further, dosimetry studies will also be required to better understand esophageal toxicity. Many ongoing clinical trials are using an intermediate dose of 66 Gy as the definitive dose.

3.5 Induction Chemotherapy Prior to Definitive Chemoradiation

With distant disease as the predominant pattern of relapse, the added benefit of induction chemotherapy was explored in the CALGB 39801 trial [23]. A total of 366 patients with unresectable IIIa/IIIb were randomized to induction carboplatin–paclitaxel for 2 cycles followed by concurrent carboplatin–paclitaxel with radiation to 66 Gy, versus the identical chemo-radiotherapy regimen alone. Median OS on the induction arm was 12 months, compared to 14 months on the concurrent chemo-XRT arm ($p = 0.3$). Survival at 2 years was 29 and 31 %, respectively. The only factors predictive for survival were weight loss prior to treatment, age, and performance status. The induction arm had similar rates of grade 3–4 esophageal (32% vs. 36 %) and pulmonary toxicity (14% vs. 19 %) as the concurrent-only arm.

In a randomized three-arm phase II trial by Belani et al., one of the arms included patients receiving induction carboplatin/paclitaxel followed by concurrent CRT to 63 Gy. This was compared to standard concurrent chemo-RT and sequential chemo-RT. With a median follow-up of 40 months, the induction arm demonstrated the poorest survival 12.7 months, although none of the arms were found to be statistically superior to each other. The induction arm was stopped early due to 20 % of patients not being able to receive chemotherapy concurrently with the radiation. Grade 3-4 esophagitis was similar between the induction and concurrent-only groups.

In phase II three-arm randomized trial conducted by Belani et al. [24], 276 unresectable IIIA/IIIB patients received either induction chemotherapy followed by 63 Gy XRT (arm 1), induction chemotherapy followed by concurrent CRT (arm 2), or concurrent CRT followed by consolidation chemotherapy (arm 3). Median OS was highest in arm at 16.3 months, although the study was not powered for individual comparisons between arms. Arms 2 and 3 had higher rates of grade 3/4 esophagitis (19 and 28 %, respectively).

3.6 Role of Consolidation Chemotherapy Following Concurrent Chemoradiation

The Hoosier Oncology Group reported results on 203 patients who were randomized between standard cisplatin/etoposide concurrent with XRT, versus the same concurrent CRT followed by 3 cycles of consolidation docetaxel [25]. The primary end point was overall survival. The study was terminated early due to an interim analysis that showed futility in the consolidation arm. Median OS was 23.2 months in the concurrent CRT alone arm and 21.2 months in the consolidation arm. Approximately 29 % of patients in the consolidation arm required hospitalization, versus 8 % in CRT alone arm, with 5.5 % grade 5 toxicity as a result of docetaxel. The conclusions made were that toxicities were increased with the addition of consolidation chemotherapy without a gain in survival.

SWOG S0023 was a phase III placebo-controlled trial examining the efficacy of adding maintenance targeted therapy following definitive chemoradiation and consolidation chemotherapy. The study closed after accruing 243 patients with stage III disease. Median survival was worse on the gefintib arm (23 vs. 35 months for placebo, $p = 0.013$). As a result, maintenance systemic therapy following chemoradiation was largely discouraged. Recently however, with the advent checkpoint-blockade inhibitors, their role as maintenance therapy is now being examined in clinical trials.

4 Stage IV Patients and Oligometastases

Historically, survival for stage IV NSCLC patients has been poor, with a median value of 6–12 months. However, the idea of 'oligometastases,' first proposed by Hellman and Weichselbaum [26], is now gaining traction in patients with NSCLC, such as thoracic radiation or SABR to further extend their progression-free survival.

4.1 Synchronous Brain Metastases

Hu and colleagues [27] from the MD Anderson Cancer Center reviewed 84 cases presenting with solitary brain metastasis, treated with stereotactic radiosurgery or neurosurgical resection. Eight patients received thoracic radiotherapy alone, 23 patients received chemotherapy alone and 13 received both. Median survival times by local thoracic stage were 25.6, 9.5, and 9.9 months, for stage I, II, and III, respectively. The authors concluded that aggressive local therapy may be justified for local stage I patients, not for locally advanced disease.

A Turkish group reported on 63 NSCLC patients who received brain-directed therapy for solitary brain metastasis, followed by thoracic radiation to 66 Gy with concurrent chemotherapy (2 cycles, cisplatin-based) [28]. With a median follow-up over 2 years, median survival was 28.6 months. Local tumor stage (T1-2 vs. T3-4) and nodal stage (N0-1 vs. N2-3) were a significant predictor for survival on

multivariable analysis. The results illustrate that there exists a select group of favorable patients with brain metastases who exhibit similar survival to stage III patients, warranting the need for aggressive treatment strategies.

Finally, a joint report by Gray et al. [29] reported similarly high median survival rates in 66 patients with 1-4 synchronous brain-only metastases. Only 7 patients had surgery has a component of their brain-directed therapy, while the remaining received a mixture of SRS alone, whole brain RT alone, or a combination of the two. Local tumor–nodal stage breakdown were as follows: 9 stage I, 10 stage II, and 47 stage III. Thoracic radiation to a dose greater than 45 Gy was given in 38 pts (five in conjunction with thoracic surgery), while 28 patients did not receive thoracic RT (17 had chemotherapy alone, 14 had thoracic surgery alone). Those receiving thoracic RT had a median OS of 26.4, versus 10.5 months in the chemotherapy alone group ($P < 0.001$). A reduction in the rate of first failure in brain was found to be significantly associated with those receiving either surgery or SRS in combination with whole brain RT. Similar to previous studies, neurological disease progression was the main factor in determining overall survival. Aggressive brain-directed therapy is considered to be crucial when evaluating the benefit of adding thoracic RT.

Overall, these series indicate better than expected outcomes in stage IV patients receiving thoracic radiotherapy. A major limitation of these studies is that molecular status information has not been uniformly available. The presence of the *epithelial-growth factor receptor (EGFR)* mutation and translocation of the *anaplastic lymphoma kinase-echinoderm microtuble ligand-4 (ALK-EML4)* chromosome translocation are now considered favorable prognostic factors with the advent of more efficacious and selectively targeted agents. Moving forward, having such data may help clinicians better select those stage IV patients who benefit the most from radiation to both local and distant disease.

4.2 SABR in Stage IV Disease

Colleagues at University of Texas Southwestern and University of Colorado published results of a phase II trial utilizing SABR to treat all sites of metastatic disease in patients with stage IV NSCLC receiving concurrent erlotinib [30]. Eligibility was limited to those six or fewer sites of extracranial disease who failed first-line systemic chemotherapy. A total of 24 patients were enrolled. Only 2 patients had previously treated brain metastases. The numbers of SABR sites treated by patient were as follows: 1 ($n = 8$), 2 ($n = 8$), 3 ($n = 5$), 4 ($n = 2$), and 5 ($n = 1$). Common fractionation schemes were 27–33 Gy/3 fractions and 35–40 Gy/5 fractions. The lung parenchyma was the most common site to be treated (35 %), followed by mediastinum/hilum (25 %), and adrenal glands (13 %). The results were promising, with a median PFS of 14.7 months and median OS of 20.4 months, both meaningfully longer than what is observed with historical results with second-line systemic therapy alone. What is remarkable is that only 3/21 patients had a local failure from SABR, and 10 patients had not progressed (both distantly and at the radiation field) at last follow-up. Molecular testing status was not provided, and therefore the

relationship between *EGFR* status and outcome is unknown. These data provide encouragement that aggressive localized therapy with SABR in selected patients with limited metastatic disease burden may translate to more protracted PFS compared to systemic therapy alone.

4.3 Future Directions

With the disappointing results of RTOG 0617, there is a resurging debate on the utility of radiation dose escalation in NSCLC. The protocols to come forward will need to more carefully study the impact of radiation on adjacent normal structures, such as esophagus and heart. Adapting the radiation treatment field midcourse during a patient's radiation treatment is being studied in the open RTOG 1106 trial. This trial incorporates data from a PET/CT acquired during treatment and calls for tailoring the treatment field to match the shrinking areas of PET avidity.

Proton beam therapy is being studied in several institutions and has the potential to deliver more favorable dose distributions to the heart, lungs, and esophagus. A recent outcome analysis with nearly five-year follow-up demonstrates comparable survival and disease-free survival compared to photon-based treatment [31].

The role of immunotherapy in the treatment of NSCLC is now beginning to gain a strong foothold with nivolumab, a programmed death receptor-1 (PD-1) inhibitor, recently receiving FDA approval for patients with squamous cell histology [32]. Recent data now show an overall survival benefit with nivolumab in non-squamous-NSCLC compared to conventional chemotherapy [33]. Therefore, nivolumab has shown to improve OS compared to conventional chemotherapy in the phase III setting for both major types of NSCLC.

There are several pre-clinical reports indicating the immunogenic potentiation from delivering higher doses of radiation in a Lewis lung cancer model, including upregulation of genes involved in antigen presentation, adhesion, and activation of innate immune system. In the report by Fotin–Mleczek et al. [34], 3 fractions of 12 Gy each resulted in increasing immune cell infiltrates, including CD4 and CD8 + T cells, CD8 + dendritic cells, and natural killer T cells. The research group of Johns Hopkins has shown in an autochthonous model that the combination of programmed death receptor ligand-1 (PDL-1) blockade with local radiation showed an abscopal effect in the contralateral non-irradiated lung [35].

These findings are now providing impetus to explore the combination of SABR with immune checkpoint blockade as a way to further provide antigen presentation and synergistically improve the efficacy of systemic therapy. There are clinical trials at New York University (NCT02221739) and MD Anderson (NCT02239900) incorporating SABR-type fractionation with the CTLA-4 inhibitor ipilimumab. Similar trials incorporating PD-1 inhibitors such as nivolumab with SABR are also on the horizon. The sequencing and timing of these targeted therapies with SABR, as well as optimal SABR dose, will require rigorous examination. Immune cytokine assays and panels may also prove useful to better understand the mechanism for a possible synergism with these two therapies.

5 Conclusions

The advent of SABR has radically and permanently altered the treatment landscape in NSCLC, especially in early stage patients who are unable to tolerate surgery. On the forefront is the role of SABR as an 'immune-potentiator' in patients receiving immunotherapies. In stage IIIA–IIIB patients, treatments have shifted from radiation alone 30 years ago to combination chemotherapy–radiation regimens. The new median survival of 29 months in the 60 Gy cohort on RTOG 0617 is now the benchmark for future comparisons, keeping in mind the highly controlled setting (90 % received PET/CT staging) and generally higher performance status patients enrolled on such studies. Despite the RTOG 0617 results, there is still impetus to improve local control outcomes with novel radiation strategies and modalities, including proton therapy. With continued advances in systemic treatments, the focus will eventually redirect to optimizing local control with radiotherapy, both in the early and in the advanced-stage setting.

References

1. Dosoretz DE et al (1992) Radiation therapy in the management of medically inoperable carcinoma of the lung: results and implications for future treatment strategies. Int J Radiat Oncol Biol Phys 24(1):3–9
2. Sibley GS et al (1998) Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys 40(1):149–154
3. Han K et al (2010) A comparison of two immobilization systems for stereotactic body radiation therapy of lung tumors. Radiother Oncol 95(1):103–108
4. Suzuki O et al (2012) Influence of rotational setup error on tumor shift in bony anatomy matching measured with pulmonary point registration in stereotactic body radiotherapy for early lung cancer. Jpn J Clin Oncol 42(12):1181–1186
5. Timmerman R et al (2006) Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 24(30):4833–4839
6. Modh A et al (2014) Local control and toxicity in a large cohort of central lung tumors treated with stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 90(5):1168–1176
7. Stephans KL et al (2012) Prediction of chest wall toxicity from lung stereotactic body radiotherapy (SBRT). Int J Radiat Oncol Biol Phys 82(2):974–980
8. Yom SS et al (2007) Initial evaluation of treatment-related pneumonitis in advanced-stage non-small-cell lung cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 68(1):94–102
9. Chen AB et al (2014) Comparative effectiveness of intensity-modulated versus 3D conformal radiation therapy among medicare patients with stage III lung cancer. J Thorac Oncol 9 (12):1788–1795
10. Bradley JD et al (2015) Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 16(2):187–199
11. Perez CA et al (1980) A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the radiation therapy oncology group. Cancer 45(11):2744–2753

12. Cox JD et al (1990) A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with radiation therapy oncology group stage iii non-small-cell lung carcinoma: report of radiation therapy oncology group 83-11. J Clin Oncol 8(9):1543–1555
13. Saunders M et al (1999) Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART steering committee. Radiother Oncol 52(2):137–148
14. Gomez DR et al (2013) Phase 1 study of dose escalation in hypofractionated proton beam therapy for non-small cell lung cancer. Int J Radiat Oncol Biol Phys 86(4):665–670
15. Dillman RO et al (1996) Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst 88 (17):1210–1215
16. Le Chevalier T et al (1994) Radiotherapy alone versus combined chemotherapy and radiotherapy in unresectable non-small cell lung carcinoma. Lung Cancer 10(Suppl 1):239–244
17. Sause W et al (2000) Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: radiation therapy oncology group, eastern cooperative oncology group, and southwest oncology group. Chest 117(2):358–364
18. BMJ (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small cell lung cancer collaborative group. 311(7010):899–909
19. Auperin A et al (2006) Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. Ann Oncol 17(3):473–483
20. Furuse K et al (1999) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 17(9):2692–2699
21. Rowell NP O'Rourke NP (2004) Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev (4):CD002140
22. Auperin A et al (2010) Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 28(13):2181–2190
23. Vokes EE et al (2007) Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: cancer and leukemia group B. J Clin Oncol 25(13):1698–1704
24. Belani CP et al (2005) Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol 23(25):5883–5891
25. Hanna N et al (2008) Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the hoosier oncology group and U.S. oncology. J Clin Oncol 26(35):5755–5760
26. Hellman S, Weichselbaum RR (1995) Oligometastases. J Clin Oncol 13(1):8–10
27. Hu C et al (2006) Nonsmall cell lung cancer presenting with synchronous solitary brain metastasis. Cancer 106(9):1998–2004
28. Parlak C et al (2014) Definitive chemoradiation therapy following surgical resection or radiosurgery plus whole-brain radiation therapy in non-small cell lung cancer patients with synchronous solitary brain metastasis: a curative approach. Int J Radiat Oncol Biol Phys 88 (4):885–891
29. Gray PJ et al (2014) Aggressive therapy for patients with non-small cell lung carcinoma and synchronous brain-only oligometastatic disease is associated with long-term survival. Lung Cancer 85(2):239–244

30. Iyengar P et al (2014) Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. J Clin Oncol 32(34):3824–3830
31. Nguyen QN et al (2015) Long-term outcomes after proton therapy, with concurrent chemotherapy, for stage II-III inoperable non-small cell lung cancer. Radiother Oncol
32. Brahmer J et al (2015) Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 373(2):123–135
33. Paz Ares L (2015) Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). J Clinical Oncol 33: Abstr LBA 109
34. Fotin-Mleczek M et al (2014) mRNA-based vaccines synergize with radiation therapy to eradicate established tumors. Radiat Oncol 9:180
35. Sharabi AB et al (2015) Stereotactic radiation therapy combined with immunotherapy: augmenting the role of radiation in local and systemic treatment. Oncology (Williston Park) 29 (5)
36. Timmerman R et al (2003) Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 124(5):1946–1955
37. Nagata Y et al (2005) Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys 63(5):1427–1431
38. Lindberg K et al (2015) Long-term results of a prospective phase II trial of medically inoperable stage I NSCLC treated with SBRT—the Nordic experience. Acta Oncol 1-9
39. Koto M et al (2007) A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer. Radiother Oncol 85(3):429–434
40. Fakiris AJ et al (2009) Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 75 (3):677–682

Chemotherapy for Advanced Non-small Cell Lung Cancer

Martin F. Dietrich and David E. Gerber

Abstract

Non-small cell lung cancer has seen an unprecedented augmentation of therapeutic options over the last couple of years. Improved understanding of molecular drivers and the role of the immune system in cancer therapy have brought new drugs to the armamentarium. Despite these advances, cytotoxic chemotherapy remains a substantial part of therapy for most patients in locally advanced and metastatic stage. Initially thought to be a chemotherapy-resistant entity, meta-analyses in the mid-1990s demonstrated modest efficacy of platinum-based therapy. Further combination trials demonstrated enhanced efficacy for several regimen in first and second lines, including the introduction of antimetabolites, taxanes, and anti-angiogenic agents. Maintenance chemotherapy has been another novel, successful approach for management of metastatic disease. Herein, we summarize the current concepts of chemotherapy, its applicability to the different histologies, and novel concepts of therapy.

Keywords

Chemotherapy · Non-small cell lung cancer · Advanced/metastatic disease

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Contents

1 Introduction

Based on the preponderance of advanced-stage diagnoses, it would be assumed that chemotherapy would be a long-standing mainstay of treatment for non-small cell lung cancer (NSCLC). Over 30 % of NSCLC cases are diagnosed as stage 4 disease, and a substantial proportion of early stage cases will eventually develop metastatic recurrence within 5 years of initial diagnosis (24 % in stage I, 84 % in stage III) [1]. However, it is only within the past 20 years that chemotherapy has been shown to have clear clinical benefits and seen widespread uptake for advanced NSCLC. Early clinical trials of alkylating agents and vinca alkaloids did not demonstrate a survival advantage over supportive care alone [2]. Toxicities were substantial, particularly given that the average age at diagnosis is 70 years [3]. Many patients felt the perceived hardships of treatment outweighing the perceived modest benefit of chemotherapy [4]. General physicians often had a nihilistic view of metastatic lung cancer, referring patients to medical oncologists less frequently than they did patients with other oncologic diagnoses such as advanced breast cancer [5]. As a result of these and other factors, historically fewer than 50 % of individuals with advanced NSCLC were treated with chemotherapy [6–9].

Although often overshadowed by advances in molecularly targeted therapies and more recently the advent of immunotherapy, there has also been considerable progress regarding conventional chemotherapy over the past two decades. In the mid-1990s, evidence emerged that platinum-based doublet regimens not only prolonged survival compared to supportive care, but also improved quality of life [2]. Since that time, a number of new cytotoxic agents featuring either improved efficacy, better tolerability, or both have emerged [10, 11]. Progress in supportive care, most notably antiemetic drugs, has substantially improved the patient treatment experience [12, 13]. These developments have led to prolongation of treatment regimens, with an associated survival benefit [14]. The addition of anti-angiogenic agents to existing chemotherapy regimens has modestly improved outcomes [15, 16]. For a minority of chemotherapy regimens, the recognition of specific patient populations that derive particular benefit has improved cost-effectiveness [17–19]. Reflecting this progress and perhaps changing societal views on lung cancer, contemporary patients with advanced NSCLC appear far more willing than their predecessors to consider undergoing treatment [20, 21].

For the foreseeable future, it is expected that chemotherapy will remain a treatment modality for the majority of individuals with advanced NSCLC. Most NSCLC cases do not have identified driver genomic alterations, so are not candidates for treatment with small molecule kinase inhibitors. For those cases treated with molecularly targeted agents, resistance generally develops within several months [22, 23]. Chemotherapy represents an important therapeutic option for both populations. This chapter will review contemporary chemotherapy regimens for advanced NSCLC, including discussion of mechanism, efficacy, toxicity, biomarkers, and other aspects of treatment delivery such as patient age and functional status.

2 First-Line Chemotherapy

The principal goals of chemotherapy in the advanced or metastatic NSCLC setting are survival improvement and symptom palliation. Platinum-based doublet chemotherapy remains the backbone of treatment for most cases. In an updated meta-analysis, cisplatin was associated with a modest improvement in survival [2]. A separate study identified cisplatin use as an independent predictor of improved outcomes [24]. Another meta-analysis demonstrated an odds ratio of survival of 0.44 in favor of chemotherapy, with an increase in median overall survival from 3.9 to 6.7 months [25].

2.1 Selection of Platinum Analog: Cisplatin Versus Carboplatin

Platinum analogs represent their own category of chemotherapy agents. These drugs form DNA adducts, resulting in double strand breaks and activation of apoptosis, through both p53-dependent and p53-independent pathways. The establishment of cisplatin as the backbone drug for advanced NSCLC regimens raised concerns about toxicity rates and severity in the non-curative setting, particularly nausea/vomiting, ototoxicity, and nephrotoxicity. Carboplatin presents a less toxic option. Chemically, carboplatin carries a bidentate dicarboxylate group, which leads to exchange of its ligand from two chloride groups to cyclobutane dicarboxylic acid (CBDCA). The DNA-binding reactivity of carboplatin is substantially lower than that of cisplatin, which likely accounts for the differences in tolerability and efficacy [26, 27]. In meta-analysis evaluating first-line chemotherapy, cisplatin was found to have a higher response rate (30 vs. 24 %) and improved median overall survival in squamous histology, but also had a less favorable toxicity profile [28]. Another study demonstrated higher response rates with cisplatin but no difference in overall survival (RR, 1.00; 95 % CI, 0.94–1.07; $p = 0.93$) [29]. Many thoracic oncologists have interpreted the ECOG E1594 trial (in which three cisplatin-based regimens had similar overall survival as carboplatin–paclitaxel) [30] as support for the use of carboplatin in the advanced disease setting. Given the equivalent survival, carboplatin has since routinely been the preferred agent of choice in metastatic non-small cell lung cancer in Western countries due its superior side effect profile compared to cisplatin-based regimens. In selected patients with symptomatic disease, cisplatin may be preferred due to its superior response rate. By contrast, in early stage non-small cell lung cancer, where patients are treated with curative intent, cisplatin has generally remained the drug of choice. In recent years, improvements in supportive care regimens—including neurokinin 1 antagonists, 5-hydroxytryptamine antagonists and myeloid growth factors—have improved the toxicity profiles of both agents [12, 13].

2.2 Dosing of Platinum

Cisplatin is routinely given based on body surface area with dose adjustments or consideration of alternative agents required for glomerular filtration rates (GFR) less than 60 milliliters per minute (mL/min). The half-life of cisplatin is significantly prolonged in renal impairment, increasing from 2 to 6 h with normal renal function to 18–24 h with moderate renal impairment. An increase in side effects with renal impairment has been well documented. For carboplatin, the target area under curve (AUC) ranges from 2 to 7, with most palliative regimens in the metastatic setting favoring an AUC of 5 or 6. The standard formula for calculating the appropriate carboplatin dose is the Calvert Formula (Total Carboplatin Dose = Target AUC × (GFR + 25)). Long-standing controversy has accompanied the exact determination of the appropriate carboplatin dose. Most institutions base the GFR on the Cockroft-Gault formula based on the measured blood level of creatinine. Several issues to contribute to inappropriate dosing have been identified, including individual assay and inter-laboratory variation. Physiologically, creatinine is a product of muscle metabolism. Its level is therefore influenced by the patient's existing muscle mass, nutrition, weight, and activity level. Thus, it is often recommended to utilize a minimum creatinine value of 0.6 mg/dL (or maximum GFR of 125 mL/min) to avoid overestimation of creatinine clearance. More accurate measurements may be obtained through 24-h urine collections, although these assessments are prone to over- or under-collection [31]. Infusional surrogate markers such as inulin, are considered more accurate but are not routinely available in clinical practice.

2.3 Platinum Doublet Chemotherapy

Depending on performance status, histology, treatment preference, and clinical experience, the combination of cisplatin or carboplatin with paclitaxel, docetaxel, gemcitabine, pemetrexed, or vinorelbine ("platinum doublet") is the standard preferred regimen for first-line treatment of advanced NSCLC. Individually, these drugs have demonstrated clinical benefit, and a number are routinely employed as monotherapy in later lines of treatment [18, 32, 33]. In some instances, monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) or the vascular endothelial growth factor (VEGF) axis may be added to this backbone (see Sect. 8). With the exception of the histology-specific effects of pemetrexed, any differences in efficacy among these agents appear to be of little significance. Accordingly, treatment selection is frequently based on toxicity profile, schedule, and other practical considerations.

3 Taxanes

3.1 Paclitaxel

Paclitaxel is a derivative from the western yew tree, *Taxus brevifolia*. Paclitaxel interrupts cell cycle progression through enhancement of tubulin assembly into microtubules, inhibiting depolymerization of microtubules. In proliferating cells, this interference results in p53-independent cell death during the M phase of the mitotic cycle. Paclitaxel was one of the first agents to demonstrate superior outcomes compared to best supportive care in advanced NSCLC [34, 35]. It was subsequently combined with cisplatin in a three-arm ECOG study that compared high- and low-dose paclitaxel (250 and 135 mg/m^2, respectively) combinations with standard cisplatin/etoposide [36]. Due to lack of statistical significance, the study was retrospectively analyzed by combining the two paclitaxel arms. Median survival was also improved in the paclitaxel arms versus the etoposide arm (9.9 vs. 7.6 months, $p = 0.048$). Subsequently, cisplatin–paclitaxel was adopted by ECOG as the reference regimen for future trials. In a European study, the addition of paclitaxel to cisplatin failed to prolong survival compared to cisplatin alone (9.9 vs. 9.7 months, $p = 0.973$); however, a higher response rate (26 vs. 17 %; $p = 0.028$) was reported with combination therapy [37].

Two prospective randomized phase 3 trials, ECOG1594 [30] and SWOG 9509 [38], evaluated the efficacy and tolerability of several cisplatin-based combinations with paclitaxel, docetaxel, and gemcitabine against paclitaxel–carboplatin. Both trials found equivalent efficacy with favorable toxicity profile and tolerance in the paclitaxel–carboplatin arm. These findings led to paclitaxel–carboplatin becoming one of the most widely used regimens in NSCLC.

3.2 Nanoparticle Albumin-Bound (Nab)-Paclitaxel

Allergic reactions are an infrequent but potentially severe side effect of solvent (cremophor) based (sb)-paclitaxel that require prophylactic steroid and antihistamine administration. Nanoparticle albumin-bound paclitaxel is a bio-identical version of paclitaxel. However, due to its composition, it is soluble in sodium chloride. With no cremophor component, there is no requirement for prophylactic steroid or antihistamine dosing. In direct comparison in the first-line setting, carboplatin plus nab-paclitaxel achieved a higher response rate than did carboplatin plus sb-paclitaxel (33 vs. 25 %; 95 % CI 1.082–1.593, $p = 0.005$), with particular benefit in squamous histology (41 vs. 24 %; 95 % CI 1.271–2.221; $p < 0.001$) [10]. There was a numerical but nonsignificant improvement in progression-free (6.3 vs. 5.8 months; $p = 0.214$) and overall survival (12.1 vs. 11.2 months; $p = 0.271$). Lower rates of grade ≥3 neuropathy, neutropenia, arthralgia, and myalgia were reported in the nab-paclitaxel arm. In the solvent-based paclitaxel arm, less grade 3 thrombocytopenia and anemia occurred. Criticism of the study design was based on

different dosing schedules, with solvent-based paclitaxel given once every 3 weeks at 200 mg/m^2, while nab-paclitaxel was given at 100 mg/m^2 weekly for on days 1, 8, and 15 of each cycle.

Factors impacting the choice between sb- and nab-paclitaxel include patient preference, feasibility of accommodating the different dosing schemes, comorbidities—in particular diabetes mellitus (potentially exacerbated by high-dose steroid administration) and preexisting neuropathy—and cost.

3.3 Docetaxel

Docetaxel is derived from the European yew tree, *Taxus baccata*. Docetaxel has been extensively evaluated in the first- and setting-line treatment settings of advanced NSCLC. In the first-line setting, single-agent response rates range from 18 to 38 % with a median survival of 6–11 months [39, 40]. The response rates and 1-year survival rates were generally higher in combination with cisplatin (33–39 % and 33–35 %, respectively). In a Japanese phase 3 trial, the combination of docetaxel with cisplatin achieved higher response rates (37 vs. 21 %, $p < 0.01$) and improved median overall survival (11.4 vs. 9.6 months, $p = 0.014$) and 1-year survival (48 vs. 41 %, $p = 0.014$) compared to docetaxel monotherapy [41]. In a direct head-to-head comparison, cisplatin–docetaxel was found to have a comparable response rate (17 vs. 17 %, p=0.001) and overall survival to paclitaxel–carboplatin, with significantly higher rates of myelosuppression [30]. Docetaxel is thus frequently given as single-agent therapy in the second-line setting. Of note, despite similar biologic mechanisms of actions, there does not appears to be meaningful overlap with efficacy if paclitaxel has been given in first line, and no significant development of cross-resistance in taxanes can be detected when given in sequential lines of therapy. Sequential treatment with paclitaxel-containing platinum doublet followed by docetaxel is one of the most frequent treatment algorithms currently used in clinical practice. Due to potential allergic reactions related to the Tween 20 solvent and risk of peripheral edema, dexamethasone is administered the day before, day of, and day after docetaxel.

4 Antimetabolites

4.1 Gemcitabine

Gemcitabine is a pyrimidine analog in which the hydrogen atoms at 2′ are replaced by fluorine atoms. It competitively integrates into replicating deoxyribonucleic acid (DNA) strands and causes single-strand breaks by outcompeting cytidine during the S phase of cell cycle replication. Through the same active site, it binds ribonucleotide reductase (RNR) irreversibly, which leads to reduced levels of deoxyribonucleotides that are required for DNA replication and repair. The inhibition of RNA synthesis results in cell cycle-independent apoptosis. Gemcitabine was

initially introduced in clinical practice for the treatment of pancreatic cancer as a potent analog to 5-fluorouracil. Due to its tolerable side effect profile, gemcitabine was then evaluated in NSCLC, both as single-agent therapy and in combination with cisplatin. The addition of gemcitabine (1000 mg/m^2 on D1, 8, and 15 every 28 days) to cisplatin (100 mg/m^2 on D1) led to significant improvement in response rates, median, and 1-year survival (30 vs. 11 %; 9.1 vs. 7.6 months; and 39 vs. 28 %) [42]. In a Spanish study, investigators compared gemcitabine–cisplatin to etoposide–cisplatin [43]. The overall response rates were better in the gemcitabine-containing arm (41 vs. 22 %) with a nonsignificant trend toward improved median survival and 1-year survival. Three additional phase 3 studies demonstrated a modest overall survival advantage for gemcitabine-based platinum doublets compared to cisplatin monotherapy [44, 45]. This trend was confirmed in a meta-analysis evaluating 13 trials involving 4500 patients. The gemcitabine–platinum doublets had a small but statistically significant improvement in 1-year survival from 35 to 39 % (HR. 0.88; CI: 0.82–0.93; $p < 0.01$), supporting gemcitabine as a reasonable addition to platinum.

4.2 Pemetrexed

Pemetrexed is a folate antagonist and chemically related to methotrexate. It is a widely utilized agent in metastatic non-squamous NSCLC in first-line platinum doublet regimens and as single-agent maintenance and second-line therapy. Given its mechanism of action, it is coadministered with folate and cyanocobalamin (vitamin B12), which decreases the rates of hematologic and gastrointestinal toxicities without reducing efficacy [46]. Similar to docetaxel, due to the frequent development of peripheral edema arising from increased vascular permeability, dexamethasone is added the day before, day of, and day after chemotherapy. Several trials established pemetrexed as combination partner for a platinum in first-line metastatic NSCLC. Scagliotti et al. [47] compared cisplatin/pemetrexed to cisplatin/gemcitabine and found equal median survival (10.3 vs. 10.3 months, HR = 0.94, 95 % CI, 0.84–1.05). The same study also established the histology-specific efficacy of pemetrexed. Specifically, this trial and multiple other studies have demonstrated improved efficacy of pemetrexed in non-squamous NSCLC [11], an observation that may reflect higher levels of thymydilate synthase (TS) in squamous tumors [48]. Importantly, "non-squamous" includes large cell histology in addition to adenocarcinoma, and multiple studies have shown particular benefit in this rare subtype. Finally, pemetrexed is indicated only for patients with creatinine clearance >45 mL/min. Among patients with advanced NSCLC, it is estimated that over 10 % of patients will develop creatinine clearance less than this threshold during the course of their disease, with more than one-third of these individuals having no documented recovery [49]. With established indications in first-line, second-line, and maintenance therapy, along with convenient administration (10-min infusion) and a favorable toxicity profile, pemetrexed is currently one of the most frequently used agents for the treatment of non-squamous NSCLC.

Due to chemical similarities with methotrexate, initially there were concerns about the influence of third-space fluid collections such as pleural effusions (a frequent occurrence in advanced NSCLC) on pemetrexed pharmacokinetic properties. In the presence of third-space fluid collections, methotrexate clearance is substantially delayed, resulting in a marked increase in hematologic and hepatic toxicities [50]. This concern was prospectively addressed in a clinical study of pemetrexed enrolling patients with either advanced NSCLC or mesothelioma who had clinically detectable and stable-appearing pleural or peritoneal effusions [51]. Pharmacokinetics and toxicities were compared to a matched group of patients without third-space fluid collections. The presence of effusions did not affect plasma pemetrexed concentrations or hematologic or other toxicities. Based on this trial and vast clinical experience with pemetrexed, it has become common clinical practice—in contrast to methotrexate—not to drain third-space fluid collections prior to pemetrexed administration. The US FDA package insert for pemetrexed labels the effect of present fluid collections as unknown due to lack of systematic, prospective studies.

5 Vinca Alkaloids

5.1 Vinorelbine

Vinorelbine, a semi-synthetic vinca-alkaloid, has been shown to have activity in both single-agent and combination settings for NSCLC. In an initial monotherapy trial (ELVIS), vinorelbine was compared to best supportive care in a geriatric study with enrollment of patients older than 70 years [52]. A median survival improvement from 21 to 28 weeks ($p < 0.001$) was noted with the administration of vinorelbine, and one-year survival improved from 14 to 32 % ($p = 0.04$). The SWOG 9308 trial demonstrated the efficacy of adding vinorelbine to cisplatin, which improved both radiographic response rate and overall survival [53]. Specifically, 1-year survival was 36 % in the combination arm and 20 % in the cisplatin only arm (Table 1).

Table 1 Summary of phase 3 trials comparing platinum-based doublets

Trial	Regimen	Response rate (%)	Progression-free survival (months)	Overall survival (months)	Statistics
Schiller [30] ECOG 1594	Cisplatin–paclitaxel cisplatin–gemcitabine cisplatin–docetaxel carboplatin–paclitaxel	21 22 17 17	3.4 4.2 3.7 3.1	7.8 8.1 7.4 8.1	Not significant
Van Meerbeeck [54] EORTC	Cisplatin–paclitaxel cisplatin–gemcitabine	31 36	NA NA	8.1 8.8	Not significant

(continued)

Table 1 (continued)

Trial	Regimen	Response rate (%)	Progression-free survival (months)	Overall survival (months)	Statistics
Kelly [38] SWOG 9509	Cisplatin–vinorelbine carboplatin–paclitaxel	28 25	4 4	8 8	Not significant
Scagliotti [55]	Cisplatin–paclitaxel carboplatin–paclitaxel cisplatin–vinorelbine	30 32 30	5.3 5.5 4.6	9.8 9.9 9.5	Not significant
Scagliotti [47]	Cisplatin–pemetrexed cisplatin–gemcitabine	30.6 28.2	4.8 5.1	10.3 10.3	
Socinski [10]	Carboplatin–paclitaxel carboplatin–nab-paclitaxel	25 33	5.8 6.3	11.2 12.1	

6 Platinum-Based Triplet Therapy

Several trials have been conducted to investigate the efficacy of triplet regimens with a platinum backbone. The overall trend in these studies was the demonstration of an increased frequency of hematologic and non-hematologic side effects without improvement of overall survival, although higher response rates have been reported in some studies [56–58]. Notably, two Italian studies have demonstrated improved survival with three-drug combinations. In a phase 3 trial of the Southern Italy Cooperative Oncology Group, the regimen of cisplatin–gemcitabine–vinorelbine was compared to cisplatin–gemcitabine or cisplatin–vinorelbine [56]. Response rates were 47, 30, and 25 %, respectively. One-year survival rates were 45, 40, and 34 % respectively ($p < 0.01$). Another phase 3 trial by the same group evaluated cisplatin–gemcitabine with or without vinorelbine or paclitaxel [57]. Median survival was 51 weeks for both triplet combinations, compared to 38 weeks for cisplatin–gemcitabine ($P < 0.05$ for both comparisons). Nevertheless, other studies have been unable to reproduce these improved outcomes, or even had inferior outcomes with triple therapy [59]. Given the well-documented increase in toxicity associated with the addition of a third chemotherapeutic agent, triple cytotoxic therapy is not routinely recommended for the treatment of advanced NSCLC.

7 Addition of Targeted Therapies to Chemotherapy

The strategy of combining conventional chemotherapy with molecularly targeted therapeutic agents has been investigated in dozens of NSCLC clinical trials. Underpinning these efforts were strong preclinical data, potential for synergistic efficacy, and nonoverlapping toxicities. Drug classes explored in these novel combinations include matrix metalloproteinase inhibitors [60], poly ADP ribose

polymerase (PARP) inhibitors [61], histone deacetylase (HDAC) inhibitors [62], EGFR inhibitors, anti-angiogenic agents, insulin growth factor (IGF) [63], and heat shock protein (HSP)-90 inhibitors [64], among others. Despite the promise of this approach, most trials failed to demonstrate improved clinical outcomes. To date, drugs targeting the VEGF-VEGFR axis and drugs targeting EGFR have shown the greatest promise in such combinations.

8 Monoclonal Antibodies in NSCLC Therapy

8.1 Antiangiogenic Agents

Neo-angiogenesis has been a long documented requirement for local tumor growth, invasion and enhanced metastatic potential [65]. On a cellular level, the principal molecular driver of this process is vascular endothelial growth factor (VEGF), which exerts growth propagating effects on existing and developing vasculature. VEGF is a direct transcriptional target of the hypoxia-inducible factors and is tightly regulated via multiple oncogenic pathways [66–68]. It therefore presented itself as a promising target for cancer therapy.

8.2 Addition of Anti-angiogenic Therapy in First Line

The monoclonal antibody bevacizumab, a humanized IgG1 antibody targeting VEGF-A, was the first phase 3 trial in advanced NSCLC to demonstrate improved survival outcomes with the addition of a biologic agent to chemotherapy. In an initial phase 2 study enrolling 99 unselected patients with metastatic lung cancer, the addition of bevacizumab to carboplatin–paclitaxel compared to carboplatin–paclitaxel alone demonstrated a near doubling of response rate (31.5 vs. 18.8 %), improved PFS (7.4 vs. 4.2 months, $p = 0.023$), and a nonsignificant increase in overall survival (17.7 vs. 14.9 months, $p = 0.63$) [69]. The main complication of anti-VEGF therapy was major bleeding events (specifically hemoptysis), which occurred in 9 % of patients and resulted in 4 deaths. Tumor necrosis, squamous cell histology, cavitation, and central location were identified as major risk factors. Therefore, squamous cell histology was excluded from subsequent trials of bevacizumab due to safety concerns. Other mechanism-related side effects included gastrointestinal perforation, delayed wound healing, proteinuria, and hypertension.

The ECOG E4599 phase 3 trial confirmed the benefit of adding bevacizumab to carboplatin-based chemotherapy. In this trial, carboplatin–paclitaxel was compared to carboplatin–paclitaxel plus bevacizumab 15 mg/kg every 3 weeks [15]. Chemotherapy was administered for a maximum of 6 cycles in patients with disease control and acceptable toxicities, while bevacizumab monotherapy was continued until disease progression. Median survival was 12.3 months with the addition of bevacizumab, compared to 10.3 months in the chemotherapy-alone group (hazard ratio 0.79; $p = 0.003$). The median progression-free survival and response rates

were also improved: 6.2 versus 4.5 months (HR 0.66, $p < 0.001$) and 35 versus 15 % ($p < 0.001$) with the addition of bevacizumab. Five treatment-related pulmonary hemorrhages were reported in the bevacizumab arm. These results led to US FDA approval for the combination of carboplatin–paclitaxel plus bevacizumab. The European AVAiL trail evaluated the effects of bevacizumab added to cisplatin–gemcitabine chemotherapy [70]. The trial design included a placebo group and two investigational arms with bevacizumab at either low dose (7.5 mg/kg) or high dose (15 mg/kg) given every three weeks with chemotherapy. The results demonstrated improved response rates (34 % (low) vs. 30 % (high) vs. 20 % (placebo); $p = 0.03$). However, the addition of bevacizumab only modestly improved progression-free survival (13.6 (low) vs. 13.4 (high) and 13.1 (placebo) months, $p = 0.03$) and did not improve overall survival. It is noteworthy that the results between the FDA-approved dose of 15 mg/kg and the lower dose of 7.5 mg/kg did not differ significantly with regard to response rate, progression-free survival, or experienced side effects, although the trial was not prospectively powered to compare these two arms.

Given the relatively modest clinical benefit of bevacizumab, the potential for additional toxicities, and the substantial costs of this therapy, much effort has been directed toward identifying biomarkers predictive of efficacy. In an analysis of multiple cytokines and circulating angiogenic factors, baseline and dynamic changes in intracellular adhesion molecule (ICAM) were associated with bevacizumab benefit with improved response rates (32 vs. 14 %, $p = 0.02$) and 1 year-survival (65 vs. 25 %) [71]. Additionally, the development of treatment-emergent hypertension is associated with clinical benefit [72]. Although bevacizumab remains a key component of first-line treatment of advanced non-squamous NSCLC, to date there are no pretreatment biomarkers routinely employed to select patients for this treatment strategy.

Further complicating considerations of incorporating anti-angiogenic therapies in first-line treatment regimens are pivotal clinical trials with negative, and perhaps detrimental, outcomes. Scagliotti et al. conducted a randomized placebo-controlled phase 3 trial of carboplatin–paclitaxel ± the multi-kinase inhibitor sorafenib. The study was terminated prematurely after no expected benefit was predicted after the first interim analysis (OS 10.7 months in sorafenib arm vs. 10.6 months in placebo arm, HR = 1.15; $p = 0.915$). In a prespecified analysis, patients with squamous cell histology had greater mortality in the sorafenib arm (HR = 1.85; 95 % CI, 1.22–2.81), which did not necessarily appear to reflect heightened toxicities.

8.3 Role of Anti-angiogenic Agents in Second-Line Therapy

Given the apparent clinical benefit of bevacizumab as a component of first-line treatment for advanced NSCLC, as well as analyses in other malignancies suggesting that continued anti-angiogenic therapy after disease progression may provide additional benefit [73], a number of trials have examined the role of anti-angiogenic therapy in second-line treatment regimens. The phase 3 REVEL

trial compared docetaxel monotherapy to docetaxel plus the anti-VEGF receptor 2 (VEGFR2) monoclonal antibody ramucirumab [16]. VEGFR2 is primarily expressed on the surface of endothelial cells and is the corresponding binding partner to VEGF. Modest improvements in overall survival (10.5 vs. 9.1 months; HR = 0.86, $p = 0.023$) and progression-free survival (4.5 vs. 3.0 months; HR = 0.76, $p < 0.001$) were reported. Hematologic side effects were comparable and generally in line with expected toxicities from docetaxel. There was an increased rate of minor bleeding (epistaxis, wound healing) and hypertension with the addition of ramucirumab, but no significant difference in life-threatening pulmonary hemorrhage events or gastrointestinal perforations was reported. Importantly, unlike phase 3 trials of bevacizumab, the trial enrolled patients with squamous NSCLC (26 % of the trial population). This subset of patients appeared to have efficacy and toxicity rates similar to non-squamous cases. Whether the apparent safety in squamous populations in this trial reflects inherent differences in therapeutic agent (anti-VEGFR2 rather than anti-VEGF) or a pretreated clinical state (second-line study versus first-line bevacizumab trials) or other factors is not clear. Currently, the combination of docetaxel plus ramucirumab is US FDA-approved for treatment of previously treated advanced NSCLC of any histology.

Another anti-angiogenic agent with potential activity in advanced NSCLC is the multi-targeted angiokinase inhibitor nintedanib. This oral agent is administered on a daily basis and provides relatively balanced inhibition of the VEGF receptor, platelet-derived growth factor (PDGF) receptor, and fibroblast growth factor (FGF) receptor kinases. In the international LUME-Lung 1 study involving 27 countries, 655 patients were randomly assigned to receive docetaxel plus nintedanib and 659 to receive docetaxel plus placebo [74]. Patients were eligible to enroll after progression on first-line therapy. Patients were randomly assigned to receive docetaxel at 75 mg/m^2 every three weeks plus oral nintedanib at 200 mg twice daily on days 2–21 or docetaxel plus corresponding placebo. In this study, median progression-free survival was improved in the combination arm (3.4 vs. 2.7 months; HR 0.79 995 % CI 0.68–0.92), $p = 0.0019$). Among patients who progressed within 9 months of first-line therapy with adenocarcinoma histology, overall survival was significantly improved in the combination arm (median 10.9 vs. 7.9 months, HR 0.75 [95 % CI 0.60–0.92], $p = 0.0073$). Grade 3 side effects more commonly observed in the docetaxel–nintedanib combination arm were diarrhea (6.6 vs 2.6 %), reversible increases in alanine aminotransferase (7.8 vs. 0.9 %), and reversible increases in aspartate aminotransferase (3.4 vs. 0.5 %). Based on these results, the National Institute of Health and Care Excellence (NICE) in Great Britain issued a recommendation to the National Health Services (NHS) to approve nintedanib in combination with docetaxel for second-line NSCLC (26209505). The drug is currently not approved by the FDA and other licensing authorities.

9 Antibodies Targeting the Epidermal Growth Factor Receptor (EGFR)

EGFR is overexpressed in up to 85 % of NSCLC cases [75]. This upregulation is independent of activating mutations in exons 19 and 21. Targeting the EGFR receptor via monoclonal antibody blockade has been a successful concept in head and neck and colorectal carcinomas. Two mechanisms are thought to be central to this anti-tumor effect: (1) prevention of dimerization and subsequent intracellular kinase activation leading to proliferation; (2) immune-mediated antibody-dependent cell-mediated cytotoxicity (ADCC). Initial promising data suggesting a clinical benefit with the addition of cetuximab to chemotherapy came from the Lung Cancer Cetuximab Study (LUCAS). The overall response rate in this trial improved from 35 to 28 %. This led to the First-Line Erbitux in Lung Cancer (FLEX) landmark phase 3 trial [76]. In this trial, the addition of cetuximab to cisplatin–vinorelbine modestly but significantly improved overall survival (median 11.3 vs. 10.1 months; HR: 0.871, $p = 0.044$). There was no significant difference in progression-free survival (4.8 vs. 4.8 months; HR: 0.943, $p = 0.039$). Early onset acneiform rash of any grade was associated with improved median survival (15.0 vs. 8.8 months (HR: 0.63, $p < 0.001$). In a retrospective analysis, clinical benefit appeared limited to the subset of patients with tumors having high EGFR expression (defined as immunohistochemical *H* score ≥200): median OS 12.0 versus 9.6 months; HR 0.73, $p = 0.011$). The low expression group (defined as immunohistochemical *H* score <200) did not derive a clinical benefit: median OS, 9.8 versus 10.3 months; HR 0.99, $p = 0.88$. Cetuximab is not approved by the FDA for NSCLC, and in 2015 the National Comprehensive Cancer Network (NCCN) removed cetuximab from its guidelines due to minimal benefits, poor tolerance, and difficulties of administration of this regimen.

10 Maintenance Therapy

Initial response rates with induction chemotherapy with a platinum-containing regimen, depending on the reporting study, vary greatly and are of limited duration. Eventually, all advanced NSCLC tumors progress. The task to consolidate and maintain the achieved initial responses has been difficult, initially due to the uncertainty about optimal length of induction therapy. In a pivotal randomized controlled trial, Socinski et al. compared treatment with up to four cycles of carboplatin–paclitaxel versus continued carboplatin–paclitaxel until disease progression [77]. Both arms had a median of 4 cycles of chemotherapy administered, and no significant difference in overall survival was detected. Expectedly, cumulative toxicity was higher in the continuation arm. Soon et al. performed a meta-analysis of 13 clinical trials with 3027 available patients, attesting to improved progression-free survival with increasing toxicity with length of chemotherapy, while only providing a modest survival benefit, albeit statistically significant [78].

Based on this collective experience, the continuation of first-line combination chemotherapy beyond 4–6 cycles is generally not recommended. Accordingly, clinical trials have evaluated the impact of "maintenance" therapy with less toxic regimens, most commonly single-agent therapy. This strategy has two main approaches: **Continuation maintenance** entails the continuation of an agent previously administered with induction therapy; with **switch maintenance**, a new agent not previously administered is introduced. Potential rationales for maintenance therapy include increased exposure to effective therapies, decreasing chemotherapy resistance (Goldie and Coldman Hypothesis), maximizing efficacy of chemotherapeutic agents (Norton-Simon Hypothesis), anti-angiogenic effects, and altering anti-tumor immunity [79]. Currently, bevacizumab is FDA-approved as continuation maintenance therapy, while pemetrexed is approved as both continuation and switch maintenance therapy. The EGFR tyrosine kinase inhibitor erlotinib is also approved as switch maintenance therapy.

10.1 Bevacizumab

Both previously discussed registration trials of Bevacizumab in first-line setting, ECOG E4599 and AVAiL, included continuation of bevacizumab after chemotherapy was completed until disease progression or intolerable toxicity in all bevacizumab arms. As a result, neither trial directly addressed the relative benefit of concurrent and maintenance therapy with bevacizumab. In a retrospective landmark analysis of E4599, patients who received maintenance bevacizumab after completion of chemotherapy had longer progression-free survival than patients who did not continue bevacizumab beyond combination chemotherapy cycles (4.4 vs. 2.8 months, HR = 0.64, $p < 0.001$) [80]. Median overall survival was 12.8 and 11.4 months, respectively (HR = 0.75, $p = 0.03$). Further insight into the potential benefit of continuation maintenance bevacizumab is available from a three-arm trial in ovarian cancer, in which patients were randomly assigned to carboplatin–paclitaxel, carboplatin–paclitaxel plus concurrent bevacizumab, or carboplatin–paclitaxel plus concurrent bevacizumab followed by up to 10 months of maintenance bevacizumab monotherapy [81]. Median progression-free survival was 10.3, 11.2 months (HR 0.91; $p = 0.16$), and 14.1 months (HR 0.72; $p < 0.001$), respectively. Based on these data and the convenience and acceptable safety profile of bevacizumab monotherapy, bevacizumab is generally continued until disease progression or toxicity.

10.2 Pemetrexed

As continuation maintenance therapy, pemetrexed has been evaluated in the randomized controlled PARAMOUNT trial [11, 82]. Patients received a total of four cycles of cisplatin–pemetrexed and were then randomized 2:1 to either best supportive care or continuation of pemetrexed at 500 mg/m^2 every 3 weeks until

disease progression or unacceptable toxicities. Vitamin B12, folate, and dexamethasone were standard adjunct medications in this regimen. Slightly higher rates of neutropenia (5.8 vs. 0 %), anemia (6.4 vs. 0.6 %), and fatigue (4.7 vs. 1.1 %) were observed in the maintenance arm. The median progression-free survival was 4.1 months in the maintenance group and 2.8 months in the best supportive care arm. Furthermore, there was a significant improvement in overall survival: median 4.1 versus 2.8 months ($p < 0.001$), measured from the time of randomization. This trial led to approval of the continuation pemetrexed maintenance after induction therapy with four cycles of a platinum-containing regimen.

Pemetrexed switch maintenance therapy was studied in the phase 3 JMEN trial [83]. Patients were randomly assigned to receive pemetrexed or placebo if they had not progressed after four cycles of platinum-based chemotherapy that did not contain pemetrexed. Progression-free survival in the maintenance arm was extended from 2.6 to 4.3 months ($p < 0.0001$), and overall survival was extended from 10.6 to 13.4 months ($p = 0.012$). Discontinuation due to drug-related toxicity was slightly higher in the pemetrexed group (5 vs. 1 % in placebo group). Notably, only 11 % of patients in the supportive care arm ever received pemetrexed after disease progression, a pattern that may reflect the primarily Eastern European setting of the trial, where pemetrexed may not have been widely available off protocol.

In the standard clinical setting, both bevacizumab and pemetrexed have proven benefits to extend length and quality of life. Both have relatively tolerable side effect profiles. Whether maintenance therapy with bevacizumab, pemetrexed, or both agents would be most beneficial for patients remains unknown and is under investigation in the ECOG E5508 trial.

Notably, both pemetrexed and bevacizumab are indicated only in non-squamous histology. Squamous cell carcinomas, maintenance therapy options are less clear. Erlotinib is FDA-approved as switch maintenance therapy in all histologic subtypes, but clinical benefit is generally viewed as modest [84, 85]. Other options endorsed by the National Comprehensive Cancer Network (NCCN) include docetaxel [86] and gemcitabine [87, 88] (Table 2).

11 Second-Line Chemotherapy

11.1 Docetaxel

Docetaxel has been extensively studied in relapsed or refractory NSCLC. Response rates have been reported between 16 and 25 % and median survival between 7 and 10 months [90–92]. Standard dosing is given at 75 mg/m^2 every 3 weeks. This standard docetaxel regimen was compared head-to-head against weekly dosing with 25 mg/m^2 [93]. Median survival was significantly better in the 3 week group (7.1 vs. 5.4 months, $p = 0.04$). The principal difference in toxicity was higher rates of neutropenia with the 3-week dosing. The 75 mg/m^2 dosing was confirmed in another phase 3 study by Shepherd et al., in which the 100 mg/m^2 dose resulted in up to five treatment-related deaths in 40 treated patients [93]. Although objective

Table 2 Selected phase 3 trials with bevacizumab or pemetrexed-containing maintenance regimen

Trial	Induction regimen	Maintenance regimen	Response rates (%)	Progression-free survival (months)	Overall survival	Significance
E4599 [15]	Carboplatin–paclitaxel	Bevacizumab (15 mg/kg) observation	35 15	6.2 4.5	12.3 10.3	HR = 0.79, 95 % CI = 0.67–0.92, $p = 0.003$
AVAiL [70]	Carboplatin–gemcitabine	Bevacizumab (15 mg/kg) bevacizumab (7.5 mg/kg) observation	30 34 20	6.5 6.7 6.1	13.4 13.6 13.1	HR = 0.93, 95 % CI = 0.78–1.11; $p = 0.42$ (low) HR = 1.03; 95 % CI = 0.86–1.23; $p = 0.76$ (high)
JMEN [83]	Platinum-based doublet* × 4 cycles	Pemetrexed 500 mg/m^2 + BSC placebo + BSC	47 52	4.3 2.6	13.4 10.6	HR = 0.79; 95 % CI 0.65–0.95, $p = 0.012$
PARAMOUNT [11]	Cisplatin 75 mg/m^2 − pemetrexed 75 mg/m^2 × 4 cycles	Pemetrexed 500 mg/m^2 + BSC placebo + BSC	46 42	4.1 2.8	13.9 11	HR = 0.78; 95 % CI, 0.64–0.96; $p = 0.0195$
AVAPERL [89]	Cisplatin 75 mg/m^2 − pemetrexed 500 mg/m^2 + bevacizumab 7.5 mg/kg × 4 cycles	Pemetrexed 500 mg/m^2 plus bevacizumab 7.5 mg/kg bevacizumab 7.5 mg/kg	NR NR	7.4 3.7	Not achieved ($p = 0.22$)	HR = 0.48; 95 % CI, 0.35–0.66; $p < 0.001$

*Cisplatin or carboplatin plus gemcitabine, docetaxel, or paclitaxel

response rates were low (6.3 and 5.5 % in the 100 and 75 mg/m^2 arms, respectively), compared to best supportive care, significant improvement in median (7.5 vs. 4.6 months) and 1-year survival (37 vs. 19 %) was demonstrated. The overall survival benefit remained statistically significant even after combining both groups.

11.2 Pemetrexed

In a phase 3 non-inferiority trial [90], pemetrexed was established as an alternative to docetaxel. Patients received pemetrexed at 500 mg/m^2 in combination with Vitamin B12, folate and dexamethasone, or docetaxel 75 mg/m^2 every three weeks with dexamethasone. The primary end point for this study was overall survival. Median progression-free survival was 2.9 months for each arm, and median survival time was 8.3 months for pemetrexed and 7.9 months for docetaxel (p = not significant). While the two regimens were felt to be equally efficacious, the docetaxel arm experienced a significant higher rate of grade 3/4 neutropenia (40.2 vs. 5.3 %; $p < 0.001$), febrile neutropenia (12.7 vs. 1.9 %, $p < 0.001$), and neutropenic fever admissions (13.4 vs. 1.5 %, $p < 0.001$). As has been demonstrated in other trials of pemetrexed, clinical benefit of this agent was more pronounced in the non-squamous population. Given the convenience and favorable toxicity profile, pemetrexed has generally been preferred over docetaxel as second-line treatment of non-squamous NSCLC. However, in recent years, widespread use of pemetrexed in the first-line and maintenance settings has resulted in decreased use in the second-line setting.

11.3 Erlotinib

Although contemporary use of the EGFR inhibitor erlotinib is increasingly confined to the subset of NSCLC cases harboring activating exon 19 or exon 21 mutations in the EGFR gene (see Chapter 'Resistance to Therapy'), erlotinib remains FDA-approved as second and third therapy in unselected NSCLC populations. In *EGFR* wild-type populations, clinical benefit is far less pronounced than seen with *EGFR* mutant cases. In the NCI-Canada (NCI-C) BR.21 trial, patients with previously treated advanced NSCLC of any histology were randomized 2:1 to erlotinib 150 mg orally daily or placebo [94]. Response rate was 8.9 % in the erlotinib group, and less than 1 % in the placebo group. Progression-free survival was 2.2 and 1.8 months, respectively (hazard ratio, 0.61, $p < 0.001$). Overall survival was 6.7 and 4.7 months, respectively (hazard ratio, 0.70; $p < 0.001$). In deciding whether erlotinib is a reasonable alternative to chemotherapy in this setting, the Veristrat test has been introduced based on results from the PROSE study [95]. Veristrat is a serum proteomic assay with an eight-peak signature that predicts benefit from erlotinib, regardless of tumor mutational status. A "good" result equivalently benefit from erlotinib and single-agent chemotherapy. A "poor" result suggests that erlotinib may yield inferior results compared to chemotherapy.

It is noteworthy that the recent advent of immunotherapy (see Chapter 'Palliative Care in Lung Cancer') is likely to supplant the aforementioned agents as second-line therapy. Recently, the anti-programmed death 1 (PD1) monoclonal antibody nivolumab was found to yield superior overall survival compared to docetaxel in both squamous and non-squamous previously advanced NSCLC, leading to broad FDA approval in the second-line setting and beyond (Table 3).

12 Histology and Biomarkers as Predictors of Chemotherapy Effect

A major limitation of chemotherapy administration for advanced NSCLC is the ongoing lack of predictive biomarkers to guide selection of specific agents. Specific genomic alterations such as *EGFR* mutations and *ALK* rearrangements predict benefit from kinase inhibitors directed against these targets. Within several months of the emergence of immune checkpoint inhibitors for lung cancer therapy (see Chapter 'Palliative Care in Lung Cancer'), companion diagnostics such as tumor programmed death ligand 1 (PDL1) expression were demonstrating clinical promise. By contrast, decades of investigation—ranging from ex vivo chemosensitivity assays to next-generation sequencing—have yet to yield clinically useful biomarkers, with the exception of histology for pemetrexed consideration.

Nevertheless, a number of promising predictive biomarkers are under investigation, with selected examples reviewed in this section.

12.1 Excision Repair Cross-Complementation Group 1 (ERCC1)

The excision repair cross-complementation group 1 is a protein involved in nucleotide excision repair and interstrand cross-link repair [97]. Immunohistochemical expression of ERCC1 has been associated with resistance to platinum treatment effects. In the adjuvant IALT trial for early stage NSCLC, ERCC1-negative tumors had significantly prolonged survival with adjuvant cisplatin-based chemotherapy (HR 0.65; 95 % CI, 0.50–0.86, $p = 0.002$) [98]. ERCC1-positive tumors (44 % of all samples) did not derive a survival benefit from adjuvant, platinum-based therapy (adjusted hazard ratio for death, 1.14; 95 % CI, 0.84–1.55; $p = 0.40$). Conversely, among patients who did not receive adjuvant chemotherapy, patients with ERCC1-positive tumors had improved outcomes compared to ERCC1-negative cases (HR, 0.66; 95 % CI, 0.49–0.90; $p = 0.009$). These retrospective data are currently being validated in prospective biomarker trials. In a second analysis of two clinical trials, the National Cancer Institute of Canada Clinical Trials Group JBR.10 and the Cancer and Leukemia Group B 9633 trial from the Lung Adjuvant Cisplatin Evaluation Biology project, a correlation between ERCC1 expression detected by immunohistochemistry and prognosis could not be confirmed [99]. This was partly attributed to change in antibody

Table 3 Summary of trials for second-line chemotherapy regimen in NSCLC

Trial	Regimen	Response rate (%)	Progression-free survival	Overall survival (months)	Statistics
Shepherd (2001) [55]	Docetaxel 100 mg/m^2 docetaxel 75 mg/m^2 BSC	7.1 7.1 NR	10.6 weeks (combined) 6.7 weeks	7.5 5.9 4.6	log-rank test, p = .01 for low-dose docetaxel group
Camps (2006) [96]	Docetaxel 75 mg/m^2 q3 weeks docetaxel 25 mg/m^2 weekly	9.3 4.8	6.6 months 5.4 months	NR NR	p = 0.076 for PFS between two arms
Hanna [90]	Docetaxel 75 mg/m^2 q3 weeks pemetrexed 500 mg/m^2 q3 weeks	8.8 9.1	2.9 months 2.9 months	7.9 8.3	Not statistically significant
Shepherd [94]	Erlotinib 150 mg daily placebo	8.9 <1	2.2 months 1.8 months	6.7 4.7	HR = 0.70; $p < 0.001$
Garon [16]	Docetaxel + ramucirumab docetaxel	23 14	4.5 months 3.0 months	10.5 months 9.1 months	HR = 0.76, CI = 0.68–0.86; $p < 0.0001$

specificity between the different ERCC1 isoforms, and the authors concluded that the current analysis of tissue is currently of limited applicability for clinical practice.

12.2 Ribonucleotide Reductase Messenger 1 (RRM1)

Ribonucleotide reductase messenger 1 (RRM1) is a regulator of ribonucleotide reductase. With its involvement in DNA repair and ribonucleotide synthesis, it counteracts the molecular effects of gemcitabine and leads to gemcitabine resistance in preclinical models [100]. A meta-analyses including 18 studies and 1243 patients evaluated the effect of RRM1 on gemcitabine sensitivity and found that overall response rates were significantly improved with low or absent RRM1 expression (OR = 0.31, 95 % CI 0.21–0.45, $p < 0.00001$). A prospective, randomized phase 3 trial evaluated combined RRM1 and ERCC1 as predictive markers and found an improved response rate based on low RRM1 expression ($r = -0.41$; $p = 0.001$ for RRM1) [101]. However, no statistically significant difference in progression-free or overall survival was detected.

12.3 Thymidylate Synthase (TS)

TS is among the molecular targets of the folate analog pemetrexed. A number of studies have demonstrated that greater tumor expression of TS is associated with resistance to pemetrexed [102]. Indeed, higher average TS expression in squamous tumors is thought to account for the relative lack of efficacy in that subset of NSCLC. Specifically, pemetrexed is a competitive inhibitor of TS, the enzyme responsible for the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). Elevated levels of TS likely outcompete pemetrexed stoichiometrically and lead to relative lack of effect in this subtypes. Due to inter-study variability, differences in analysis technique and read out, TS quantification has not been standardized. Thus, histology continues to serve as a treatment selection biomarker for pemetrexed.

12.4 Gene Expression Profiling

Numerous attempts have been made to identify common multi-gene expression signatures that would predict benefit from chemotherapy. Some of these are in clinical practice, e.g., OncoTypeDX and Mammaprint for breast cancer, but none are available for the routine clinical use in NSCLC. Attempts to include next-generation sequencing into prognostication and prediction of chemotherapy are underway, but have not matured to the point of integration into clinical practice [103–105].

13 Special Populations

13.1 Elderly Patients

Advanced patient age has emerged a significant concern with regard to clinical benefit, tolerance, and toxicity of chemotherapy for advanced NSCLC. With anticipated demographic changes, the elderly population will likely compose an even larger share of the lung cancer population. Two retrospective analyses of large ECOG trials, 5592 and 1594, were undertaken to answer this question. In the analysis of ECOG 5592, comparing cisplatin/etoposide to cisplatin/paclitaxel, elderly patients (defined as patients older than 70 years) had similar response rates, survival outcome, and quality of life measures compared to younger patients [106]. However, elderly patients experienced a higher rate of side effects, including grade 3–4 leukopenia (64 vs. 49 %, $p = 0.05$) and grade 3 neuropsychiatric events (7 vs. 3 %, $p = 0.02$). Rates of other toxicities were not significantly different between age groups. A retrospective subgroup analysis of ECOG 1594 confirmed that patients with matched characteristics received similar clinical benefit from therapy, independent of their age [107].

In the prospective ELVIS trial [52], patients aged 70 years or older were randomized to vinorelbine plus best supportive care versus best supportive care alone. In the vinorelbine arm, 1-year survival rate was higher (32 vs. 14 %; $p < 0.01$), and patients had less cancer-related symptoms and comparable quality of life, even when accounting for treatment-related toxicity.

Other studies have reported incremental benefit of combination therapy with platinum backbone over single-arm therapy alone in elderly populations. In the Cancer and Leukemia Group B (CALGB) trial 9730 [108], elderly patients receiving carboplatin–paclitaxel had a median survival of 8.8 months compared to 6.7 months in the paclitaxel only arm, although statistical significance was not reached (HR = 0.91 (95 % CI, 0.77–1.17; $p = 0.25$). A Japanese trial reported by Abe et al. found no significant difference between single-agent and doublet chemotherapy in elderly populations. Median overall survival was 14.8 months with docetaxel (60 mg/m^2) every 3 weeks, compared to 13.3 months with cisplatin (25 mg/m^2) plus docetaxel (20 mg/m^2) weekly three weeks on, one week off (HR, 1.18; 95 % CI, 0.83–1.69) [109]. Selection of patients that were unfit for regular dose cisplatin, the dosing scheme, or other factors could have contributed to the outcome of this trial. Lilienbaum et al. reported further clinical benefit in elderly patient populations comparing weekly docetaxel (30 mg/m^2) to docetaxel given at conventional doses (75 mg/m^2 every three weeks). Although weekly dosing seemed to have a favorable side effect profile, overall measures of tolerance were comparable. Better performance status (ECOG 0-1) was associated with improved outcomes compared to borderline performance status (ECOG 2) (7.8 vs. 2.9 months; $p < 0.001$). This trend was confirmed in a subset of octagenarians ($n = 30$). Quoix and colleagues reported the results of Intergroupe Francophone de Cancérologie Thoracique (IFCT)-0501, a randomized phase 3 trial of combination

chemotherapy versus single-agent chemotherapy in patients with advanced NSCLC between the ages of 70 and 89 [110]. Patients with performance status 0–2 received doublet chemotherapy or monotherapy. Doublet chemotherapy consisted of carboplatin on day 1 and paclitaxel weekly (3 weeks on, one week off in a 4-week cycle). The monotherapy group was treated with vinorelbine or gemcitabine on days 1 and 8 of a three-week cycle. The study demonstrated a significant improvement in OS (10.3 vs. 6.2 months) and PFS in the doublet chemotherapy group (6.0 vs. 2.8 months). In a multivariate analysis, doublet chemotherapy, PS 0–1, never having smoked, adenocarcinoma histology, activities of daily living score of 6, and weight loss of 5 % or less were the favorable prognostic factors. Grade 3–5 toxicities were increased in the doublet chemotherapy group, including 4 % treatment-related deaths on study.

Although elderly patients are frequently underrepresented in clinical trials, the currently available data argue that choice of chemotherapy should be made based on performance status, comorbidities, histology, and patient expectation, rather than an age-based decision alone. In elderly patients with concern for acceptable toxicity and tolerance of therapy, single-agent chemotherapy has been shown to demonstrate benefit and should be considered as a treatment alternative.

13.2 Poor Performance Status

Poor performance status is a frequently encountered clinical challenge. Poor performance status is commonly classified as ECOG status 2 or greater (or alternatively as Karnofsky index of 70 % or less). When assessing a patient's candidate for therapy, it appears important to distinguish between a more acute clinical decline attributed to cancer-related symptoms, or a longer-term poor health prior to diagnosis. While patients with poor performance status are estimated to make up 30–40 % of total lung cancer cases, they are historically excluded or underrepresented in clinical trials [110]. Thus, few trials are available to address the question of treatment benefit in poor performance status patients. Based on data from Selective Targeting for Efficacy in Lung Cancer, Lower Adverse Reaction (STELLAR) 3 and 4, Lilienbaum et al. described four factors that predict worse outcome, including low albumin (≤3.5 g/dL), elevated serum LDH (>200 IU/L), extra-thoracic metastases and presence of two or more comorbidities [111, 112]. In a retrospective analysis of two multicenter trials, patients with poor performance status had similar response rates but worse survival compared to those with good performance status, suggesting worse tolerance of and less benefit from treatment in this population [113]. Zukin et al. prospectively demonstrated a clinical benefit from combination carboplatin–pemetrexed over pemetrexed monotherapy (response rate 23.8 vs. 10.3 %, $p = 0.032$; median overall survival 9.3 vs. 5.3 months; HR, 0.62; 95 % CI, 0.46–0.83; $p = 0.001$) in a patient population with reduced performance status (ECOG 2) [114].

Although molecularly targeted therapies such as EGFR inhibitors have demonstrated high efficacy rates in patients with poor performance status whose

tumors harbor druggable genomic alterations [115], it is not clear that these treatments provide benefit to patients with poor functional status whose tumors lack specific activating mutations [116]. In unselected patients with poor performance status, there was no difference in response rate and survival between the EGFR inhibitor gefitinib and placebo [117].

14 Conclusion

Chemotherapy is now a well-established treatment modality in advanced non-small cell lung cancer. In recent years, we have seen improved outcomes, better tolerated and more convenient therapies, and promising combinations of biologic agents with conventional cytotoxic drugs. As a result of these developments, chemotherapy is now viewed as a more attractive option by both patients and physicians than it had been previously. To date, candidate biomarkers have not reliably predicted benefit from specific chemotherapeutic agents. Even as new treatment options such as molecularly targeted therapies and immune checkpoint inhibitors expand their role in lung cancer treatment, chemotherapy will remain an essential component of combination therapy and an essential treatment option after progression on these other drugs.

References

1. Goodgame B, Viswanathan A, Zoole J et al (2009) Risk of recurrence of resected stage I non-small cell lung cancer in elderly patients as compared with younger patients. J Thorac Oncol 4:1370–4
2. BMJ (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ 311:899–909
3. Jemal A, Thun MJ, Ries LA et al (2008) Annual report to the nation on the status of cancer, 1975–2005, featuring trends in lung cancer, tobacco use, and tobacco control. J Natl Cancer Inst 100:1672–94
4. Silvestri G, Pritchard R, Welch HG (1998) Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. BMJ 317:771–5
5. Wassenaar TR, Eickhoff JC, Jarzemsky DR, Smith SS, Larson ML, Schiller JH (2007) Differences in primary care clinicians' approach to non-small cell lung cancer patients compared with breast cancer. J Thorac Oncol 2:722–8
6. Rasco DW, Yan J, Xie Y, Dowell JE, Gerber DE (2010) Looking beyond surveillance, epidemiology, and end results: patterns of chemotherapy administration for advanced non-small cell lung cancer in a contemporary, diverse population. J Thorac Oncol 5:1529–35
7. Earle CC, Neumann PJ, Gelber RD, Weinstein MC, Weeks JC (2002) Impact of referral patterns on the use of chemotherapy for lung cancer. J Clin Oncol 20:1786–92
8. Earle CC, Venditti LN, Neumann PJ et al (2000) Who gets chemotherapy for metastatic lung cancer? Chest 117:1239–46
9. Ramsey SD, Howlader N, Etzioni RD, Donato B (2004) Chemotherapy use, outcomes, and costs for older persons with advanced non-small-cell lung cancer: evidence from surveillance, epidemiology and end results-Medicare. J Clin Oncol 22:4971–8

10. Socinski MA, Bondarenko I, Karaseva NA et al (2012) Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol 30:2055–62
11. Paz-Ares L, de Marinis F, Dediu M et al (2012) Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 13:247–55
12. Navari RM, Reinhardt RR, Gralla RJ et al (1999) Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. L-754,030 Antiemetic Trials Group. N Engl J Med 340:190–5
13. Nichols CR, Fox EP, Roth BJ, Williams SD, Loehrer PJ, Einhorn LH (1994) Incidence of neutropenic fever in patients treated with standard-dose combination chemotherapy for small-cell lung cancer and the cost impact of treatment with granulocyte colony-stimulating factor. J Clin Oncol 12:1245–50
14. Temel JS, Greer JA, Muzikansky A et al (2010) Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363:733–42
15. Sandler A, Gray R, Perry MC et al (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355:2542–50
16. Garon EB, Ciuleanu TE, Arrieta O et al (2014) Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 384:665–73
17. de Marinis F, De Santis S, De Petris L (2006) Second-line treatment options in non-small cell lung cancer: a comparison of cytotoxic agents and targeted therapies. Semin Oncol 33: S17–24
18. Smit EF, Mattson K, von Pawel J, Manegold C, Clarke S, Postmus PE (2003) ALIMTA (pemetrexed disodium) as second-line treatment of non-small-cell lung cancer: a phase II study. Ann Oncol 14:455–60
19. Smit EF, Socinski MA, Mullaney BP et al (2012) Biomarker analysis in a phase III study of pemetrexed-carboplatin versus etoposide-carboplatin in chemonaive patients with extensive-stage small-cell lung cancer. Ann Oncol 23:1723–9
20. Bridges JF, Mohamed AF, Finnern HW, Woehl A, Hauber AB (2012) Patients' preferences for treatment outcomes for advanced non-small cell lung cancer: a conjoint analysis. Lung Cancer 77:224–31
21. Peeters L, Sibille A, Anrys B et al (2012) Maintenance therapy for advanced non-small-cell lung cancer: a pilot study on patients' perceptions. J Thorac Oncol 7:1291–5
22. Katayama R, Shaw AT, Khan TM et al (2012) Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. Science Trans Med 4:120ra17
23. Kobayashi S, Boggon TJ, Dayaram T et al (2005) EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 352:786–92
24. Albain KS, Crowley JJ, LeBlanc M, Livingston RB (1991) Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience. J Clin Oncol 9:1618–26
25. Marino P, Pampallona S, Preatoni A, Cantoni A, Invernizzi F (1994) Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. Chest 106:861–5
26. Los G, Verdegaal E, Noteborn HP et al (1991) Cellular pharmacokinetics of carboplatin and cisplatin in relation to their cytotoxic action. Biochem Pharmacol 42:357–63
27. Peng B, Tilby MJ, English MW et al (1997) Platinum-DNA adduct formation in leucocytes of children in relation to pharmacokinetics after cisplatin and carboplatin therapy. Br J Cancer 76:1466–73

28. Ardizzoni A, Boni L, Tiseo M et al (2007) Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. J Natl Cancer Inst 99:847–57
29. Jiang J, Liang X, Zhou X, Huang R, Chu Z (2007) A meta-analysis of randomized controlled trials comparing carboplatin-based to cisplatin-based chemotherapy in advanced non-small cell lung cancer. Lung Cancer 57:348–58
30. Schiller JH, Harrington D, Belani CP et al (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92–8
31. Gerber DE, Grossman SA, Batchelor T, Ye X (2007) Calculated versus measured creatinine clearance for dosing methotrexate in the treatment of primary central nervous system lymphoma. Cancer Chemother Pharmacol 59:817–23
32. Ranson M, Davidson N, Nicolson M et al (2000) Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 92:1074–80
33. Roszkowski K, Pluzanska A, Krzakowski M et al (2000) A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). Lung Cancer 27:145–57
34. Chang AY, Kim K, Glick J, Anderson T, Karp D, Johnson D (1993) Phase II study of taxol, merbarone, and piroxantrone in stage IV non-small-cell lung cancer: The Eastern cooperative oncology group results. J Natl Cancer Inst 85:388–94
35. Murphy WK, Fossella FV, Winn RJ et al (1993) Phase II study of taxol in patients with untreated advanced non-small-cell lung cancer. J Natl Cancer Inst 85:384–8
36. Bonomi P, Kim K, Fairclough D et al (2000) Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern cooperative oncology group trial. J Clin Oncol 18:623–31
37. Giaccone G, Splinter TA, Debruyne C et al (1998) Randomized study of paclitaxel-cisplatin versus cisplatin-teniposide in patients with advanced non-small-cell lung cancer. The European organization for research and treatment of cancer lung cancer cooperative group. J Clin Oncol 16:2133–41
38. Kelly K, Crowley J, Bunn PA Jr et al (2001) Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest oncology group trial. J Clin Oncol 19:3210–8
39. Miller VA, Rigas JR, Francis PA et al (1995) Phase II trial of a 75-mg/m^2 dose of docetaxel with prednisone premedication for patients with advanced non-small cell lung cancer. Cancer 75:968–72
40. Kunitoh H, Watanabe K, Onoshi T, Furuse K, Niitani H, Taguchi T (1996) Phase II trial of docetaxel in previously untreated advanced non-small-cell lung cancer: a Japanese cooperative study. J Clin Oncol 14:1649–55
41. Burris HA 3rd, Fields S, Peacock N (1995) Docetaxel (Taxotere) in combination: a step forward. Semin Oncol 22:35–40
42. Sandler AB, Nemunaitis J, Denham C et al (2000) Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 18:122–30
43. Cardenal F, Lopez-Cabrerizo MP, Anton A et al (1999) Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 17:12–8
44. Saha A, Rudd R (2006) Gemcitabine and carboplatin: is this the best combination for non-small cell lung cancer? Expert Rev Anticancer Ther 6:165–73
45. Grigorescu AC, Draghici IN, Nitipir C, Gutulescu N, Corlan E (2002) Gemcitabine (GEM) and carboplatin (CBDCA) versus cisplatin (CDDP) and vinblastine (VLB) in

advanced non-small-cell lung cancer (NSCLC) stages III and IV: a phase III randomised trial. Lung Cancer 37:9–14
46. Vogelzang NJ, Rusthoven JJ, Symanowski J et al (2003) Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21:2636–44
47. Scagliotti GV, Parikh P, von Pawel J et al (2008) Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 26:3543–51
48. Shimizu T, Nakagawa Y, Takahashi N, Hashimoto S (2015) Thymidylate synthase gene amplification predicts pemetrexed resistance in patients with advanced non-small cell lung cancer. Clin Transl Oncol 18(1):107–112
49. Kutluk Cenik B, Sun H, Gerber DE (2013) Impact of renal function on treatment options and outcomes in advanced non-small cell lung cancer. Lung Cancer 80:326–332
50. Evans WE, Pratt CB (1978) Effect of pleural effusion on high-dose methotrexate kinetics. Clin Pharmacol Ther 23:68–72
51. Dickgreber NJ, Sorensen JB, Paz-Ares LG et al (2010) Pemetrexed safety and pharmacokinetics in patients with third-space fluid. Clin Cancer Res 16:2872–80
52. Gridelli C, Perrone F, Gallo C et al (1997) Vinorelbine is well tolerated and active in the treatment of elderly patients with advanced non-small cell lung cancer. A two-stage phase II study. Eur J Cancer 33:392–7
53. Wozniak AJ, Crowley JJ, Balcerzak SP et al (1998) Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest oncology group study. J Clin Oncol 16:2459–2465
54. van Meerbeeck JP, Legrand C, van Klaveren RJ, Giaccone G (2001) Group ELC. Chemotherapy for non-small-cell lung cancer. Lancet 358:1271–1272
55. Scagliotti GV, De Marinis F, Rinaldi M et al (2002) Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 20:4285–4291
56. Comella P, Panza N, Manzione L, et al (2000) Interim analysis of a phase III trial comparing cisplatin, gemcitabine, and vinorelbine versus either cisplatin and gemcitabine or cisplatin and vinorelbine in advanced non small-cell lung cancer. A Southern italy cooperative oncology group study. Clin Lung Cancer 1:202–207; discussion 8
57. Comella P (2001) Southern Italy cooperative oncology G. phase III trial of cisplatin/gemcitabine with or without vinorelbine or paclitaxel in advanced non-small cell lung cancer. Semin Oncol 28:7–10
58. Kodani T, Ueoka H, Kiura K et al (2002) A phase III randomized trial comparing vindesine and cisplatin with or without ifosfamide in patients with advanced non-small-cell lung cancer: long-term follow-up results and analysis of prognostic factors. Lung Cancer 36:313–319
59. Souquet PJ, Tan EH, Rodrigues Pereira J et al (2002) GLOB-1: a prospective randomised clinical phase III trial comparing vinorelbine-cisplatin with vinorelbine-ifosfamide-cisplatin in metastatic non-small-cell lung cancer patients. Ann Oncol 13:1853–61
60. Goffin JR, Anderson IC, Supko JG et al (2005) Phase I trial of the matrix metalloproteinase inhibitor marimastat combined with carboplatin and paclitaxel in patients with advanced non-small cell lung cancer. Clin Cancer Res 11:3417–24
61. Morra F, Luise C, Visconti R et al (2015) New therapeutic perspectives in CCDC6 deficient lung cancer cells. Int J Cancer 136:2146–57
62. Tarhini AA, Zahoor H, McLaughlin B et al (2013) Phase I trial of carboplatin and etoposide in combination with panobinostat in patients with lung cancer. Anticancer Res 33:4475–81
63. Langer CJ, Novello S, Park K et al (2014) Randomized, phase III trial of first-line figitumumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone in patients with advanced non-small-cell lung cancer. J Clin Oncol 32:2059–66

64. Socinski MA, Goldman J, El-Hariry I et al (2013) A multicenter phase II study of ganetespib monotherapy in patients with genotypically defined advanced non-small cell lung cancer. Clin Cancer Res 19:3068–77
65. Fidler IJ, Ellis LM (2004) Neoplastic angiogenesis—not all blood vessels are created equal. N Engl J Med 351:215–6
66. Forsythe JA, Jiang BH, Iyer NV et al (1996) Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. Mol Cell Biol 16:4604–4613
67. Jiang BH, Agani F, Passaniti A, Semenza GL (1997) V-SRC induces expression of hypoxia-inducible factor 1 (HIF-1) and transcription of genes encoding vascular endothelial growth factor and enolase 1: involvement of HIF-1 in tumor progression. Cancer Res 57:5328–5335
68. Xu Q, Briggs J, Park S et al (2005) Targeting Stat3 blocks both HIF-1 and VEGF expression induced by multiple oncogenic growth signaling pathways. Oncogene 24:5552–5560
69. Johnson DH, Fehrenbacher L, Novotny WF et al (2004) Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 22:2184–2191
70. Reck M, von Pawel J, Zatloukal P et al (2009) Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 27:1227–1234
71. Dowlati A, Gray R, Sandler AB, Schiller JH, Johnson DH (2008) Cell adhesion molecules, vascular endothelial growth factor, and basic fibroblast growth factor in patients with non-small cell lung cancer treated with chemotherapy with or without bevacizumab—an Eastern cooperative oncology group study. Clin Cancer Res 14:1407–1412
72. Dahlberg SE, Sandler AB, Brahmer JR, Schiller JH, Johnson DH (2010) Clinical course of advanced non-small-cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel on ECOG 4599. J Clin Oncol 28:949–954
73. Iwamoto S, Takahashi T, Tamagawa H et al (2015) FOLFIRI plus bevacizumab as second-line therapy in patients with metastatic colorectal cancer after first-line bevacizumab plus oxaliplatin-based therapy: the randomized phase III EAGLE study. Ann Oncol 26: 1427–1433
74. Reck M, Kaiser R, Mellemgaard A et al (2014) Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol 15:143–155
75. Pirker R (2012) EGFR-directed monoclonal antibodies in non-small cell lung cancer: how to predict efficacy? Transl Lung Cancer Res 1:269–75
76. Pirker R, Pereira JR, Szczesna A et al (2009) Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 373:1525–1531
77. Socinski MA, Schell MJ, Peterman A et al (2002) Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. J Clin Oncol 20:1335–1343
78. Soon YY, Stockler MR, Askie LM, Boyer MJ (2009) Duration of chemotherapy for advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomized trials. J Clin Oncol 27:3277–83
79. Gerber DE, Schiller JH (2013) Maintenance chemotherapy for advanced non-small-cell lung cancer: new life for an old idea. J Clin Oncol 31:1009–1020
80. Lopez-Chavez A, Young T, Fages S et al (2012) Bevacizumab maintenance in patients with advanced non-small-cell lung cancer, clinical patterns, and outcomes in the Eastern cooperative oncology group 4599 Study: results of an exploratory analysis. J Thorac Oncol 7:1707–1712

81. Burger RA, Brady MF, Bookman MA et al (2011) Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 365:2473–83
82. Gridelli C, de Marinis F, Pujol JL et al (2012) Safety, resource use, and quality of life in paramount: a phase III study of maintenance pemetrexed versus placebo after induction pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Thorac Oncol 7:1713–21
83. Ciuleanu T, Brodowicz T, Zielinski C et al (2009) Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 374:1432–1440
84. Brugger W, Triller N, Blasinska-Morawiec M et al (2011) Prospective molecular marker analyses of EGFR and KRAS from a randomized, placebo-controlled study of erlotinib maintenance therapy in advanced non-small-cell lung cancer. J Clin Oncol 29:4113–20
85. Cappuzzo F, Ciuleanu T, Stelmakh L et al (2010) Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 11:521–529
86. Fidias PM, Dakhil SR, Lyss AP et al (2009) Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 27:591–598
87. Brodowicz T, Krzakowski M, Zwitter M et al (2006) Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer 52:155–163
88. Belani CP, Dakhil S, Waterhouse DM et al (2007) Randomized phase II trial of gemcitabine plus weekly versus three-weekly paclitaxel in previously untreated advanced non-small-cell lung cancer. Ann Oncol 18:110–115
89. Barlesi F, Scherpereel A, Rittmeyer A et al (2013) Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). J Clin Oncol 31:3004–3011
90. Hanna N, Shepherd FA, Fossella FV et al (2004) Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22:1589–1597
91. Alexopoulos K, Kouroussis C, Androulakis N et al (1999) Docetaxel and granulocyte colony-stimulating factor in patients with advanced non-small-cell lung cancer previously treated with platinum-based chemotherapy: a multicenter phase II trial. Cancer Chemother Pharmacol 43:257–262
92. Gandara DR, Vokes E, Green M et al (2000) Activity of docetaxel in platinum-treated non-small-cell lung cancer: results of a phase II multicenter trial. J Clin Oncol 18:131–135
93. Shepherd FA, Dancey J, Ramlau R et al (2000) Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095–2103
94. Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al (2005) Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123–132
95. Gregorc V, Novello S, Lazzari C et al (2014) Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker-stratified, randomised phase 3 trial. Lancet Oncol 15:713–721
96. Camps C, Massuti B, Jimenez A et al (2006) Randomized phase III study of 3-weekly versus weekly docetaxel in pretreated advanced non-small-cell lung cancer: a Spanish Lung Cancer Group trial. Ann Oncol 17:467–472
97. Al-Minawi AZ, Lee YF, Hakansson D et al (2009) The ERCC1/XPF endonuclease is required for completion of homologous recombination at DNA replication forks stalled by inter-strand cross-links. Nucleic Acids Res 37:6400–6413
98. Olaussen KA, Dunant A, Fouret P et al (2006) DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 355:983–991

99. Friboulet L, Olaussen KA, Pignon JP et al (2013) ERCC1 isoform expression and DNA repair in non-small-cell lung cancer. N Engl J Med 368:1101–1110
100. Gong W, Zhang X, Wu J et al (2012) RRM1 expression and clinical outcome of gemcitabine-containing chemotherapy for advanced non-small-cell lung cancer: a meta-analysis. Lung Cancer 75:374–380
101. Reynolds C, Obasaju C, Schell MJ et al (2009) Randomized phase III trial of gemcitabine-based chemotherapy with in situ RRM1 and ERCC1 protein levels for response prediction in non-small-cell lung cancer. J Clin Oncol 27:5808–5815
102. Sun JM, Ahn JS, Jung SH et al (2015) Pemetrexed plus cisplatin versus gemcitabine plus cisplatin according to thymidylate synthase expression in nonsquamous non-small-cell lung cancer: a biomarker-stratified randomized phase II trial. J Clin Oncol 33:2450–2456
103. Tang H, Xiao G, Behrens C et al (2013) A 12-gene set predicts survival benefits from adjuvant chemotherapy in non-small cell lung cancer patients. Clin Cancer Res 19:1577–1586
104. Kim HS, Mendiratta S, Kim J et al (2013) Systematic identification of molecular subtype-selective vulnerabilities in non-small-cell lung cancer. Cell 155:552–566
105. Byers LA, Diao L, Wang J et al (2013) An epithelial-mesenchymal transition gene signature predicts resistance to EGFR and PI3 K inhibitors and identifies Axl as a therapeutic target for overcoming EGFR inhibitor resistance. Clin Cancer Res 19:279–290
106. Langer CJ, Manola J, Bernardo P et al (2002) Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern cooperative oncology group 5592, a randomized trial. J Natl Cancer Inst 94:173–181
107. Wakelee HA, Dahlberg SE, Brahmer JR et al (2012) Differential effect of age on survival in advanced NSCLC in women versus men: analysis of recent Eastern cooperative oncology group (ECOG) studies, with and without bevacizumab. Lung Cancer 76:410–415
108. Lilenbaum RC, Herndon JE 2nd, List MA et al (2005) Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: the cancer and leukemia group B (study 9730). J Clin Oncol 23:190–196
109. Abe T, Takeda K, Ohe Y et al (2015) Randomized phase III trial comparing weekly docetaxel plus cisplatin versus docetaxel monotherapy every 3 weeks in elderly patients with advanced non-small-cell lung cancer: the intergroup trial JCOG0803/WJOG4307L. J Clin Oncol 33:575–581
110. Quoix E, Zalcman G, Oster JP et al (2011) Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 378:1079–1088
111. Lilenbaum RC, Cashy J, Hensing TA, Young S, Cella D (2008) Prevalence of poor performance status in lung cancer patients: implications for research. J Thorac Oncol 3:125–129
112. Lilenbaum R, Rubin M, Samuel J et al (2007) A randomized phase II trial of two schedules of docetaxel in elderly or poor performance status patients with advanced non-small cell lung cancer. J Thorac Oncol 2:306–311
113. Lilenbaum R, Villaflor VM, Langer C et al (2009) Single-agent versus combination chemotherapy in patients with advanced non-small cell lung cancer and a performance status of 2: prognostic factors and treatment selection based on two large randomized clinical trials. J Thorac Oncol 4:869–874
114. Stinchcombe TE, Buzkova P, Choksi J et al (2006) A phase I/II trial of weekly docetaxel and gefitinib in elderly patients with stage IIIB/IV non-small cell lung cancer. Lung Cancer 52:305–311
115. Zukin M, Barrios CH, Pereira JR et al (2013) Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. J Clin Oncol 31:2849–2853

116. Inoue A, Kobayashi K, Usui K et al (2009) First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. J Clin Oncol 27:1394–1400
117. Lilenbaum R, Axelrod R, Thomas S et al (2008) Randomized phase II trial of erlotinib or standard chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2. J Clin Oncol 26:863–869
118. Goss G, Ferry D, Wierzbicki R et al (2009) Randomized phase II study of gefitinib compared with placebo in chemotherapy-naive patients with advanced non-small-cell lung cancer and poor performance status. J Clin Oncol 27:2253–2260

Multimodality Therapy for NSCLC

Lingling Du, Saiama N. Waqar and Daniel Morgensztern

Abstract

The standard therapy for patients with unrespectable stage III non-small-cell lung cancer (NSCLC) is the combination of chemotherapy and radiotherapy. Although the concurrent use of both treatment modalities has been shown to be superior to sequential therapy, the role for additional chemotherapy, either as induction or as consolidation, remains unclear. Targeted therapy has met limited success in the treatment of unselected patients with stage III NSCLC. New studies using induction therapy with erlotinib or crizotinib for molecularly selected patients and consolidation therapy with checkpoint inhibitors are currently ongoing, and the results are eagerly awaited.

Keywords

Stage III NSCLC · Chemoradiotherapy · Molecularly targeted therapy · Immunotherapy

Contents

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1 Introduction

Lung cancer is both the most commonly diagnosed malignancy and cause of cancer death in the United States for men and women combined, with 240,000 new cases and 162,000 deaths estimated for the year 2015 [1]. Among patients with lung cancer, approximately 85 % have one of the non-small-cell lung cancer (NSCLC) histologies [2]. Stage III NSCLC was present in approximately 27 % of patients according to the sixth edition of the American Joint Commission on Cancer (AJCC) [3]. However, the proportion of stage III is currently lower due to the reclassification of the approximately 15–20 % of those with malignant pleural effusion to stage M1a in the seventh edition of AJCC [4, 5]. Stage III lung cancer is a heterogeneous disease, with several broad subgroups including T3N1 and selected cases of T4N0-1 which may be treated with surgery followed by adjuvant chemotherapy, T1-3N2 which is potentially resectable but usually treated with chemoradiation, and patients with invasive T4 or N3, which are unresectable and treated with chemoradiation [6].

2 Chemoradiotherapy

2.1 Initial Studies with Chemoradiotherapy

The role of chemotherapy in the management of locally advanced NSCLC was established with the results of the Cancer and Leukemia Group B (CALGB) 8433 trial, which randomly assigned 155 patients with stage III NSCLC to sequential chemotherapy with cisplatin (100 mg/m^2 on days 1 and 29) and vinblastine (5 mg/m^2 weekly for 5 weeks) followed by radiotherapy with 60 Gy over six weeks, starting on day 50, or radiotherapy alone [7]. The response rate was 46 % for sequential chemoradiation and 35 % for radiation alone ($p = 0.092$). The addition of chemotherapy significantly prolonged the median failure-free survival (PFS; 8.2 vs. 6.0 months; $p = 0.041$), overall survival (OS; 13.8 vs. 9.7 months; $p = 0.006$), and 3-year OS (23 % vs. 11 %) compared to radiation therapy alone. Chemo radiotherapy was more commonly associated with serious infection (7 % vs. 3 %) and significant weight loss (14 % vs. 6 %), but there were no treatment-related deaths in either arm.

Several trials have been conducted in an attempt to establish the optimal way to deliver chemotherapy and radiation. The Radiation Therapy Oncology Group

(RTOG) 9410 trial randomly assigned 610 patients to sequential cisplatin (100 mg/m^2 on days 1 and 29) and vinblastine (5 mg/m^2 weekly for 5 weeks) followed by radiotherapy 60 Gy starting on day 50, the same regimen with concurrent radiation starting on day 1, or concurrent radiation with 69.6 at 1.2 Gy twice daily beginning on day 1 with cisplatin (50 mg/m2 on days 1, 8, 29, and 36) and oral etoposide (50 mg twice daily on days 1, 2, 5, and 6 for 10 weeks) [8]. The median OS for arms 1 to 3 was 14.6, 17.0, and 15.6 months. Concurrent chemoradiation conferred a slightly better 5-year survival rate compared to sequential chemoradiation (16 % vs. 10 %; hazard ratio [HR] 0.812; 95 % confidence interval [CI] 0.663–0.996; $p = 0.046$). Acute grade 3–5 adverse events, mostly esophagitis, mucositis, nausea, and vomiting, were more commonly seen in the concurrent therapy arms. Late toxicities were similar among the three groups.

A meta-analysis of six randomized trial comparing concurrent to sequential chemoradiation in locally advanced NSCLC showed a significant improvement in median OS with the concurrent strategy (HR 0.84; 95 % CI 0.74–.95; $p = 0.004$) [9]. The absolute survival benefit was 5.7 % at 3 years, and 4.5 % at 5 years. Compared to the sequential strategy, concurrent chemoradiation was associated with increased grade 3–4 acute esophageal toxicity (18 % vs. 4 %; $p < 0.001$).

2.2 Paclitaxel-Based Studies

The phase II Locally Advanced Multimodality Protocol (LAMP) study tested the regimen of paclitaxel and carboplatin combined with radiotherapy in stage III NSCLC [10]. A total of 276 patients were randomly assigned to sequential arm with two cycles of paclitaxel (200 mg/m^2) and carboplatin (AUC = 6) followed by radiotherapy with 63 Gy, induction arm with two cycles of induction paclitaxel (200 mg/m^2) and carboplatin (AUC = 6) followed by weekly paclitaxel (45 mg/m^2) and carboplatin (AUC = 2) with concomitant radiotherapy 63 Gy, or consolidation arm with weekly paclitaxel (45 mg/m^2) and carboplatin (AUC = 2) with concurrent RT 63 Gy followed by two cycles of consolidation paclitaxel (200 mg/m^2) and carboplatin (AUC = 6). At a median follow-up of 39.6 months, the median OS of the sequential, induction, and consolidation arms was 13.0, 12.7, and 16.3 months, respectively. The 3-year survival rates were almost identical among the three arms (17 % for sequential, 15 % for induction, 17 % for consolidation). Median PFS and 1-year progression-free rates were, respectively, 9.0 months and 54 % for the sequential arm, 6.7 months and 46 % for the induction arm, and 8.7 months and 46 % for the consolidation arm. The consolidation arm was associated with increased rates of grade 3–4 esophagitis, lung toxicities, and myelosuppression.

The RTOG 0617 was a phase III study evaluating the role of high-dose versus standard-dose radiotherapy and the effect of additional cetuximab [11]. Patients with unresectable stage III NSCLC were randomly assigned to either standard-dose radiotherapy (60 Gy) with or without cetuximab, or high-dose radiotherapy (74 Gy)

with or without cetuximab. All patients received concurrent paclitaxel (45 mg/m^2) and carboplatin (AUC = 2) with radiation followed by consolidation paclitaxel (200 mg/m^2) and carboplatin (AUC = 6) for two cycles. For patients randomized to receive cetuximab, cetuximab was administered at 400 mg/m2 on day 1 followed by 250 mg/m^2 weekly that continued through consolidation treatment. A total of 544 patients were enrolled. Standard-dose radiation was associated with improved median OS (28.7 vs. 20.3 months; HR 1.38; 95 % CI 1.09–1.76; $p = 0.004$) compared to high-dose radiotherapy, with the latter causing increased rates of severe esophagitis (21 vs. 7, %; $p < 0.0001$). The addition of cetuximab did not improve the median OS (25 vs. 24 months; HR 1.07; 95 % CI 0.84–1.35; $p = 0.29$) or median PFS (median 10.8 vs. 10.7 months and 27.5 %; HR 0.99; 95 % CI 0.80–1.22; $p = 0.89$) compared to chemotherapy alone. However, in a planned subset analysis, patients with over-expression of EGFR (H-score ≥200) had improved median OS with the use of cetuximab (42.0 vs. 21.2 months; HR 1.72; 95 % CI 1.04–2.84; $p = 0.032$). Since the study did not suggest a survival benefit with high-dose radiotherapy or cetuximab in the overall population with stage III NSCLC, concurrent paclitaxel and carboplatin with standard-dose radiotherapy followed by two cycles of consolidation paclitaxel and carboplatin remains one of the standard treatments for unresectable stage III NSCLC.

2.3 Etoposide-Based Studies

The phase II Southwest Oncology Group (SWOG) 9019 trial evaluated the regimen of cisplatin and etoposide with radiotherapy [12]. Patients with stage III NSCLC were treated with cisplatin (50 mg/m^2 on days 1, 8, 29, and 36) and etoposide (50 mg/m^2/day on days 1–5, and 29–33) along with concurrent radiation 45 Gy. In the absence of disease progression, patients then received further radiotherapy to a total dose of 61 Gy with 2 additional cycles of cisplatin and etoposide. The median OS for the 50 enrolled patients was 15 months, with 3-year OS and 5-year OS of 17 and 15 %, respectively. Major adverse events include neutropenia (grade 4 in 32 %), anemia (grade 3–4 in 28 %), esophagitis (grade 3–4 in 20 %), and respiratory infection (grade 3–4 in 8 %). This study established the role of cisplatin and etoposide with concurrent radiotherapy as one of the standard treatments for locally advanced NSCLC.

In the phase II SWOG 9504 study, patients with stage IIIB NSCLC received the same chemoradiation regimen used in SWOG 1909, with two cycles of consolidation docetaxel (75 mg/m^2) 4–6 weeks after completion of chemoradiation in the absence of tumor progression [13]. The response rates, median PFS, and median OS for the 83 patients accrued were 67 %, 16 months, and 26 months, respectively. The 3-year survival was 37 %. Neutropenia (74 %), infection (21 %), and esophagitis (17 %) were the most common severe adverse events. Four patients died of treatment-related toxicities, two from pneumonitis and two from infection.

2.4 Pemetrexed-Based Studies

The phase II CALGB 30407 study examined the role of concurrent chemoradiation with pemetrexed and carboplatin with or without cetuximab in patients with stage III NSCLC [14]. Patients were randomly assigned to four cycles of pemetrexed (500 mg/m^2) and carboplatin (AUC = 5) with concomitant radiation 70 Gy or the same chemoradiation regimen with the addition of cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly for 12 weeks). All patients received four cycles of consolidation pemetrexed (500 mg/m^2). Among the 101 enrolled, 65 % had non-squamous histologies. The median OS for patients treated with and without cetuximab was 25.2 and 21.2 months, respectively. Toxicities were similar between the two treatment arms. Common grade 3 and greater adverse events include myelosuppression, esophagitis, dysphagia, pneumonitis, dehydration, nausea, and vomiting. This study demonstrated the feasibility of concurrent chemoradiation with carboplatin and pemetrexed, with no benefits from the addition of cetuximab.

Choy and colleagues compared cisplatin to carboplatin during pemetrexed-based chemoradiation regimen in a phase II trial [15]. When the study first opened, patients with squamous cell histology were eligible. After the preferential efficacy of pemetrexed in non-squamous histology was revealed in a phase III study [16], the protocol was amended in 2008 to exclude squamous cell histology. A total of 98 patients with unresectable stage III NSCLC were randomly assigned to receive pemetrexed (500 mg/m^2) in combination with carboplatin (AUC = 5) or cisplatin (75 mg/m^2). Concurrent radiotherapy was delivered to a total dose of 64 to 68 Gy. Patients also received three cycles of consolidation pemetrexed. The cisplatin arm was associated with increased median OS (27 vs. 18.7 months), 2-year OS (58.4 % vs. 45.4 %), and median PFS (13.1 vs. 8.8 months). Due the small sample size and study design, the comparison between the two regimens was not performed. Nevertheless, both regimens were considered active and well tolerated. Dehydration was the most common grade 3–4 non-hematologic toxicity in both arms (6.5 % in the carboplatin arm and 9.6 % in the cisplatin arm). Esophagitis was experienced in 4.3 % in the carboplatin group and 5.7 % in the cisplatin group. The carboplatin arm had more severe hematologic adverse events compared to the cisplatin arm (anemia 10.9 % vs. 7.7 %; febrile neutropenia 4.3 % versus 0 %; thrombocytopenia 8.6 % vs. 5.7 %, respectively).

2.5 Comparison of Chemotherapy Regimens

The two most commonly used chemotherapy regimens in combination with radiotherapy in stage III NSCLC are cisplatin plus etoposide and carboplatin plus paclitaxel. In a small study conducted by Dr. Wang and colleagues, 65 patients with stage III NSCLC were randomized to cisplatin plus etoposide or carboplatin plus paclitaxel during concurrent radiotherapy with 60 Gy [17]. Cisplatin and etoposide was associated with increased median OS (20.2 vs. 13.5 months) and 3-year OS (33.1 vs. 13 %, $p = 0.04$).

In a retrospective analysis using the Department of Veterans Affairs Central Cancer Registry, 1,842 patients treated with either cisplatin plus etoposide or carboplatin plus paclitaxel with concomitant radiation from 2001 to 2010 were identified [18]. Cisplatin plus etoposide was used in 27 % of patients and was associated with increased median OS in univariable analysis (17.3 vs. 14.6 months, HR 0.88; 95 % CI 0.79–.98, $p = 0.02$). Nevertheless, since the population of patients receiving cisplatin plus etoposide had a higher proportion of overall favorable features such as younger age, less weight loss, and better comorbidity scores, a propensity score-match data set was performed. With this analysis, the improvement in OS from cisplatin plus etoposide did not reach statistical significance (HR 0.97; 95 % CI 0.85–1.10). The rates of hospitalization (2.4 vs. 1.7; $p < 0.001$), outpatient visits (17.6 vs. 12.6; $p < 0.001$), infections (47.3 vs. 39.4 %; $p = 0.002$), acute kidney disease/dehydration (30.5 % vs. 21.2 %; $p < 0.001$), and mucositis plus esophagitis (18.6 % vs. 14.4 %; $p = 0.0246$) were increased in the cisplatin plus etoposide regimen compared to carboplatin plus paclitaxel.

The PROCLAIM study is a phase III trial comparing cisplatin plus pemetrexed to cisplatin plus etoposide during concurrent chemoradiotherapy [19]. Patients with stage III NSCLC were randomly assigned to receive three cycles of cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) every 3 weeks or cisplatin (50 mg/m^2 on days 1, 8, 29, and 36) plus etoposide (50 mg/m^2 on days 1–5 and 29–33) during concurrent radiotherapy with 66 Gy. After concomitant chemoradiation, patients received further consolidation chemotherapy with four cycles of pemetrexed in the cisplatin plus pemetrexed arm or a choice of 3 regimens in the cisplatin plus etoposide arm. The cisplatin plus pemetrexed was associated with a numerically superior response rate (36 % vs. 33 %, $p = 0.458$), median PFS (11.4 vs. 9.8 months; HR 0.86; 95 % CI 0.71–1.04), and median OS (26.8 vs. 25.0 months; HR 0.98; 95 % CI 0.79–1.20; $p = 0.831$), although none reached statistical significance. The pemetrexed arm was associated with decreased rates of severe neutropenia (24.4 % vs. 44.5 %) and esophagitis (15.5 % vs. 20.6 %). This study demonstrated that cisplatin plus pemetrexed with concurrent radiotherapy was as effective as cisplatin plus etoposide, but with a better safety profile.

2.6 Consolidation Chemotherapy

Although several studies include the use of consolidation chemotherapy, its role in the management of patients with unresectable stage III NSCLC remains undefined (Table 1).

In the HOG/USO study, the chemoradiation followed by consolidation docetaxel, as used in the SWOG 9504 regimen, was compared to chemoradiation alone [20]. Although the planned accrual was for 259 patients, the trial was closed early, after enrollment of 203 patients, when an interim analysis suggested evidence of futility. Compared to observation, the docetaxel arm was associated with similar median OS (21.2 vs. 23.2 months, $p = 0.883$) and 3-year OS (27.1 % vs. 26.1 %). Consolidation docetaxel was associated with increased rates of febrile neutropenia

Table 1 Clincal trials of consolidation chemotherapy for stage III NSCLC

Trial	Year	Study arms	Median OS (months)	Survival rate
HOG/USO[20]	2008	Cis/Etop + RT - > Obs versus Cis/Etop + RT - > Doc	23.2 versus 21.2 (p = 0.08)	(3-yr) 26.1 % versus 27.1 %
GILT[21]	2012	Cis/Vin + RT - > Obs versus Cis/Vin + RT - > Cis/Vin	18.5 versus 20.8 (p = 0.87)	(4-yr) 21.4 % versus 25.3 %
KCSG-LU05-04[22]	2015	Cis/Doc + RT - > Obs versus Cis/Doc + RT - > Cis/Doc	20.6 versus 21.8 (p = 0.44)	NA

Cis cisplatin; *Etop* etoposide; *RT* radiotherapy; *Obs*,observation; *Doc* docetaxel; *Vin* vinorelbine

and grade 3–5 pneumonitis (9.6 % vs. 1.4 %). Five percent of patients in the docetaxel arm died of grade 5 toxicities.

The phase III GILT study examined the role of consolidation cisplatin and oral vinorelbine after concurrent chemoradiotherapy [21]. Patients received two cycles of oral vinorelbine (50 mg/m^2 on days 1, 8, and 15) and cisplatin (20 mg/m^2 on days 1–4) every 4 weeks with concomitant radiotherapy at 66 Gy. Patients without disease progression were further randomized to two cycles of consolidation therapy with oral vinorelbine (60–80 mg/m^2 on days 1 and 8) and cisplatin (80 mg/m^2 on day 1) every 3 weeks versus observation. A total of 279 patients were enrolled. The overall response rate of chemoradiation was 60.7 %. Consolidation chemotherapy did not improve median PFS (6.4 vs. 5.5 months, p = 0.63) or median OS (20.8 vs. 18.5 months, p = 0.87). The 4-year survival rates were 25.3 and 21.4 % for the consolidation and the observation arm, respectively. Concurrent chemoradiation caused esophagitis in 8.6 %, nausea in 5.0 %, fatigue in 3.3 %, and pneumonia/pneumonitis in 2.6 %. Neutropenia and anemia were the most common severe hematologic toxicities (neutropenia in 11.2 % and anemia in 3.2 %). Consolidation chemotherapy caused more neutropenia (11.7 % vs. 5.7 %), anemia (3.5 % vs. 1.1 %), nausea (4.7 % vs. 2.9 %), and fatigue (2.3 % vs. 1.0 %) compared to observation.

The KCSG-LU05-04 trial was a phase III study examining the efficacy of consolidation cisplatin plus docetaxel following concurrent chemoradiation with the same regimen [22]. Concurrent chemoradiation entailed weekly cisplatin (20 mg/m^2) and docetaxel (20 mg/m^2) for 6 weeks with 66 Gy of radiotherapy. Consolidation docetaxel was given at 35 mg/m^2 on days 1 and 8 every 3 weeks for three cycles. A total of 437 patients in Korea, China, and Taiwan were randomly assigned to concurrent chemoradiation alone versus chemoradiation followed by consolidation docetaxel. Although numerically superior, the improvement in median PFS (9.1 vs. 8.1 months, HR 0.91; 95 % CI 0.73–1.12; p = 0.36) and median OS (20.6 vs. 21.8 months; HR 0.91; 95 % CI 0.72–1.25; p = 0.44) did not reach statistical significance. The most common grade 3–4 toxicities in the

chemoradiotherapy phase were esophagitis (9.5 %), infection (6.4 %), anorexia (4.0 %), and anemia (5.4 %). Consolidation chemotherapy induced more neutropenia (6.9% vs. 2.9 %), febrile neutropenia (1.8% vs. 0 %), fatigue (4.6 versus 0 %), and anorexia (3.5 versus 1.2 %) compared to observation.

In a pooled analysis including 3,479 patients from 41 studies, consolidation chemotherapy did not prolong median OS compared to observation alone (19.0 vs. 17.9 months; HR 0.94; 95 % CI 0.81–1.09; $p = 0.40$) [23]. The 3-year survival rates were also similar between the consolidation and the observation group (27.0 % vs. 24.8 %). Grade 3-5 neutropenia, esophagitis, pneumonitis, and treatment-related deaths were similar in the two study groups.

With the lack of established benefit from consolidation chemotherapy in 3 randomized Clincal trials and a pooled analysis, the American Society for Radiation Oncology (ASTRO) guideline recommended against routine use of consolidation chemotherapy after concurrent chemoradiation [24]. However, patients who did not receive full doses of systemic chemotherapy during radiotherapy can be considered for consolidation chemotherapy.

3 Molecularly Targeted Therapy

Several targeted drugs used in advanced stage NSCLC have been tried in patients with locally advanced disease. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor receptor (VEGFR), is an approved therapy for patients with advanced non-squamous NSCLC [25]. The use of bevacizumab during chemoradiation, however, was associated with increased risk of bleeding and development of trachea–esophageal fistula [26]. Due to the severe toxicities, bevacizumab is no longer being investigated during chemoradiotherapy.

The epidermal growth factor receptor has been studied in patients with stage III NSCLC with trial including both the monoclonal antibody cetuximab and the tyrosine kinase inhibitors gefitinib and erlotinib. In the NEAR trial, 30 patients who were unfit or unwilling to receive chemoradiation received weekly cetuximab during radiotherapy followed by 13 weeks of consolidation [27]. The treatment was well tolerated, and the outcomes including median OS of 19.5 months and 2-year OS of 34.9 % are comparable to those obtained from standard chemoradiation. Using a similar design except for the consolidation cetuximab, the N0422 study showed a median OS of 15.1 months in 57 patients with stage III NSCLC who were elderly or had poor performance status [28]. The Swedish Lung Cancer Group trial examined the role of concurrent weekly cetuximab in combination with thoracic radiation therapy (68 Gy over 7 weeks), following 2 cycles of induction chemotherapy with cisplatin and docetaxel [29]. The clinical benefit rate at 12 months was 30 % and median OS was 17 months. Grade 3 esophagitis was seen in 1.4 % and grade 3 skin toxicity in 4.2 %. Ramalingam and colleagues conducted a multicenter single-arm phase II trial in which 40 patients with unresectable IIIA or IIIB NSCLC were treated with thoracic radiotherapy to a dose of 73.5 Gy in 35 fractions over 7 weeks in combination with weekly cetuximab, which was

continued during consolidation therapy with carboplatin and paclitaxel for a maximum of 26 doses [30]. The median OS, primary endpoint of the study, was 19.4 months. Cetuximab addition to chest radiation and consolidation chemotherapy was well tolerated with 3 patients experiencing a grade 3 rash. No grade 3 or 4 esophagitis was observed. EGFR gene copy number by fluorescence in situ hybridization (FISH) was not predictive of outcomes in this study. The safety of cetuximab in combination with definitive chemoradiation in NSCLC has also been demonstrated by the Radiation Therapy Oncology Group (RTOG) 0324 and Cancer and Leukemia Group B (CALGB) 30407 trials, where toxicities observed in the arms with combined chemotherapy and cetuximab were comparable to those with chemotherapy alone [14, 31].

The Southwest Oncology Group (SWOG) S0023 trial was designed to evaluate whether the addition of gefitinib maintenance therapy improved overall survival following concurrent chemoradiation with cisplatin and etoposide followed by three cycles of consolidation docetaxel [32]. A total of 243 molecularly unselected patients with stage III NSCLC were randomized to receive gefitinib or placebo following concurrent chemoradiation with cisplatin and etoposide and consolidation docetaxel. Although gefitinib was well tolerated, survival was worse in the gefitinib arm, predominantly due to tumor progression. The Japanese Cooperative Oncology Group (JCOG) 0402 study examined the role of induction chemotherapy followed by gefitinib and concurrent thoracic radiation in patients with unresectable adenocarcinoma, selected by light or never smoking status only, and did not meet predefined criteria for feasibility due to increased toxicity mostly with grade 3 and 4 liver enzyme elevations [33]. In a phase II study including 46 unselected patients with stage III NSCLC treated with erlotinib 150 mg daily during standard chemoradiation with weekly carboplatin plus paclitaxel followed by two cycles of consolidation with chemotherapy alone, the median and 5-year OS were encouraging at 36.5 months and 39.5 %, respectively [34]. Of note, there were 4 patients with *EGFR* mutation and 5 patients with unknown *EGFR* status in the study, precluding the evaluation of the effects of this mutation in the outcome.

The RTOG 1306 is a phase II study evaluating the role of targeted agents in molecularly selected patients with locally advanced NSCLC. In this study, patients with stage III *EGFR*-mutant lung cancer and *ALK*-positive NSCLC will be

Fig. 1 RTOG 1306 schema *Targeted therapy Erlotinib* for EGFR mutation or crizotinib for *ALK* fusion for 12 weeks. If CT scan after 6 weeks of targeted therapy does not show *PR*, patients should proceed directly to chemoradiation *Chemotherapy* cisplatin plus etoposide or carboplatin plus paclitaxel *Radiation* 60 Gy in 30 fractions with intensity-modulated radiation therapy (IMRT) or 3D conformal radiation therapy (3D-CRT)

randomized to 12 weeks of induction erlotinib (*EGFR*-mutant) or crizotinib (*ALK*-positive) followed by chemoradiation, or chemoradiation alone (Fig. 1) [35].

4 Immunotherapy

In patients with stage III disease, the largest experience with immunotherapy is with tecemotide (liposomal BLP25), a peptide-based vaccine consisting of synthetic mucin 1 (MUC-1) lipopeptide combined with the adjuvant monophosphoryl lipid A and three lipids forming a liposomal product. In a phase II study, 171 patients with stage IIIB or IV NSCLC who had no tumor progression after the initial therapy were randomized to tecemotide 100 μg weekly for 8 weeks followed by maintenance every 6 weeks until tumor progression or observation [36]. Although there was no benefit from the vaccine in the study population, a post hoc analysis showed increased median (not reached vs. 13.3 months) and 2-year OS (60 % vs. 36.7 %) in the tecemotide group. The encouraging results in patients with stage III NSCLC led to the START trial, a phase III study where 1,513 patients were randomized to receive tecemotide versus placebo following definitive chemoradiation [37]. Although tecemotide was not associated with improved median OS in the entire patient population (25.6 vs. 22.3 months, HR 0.88, 95 % CI 0.75–1.03, $p = 0.12$), it improved median OS in a subset analysis of patients treated with concurrent chemoradiation (30.8 vs. 20.6 months; HR 0.78; 95 % CI 0.64–0.95, $p = 0.01$). In the updated analysis with a median follow-up of 58 months, the addition of tecemotide was associated with increased median OS in patients treated with concurrent chemoradiation (29.8 vs. 20.8 months, HR 0.81; 95 % CI 0.68–0.98, $p = 0.026$) but not in those treated with sequential therapy (20.7 vs. 25.5 months, HR 1.04; 95 % CI 0.82–1.31, $p = 0.76$) [38]. Soluble MUC and antinuclear antibodies were associated with improved survival in patients treated with tecemotide. Two large randomized studies testing tecemotide in patients treated with concurrent chemoradiation, START2 and INSPIRE, were discontinued after the results from the EMR 63325-009 study, which showed no benefit from the addition of tecemotide to chemoradiation.

Checkpoint inhibitors represent a promising new approach to the treatment of NSCLC, with nivolumab and pembrolizumab approved for patients with previously treated advanced stage NSCLC [39–41]. The role of immune checkpoint inhibitors in patients with locally advanced NSCLC is currently being investigated. Both anti-programmed death 1 (PD-1) and anti-programmed death cell ligand 1 (PDL-1) antibodies are being investigated as consolidation therapy after standard chemoradiation for patients with stage III NSCLC [42].

5 Conclusions

The cure rates for patients with locally advanced NSCLC remain suboptimal with standard chemoradiation. There are several acceptable chemotherapy regimens to be used during concurrent radiotherapy, and the escalation of the radiation dose is

not associated with improved outcomes. Consolidation chemotherapy, although commonly used, has not shown improvement in survival compared to chemoradiation alone and should be considered only in selected cases. The role for targeted therapy in molecularly selected patients is currently being evaluated in this potentially curative patient population, although its applicability is limited by the low probability of patients harboring targetable driver gene abnormalities. There are ongoing studies testing consolidation therapy with checkpoint inhibitors, and the results are eagerly awaited.

References

1. Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. CA Cancer J Clin 65(1):5–29
2. Govindan R, Page N, Morgensztern D et al (2006) Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol: Official J Am Soc Clin Oncol 24(28):4539–4544
3. Morgensztern D, Ng SH, Gao F, Govindan R (2010) Trends in stage distribution for patients with non-small cell lung cancer: a national cancer database survey. J Thorac Oncol: Official Publ Int Assoc Study of Lung Cancer 5(1):29–33
4. Morgensztern D, Waqar S, Subramanian J, Trinkaus K, Govindan R (2012) Prognostic impact of malignant pleural effusion at presentation in patients with metastatic non-small-cell lung cancer. J Thorac Oncol: Official Publ Int Assoc Study of Lung Cancer 7(10):1485–1489
5. Goldstraw P, Crowley J, Chansky K et al (2007) The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol: Official Publ Int Assoc for the Study of Lung Cancer 2(8):706–714
6. Ettinger DS, Akerley W, Borghaei H et al (2012) Non-small cell lung cancer. J Nat Compr Cancer Network: JNCCN 10(10):1236–1271
7. Dillman RO, Seagren SL, Propert KJ et al (1990) A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. The New England J Med 323(14):940–945
8. Curran WJ Jr, Paulus R, Langer CJ et al (2011) Sequential versus concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst 103(19):1452–1460
9. Auperin A, Le Pechoux C, Rolland E et al (2010) Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol: Official J Am Soc Clin Oncol 28(13):2181–2190
10. Belani CP, Choy H, Bonomi P et al (2005) Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol: Official J Am Soc Clin Oncol 23(25):5883–5891
11. Bradley JD, Paulus R, Komaki R et al (2015) Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 16(2):187–199
12. Albain KS, Crowley JJ, Turrisi AT 3rd et al (2002) Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. J Clin Oncol: Official J Am Soc Clin Oncol 20(16):3454–3460
13. Gandara DR, Chansky K, Albain KS et al (2003) Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. J Clin Oncol: Official J Am Soc of Clin Oncol 21(10):2004–2010

14. Govindan R, Bogart J, Stinchcombe T et al (2011) Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. J Clin Oncol: Official J Am Soc of Clin Oncol 29(23):3120–3125
15. Choy H, Schwartzberg LS, Dakhil SR et al (2013) Phase 2 study of pemetrexed plus carboplatin, or pemetrexed plus cisplatin with concurrent radiation therapy followed by pemetrexed consolidation in patients with favorable-prognosis inoperable stage IIIA/B non-small-cell lung cancer. J Thorac Oncol: Official Publication Int Assoc Study of Lung Cancer 8(10):1308–1316
16. Scagliotti GV, Parikh P, von Pawel J et al (2008) Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol: Official J Am Soc Clin Oncol 26 (21):3543–3551
17. Wang L, Wu S, Ou G et al (2012) Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer. Lung Cancer 77(1):89–96
18. Santana-Davila R, Devisetty K, Szabo A et al (2015) Cisplatin and etoposide versus carboplatin and paclitaxel with concurrent radiotherapy for stage III non-small-cell lung cancer: an analysis of Veterans Health Administration data. J Clin Oncol: Official J Am Soc Clin Oncol 33(6):567–574
19. Senan S, Brade AM, Wang L et al (2015) Final overall survival (OS) results of the phase III PROCLAIM trial: Pemetrexed (Pem), cisplatin (Cis) or etoposide (Eto), Cis plus thoracic radiation therapy (TRT) followed by consolidation cytotoxic chemotherapy (CTX) in locally advanced nonsquamous non-small cell lung cancer (nsNSCLC). ASCO Meet Abs. 2015;33 (15_suppl):7506
20. Hanna N, Neubauer M, Yiannoutsos C et al (2008) Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. Journal of Clincal Oncology: Official Journal of the American Society of. Clin Oncol 26(35):5755–5760
21. Huber RM, Engel-Riedel W, Kollmeier J et al (2012) GILT study: oral vinorelbine (NVBo) and cisplatin (P) with concomitant radiotherapy (RT) followed by either consolidation (C) with NVBo plus P plus best supportive care (BSC) or BSC alone in stage (st) III non-small cell lung cancer (NSCLC): final results of a phase (ph) III study. ASCO Meet Abs. 2012;30 (15_suppl):7001
22. Ahn JS, Ahn YC, Kim JH et al (2015) multinational randomized phase iii trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage iii non-small-cell lung cancer: KCSG-LU05-04. J Clin Oncol
23. Tsujino K, Kurata T, Yamamoto S et al (2013) Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung cancer?: A pooled analysis of the literature. J Thorac Oncol 8(9):1181–1189
24. Bezjak A, Temin S, Franklin G et al (2015) Definitive and adjuvant radiotherapy in locally advanced non–small-cell lung cancer: american society of Clincal oncology Clincal practice guideline endorsement of the american society for radiation oncology evidence-based Clincal practice guideline. J Clin Oncol. 2015;33(18):2100–2105
25. Sandler A, Gray R, Perry MC et al (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. The New England J Med 355(24):2542–2550
26. Spigel DR, Hainsworth JD, Yardley DA et al (2010) Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. J Clin Oncol 28 (1):43–48
27. Jensen AD, Munter MW, Bischoff HG et al (2011) Combined treatment of nonsmall cell lung cancer NSCLC stage III with intensity-modulated RT radiotherapy and cetuximab: the NEAR trial. Cancer 117(13):2986–2994

28. Jatoi A, Schild SE, Foster N et al (2010) A phase II study of cetuximab and radiation in elderly and/or poor performance status patients with locally advanced non-small-cell lung cancer (N0422). Annals of Oncol: Official J Euro Soc Med Oncol/ESMO 21(10):2040–2044
29. Hallqvist A, Wagenius G, Rylander H et al (2011) Concurrent cetuximab and radiotherapy after docetaxel-cisplatin induction chemotherapy in stage III NSCLC: satellite–a phase II study from the Swedish Lung Cancer Study Group. Lung Cancer 71(2):166–172
30. Ramalingam SS, Kotsakis A, Tarhini AA et al (2013) A multicenter phase II study of cetuximab in combination with chest radiotherapy and consolidation chemotherapy in patients with stage III non-small cell lung cancer. Lung Cancer 81(3):416–421
31. Blumenschein GR Jr, Paulus R, Curran WJ et al (2011) Phase II study of cetuximab in combination with chemoradiation in patients with stage IIIA/B non-small-cell lung cancer: RTOG 0324. J Clin Oncol: Official J Am Soc Clin Oncol 29(17):2312–2318
32. Kelly K, Chansky K, Gaspar LE et al (2008) Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol 26(15):2450–2456
33. Niho S, Ohe Y, Ishikura S et al (2012) Induction chemotherapy followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced adenocarcinoma of the lung: a multicenter feasibility study (JCOG 0402). Annals of Oncol: Official J Euro Soc Med Oncol/ESMO 23(9):2253–2258
34. Komaki R, Allen PK, Wei X et al (2015) Adding Erlotinib to Chemoradiation Improves Overall Survival but Not Progression-Free Survival in Stage III Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 92(2):317–324
35. Devarakonda S, Morgensztern D, Govindan R (2013) Molecularly targeted therapies in locally advanced non-small-cell lung cancer. Clin lung Cancer 14(5):467–472
36. Butts C, Murray N, Maksymiuk A et al (2005) Randomized phase IIB trial of BLP25 liposome vaccine in stage IIIB and IV non-small-cell lung cancer. J Clin Oncol: Official J Am Soc Clin Oncol 23(27):6674–6681
37. Butts C, Socinski MA, Mitchell PL et al (2014) Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. Lancet Oncol 15(1):59–68
38. Mitchell P, Thatcher N, Socinski MA, et al (2015) Tecemotide in unresectable stage III non-small-cell lung cancer in the phase III START study: updated overall survival and biomarker analyses. Ann Oncol
39. Brahmer J, Reckamp KL, Baas P et al (2015) Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. The New England J Med 373(2):123–135
40. Sul J, Blumenthal GM, Jiang X, He K, Keegan P, Pazdur R (2016) FDA approval summary: Pembrolizumab for the treatment of patients with metastatic non-small cell lung cancer whose tumors express programmed death-ligand 1. Oncologist 21(5):643–650
41 Kazandjian D, Suzman DL, Blumenthal G, Mushti S, He K, Libeg M, Keegan P, Pazdur R. FDA approval summary: Nivolumab for the treatment of metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy. Oncologist 2016 May; 21(5):634-642
42 Mamdani H, Jalal SI, Hanna N (2015) Locally advanced non-small cell lung cancer: Optimal chemotherapeutic agents and duration. Curr Treat Options Oncol 16(10):364

Targeted Therapies for Lung Cancer

Thomas E. Stinchcombe

Abstract

Targeted therapies have become standard therapies for patients with non-small cell lung cancer (NSCLC). A phase III trial of carboplatin and paclitaxel with and without bevacizumab in patients with advanced NSCLC with non-squamous histology demonstrated a statistically significant improvement in efficacy. In patients with NSCLC with an activating epidermal growth factor receptor (*EGFR*) mutation (defined as exon 19 deletion and exon 21 L858R point mutation), phase III trials of EGFR tyrosine kinase inhibitors (TKI) compared to platinum-based chemotherapy have demonstrated superior efficacy in the first-line setting. In patients with NSCLC with anaplastic lymphoma kinase (*ALK*) rearrangements, phase III trials of crizotinib have demonstrated superior efficacy compared to platinum–pemetrexed in the first-line setting and standard chemotherapy in the second-line setting. A second-generation ALK inhibitor, ceritinib, is available for patients who have progressed after or were intolerant of crizotinib. Crizotinib has also demonstrated activity on patients with ROS1 rearrangements, and BRAF inhibitors (dabrafenib, vemurafenib) have demonstrated activity in patients with NSCLC with *BRAF* V600E mutation. The oncogenic mutations that are susceptible to targeted therapy are mainly found in non-squamous NSCLC. The development of targeted therapy in patients with squamous NSCLC has been more challenging due to the genomic complexity observed in the squamous histology and the low prevalence of *EGFR*, *ALK*, and *ROS1* molecular alterations. A phase III trial of cisplatin and gemcitabine with and without necitumumab in patients with advanced NSCLC with squamous histology demonstrated a statistically significant improvement in progression-free and overall survival.

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Contents

1 Introduction

Lung cancer remains a leading cause of cancer-related mortality in the United States and globally [1–3]. The majority of patients have the non-small cell lung cancer (NSCLC) subtype and present with advanced stage disease at the time of diagnosis [4]. In patients with advanced NSCLC, defined as stage IIIB or IV disease, platinum-based chemotherapy was the mainstay of systemic therapy for several decades. However, clinical trials of various combinations of platinum doublets revealed a therapeutic plateau had been reached [5, 6]. Consequently, the focus of drug development became agents that targeted a critical cell signaling pathway or a specific oncogenic process. Several targeted agents have become standard of care in the treatment of NSCLC, and others are currently in development. The identification and development of predictive biomarkers for targeted therapies have accelerated the pace of drug development and significantly improved the clinical care of patients with advanced NSCLC. The currently available targeted therapies are most frequently used in patients with NSCLC with non-squamous histology. The development of targeted therapies for small cell lung cancer (SCLC) and NSCLC with squamous histology has been more challenging.

2 Anti-angiogenesis Agents

The ability to develop new blood vessels is one the hallmarks of cancer and new blood vessels provide oxygen and nutrients to sustain tumor growth and can provide a conduit for development of new metastatic lesions [7]. Disrupting the process of angiogenesis was a focus of extensive research. The first anti-angiogenesis agent available for advanced NSCLC was bevacizumab, a monoclonal antibody that target vascular endothelial growth factor (VEGF) A, which is a ligand that binds to VEGF receptors. A randomized phase II trial investigated carboplatin and paclitaxel alone and with bevacizumab at 7.5 mg/kg every three weeks or 15 mg/kg every three weeks in advanced NSCLC (all histologies) [8]. This trial established the bevacizumab dose of 15 mg/kg every three weeks as the preferred dose for further investigation in combination with carboplatin and paclitaxel. A prohibitive rate of pulmonary hemorrhage was observed in patients with squamous histology treated with bevacizumab, and patients with squamous histology were excluded from subsequent trials. The phase III trial compared carboplatin and paclitaxel with and without bevacizumab in patients with advanced NSCLC with non-squamous histology. Patients with hemoptysis, uncontrolled hypertension, clinically significant cardiovascular disease, and on therapeutic anticoagulation were excluded. This trial revealed a statistically superior objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) with the addition of bevacizumab (Table 1) [9]. A three arm phase III trial investigated cisplatin and gemcitabine with placebo, bevacizumab 7.5 mg/kg every three weeks, or 15 mg/kg every three weeks in patients with advanced NSCLC with non-squamous histology (Table 1) [10, 11]. The primary end-point was PFS, and the trial was not designed to compare the efficacy of the two bevacizumab arms. Patients assigned to bevacizumab 7.5 mg/kg or 15 mg/kg every three weeks arms compared to the placebo arm had a statistically superior ORR and PFS; a statistically significant difference in the secondary end-point of OS was not observed between the individual bevacizumab arms compared to placebo. The unique grade 3 or 4 bevacizumab-related toxicities observed in these trials were hypertension, proteinuria, and hemorrhage (pulmonary or gastrointestinal). Bevacizumab in combination with platinum-based therapy was the first targeted therapy, demonstrating an improvement in outcome compared to platinum-based chemotherapy alone. However, concerns about toxicities, treatment restrictions related to the comorbidities, and the lack of a predictive biomarker have limited the future development of the agent.

Ramucirumab is a monoclonal antibody against the extracellular domain of VEGF receptor 2, and a phase III trial investigated docetaxel with placebo or ramucirumab in patients who had experienced disease progression after platinum-based therapy [12]. There were no eligibility restrictions related to histology, and approximately 25 % of the patients enrolled had squamous NSCLC. A statistically significant higher ORR, longer PFS, and longer OS were observed in patients assigned to the ramucirumab compared to the placebo arm (Table 1).

Table 1 Select phase III trials of anti-angiogenesis agents in advanced non-small cell lung cancer

Comparison (# of patients)	Line of therapy	Objective response rate	Median progression-free survival	Median overall survival
Carboplatin and paclitaxel ± bevacizumab [9] (n = 838)	First-line	35 % versus 15 % $p < 0.001$	6.2 versus 4.5 months HR = 0.66, $p < 0.001$	12.3 versus 10.3 months HR = 0.79, $p = 0.003$
Cisplatin/gemcitabine with placebo [10, 11] bevacizumab 7.5 mg/kg bevacizumab 15 mg/kg (n = 1043)[a]	First-line	20.1 % 34.1 % ($p < 0.0001$) 30.4 % ($p = 0.0023$)	6.1 months 6.7 months, HR = 0.75, $p = 0.003$ 6.5 months, HR = 0.82, $p = 0.03$	13.1 months 13.6 months, HR = 0.93, $p = 0.420$ 13.4 months, HR = 1.03, $p = 0.761$
Docetaxel with placebo or ramucirumab [12] (n = 1253)	Second-line	23 % versus 14 % $P < 0.0001$	4.5 versus 3.0 months HR = 0.76, $p < 0.0001$	10.5 versus 9.1 months HR = 0.86, $p = 0.023$

[a]This is a 3-arm trials and bevacizumab 7.5 mg/kg and 15 mg/kg were compared to placebo arm
HR: hazard ratio

A higher rate of toxicity was not observed in the squamous histology subset. In the ramucirumab compared to the docetaxel alone arm, a higher rate of febrile neutropenia was observed (10 % vs. 6 %); a similar rate of grade ≥3 hemorrhage (2 % in each arm) and hypertension (6 % vs. 2 %) were observed in the two arms. A predictive biomarker for ramucirumab has not been identified.

3 Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors in EGFR Mutant NSCLC

In the early trials of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), patients with history of light or never smoking, adenocarcinoma histology, and Asian ethnicity were observed to higher response rate [13]. Patients with these clinical characteristics were subsequently found to have a high rate of activating *EGFR* mutations, defined as exon 19 deletions or exon 21 L858R point mutations [14, 15]. Based on these clinical observations, a prospective phase III trial compared gefitinib to carboplatin/paclitaxel in patients with a history of light or never smoking and advanced NSCLC with adenocarcinoma histology was performed in Asia [16]. Patients assigned to the gefitinib compared to carboplatin and paclitaxel arm experienced a statistically significant higher ORR and longer PFS in the intent-to-treat patient population. In the subgroup of patients with a confirmed EGFR mutation (n = 261), patients assigned to gefitinib compared to carboplatin and paclitaxel experienced a statistically significant higher ORR and PFS (Table 2). Patients who did not have an *EGFR* mutation (n = 176) assigned to the gefitinib

arm compared to the carboplatin and paclitaxel arm had a statistically significant lower ORR (1.1 % vs. 23.5 %, $p < 0.001$) and shorter PFS (HR of 2.85; 95 % CI, 2.05–3.98, $p < 0.001$; median PFS of 1.5 and 5.5 months) [16, 17]. The rate of *EGFR* mutations in this clinically enriched cohort was approximately 60 %. This trial established *EGFR* mutation as opposed to *EGFR* fluorescence in situ hybridization (FISH) and EGFR immunohistochemistry (IHC) as the preferred biomarker for selection of EGFR TKI therapy [17]. It also established that clinical characteristics were not sufficient to select patients for first-line EGFR TKI and *EGFR* mutation testing was required. Additional trials comparing EGFR TKI to platinum doublets have been performed which required the presence of an *EGFR* mutation for enrollment (Table 2). These trials have consistently shown a

Table 2 Select trials of epidermal growth factor receptor tyrosine kinase inhibitors compared to platinum-based chemotherapy

Trial (# of patients)	Comparison	Objective response rate	Median progression-free survival	Median overall survival
IPASS [16, 17] ($n = 261$)[a]	Gefitinib versus carboplatin and paclitaxel	71.2 % versus 47.3 % $p < 0.001$	9.5 versus 6.3 months HR = 0.48, $p < 0.001$	21.6 versus 21.9 HR = 1.00, $p = 0.990$
NEJSG [18] ($n = 200$)	Gefitinib versus carboplatin and paclitaxel	73.7 % versus 30.7 % $P < 0.001$	10.8 versus 5.4 months HR = 0.30, $p < 0.001$	30.5 versus 23.6 months $P = 0.31$
WJTOG [19] ($n = 172$)	Gefitinib versus cisplatin and docetaxel	62.1 % versus 32.2 % $P < 0.0001$	9.2 versus 6.3 months HR = 0.489, $p < 0.0001$	30.9 versus not reached HR = 1.638, $p = 0.211$
CTONG [24] ($n = 165$)	Erlotinib versus carboplatin and gemcitabine	83.0 % versus 36 % $P < 0.0001$	13.1 versus 4.6 months HR = 0.16, $p < 0.001$	22.69 versus 28.85 months HR = 1.04, $p = 06915$
EURTAC [23] ($n = 174$)	Erlotinib versus platinum-doublet	58 % versus 15 %	9.7 versus 5.2 months HR = 0.37, $p < 0.0001$	19.3 versus 19.5 months HR = 1.04, $p = 0.87$
LUX Lung-3 [21] ($n = 345$)	Afatinib versus cisplatin and pemetrexed	56 % versus 23 % $P < 0.001$	11.1 versus 6.9 months HR = 0.58, $p < 0.001$	28.2 versus 28.2 months HR = 0.88, $p = 0.39$
LUX Lung-6 [20] ($n = 364$)	Afatinib versus cisplatin and gemcitabine	66.9 % versus 23.0 % $P < 0.0001$	11.0 versus 5.6 months HR = 0.28, $p < 0.0001$	23.1 versus 23.5 months HR = 0.93, $p = 0.61$

IPASS Iressa Pan Asia Study, *NEJSG* North East Japan Study Group, *WJTOG* West Japan Thoracic Oncology Group, *CTONG* Chinese Thoracic Oncology Group, *EURTAC* European Tarceva versus Chemotherapy, *HR* hazard ratio

[a]The data represent the subgroup with a confirmed *EGFR* mutation

superiority in ORR, PFS, and quality of life in the EGFR TKI arm [18–26]. The most common adverse events observed with this class of agents are rash and diarrhea, and less common serious adverse events include stomatitis, paronychia, and interstitial pneumonitis.

Retrospective analyses observed that patients with *EGFR* exon 19 deletions compared to exon 21 L858R had better outcomes with EGFR TKIs, but clinically patients with exon 19 or 21 *EGFR* mutations were treated the same. A recent combined analysis of two trials of afatinib compared to platinum-based chemotherapy has challenged the assumption *EGFR* exon 19 and exon 21 should be treated similarly [27]. In the combined analysis of the two trials, in patients with an *EGFR* exon 19 and exon 21 L858R mutations ($n = 631$) a statistically significant longer OS was observed in patients assigned to afatinib compared to platinum-based therapy (hazard ratio (HR) of 0.81, 95 % confidence interval (CI), 0.66–0.99; $p = 0.037$; median OS of 27.3 and 24.3 months, respectively). When patients were analyzed by mutation type, the OS difference remained statistically significant in the exon 19 deletion patient subgroup ($n = 355$, HR of 0.59, 95 % CI, 0.45–0.77; $p = 0.0001$; median OS of 31.7 and 20.7 months, respectively). However, a statistically significant difference in OS was not observed in the exon 21 L858R deletion subgroup ($n = 276$, HR of 1.25, 95 % CI, 0.92–1.71; $p = 0.16$; median OS of 22.1 and 26.9 months, respectively). This observation raises the question whether afatinib is a better EGFR TKI for patients with *EGFR* exon 19 deletions since previous trials of EGFR TKI compared to platinum-based therapy have revealed an improvement in ORR and PFS, but not an OS improvement in the intent-to-treat patient population.

The development of EGFR TKI therapy in patients with *EGFR* mutant NSCLC has been a significant therapeutic advance; however, disease progression is inevitable and generally occurs within 10–15 months. Multiple mechanisms of resistance have been identified, but approximately 50–60 % of *EGFR* mutant NSCLC develop a T790M resistance mutation [28–30]. A separate chapter focuses of the mechanisms of resistance and drugs in development for this patient population.

4 EGFR Tyrosine Kinase Inhibitors in Second- or Third-Line Setting

Erlotinib is currently available for patients who have progressed on platinum-based chemotherapy based on a phase III trial of erlotinib compared to best supportive care which revealed an improvement in ORR, PFS, OS, and QoL [31, 32]. An analysis of the benefit according to tumor molecular characteristics revealed that OS was not influenced by *EGFR* mutation status [33]. Thus, erlotinib is available as a treatment in the second- and third-line settings regardless of *EGFR* mutation status. However, the limited activity observed in the *EGFR* wild-type NSCLC in the first-line setting raised questions about the efficacy of EGFR TKIs in the second- and third-line settings. A prospective trial enrolled patients who had experienced disease progression after platinum-based therapy with *EGFR* wild-type tumors to

docetaxel or erlotinib (n = 222) [34]. Patients assigned to the docetaxel compared to erlotinib experienced a superior OS (HR of 0.73, 95 % CI, 0.523–1.00; p = 0.05; median OS of 8.2 and 5.4 months, respectively) and PFS (HR of 0.71, 95 % CI, 0.53–0.95; p = 0.02; median 2.9 and 2.4 months). These data support the use of chemotherapy as the preferred second-line therapy for patients who are candidates for second-line chemotherapy.

There has been considerable interest in defining an *EGFR* mutation wild-type patient population who may benefit from EGFR TKIs in the second- and third-line setting based on clinical factors or a predictive biomarker. A multivariate serum proteomic test can classify patients into two categories related to good or poor outcome from EGFR TKI therapy [35]. A phase III trial prospectively assessed the proteomic signature and stratified patients based on good or poor status and then randomized patients to erlotinib or second-line chemotherapy [36]. A statistically significant interaction between treatment and proteomic classification was observed (p = 0.017). Among patient with proteomic classification of good, patients assigned to the chemotherapy compared to erlotinib had a similar OS (HR of 1.06, 95 % CI, 0.77–1.47; p = 0.714; median OS of 10.9 and 11.0 months). Among patients with proteomic classification of poor, patients assigned to the erlotinib arm compared to the chemotherapy arm had a statistically significant worse OS (HR of 1.72, 95 % CI, 1.08–2.74, p = 0.022; median of OS of 3.0 and 6.4 months). Patients with the serum proteomic status of poor should not receive erlotinib, and the primary utility of the test is in *EGFR* wild-type NSCLC.

5 Adjuvant Epidermal Growth Factor Tyrosine Kinase Inhibitors

Given the promising activity of EGFR TKIs in patients with metastatic *EGFR* mutant NSCLC, there is significant interest in developing the agents as adjuvant therapy for patients with completely resected *EGFR* mutant NSCLC. A single-arm phase II trial investigated erlotinib 150 mg daily for two years in patients with resected stage IA to IIIA *EGFR* mutant NSCLC [37]. The primary end-point was 2-year disease-free survival (DFS) of 86 %, and a 100 patients were enrolled. Of the patients enrolled, 69 % of patients tolerated at least 22 months of erlotinib, and 40 % need at least one dose reduction. The 2-year DFS observed was 89 %, and median DFS has not yet been reached. Twenty-nine patients have recurred, and the median time recurrence after stopping erlotinib was 8.5 months (range 0–47 months). The OS data is immature.

A phase III trial investigated adjuvant erlotinib compared to placebo in patients with resected stage IB to IIIA NSCLC with EGFR-positive IHC or FISH. Patients could have received adjuvant chemotherapy. The primary end-point was DFS, and the patients assigned to adjuvant erlotinib compared to placebo experienced a similar DFS in the intent-to-treat patient population (HR of 0.90; 95 % CI, 0.741–1.104; p = 0.3235; median DFS 50.2 and 48.2 months, respectively). Of the 973

patients enrolled, 161 patients had NSCLC harboring an *EGFR* mutation. Patients with *EGFR* mutant NSCLC assigned to the erlotinib compared to the placebo arm had a longer DFS (HR of 0.61, 95 % CI, 0.384–0.981; $p = 0.0391$). Due to the hierarchical testing procedure, this result is not considered statistically significant.

At this time, the data do not support the use of adjuvant EGFR TKI in unselected patients. In *EGFR* mutant NSCLC, adjuvant EGFR TKI appears to delay disease recurrence, but data demonstrating improvement in OS are not available. There remain several significant concerns about the use of adjuvant EGFR TKI including the potential to development of acquired resistance to EGFR TKIs, and the questions about the appropriate dose and duration of therapy. The National Cancer Institute Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST, NCT02194738) is currently screening surgically resected patients for molecular abnormalities [38]. Patients with *EGFR* mutant NSCLC will be enrolled on a clinical trial ALCHEMIST-EGFR (NCT02193282) which investigates adjuvant erlotinib 150 mg daily for two years compared to placebo. The primary end-point is OS, and the trial will enroll 410 patients. At this time, the use adjuvant EGFR TKI cannot be recommended outside the context of a clinical trial, and patients should be encouraged to enroll in the ALCHEMIST trial.

6 Anaplastic Lymphoma Kinase Inhibitors

Anaplastic lymphoma kinase (*ALK*) rearrangements were first detected in NSCLC in 2007, and the rate of *ALK* translocations among patients with adenocarcinoma is estimated to be approximately 8 % [3]. *ALK* rearrangements are more common in patients with adenocarcinoma histology and a history of never or light smoking [39, 40]. The anaplastic lymphoma kinase inhibitor crizotinib was approved in 2011 based on the promising activity observed in a phase I study with an expansion cohort in patients with advanced NSCLC and a confirm *ALK* rearrangement [41]. The early identification of a predictive biomarker significantly accelerated the drug development and approval process of crizotinib. Two subsequent trials investigated crizotinib in patients with advanced NSCLC with a confirmed *ALK* rearrangement compared to platinum–pemetrexed in first-line setting or compared to docetaxel or pemetrexed in the second-line setting [42, 43]. In both trials, patients assigned to crizotinib compared to chemotherapy had a statistically significant higher ORR and longer PFS, and better QoL (Table 3). Patients with *ALK* rearrangement appear to have a higher ORR with pemetrexed compared to historical controls of unselected patients with non-squamous histology who received pemetrexed [43, 44]. The most common adverse events observed with crizotinib are visual disturbances, diarrhea, edema, vomiting, constipation, and elevated liver enzymes. The most common grade 3 or 4 adverse events occurring at a rate of >5 % are elevated liver enzymes and neutropenia.

Ceritinib is a second-generation ALK inhibitor that is 20 times as potent ALK inhibitor as crizotinib. Ceritinib has revealed activity in patients who have progressed after crizotinib or who were intolerant of crizotinib and crizotinib-naïve

Table 3 Select trials of ALK inhibitors in patients with NSCLC with ALK rearrangements

Comparison (# of patients)	Objective response rate	Median progression-free survival	Median overall survival
Crizotinib versus chemotherapy (docetaxel or pemetrexed) (n = 347) [43]	65 % versus 20 % $p < 0.001$	7.7 versus 3.0 months HR = 0.49, $p < 0.001$	20.3 versus 22.8 months HR = 1.02, $p = 054$
Crizotinib versus platinum–pemetrexed (n = 343) [42]	74 % versus 45 % $P < 0.001$	10.9 versus 7.0 months HR = 0.45, $p < 0.001$	Not reached HR = 0.82, $p = 0.36$
Ceritnib [45] (n = 114) Ceritinib (prior crizotinib) (n = 80) Ceritinib (crizotinib naïve) (n = 34)	58 % 56 % 62 %	7.0 months 6.9 months Not reached	Not reached Not reached Not reached
Alectinib (prior crizotinib) [47] (n = 47) Alectinib (crizotinib naïve) [46] (n = 43)	55 % 93.5 %	Not reached Not reached	Not reached Not reached

ALK anaplastic lymphoma kinase, *HR* hazard ratio
[a]Data represent patients receiving a minimum of ceritinib 400 mg daily

patients (Table 3) [45]. The grade 3 or 4 adverse events occurring at a rate of >5 % are elevated liver enzymes, diarrhea, elevated lipase, nausea, fatigue, and vomiting. Approximately 60 % of patients treated at the approved dose of 750 mg required at least one dose reduction. Responses were observed in patients with untreated CNS lesions which is clinically relevant since many patients are presented with or develop brain metastases.

Alectinib is a highly selective ALK inhibitor that has demonstrated activity against the L1196M crizotinib resistance mutation [46]. Alectinib was investigated in phase I/II trial in patients with *ALK* rearranged NSCLC who ALK inhibitor naïve; the primary end-point of the phase II was ORR. The recommended dose for phase II was 300 mg twice daily, and the ORR observed in the phase II cohort was 93.5 % (95 % CI, 82.1–98.6 %). The grade 3 treatment-related adverse events observed were decreased neutrophil count (4 %), increased creatinine phosphokinase (4 %), increased liver enzymes (2 %), increased bilirubin (2 %), and rash (2 %). The data on PFS was immature at the time publication. Activity was demonstrated in patients with treated and untreated brain metastases. Alectinib was investigated in a separate phase I/II trial in patients with *ALK* rearranged NSCLC who had progressed on or were intolerant of crizotinib; the primary end-point of the phase II trial was ORR [47]. Alectinib 600 mg twice a day was selected based on the toxicities and tolerability observed in the phase I portion of the trial for further investigation in the phase II portion of the trial. The ORR observed was 55 %, and the PFS data were immature at the time of publication. Of the 21 patients with CNS

disease at baseline, 52 % had an objective response and 38 % had stable disease. The most common grade 3 or 4 adverse events were increased gamma-glutamyl transpeptidase, decreased neutrophil count, and hypophosphatemia. Both alectinib and ceretinib have demonstrated activity in patients who have progressed on or were intolerant of crizotinib, in patients with CNS disease, and ALK inhibitor-naïve patients.

ROS1 rearrangements are detected in approximately 1 % of cases of NSCLC and are more commonly found in patients with a history of never or light smoking and adenocarcinoma histology [48]. Preclinical data revealed significant activity of crizotinib in cell lines with *ROS1* rearrangements [48]. A single-arm phase II trial investigated crizotinib in 50 patients who tested for *ROS1* rearrangement revealed an ORR of 72 % (95 % CI, 58–84 %), and a median PFS of 19.2 months (95 % CI, 14.4 to not reached) [49]. A second study of 30 patients revealed an ORR of 80 % and a median PFS of 9.1 months [50]. Both of these trials are small, but demonstrate significant activity of crizotinib in patients NSCLC with *ROS1* rearrangements.

7 BRAF Inhibitors

BRAF mutations are detected in approximately 2–3 % of NSCLC with adenocarcinoma histology and are more frequently detected in patients with a history of tobacco use, and approximately 50–75 % of the *BRAF* mutations are the *BRAF* V600E mutation seen in melanoma [3, 51]. Vemurafenib and dabrafenib have demonstrated significant activity in patients with metastatic melanoma who harbor a *BRAF* V600E mutation. A single-arm phase II trial investigated dabrafenib in patients with advanced stage NSCLC with *BRAF* V600E mutant NSCLC (n = 84). The ORR by independent review committee was 28 % (95 % CI, 18–41 %) [52]. Given the activity of the BRAF inhibitors in combination with MEK inhibitors observed in BRAF V600E mutant melanoma, the combination of dabrafenib and trametinib was investigated in a single-arm phase II trial in patients with *BRAF* V600E mutant NSCLC (n = 33) [53]. An interim analysis revealed an ORR of 63 % (95 % CI, 40.6–81.2 %), and the trial meet the criteria to continue to the second stage. Grade 3 adverse events occurred in 39 % of patients, and the most frequent grade 3 adverse events were hyponatremia (6 %), neutropenia (6 %), and dehydration (6 %). One patient had grade 4 hyponatremia and one patient had grade 5 pleural effusion. Case reports have demonstrated activity of vemurafenib in patients with *BRAF* mutant V600E NSCLC [54, 55]. While these data are not definitive, they do suggest potential activity of BRAF inhibitors alone and in combination with MEK inhibitors in patients with NSCLC with a *BRAF* V600E mutation.

8 Squamous NSCLC

The development of targeted therapies for NSCLC with squamous histology has been more difficult, and this subtype of NSCLC has a lower rate of *EGFR* mutations and *ALK* rearrangements. A retrospective found the rate of EGFR mutations in patients with squamous histology based on immunohistochemistry testing was 0 % (95 % CI, 0–3.8 %) [56]. Given the low prevalence of *EGFR* mutations and *ALK* rearrangements, routine molecular testing is not recommended. NSCLC with squamous histology also have greater genomic complexity and frequently a single tumor will have multiple oncogenic mutations which makes it less susceptible to an agent that inhibits a single oncogenic pathway [57].

A phase III trial investigated cisplatin and gemcitabine with and without necitumumab, a monoclonal antibody against the extracellular domain of the EGFR receptor, in patients with advanced NSCLC with squamous histology [58]. Patients assigned to the necitumumab containing arm compared to the chemotherapy alone arm experienced a similar response rate (31.2 % vs. 28.8 %, $p = 0.400$), but a statistically significant longer PFS (HR of 0.85; 95 % CI, 074–098; $p = 0.20$; median 5.7 and 5.5 months, respectively) and OS (HR of 0.84, 95 % CI, 074–0.96; $p = 0.012$; median OS of 11.5 and 9.9 months). Patients assigned to the necitumumab compared to the chemotherapy alone arm experienced a higher rate of grade ≥3 hypomagnesemia (9.3 % vs. 1.1 %), and skin rash (7.1 % vs. 0.4 %). An exploratory analysis of EGFR expression using the H-score found that the H-score was not predictive of PFS or OS benefit with necitumumab. While the OS benefit is modest, this trial does represent the first improvement in OS with a targeted therapy in combination with platinum-based chemotherapy compared to platinum-based chemotherapy alone in patients with squamous NSCLC.

A phase III study investigated afatinib compared to erlotinib as second-line therapy in patients with squamous histology who had experienced disease progression after platinum-based therapy ($n = 795$) [59]. The primary end-point was PFS, and a secondary end-point was OS. Patients assigned to afatinib compared to erlotinib experienced a statistically significant longer PFS (HR of 0.81, 95 % CI, 0.69–0.96; $p = 0.01$; median PFS of 2.6 and 1.9 months, respectively) and OS (HR of 0.81, 95 % CI, 0.69–0.95; $p = 0.008$; median OS of 7.9 and 6.8 months, respectively). Patients assigned to the afatinib compared to the erlotinib arm experienced a higher rate of treatment-related grade 3 or 4 diarrhea (10.4 % vs. 2.6 %), grade 3 stomatitis (4.1 % vs. 0 %), and a lower rate of grade 3 rash (5.9 % vs. 10.4 %). Patients assigned to afatinib compared to erlotinib experienced a statistically significant improvement in global quality of life and improvement in the symptoms of cough and dyspnea. Afatinib is currently available for first-line therapy for patients with NSCLC with *EGFR* exon 19 and 21 mutations and as second-line therapy for patients with metastatic squamous NSCLC.

9 Small Cell Lung Cancer

Small cell lung cancer (SCLC) frequently demonstrates multiple oncogenic mutations and has inactivation of the tumor suppressor genes *p53* and *RB1*, and to date, a mutation that is susceptible to tyrosine kinase inhibitor has not been identified [60, 61]. Anti-angiogenesis therapy has been investigated in extensive stage (ES-SCLC), and agents have been shown to extend PFS but not OS. A randomized phase II investigate platinum etoposide with and without bevacizumab, and the primary end-point was PFS (n = 102) [62]. Patients assigned to the bevacizumab arm experienced a statistically significant longer PFS (HR of 0.53; 95 % CI, 0.32–0.86; median 5.5 and 4.40 months, respectively) and similar OS (HR of 1.16; 95 % CI, 0.66–2.04; median 9.4 and 10.9 months, respectively). A randomized phase II trial investigated maintenance sunitinib compared to placebo in patients who had stable disease or response to four or six cycles of platinum–etoposide [63]. Of the 138 patients who initiated chemotherapy, 85 patients were randomized to sunitinib or placebo. Patients assigned to placebo compared to sunitinib had a statistically significant worse PFS (HR of 1.62; 95 % CI, 1.02–2.60; p = 0.02; median PFS 2.1 and 3.7 months, respectively) and similar OS (HR of 1.28; 95 % CI, 0.79–2.10; p = 0.16; median OS of 6.9 and 9.0 months, respectively). While both of these trials met the primary end-point of improvement in PFS, it is unlikely that either of these agents will be investigated in a phase III trial.

10 Conclusions

There are currently several standard targeted therapies available for patients with advanced NSCLC, and the targeted therapies generally fall into two classes: monoclonal antibodies against a specific target or tyrosine kinase inhibitors. In general, the monoclonal antibodies have demonstrated modest differences in efficacy and do not have a biomarker to select patients for treatment. TKIs have demonstrated significant efficacy, and several predictive molecular markers are available (e.g., *EGFR* mutation status, and *ALK* or *ROS1* rearrangements). The development of predictive biomarker for targeted therapies has significantly accelerated drug development and improved clinical care in a relatively short period of time. Targeted therapies are the focus of drug development in lung cancer, and a number of promising agents are in development. The development of widely available next-generation tumor sequencing has made the identification of patients for targeted therapies much convenient and efficient.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015) Global cancer statistics, 2012. CA Cancer J Clin 65: 87–108
2. Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer statistics, 2014. CA Cancer J Clin 64:9–29

3. Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, Varella-Garcia M, Franklin WA, Aronson SL, Su PF, Shyr Y, Camidge DR, Sequist LV, Glisson BS, Khuri FR, Garon EB, Pao W, Rudin C, Schiller J, Haura EB, Socinski M, Shirai K, Chen H, Giaccone G, Ladanyi M, Kugler K, Minna JD, Bunn PA (2014) Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 311:1998–2006
4. Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, Spitznagel EL, Piccirillo J (2006) Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 24:4539–4544
5. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92–98
6. Breathnach O, Freidlin B, Conley B, Green M, Johnson D, Gandara D, O'Connell M, Shepherd F, Johnson B (2001) Twenty-two years of phase III trials for patients with advanced non-small cell lung cancer: sobering results. J Clin Oncol 19:1734–1742
7. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674
8. Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, Langer CJ, DeVore RF 3rd, Gaudreault J, Damico LA, Holmgren E, Kabbinavar F (2004) Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 22:2184–2191
9. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355:2542–2550
10. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N, Manegold C (2009) Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 27:1227–1234
11. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N, Manegold C (2010) Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 21:1804–1809
12. Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, Park K, Gorbunova V, Kowalyszyn RD, Pikiel J, Czyzewicz G, Orlov SV, Lewanski CR, Thomas M, Bidoli P, Dakhil S, Gans S, Kim JH, Grigorescu A, Karaseva N, Reck M, Cappuzzo F, Alexandris E, Sashegyi A, Yurasov S, Perol M (2014) Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 384:665–673
13. Miller VA, Riely GJ, Zakowski MF, Li AR, Patel JD, Heelan RT, Kris MG, Sandler AB, Carbone DP, Tsao A, Herbst RS, Heller G, Ladanyi M, Pao W, Johnson DH (2008) Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. J Clin Oncol 26:1472–1478
14. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129–2139
15. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M (2004) EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 304:1497–1500
16. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H,

Duffield EL, Watkins CL, Armour AA, Fukuoka M (2009) Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947–957
17. Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V, Chao TY, Nakagawa K, Chu DT, Saijo N, Duffield EL, Rukazenkov Y, Speake G, Jiang H, Armour AA, To KF, Yang JC, Mok TS (2011) Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol 29:2866–2874
18. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S, Nukiwa T (2010) Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362:2380–2388
19. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, Asami K, Katakami N, Takada M, Yoshioka H, Shibata K, Kudoh S, Shimizu E, Saito H, Toyooka S, Nakagawa K, Fukuoka M (2010) Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 11:121–128
20. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 31:3327–3334
21. Yang JC, Hirsh V, Schuler M, Yamamoto N, O'Byrne KJ, Mok TS, Zazulina V, Shahidi M, Lungershausen J, Massey D, Palmer M, Sequist LV (2013) Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol 31:3342–3350
22. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, Li W, Hou M, Shi JH, Lee KY, Xu CR, Massey D, Kim M, Shi Y, Geater SL (2014) Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 15:213–222
23. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Milella M, Reguart N, Altavilla G, Jimenez U, Provencio M, Moreno MA, Terrasa J, Munoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baize N, Garcia-Campelo R, Robinet G, Rodriguez-Abreu D, Lopez-Vivanco G, Gebbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearz A, Artal A, Cortesi E, Rolfo C, Sanchez-Ronco M, Drozdowskyj A, Queralt C, de Aguirre I, Ramirez JL, Sanchez JJ, Molina MA, Taron M, Paz-Ares L (2012) Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 13:239–246
24. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, Zhang L, You C (2011) Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 12:735–742
25. Thongprasert S, Duffield E, Saijo N, Wu YL, Yang JC, Chu DT, Liao M, Chen YM, Kuo HP, Negoro S, Lam KC, Armour A, Magill P, Fukuoka M (2011) Health-related quality-of-life in a randomized phase III first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients from Asia with advanced NSCLC (IPASS). J Thorac Oncol 6:1872–1880

26. Oizumi S, Kobayashi K, Inoue A, Maemondo M, Sugawara S, Yoshizawa H, Isobe H, Harada M, Kinoshita I, Okinaga S, Kato T, Harada T, Gemma A, Saijo Y, Yokomizo Y, Morita S, Hagiwara K, Nukiwa T (2012) Quality of life with gefitinib in patients with EGFR-mutated non-small cell lung cancer: quality of life analysis of North East Japan study group 002 trial. Oncologist 17:863–870
27. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, Zhou C, Hu CP, O'Byrne K, Feng J, Lu S, Huang Y, Geater SL, Lee KY, Tsai CM, Gorbunova V, Hirsh V, Bennouna J, Orlov S, Mok T, Boyer M, Su WC, Lee KH, Kato T, Massey D, Shahidi M, Zazulina V, Sequist LV (2015) Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 16:141–151
28. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, Kris MG, Miller VA, Ladanyi M, Riely GJ (2013) Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 19:2240–2247
29. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, Bergethon K, Shaw AT, Gettinger S, Cosper AK, Akhavanfard S, Heist RS, Temel J, Christensen JG, Wain JC, Lynch TJ, Vernovsky K, Mark EJ, Lanuti M, Iafrate AJ, Mino-Kenudson M, Engelman JA (2011) Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 3:75ra26
30. Ohashi K, Sequist LV, Arcila ME, Moran T, Chmielecki J, Lin YL, Pan Y, Wang L, de Stanchina E, Shien K, Aoe K, Toyooka S, Kiura K, Fernandez-Cuesta L, Fidias P, Yang JC, Miller VA, Riely GJ, Kris MG, Engelman JA, Vnencak-Jones CL, Dias-Santagata D, Ladanyi M, Pao W (2012) Lung cancers with acquired resistance to EGFR inhibitors occasionally harbor BRAF gene mutations but lack mutations in KRAS, NRAS, or MEK1. Proc Natl Acad Sci U S A 109:E2127–E2133
31. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabarbara P, Seymour L (2005) Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123–132
32. Bezjak A, Tu D, Seymour L, Clark G, Trajkovic A, Zukin M, Ayoub J, Lago S, de Albuquerque Ribeiro R, Gerogianni A, Cyjon A, Noble J, Laberge F, Chan RT, Fenton D, von Pawel J, Reck M, Shepherd FA (2006) Symptom improvement in lung cancer patients treated with erlotinib: quality of life analysis of the National Cancer Institute of Canada clinical trials group study BR.21. J Clin Oncol 24:3831–3837
33. Tsao MS, Sakurada A, Cutz JC, Zhu CQ, Kamel-Reid S, Squire J, Lorimer I, Zhang T, Liu N, Daneshmand M, Marrano P, da Cunha Santos G, Lagarde A, Richardson F, Seymour L, Whitehead M, Ding K, Pater J, Shepherd FA (2005) Erlotinib in lung cancer—molecular and clinical predictors of outcome. N Engl J Med 353:133–144
34. Garassino MC, Martelli O, Broggini M, Farina G, Veronese S, Rulli E, Bianchi F, Bettini A, Longo F, Moscetti L, Tomirotti M, Marabese M, Ganzinelli M, Lauricella C, Labianca R, Floriani I, Giaccone G, Torri V, Scanni A, Marsoni S, trialists T (2013) Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol 14:981–988
35. Taguchi F, Solomon B, Gregorc V, Roder H, Gray R, Kasahara K, Nishio M, Brahmer J, Spreafico A, Ludovini V, Massion PP, Dziadziuszko R, Schiller J, Grigorieva J, Tsypin M, Hunsucker SW, Caprioli R, Duncan MW, Hirsch FR, Bunn PA Jr, Carbone DP (2007) Mass spectrometry to classify non-small-cell lung cancer patients for clinical outcome after treatment with epidermal growth factor receptor tyrosine kinase inhibitors: a multicohort cross-institutional study. J Natl Cancer Inst 99:838–846
36. Gregorc V, Novello S, Lazzari C, Barni S, Aieta M, Mencoboni M, Grossi F, De Pas T, de Marinis F, Bearz A, Floriani I, Torri V, Bulotta A, Cattaneo A, Grigorieva J, Tsypin M, Roder J, Doglioni C, Levra MG, Petrelli F, Foti S, Vigano M, Bachi A, Roder H (2014)

Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker-stratified, randomised phase 3 trial. Lancet Oncol 15:713–721
37. Pennell NA, Neal JW, Chaft JE, Azzoli CG, Janne PA, Govindan R, Evans TL, Costa DB, Rosovsky RPG, Wakelee HA, Heist RS, Shaw AT, Temel JS, Shapiro MA, Muzikansky A, Lanuti M, Lynch TJ, Kris MG, Sequist LV (2014) SELECT: a multicenter phase II trial of adjuvant erlotinib in resected early-stage EGFR mutation-positive NSCLC. J Clin Oncol 32: (suppl; abstract 7514)
38. Gerber DE, Oxnard GR, Govindan R (2015) ALCHEMIST: bringing genomic discovery and targeted therapies to early-stage lung cancer. Clin Pharmacol Ther 97:447–450
39. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, Fujiwara S, Watanabe H, Kurashina K, Hatanaka H, Bando M, Ohno S, Ishikawa Y, Aburatani H, Niki T, Sohara Y, Sugiyama Y, Mano H (2007) Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 448:561–566
40. Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, Solomon B, Stubbs H, Admane S, McDermott U, Settleman J, Kobayashi S, Mark EJ, Rodig SJ, Chirieac LR, Kwak EL, Lynch TJ, Iafrate AJ (2009) Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 27:4247–4253
41. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, Ou SH, Dezube BJ, Janne PA, Costa DB, Varella-Garcia M, Kim WH, Lynch TJ, Fidias P, Stubbs H, Engelman JA, Sequist LV, Tan W, Gandhi L, Mino-Kenudson M, Wei GC, Shreeve SM, Ratain MJ, Settleman J, Christensen JG, Haber DA, Wilner K, Salgia R, Shapiro GI, Clark JW, Iafrate AJ (2010) Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 363:1693–1703
42. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, Iyer S, Reisman A, Wilner KD, Tursi J, Blackhall F, The PI (2014) First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 371:2167–2177
43. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, De Pas T, Besse B, Solomon BJ, Blackhall F, Wu YL, Thomas M, O'Byrne KJ, Moro-Sibilot D, Camidge DR, Mok T, Hirsh V, Riely GJ, Iyer S, Tassell V, Polli A, Wilner KD, Janne PA (2013) Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 368:2385–2394
44. Shaw AT, Varghese AM, Solomon BJ, Costa DB, Novello S, Mino-Kenudson M, Awad MM, Engelman JA, Riely GJ, Monica V, Yeap BY, Scagliotti GV (2013) Pemetrexed-based chemotherapy in patients with advanced, ALK-positive non-small cell lung cancer. Ann Oncol 24:59–66
45. Shaw AT, Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, Camidge DR, Vansteenkiste J, Sharma S, De Pas T, Riely GJ, Solomon BJ, Wolf J, Thomas M, Schuler M, Liu G, Santoro A, Lau YY, Goldwasser M, Boral AL, Engelman JA (2014) Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 370:1189–1197
46. Seto T, Kiura K, Nishio M, Nakagawa K, Maemondo M, Inoue A, Hida T, Yamamoto N, Yoshioka H, Harada M, Ohe Y, Nogami N, Takeuchi K, Shimada T, Tanaka T, Tamura T (2013) CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1–2 study. Lancet Oncol 14:590–598
47. Gadgeel SM, Gandhi L, Riely GJ, Chiappori AA, West HL, Azada MC, Morcos PN, Lee RM, Garcia L, Yu L, Boisserie F, Di Laurenzio L, Golding S, Sato J, Yokoyama S, Tanaka T, Ou SH (2014) Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol 15:1119–1128
48. Bergethon K, Shaw AT, Ignatius Ou SH, Katayama R, Lovly CM, McDonald NT, Massion PP, Siwak-Tapp C, Gonzalez A, Fang R, Mark EJ, Batten JM, Chen H, Wilner KD, Kwak EL, Clark JW, Carbone DP, Ji H, Engelman JA, Mino-Kenudson M, Pao W, Iafrate AJ

(2012) ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 30:863–870
49. Shaw AT, Solomon BJ (2015) Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 372:683–684
50. Mazieres J, Zalcman G, Crino L, Biondani P, Barlesi F, Filleron T, Dingemans AM, Lena H, Monnet I, Rothschild SI, Cappuzzo F, Besse B, Thiberville L, Rouviere D, Dziadziuszko R, Smit EF, Wolf J, Spirig C, Pecuchet N, Leenders F, Heuckmann JM, Diebold J, Milia JD, Thomas RK, Gautschi O (2015) Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. J Clin Oncol 33:992–999
51. Paik PK, Arcila ME, Fara M, Sima CS, Miller VA, Kris MG, Ladanyi M, Riely GJ (2011) Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. J Clin Oncol 29:2046–2051
52. Planchard D, Kim TM, Mazieres J, Quoix E, Riely GJ, Barlesi F, Souquet PJ, Smit EF, Groen HJM, Kelly RJ, Cho BC, Socinski MA, Tucker C, Ma B, Mookerjee B, Curtis J, C.M., Johnson BE (2014) Dabrafenib in patients BRAF V600E mutant advanced non-small cell lung cancer (NSCLC): a multicenter, open label, phase II trial (BRF113928). Annals of Oncology 2014;25: abstract: LBA38_PR
53. Planchard D, Groen HJM, Kim TM, Rigas JR, Souquet PJ, Baik CS, Barlesi F, Mazières J, Quoix EA, Curtis CM, Mookerjee B, Bartlett-Pandite AN, Tucker C, D'Amelio A, Johnson BE (2015) Interim results of a phase II study of the BRAF inhibitor (BRAFi) dabrafenib (D) in combination with the MEK inhibitor trametinib (T) in patients (pts) with BRAF V600E mutated (mut) metastatic non-small cell lung cancer (NSCLC). J Clin Oncol 33: abstract 8006
54. Robinson SD, O'Shaughnessy JA, Cowey CL, Konduri K (2014) BRAF V600E-mutated lung adenocarcinoma with metastases to the brain responding to treatment with vemurafenib. Lung Cancer 85:326–330
55. Peters S, Michielin O, Zimmermann S (2013) Dramatic response induced by vemurafenib in a BRAF V600E-mutated lung adenocarcinoma. J Clin Oncol 31:e341–e344
56. Rekhtman N, Paik PK, Arcila ME, Tafe LJ, Oxnard GR, Moreira AL, Travis WD, Zakowski MF, Kris MG, Ladanyi M (2012) Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations. Clin Cancer Res 18:1167–1176
57. Cancer Genome Atlas Research N (2012) Comprehensive genomic characterization of squamous cell lung cancers. Nature 489:519–525
58. Thatcher N, Hirsch FR, Szczesna A, Ciuleanu T-E, Szafranski W, Dediu M, Ramlau R, Galiulin R, Bálint B, Losonczy G, Kazarnowicz A, Park K, Schumann C, Reck M, Paz-Ares L, Depenbrock H, Nanda S, Kruljac-Letunic A, Socinski MA (2014) A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC). J Clin Oncol 32: (suppl; abstract 8008)
59. Soria J-C, Felip E, Cobo M, Lu S, Syrigos KN, Lee KH, Goker E, Georgoulias V, Li W, Isla D, Guclu SZ, Morabito A, Min YJ, Ardizzoni A, Gadgeel SM, Wang B, Chand VK, Goss GD (2015) Afatinib (A) vs erlotinib (E) as second-line therapy of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following platinum-based chemotherapy: Overall survival (OS) analysis from the global phase III trial LUX-Lung 8 (LL8). J Clin Oncol 33: abstract 8002
60. Rudin CM, Durinck S, Stawiski EW, Poirier JT, Modrusan Z, Shames DS, Bergbower EA, Guan Y, Shin J, Guillory J, Rivers CS, Foo CK, Bhatt D, Stinson J, Gnad F, Haverty PM, Gentleman R, Chaudhuri S, Janakiraman V, Jaiswal BS, Parikh C, Yuan W, Zhang Z, Koeppen H, Wu TD, Stern HM, Yauch RL, Huffman KE, Paskulin DD, Illei PB, Varella-Garcia M, Gazdar AF, de Sauvage FJ, Bourgon R, Minna JD, Brock MV, Seshagiri S

(2012) Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. Nat Genet 44:1111–1116

61. Peifer M, Fernandez-Cuesta L, Sos ML, George J, Seidel D, Kasper LH, Plenker D, Leenders F, Sun R, Zander T, Menon R, Koker M, Dahmen I, Muller C, Di Cerbo V, Schildhaus HU, Altmuller J, Baessmann I, Becker C, de Wilde B, Vandesompele J, Bohm D, Ansen S, Gabler F, Wilkening I, Heynck S, Heuckmann JM, Lu X, Carter SL, Cibulskis K, Banerji S, Getz G, Park KS, Rauh D, Grutter C, Fischer M, Pasqualucci L, Wright G, Wainer Z, Russell P, Petersen I, Chen Y, Stoelben E, Ludwig C, Schnabel P, Hoffmann H, Muley T, Brockmann M, Engel-Riedel W, Muscarella LA, Fazio VM, Groen H, Timens W, Sietsma H, Thunnissen E, Smit E, Heideman DA, Snijders PJ, Cappuzzo F, Ligorio C, Damiani S, Field J, Solberg S, Brustugun OT, Lund-Iversen M, Sanger J, Clement JH, Soltermann A, Moch H, Weder W, Solomon B, Soria JC, Validire P, Besse B, Brambilla E, Brambilla C, Lantuejoul S, Lorimier P, Schneider PM, Hallek M, Pao W, Meyerson M, Sage J, Shendure J, Schneider R, Buttner R, Wolf J, Nurnberg P, Perner S, Heukamp LC, Brindle PK, Haas S, Thomas RK (2012) Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet 44:1104–1110
62. Spigel DR, Townley PM, Waterhouse DM, Fang L, Adiguzel I, Huang JE, Karlin DA, Faoro L, Scappaticci FA, Socinski MA (2011) Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. J Clin Oncol 29:2215–2222
63. Ready NE, Pang HH, Gu L, Otterson GA, Thomas SP, Miller AA, Baggstrom M, Masters GA, Graziano SL, Crawford J, Bogart J, Vokes EE (2015) Chemotherapy with or without maintenance sunitinib for untreated extensive-stage small-cell lung cancer: a randomized, double-blind, placebo-controlled phase ii study-CALGB 30504 (Alliance). J Clin Oncol 33:1660–1665

Resistance to Therapy

Gabriel Rivera and Heather A. Wakelee

Abstract

Identification of driver mutations in adenocarcinoma of the lung has revolutionized the treatment of this disease. It is now standard of care to look for activating mutations in epidermal growth factor receptor (EGFR), and translocations in anaplastic lymphoma kinase (ALK) or ROS1 in all newly diagnosed adenocarcinoma of the lung, and in many patients with squamous cell carcinoma as well. Recognition of multiple other lung cancer driver mutations has also expanded treatment options. Targeted treatments of these mutations lead to rapid and prolonged responses, but resistance inevitably develops. Until recently, traditional chemotherapy was the only alternative at that time, but better understanding of resistance mechanisms has lead to additional therapeutic options. These mechanisms of resistance and treatments are the focus of this chapter. Understanding of mechanisms of chemotherapy resistance is touched upon, along with a brief discussion of immune checkpoint inhibitors.

Keywords

Chemotherapy resistance · EGFR resistance · ALK resistance

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Contents

1 Introduction

In a subset of non-small cell lung cancer (NSCLC), patients' somatic mutations or re-arrangements are identified within genes that produce tyrosine kinase receptor proteins that lead to constitutive activity of the receptors, thus providing a survival advantage for these cells [1]. The incidence of these "driver" mutations in NSCLC is more common in never smokers and can vary significantly by geographic region [2–4]. There is also some evidence that the identification of these mutations will increase as new technologies such as next-generation sequencing increase the sensitivity of detection [5]. The striking responses seen in patients with actionable driver mutations who are treated with the appropriate targeted therapy has revolutionized the treatment of NSCLC; however, resistance inevitably develops. This chapter will focus on what is known about the mechanisms of resistance and strategies to overcome this resistance. We will also briefly cover resistance mechanisms to common 1st-line platinum-doublet regimens used in NSCLC and discuss strategies to overcome resistance.

2 Molecular Mutations and Targeted Drugs

2.1 Epidermal Growth Factor Receptor (EGFR)

Epidermal growth factor (EGF) was discovered in 1962 by Cohen [6] from the salivary glands of mice. Then, in 1978, in an epidermoid cancer cell line, EGF was found to bind to EGFR, described as a membrane receptor that phosphorylated downstream proteins [7]. The human EGFR protein was fully sequenced in 1984 by Ullrich et al. [8] from placental tissue and a cancer cell line. The mechanism of EGFR activation was later determined to occur not only through binding of its ligand, but also requires dimerization of EGF-like receptors in the setting of adenosine

triphosphate (ATP) that results in phosphorylation of tyrosine residues leading to further downstream signaling important for cell survival and proliferation [9–12].

Considerable research had focused on the identification of EGFR in cancer cell lines as well as human cancer tissue [13–16]. The majority of that research looked at expression of EGFR and ligands through immunohistochemistry (IHC) stains. It was thought that these receptors were overexpressed and were activated in an autocrine fashion. There was also pre-clinical work that demonstrated that point mutations in the ATP-binding pocket of EGFR essentially eliminated its tyrosine kinase activity [17–21]. This led to the development of small molecule inhibitors of EGFR ultimately producing gefitinib, a reversible tyrosine kinase inhibitor (TKI), that was reported to inhibit tumor growth in a human squamous vulva cell line in a manner that did not depend on the level of EGFR expression [20, 21]. This was followed by numerous phases I and II studies with the reversible TKIs, gefitinib, and erlotinib, which demonstrated impressive tumor regression in a subset of NSCLC patients. Differential responses by histology, ethnicity, and smoking status were noted [22–29]. Both drugs were taken into phase III trials compared to placebo in unselected NSCLC patients as a second-line therapy and beyond, and only erlotinib demonstrated an overall survival benefit. This ultimately led to Food and Drug Administration (FDA) approval of erlotinib as 2nd or 3rd line NSCLC therapy in 2004 [30, 31]. Of note, gefitinib had received conditional FDA approval based on responses in a phase II study, and it was withdrawn after a negative phase III trial in unselected patients. In 2015, gefitinib was approved as a first-line therapy in those with metastatic *EGFR* mutant NSCLC [32].

Following up on the clinical benefit seen in a subset of patients, in 2004, several laboratories sequenced the *EGFR* gene and found somatic mutations, an in-frame deletion in exon 19 and missense mutation in exon 21 that predominated in adenocarcinoma histology tumors, most frequently in patients who were never smokers. Retrospectively, it was determined that these mutations correlated with response to gefitinib as well as survival outcomes [33–37]. Zhang et al. [38] demonstrated through crystallography that wild-type *EGFR* is often in an inactivated conformational state, but can be activated by EGF-like molecules in a concentration dependent manner or if *EGFR* is mutated in the kinase domain. Others determined that mutations such as L858R in the kinase domain of *EGFR* made it less avid for ATP and more avid for gefitinib or erlotinib [39, 40]. There have been several subsequent trials that were designed to evaluate patients with known *EGFR* somatic mutations either by pre-planned subset analysis or primary inclusion that determined gefitinib or erlotinib to be superior for response and progression-free survival (PFS) compared to chemotherapy in the first-line setting [41–44]. Afatinib, an irreversible pan-human epidermal growth factor receptor (HER) inhibitor, similarly demonstrated superior PFS compared to chemotherapy in lung adenocarcinoma as a first-line agent [45]. A head-to-head comparison of afatinib versus gefitinib in the first-line setting for *EGFR* mutation-positive NSCLC was completed, and early results were presented. The data demonstrated a statistically improved PFS of 11 versus 10.9 months in patients who received afatinib over gefitinib and an increase in response rate, 70 % versus 56 %, respectively. Despite

these remarkable outcomes, resistance inevitably develops with these agents. Resistance mechanisms along with novel therapeutics will be discussed in the section following a discussion of *anaplastic lymphoma kinase* (*ALK)* and *ROS proto-oncogene 1* (*ROS1*) rearrangements.

2.2 ALK and ROS1 Rearrangements

An *ALK* gene rearrangement was first reported in anaplastic large cell lymphoma [46]. In 2007, the rearrangements were identified by Soda et al. in human lung cancer specimens as echinoderm microtubule-associated protein-like 4 (*EML4*)-*ALK*, among other oncogenic fusion partners, using reverse-transcriptase polymerase chain reaction (RT-PCR) [47]. Similarly, *ROS1* rearrangements were first described in a glioblastoma multiforme cell line [48] and then later in lung cancer tissue samples in 2011 [49]. These gene rearrangements produce fusion protein receptors that are constitutively activated, promoting cell survival and division [50]. The cell location for ALK fusion protein appears to be in the plasma membrane and requires dimerization like EGFR; however, it is less clear in *ROS1* as there have been reports of membrane bound as well as golgi apparatus bound ROS1. Either way, ROS1 appears to use the same pathway as EGFR and ALK, specifically the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (PKB or Akt) pathway leads to proliferative and cell survival effects [51]. The first in human trial of the ALK inhibitor crizotinib in patients with fluorescence in situ hybridization (FISH) break-apart probe *ALK*-positive tumors began in 2006 with responses seen in two NSCLC patients. The NSCLC cohort was later expanded in 2008, which demonstrated a 60 % response rate and progression-free survival (PFS) of 9.2 months in patients who received crizotinib as second-line therapy and 18.3 months for those who received it in the first-line [52]. An additional 50 patients were identified with *ROS1* translocation by FISH and included within the dose expansion phase with an overall response rate of 72 % and median PFS of 19.2 months [53]. Crizotinib was also studied in the second-line setting in those with *ALK*-positive NSCLC who had failed first-line platinum therapy. In this phase III study, the comparator chemotherapy arm was docetaxel or pemetrexed. Response rates and PFS for crizotinib versus chemotherapy were 65 % versus 20 % and 7 months versus 3 months, respectively [54]. In a phase III study, crizotinib compared to cisplatin plus pemetrexed was found to have a higher response rate, better quality of life, and superior PFS in *ALK* rearranged lung adenocarcinoma in the first-line setting [55]. Unfortunately, like the EGFR small molecular inhibitors, these agents also lose their effectiveness by similar and different mechanisms that will be described in a later section along with current therapeutics that overcome this resistance.

3 Acquired Drug Resistance

3.1 Mechanisms of Resistance and Current Targeted Therapies

The majority of literature reports on models of drug resistance through three main mechanisms including gene alteration either through point-mutation or amplification, bypass pathways either at the cell membrane through another receptor or downstream of the mutated receptor, or through histological transformation. This section will not cover exhaustively every mutation or reported mechanism, but will cover the most commonly reported and most clinically relevant.

3.1.1 EGFR

Sequist et al. comprehensively described patterns of molecular resistance through evaluation of pre-therapy and at-progression biopsies from 37 lung adenocarcinoma *EGFR* mutant samples. The group found that an acquired T790M mutation was the most common mechanism of resistance comprising 49 % of the samples with 30 % unknown followed by small cell lung cancer (SCLC) transformation, hepatocyte growth factor receptor (HGFR)/MET proto-oncogene (MET) amplification, and PIK3CA mutations [56]. Several other authors identified a similar distribution of resistance mechanisms as Sequist, in addition to several bypass pathways [57, 58]. Each of these mutations and pathways are described individually below followed by current therapeutics under investigation.

3.1.2 T790M

Pao et al. and Kobayashi et al. first identified a resistance mutation in *EGFR*-mutated patients who progressed on erlotinib known as *T790M*. The mutation was found in exon 20 within the ATP-binding pocket of the tyrosine kinase domain. They found a cytosine to thymidine base pair change resulted in a change in amino acid residue 790 from threonine to methionine. They speculated that the hydrogen bond previously described as critical for gefitinib to bind was hindered by the bulky methionine. Moreover, while this prevented gefitinib from binding, it did not prevent ATP from binding [59, 60].

3.1.3 Therapeutics

Afatinib showed the potential to overcome T790M resistance in preclinical models and has been evaluated in patients with EGFR TKI resistance. The LUX-lung 1 trial was a phase IIb/III trial that compared afatinib plus best supportive care versus placebo plus best supportive care in patients with advanced NSCLC who progressed on chemotherapy and erlotinib and had prior benefit on erlotinib. The primary endpoint, overall survival (OS), was not met but the overall response rate was 7 % and the PFS benefit in a subset of 96 patients who were *EGFR* mutation-positive was 3.3 months versus 1 months, HR 0.51. Four of the patients in the afatinib arm had T790M mutation [61]. Both the LUX-Lung 1 and LUX-lung

4 trials enriched for resistance by using the Jackman criteria [62]; however, retrospectively, the number of T790M mutations was small, and LUX-Lung 4 demonstrated a response rate of 8.2 % and PFS 4.4 months [63].

The LUX-lung trials described above were essentially negative given their low response rates in the second-line and third-line settings. The first successful approach in overcoming EGFR resistance was a phase Ib study combining cetuximab, an EGFR monoclonal antibody, with afatinib in 126 patients who were EGFR TKI resistant, and their tumors were examined for T790M status. Cetuximab was given at 500 mg/m^2 IV every two weeks and afatinib 40 mg daily. The overall response rate was 29 % and median PFS 4.7 months. The response rate for T790M + versus T790M—patients were 32 % versus 25 % and PFS 4.6 versus 4.8 months neither of which was statistically significant, respectively. However, despite the improved success from this combination, toxicities were significant, described predominantly as diarrhea at 71 % and rash at 97 % when all grades were included [64]. The toxicities have made the combination less widely adopted despite the improved response rate.

There are now single-agent small molecule inhibitors specifically targeting the *T790M* mutation currently in clinical trials that seem to have a better toxicity profile and higher efficacy than the combination of cetuximab plus afatinib. Preliminary phase I results were reported at ASCO 2014 for AZD9291 (osimertinib) and CO-1686 (rociletinib), both third-generation TKIs that target the *T790M* mutation. In the first reports of the phase I/II trial, CO-1686 was given twice a day to 88 patients with a combined overall response rate of 58 %. Nausea, fatigue, and hyperglycemia were reported common side effects [65]. Results for the phase I/II of rociletinib were later published including 130 patients with an overall response rate of 59 % for T790M-positive tumors and 29 % for those without [66]; however, the trial continued to enroll beyond this time period. At the 2015 ASCO conference, the phase 2 study results were updated for rociletinib, and included 345 patients. T790M status was confirmed by tissue genotyping or plasma genotyping. The overall response rate was 48 % in T790M patients and between 33 and 36 % in T790M-negative patients [67], however these response rates dropped with further follow-up and drug development was halted in May 2016. At the time of data presentation in 2014, AZD9291 (osimertinib) was given daily to 199 patients with unconfirmed plus confirmed responses of 51 %. In 84 centrally confirmed T790M-mutated patients, the response rate was 64 % and in 43 T790M-negative patients, the response rate was 23 %. The most common AEs reported were diarrhea, rash, and nausea [68]. Janne et al. recently published results for 222 patient demonstrating a 51 % overall response rate. The response rate for 122 centrally confirmed T790M+ patients was 61 % and in 61 T790M-patients was 21 % [69]. These results led to FDA approval of osimertinib in late 2015, and this agent is now available to patients with *EGFR* mutation-positive NSCLC who have developed the T790M resistance mutation. This area of EGFR TKI drug resistance continues to advance quickly. Additional irreversible EGFR inhibitors are in development including, EGF816 and ASP8273, HM61713, and others, which appear safe and potentially effective in treating NSCLC patients with sensitive *EGFR* mutations as

well as those with the T790M mutation [70–72]. Resistance mechanisms to the third-generation EGFR TKIs are also under investigation and include small cell transformation, and resistance mutations such as the newly described L718Q, L844V, and C797S [73].

3.1.4 Bypass Pathways

As mentioned previously, lung adenocarcinoma can circumvent inhibition of the constitutively active mutant receptor at the membrane through a co-receptor tyrosine kinase or through a separate receptor. Morgillo et al. found insulin-like growth factor-1 receptor (IGF-1R) as a mechanism of resistance in lung cancer cell lines. It was found that when IGF-1R heterodimerized with EGFR, erlotinib resistance developed through activation of the downstream pathway PI3K/AKT/mammalian target of rapamycin (mTOR) producing survivin that helps resist apoptosis [74]. Furthermore, several laboratories have identified in vitro and in vivo *MET* amplification and expression of ligand hepatocyte growth factor as a means of EGFR TKI resistance through restoring independently of EGFR the Akt pathway [75–80]. Other receptor tyrosine kinases (RTKs) reported to promote TKI resistance are fibroblast growth factor receptors (FGFR) such as FGFR1 that is thought in an autocrine fashion through its ligand FGF2 to promote cell proliferation, and AXL is thought to promote epithelial to mesenchymal transition (EMT) discussed in more detail later [81, 82]. These are examples of receptors that are important in resistance, but there are also reports of intracellular proteins such as loss of phosphatase and tensin homolog (PTEN), the tumor suppressor protein that regulates PI3K, and results in unregulated Akt signaling. Moreover, activation of Janus kinase 2/signal transducer and activator of transcription 3 (Jak2/STAT3) pathway has been another reported mechanism of resistance to TKI therapy [83, 84].

3.1.5 Hepatocyte Growth Factor (HGF)-MET Pathway

Targeting MET is an attractive target as evidenced by Engleman et al. [77] who demonstrated that *MET* amplification was a potential means of drug resistance and that treatment with a MET inhibitor re-sensitized these resistant cells to gefitinib in an *EGFR* mutant lung cancer cell line. Unfortunately, it has been an elusive one as demonstrated in a phase III study of tivantinib, a MET inhibitor, which was studied exclusively in adenocarcinoma TKI naïve lung cancer patients. Patients were stratified by V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and *EGFR* status, but were not selected by mutation. The trial was stopped after interim analysis projected futility [78]. Similarly, onartuzumab, a MET monoclonal antibody, was studied in combination with erlotinib in stage IIIB/stage IV NSCLC with MET expression by immunohistochemistry. The study was stopped early after independent review demonstrated OS of 6.8 months versus 9.1 months; HR 1.27, favoring erlotinib alone over the combination [85]. MET was recently profiled and found to occur with other mutations in a majority of cases, which adds to the complexity of this target [86].

3.1.6 IGF-1R

There is less mature data with the Insulin growth factor receptor (IGF-1R) and its ligands as potential targets, but it remains a pathway for resistance to targeted therapies. OSI-906, an oral inhibitor of IGF-1R and insulin receptor, reported phase I data in two separate publications as intermittent and continuous dosing in solid malignancies. Both trials reported gastrointestinal (GI) toxicities as well as hyperglycemia and QTc prolongation as dose-limiting toxicities [87, 88]. A phase II study evaluating erlotinib with or without OSI-906 in chemo-naïve *EGFR* mutant advanced adenocarcinoma of the lung has been completed [NCT01221077]. We await the results of this study to determine whether it is worthwhile to target. It may also be important in ALK TKI resistance.

3.1.7 PTEN/PI3K/AKT

The PI3K pathway has long been regarded as an ideal target given that it is downstream of multiple RTKs; however, it has proven difficult to target due to significant toxicities and lack of efficacy. This may be related to the lack of specificity to the subunit of PI3K and or mutations downstream of PI3K. BKM 120 (buparlisib), an oral pan-class I PI3K inhibitor, was studied with gefitinib in a phase Ib study with NSCLC patients who were determined EGFR TKI resistant by the Jackman criteria [62]. Common adverse events were diarrhea, fatigue, mucositis, and anorexia. There were also delayed grade 3 toxicities reported, and the drug is no longer in development in lung cancer [89]. As mentioned previously, downstream mutations can also occur. Another approach toward blocking this pathway is with pan-class PI3K/mTORC1/2 inhibitors. Inhibition of just mTORC1 is not sufficient to completely shut down PI3K as it can signal through mammalian target of rapamycin complex 2 mTORC2 [90]. BEZ235 is an oral pan-class PI3K/mTORC inhibitor that enrolled 3 NSCLC patients in its phase I study. Common adverse events (AEs) were nausea, vomiting, diarrhea, and fatigue [91]. There are also direct AKT inhibitors such as MK-2206. This oral compound was studied in a phase II study in combination with erlotinib in unselected NSCLC patients who had previously progressed on erlotinib and was analyzed by *EGFR* mutant or *EGFR* wild-type cohort. Unfortunately, the response rate in the mutant *EGFR* patients was only 9 %, but the *EGFR* wild-type cohort had a disease control rate of 47 % [92]. This pathway remains important and will likely be explored in the future trials.

3.1.8 Epithelial to Mesenchymal Transition (EMT)

EMT has been reported as a resistance mechanism to EGFR-targeted therapy [56]. EMT is thought to lead to invasion, metastasis, and drug resistance in certain malignancies. The hallmark is loss of epithelial markers such as E-cadherin and vimentin [93]. There are several transcriptional factors identified within malignancies that have been shown to down regulate E-cadherin such as Snail and Twist; however, the actual trigger of EMT has yet to be elucidated. It is thought to occur through external sources such as the tumor microenvironment as well internal sources such as genetic mutations that alter transcription and epigenetic

modification [94–97]. Although transcription factors have been found to down regulate E-cadherin by suppression of its promoter, singling pathways such as Raf/Ras and binding of the ligand HGF to its receptor MET have also been implicated in the transition [98–102]. NSCLC tumor samples from the Phase III TRIBUTE trial of chemotherapy plus erlotinib versus chemotherapy alone were analyzed for E-cadherin. Eighty-seven samples (8 %) were positive for E-cadherin expression, and the group found a significant PFS difference for those on the erlotinib plus chemotherapy arm who stained positive for E-cadherin in comparison with those who received chemotherapy alone. This suggests an increased sensitivity to erlotinib for those with the epithelial marker E-cadherin [103].

3.1.9 Therapeutics for EMT

There is experimental evidence that the peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists, a class of compounds known as the thiazolidinediones, such as rosiglitazone used in type II diabetes, may be candidate drugs to block EMT. A study in a lung cancer cell line demonstrated that transforming growth factor beta TGF-β signaling induces EMT through Smad3 transcriptional activity. More importantly, this study found that the synthetic PPAR-γ ligand reverted EMT and prevented it through the inhibition of TGF-β/Smad3 signaling in vitro and prevented metastasis in vivo in experimental mouse models [104]. EMT needs to be further explored to best determine how it can become a clinically meaningful target.

3.1.10 ALK & ROS1

The previous sections addressed acquired resistance mechanisms to EGFR TKI therapy and potential treatment options. The story of ALK resistance is more complex. As opposed to the *EGFR* mutant receptor that has a single dominant mutation that explains over 50 % of acquired resistance, there are several *ALK* receptor kinase domain mutations in addition to bypass pathways. Adding to the complexity is the differential sensitivity to the RTK inhibitors based on these resistance mutations. These mutations and therapeutics will be discussed in detail below.

Choi et al. [105] were one of the first to identify an ALK resistance mutation through next-generation sequencing in a patient progressing on crizotinib. Two separate clonal mutations within the tyrosine kinase domain that conferred resistance were discovered: L1196M and C1156Y. Katayama et al. soon followed by identifying three other never before described kinase domain mutations: G1202, S1206Y, and 1151Tins. They also confirmed the previously reported L1196M mutation. It was found that these mutations conferred resistance through either steric hindrance or reduced affinity for the TKI. He also found additional mechanisms of resistance such as gene amplification in *ALK* fusion, *KIT*, or *EGFR* [106]. These mechanisms of resistance are now recognized widely and have been confirmed by others as well as other novel mutations [107–110].

Awad et al. [111] similarly identified a mutation, CD47-ROS1, in the kinase domain that conferred resistance in a *ROS1*-translocated lung cancer patient. It was determined through crystallography that crizotinib ordinarily binds to ROS1 in the

ATP-binding pocket, and this gene rearrangement results in steric hindrance. Similar to the ALK resistance story, EGFR signaling has also been reported as a mechanism of resistance to crizotinib in *ROS1*-translocated lung cancer [112].

3.1.11 Therapeutics for ALK and ROS1 Resistance

There has been an explosion of new agents for *ALK*-positive lung cancer that are FDA-approved or in clinical trials for those who progress on first-line crizotinib. Ceritinib, formerly known as LDK378, is now approved for *ALK* gene rearranged lung adenocarcinoma patients who have progressed on crizotinib. Shaw et al. reported the phase I study findings for 130 patients, and the 114 who ultimately received at least 400 mg of ceritinib daily had an overall response rate of 58 % and PFS of 7 months. Some of the most intriguing findings came from their ability to sequence 19 of these patient tumors for new or the absence of new mutations and measure response. Five of these patients had a secondary kinase mutation and 2 had gene amplification, but the remaining 12 had no *ALK* mutation with 7 of those 12 demonstrating a response. The authors postulate that this could be a result of ALK tumor dependence or of yet to be discovered off target effect of ceritinib [113]. Friboulet et al. identified ceritinib sensitive kinase domain mutations such as L1196M, G1269A, S1206Y, and I1171T by utilizing these patient samples as well as known crizotinib-resistant cell lines. They were also able to identify several less sensitive kinase mutations and two resistant kinase mutations, G1202R and F1174V/C [114]. Alectinib, a second-generation ALK inhibitor, approved in Japan and the USA for *ALK*-positive adenocarcinoma patients who progressed after crizotinib, demonstrated systemic and central nervous system (CNS) responses in a phase I study [115] and received FDA approval from positive phase II data. Phase II results of alectinib demonstrated an ORR 49.2 % in 138 patients with *ALK*-positive lung cancer who progressed on crizotinib [116]. A second study evaluated 69 patients with an ORR 47.8 % [117]. Interestingly, Katayama et al. [118] have demonstrated two resistance mutations after alectinib treatment, one in a cancer cell line and the other in a patient, V1180L and I1171T, that were both sensitive to ceritinib.

The phase I/II results of brigatinib, a dual EGFR/ALK inhibitor, demonstrated a response rate of 72 % and median PFS 56 weeks in 72 evaluable patients, the majority having received prior crizotinib [119]. Similar to alectinib and ceritinib, this drug also demonstrated CNS responses in some of the patients. An ALK/tropomyosin receptor kinase (TRK) inhibitor is also being studied in a phase I trial of patient with *ALK*+ solid tumors. Dose-limiting toxicities include dysesthesia and QTc prolongation [120].

There are several other compounds currently being studied in *ALK* rearranged lung adenocarcinoma, crizotinib-resistant patients including ASP3026 [NCT01401504] and X-396 [NCT01625234] with response rates ranging from 44 to 63 % [121]. Dual inhibition of ALK and EGFR has also been reported to be a potential strategy in those without *ALK* mutation or amplification at time of progression and in those with evidence of EGFR-activated pathways [122].

There are candidate drugs under investigation for *ROS1* resistance mutations including cabozantinib, a cMET/Proto-oncogene c-Ret (RET)/vascular endothelial growth factor receptor (VEGFR) inhibitor, and the loral compound PF-06463922 that inhibits both ALK and ROS1 [123, 124]. Results in the ongoing phase I/II study with PF-06463922 were reported with side effects of hypercholesterolemia and peripheral neuropathy and with clear anti-tumor activity [125].

3.1.12 Heat Shock Protein (HSP) 90

Heat shock proteins or chaperone proteins have been studied in normal tissue as well as malignant tissue in their role of protein folding, cell signaling, and cell growth and survival. HSP 90 has been a particular target of interest due to its overexpression and overdependence in several malignant pathways [126]. It is thought that HSP 90s ability to stabilize essential oncogenic proteins such as mutated EGFR may lead to resistance through stabilization or support of other proteins involved in bypass pathways [127]. There have been several preclinical NSCLC models that have demonstrated the ability to overcome resistance in *EGFR*, *ALK*, and *ROS1* [128–130] with HSP 90 inhibitors.

Sequist et al. reported phase II results of IPI-504 (retaspimycin), an oral HSP 90 inhibitor with some activity in *EGFR* mutant, and more so in *ALK* rearranged NSCLC. Common adverse events were fatigue, nausea, and diarrhea [131]. There are currently several second-generation HSP 90 inhibitors in clinical trials as AUY-922 [NCT01784640], AT13387 [NCT01712217], and STA-9090 [NCT01031225] as single agents or in combination with chemotherapy or RTK-targeted agents [132].

3.2 Chemotherapeutics

Schiller et al. [133] reported no difference in response rate or survival between four separate platinum-doublet regimens that included a platinum with taxane or platinum with anti-metabolite gemcitabine in patients with advanced NSCLC. They did find a greater progression-free survival (PFS) with the cisplatin plus gemcitabine regimen. However, it was Scagliotti et al. [134] that demonstrated a clear survival difference in adenocarcinoma of the lung with cisplatin plus pemetrexed when compared to cisplatin plus gemcitabine, without benefit seen in squamous cell carcinoma of the lung. Squamous cell carcinoma has been found to express high thymidylate synthase (TS) by mRNA expression [135]. Pemetrexed has been found to inhibit TS along with other folate-dependent enzymes [136]. Pemetrexed tumor sensitivity may be at least in part dependent on the level of TS [137]. While these results are encouraging as a predictive biomarker of response, they are far from conclusive at this time.

Similarly, resistance develops to taxanes, a class of tubulin-binding agents that can be used as part of a platinum-doublet regimen. Beta III-tubulin overexpression has been implicated in the development of taxane resistance [138]. Cisplatin is a drug that binds to DNA, forming adducts that covalently bind and cross-link DNA

preventing DNA replication. There are DNA repair enzymes including excision repair cross-complementing group 1 (ERCC1) that was thought to be a predictive biomarker of response to cisplatin from in vitro and early clinical studies [139]. Unfortunately, a phase III study which randomized locally advanced NSCLC patients to adjuvant cisplatin-based chemotherapy based on negative ERCC1 status was stopped early when it was determined their IHC results were inconsistent thereby making randomization based on this marker not possible [140]. It was also found that the IHC antibody could not distinguish the one out of four isoforms of ERCC1 that was thought to contribute to cisplatin resistance [141]. Thus, while ERCC1 may be a means of resistance, we do not currently have a validated method to detect the resistant isoform. The hope in the future is that even systemic chemotherapy can be tailored to subtypes of lung cancer like pemetrexed to non-squamous carcinoma of the lung.

3.3 PD1/PD-L1 Pathway

It is now known that tumors express programmed death ligand 1 (PD-L1) to induce T cell anergy by binding to its receptor, programmed death 1 (PD-1) [142]. This has been described as immune evasion and is only one checkpoint in the immune cycle that a tumor can exploit to avoid destruction. Inhibition of PD1 on the T cell or PD-L1 on the tumor has proven a successful strategy in lung cancer as well as several other malignancies [143–151]. In EGFR-mutated lung cancer, PD-L1 has been found to be at higher expression with EGFR activation and downregulated with EGFR-targeted inhibition [152–154]. In wild-type EGFR lung cancer, PD-L1 has been linked to a poorer prognosis compared to those without. While concurrent inhibition of EGFR and PD-L1 in the laboratory was not found to be synergistic, a staggered approach or at point of progression on EGFR-targeted therapy without another EGFR therapy available, a PD1 or PD-L1 inhibitor may be a reasonable approach with multiple ongoing trials combining EGFR inhibitors with PD1 and PD-L1 agents. Currently, there is one clinical trial [NCT02511184] combining crizotinib plus pembrolizumab in the advanced NSCLC in the 1st-line setting, and there are several others combining chemotherapy plus a PD1 or PD-L1 inhibitor [NCT02367794, NCT02578680, NCT02409342, NCT02574598].

4 Conclusions

The field of oncology has changed drastically into one of personalized genomics. Research in lung cancer and the application of these findings into clinical trials has begun to develop quickly and lead the way. While precision medicine has been exciting for the field, with increased knowledge, comes more awareness of the complexity and adaptability of resistance mechanisms. We have moved beyond the simplicity of mutations within the catalytic domain of proteins to one of complex molecular pathways that bypass the constitutively activated protein receptor as well

as supportive, but crucial players such as transcription factors in EMT and chaperone proteins HSP 90 in oncogenic protein stability. A yet to be fully defined, but an altogether different approach, is immunotherapy with newly proven clinical efficacy, but less so in patients with known driver mutations. Its role in combination or sequential order will need to be further investigated. As we are now starting to recognize those mutations that may be driver mutations, the importance of sustaining a response and or targeting resistance mutations while minimizing toxicity will become increasingly more important.

References

1. Subramanian J, Govindan R (2008) Molecular genetics of lung cancer in people who have never smoked. Lancet Oncol 9(7):676–682
2. Chougule A et al (2013) Frequency of EGFR mutations in 907 lung adenocarcioma patients of Indian ethnicity. PLoS ONE 8(10):e76164
3. Couraud S et al (2015) BioCAST/IFCT-1002: epidemiological and molecular features of lung cancer in never-smokers. Eur Respir J 45:1403–1414
4. Zhang Y et al (2012) Frequency of driver mutations in lung adenocarcinoma from female never-smokers varies with histologic subtypes and age at diagnosis. Clin Cancer Res 18 (7):1947–1953
5. Drilon A et al (2015) Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in "driver-negative" lung adenocarcinomas. Clin Cancer Res 21:3631–3639
6. Cohen S (1962) Isolation of a mouse submaxillary gland protein accelerating incisor eruption and eyelid opening in the new-born animal. J Biol Chem 237:1555–1562
7. Carpenter G, King L Jr, Cohen S (1978) Epidermal growth factor stimulates phosphorylation in membrane preparations in vitro. Nature 276(5686):409–410
8. Ullrich A et al (1984) Human epidermal growth factor receptor cDNA sequence and aberrant expression of the amplified gene in A431 epidermoid carcinoma cells. Nature 309 (5967):418–425
9. Garrett TP et al (2002) Crystal structure of a truncated epidermal growth factor receptor extracellular domain bound to transforming growth factor alpha. Cell 110(6):763–773
10. Lemmon MA et al (1997) Two EGF molecules contribute additively to stabilization of the EGFR dimer. EMBO J 16(2):281–294
11. Ogiso H et al (2002) Crystal structure of the complex of human epidermal growth factor and receptor extracellular domains. Cell 110(6):775–787
12. Schlessinger J (1988) Signal transduction by allosteric receptor oligomerization. Trends Biochem Sci 13(11):443–447
13. Rusch V et al (1997) Over expression of the epidermal growth factor receptor and its ligand transforming growth factor alpha is frequent in resectable non-small cell lung cancer but does not predict tumor progression. Clin Cancer Res 3(4):515–522
14. Sizeland AM, Burgess AW (1992) Anti-sense transforming growth factor alpha oligonucleotides inhibit autocrine stimulated proliferation of a colon carcinoma cell line. Mol Biol Cell 3(11):1235–1243
15. Tateishi M et al (1990) Immunohistochemical evidence of autocrine growth factors in adenocarcinoma of the human lung. Cancer Res 50(21):7077–7080
16. Veale D et al (1987) Epidermal growth factor receptors in non-small cell lung cancer. Br J Cancer 55(5):513–516
17. Honegger AM et al (1987) Point mutation at the ATP binding site of EGF receptor abolishes protein-tyrosine kinase activity and alters cellular routing. Cell 51(2):199–209

18. Honegger AM et al (1987) A mutant epidermal growth factor receptor with defective protein tyrosine kinase is unable to stimulate proto-oncogene expression and DNA synthesis. Mol Cell Biol 7(12):4568–4571
19. Redemann N et al (1992) Anti-oncogenic activity of signalling-defective epidermal growth factor receptor mutants. Mol Cell Biol 12(2):491–498
20. Wakeling AE et al (1996) Specific inhibition of epidermal growth factor receptor tyrosine kinase by 4-anilinoquinazolines. Breast Cancer Res Treat 38(1):67–73
21. Wakeling AE et al (2002) ZD1839 (Iressa): an orally active inhibitor of epidermal growth factor signaling with potential for cancer therapy. Cancer Res 62(20):5749–5754
22. Fukuoka M et al (2003) Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. J Clin Oncol 21(12):2237–2246
23. Herbst RS et al (2002) Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: results of a phase I trial. J Clin Oncol 20(18):3815–3825
24. Hidalgo M et al (2001) Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. J Clin Oncol 19(13):3267–3279
25. Kris MG et al (2003) Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 290(16):2149–2158
26. Miller VA et al (2004) Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. J Clin Oncol 22(6):1103–1109
27. Nakagawa K et al (2003) Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Japanese patients with solid malignant tumors. Ann Oncol 14(6):922–930
28. Perez-Soler R et al (2004) Determinants of tumor response and survival with erlotinib in patients with non–small-cell lung cancer. J Clin Oncol 22(16):3238–3247
29. Ranson M et al (2002) ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. J Clin Oncol 20(9):2240–2250
30. Shepherd FA et al (2005) Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353(2):123–132
31. Thatcher N et al (2005) Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa survival evaluation in lung cancer). Lancet 366(9496):1527–1537
32. Peddicord S (2015) FDA approves targeted therapy for first-line treatment of patients with a type of metastatic lung cancer. US Food and Drug Administration
33. Kosaka T et al (2004) Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. Cancer Res 64(24):8919–8923
34. Lynch TJ et al (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350 (21):2129–2139
35. Paez JG et al (2004) EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 304(5676):1497–1500
36. Pao W et al (2004) EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 101(36):13306–13311
37. Shigematsu H et al (2005) Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst 97(5):339–346
38. Zhang X et al (2006) An allosteric mechanism for activation of the kinase domain of epidermal growth factor receptor. Cell 125(6):1137–1149

39. Carey KD et al (2006) Kinetic analysis of epidermal growth factor receptor somatic mutant proteins shows increased sensitivity to the epidermal growth factor receptor tyrosine kinase inhibitor, erlotinib. Cancer Res 66(16):8163–8171
40. Yun CH et al (2008) The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc Natl Acad Sci U S A 105(6):2070–2075
41. Fukuoka M et al (2011) Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol 29(21):2866–2874
42. Mitsudomi T et al (2010) Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 11(2):121–128
43. Rosell R et al (2012) Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 13(3): 239–246
44. Zhou C et al (2011) Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 12(8):735–742
45. Sequist LV et al (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 31(27):3327–3334
46. Sandlund JT et al (1994) Clinicopathologic features and treatment outcome of children with large-cell lymphoma and the t(2;5)(p23;q35). Blood 84(8):2467–2471
47. Soda M et al (2007) Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 448(7153):561–566
48. Birchmeier C, Sharma S, Wigler M (1987) Expression and rearrangement of the ROS1 gene in human glioblastoma cells. Proc Natl Acad Sci U S A 84(24):9270–9274
49. Li C et al (2011) Spectrum of oncogenic driver mutations in lung adenocarcinomas from East Asian never smokers. PLoS ONE 6(11):e28204
50. Kwak EL et al (2010) Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 363(18):1693–1703
51. Davies KD, Doebele RC (2013) Molecular pathways: ROS1 fusion proteins in cancer. Clin Cancer Res 19(15):4040–4045
52. Camidge DR et al (2012) Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 13(10): 1011–1019
53. Shaw AT et al (2014) Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 371(21):1963–1971
54. Shaw AT et al (2013) Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 368(25):2385–2394
55. Solomon BJ et al (2014) First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 371(23):2167–2177
56. Sequist LV et al (2011) Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 3(75):75ra26
57. Arcila ME et al (2011) Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay. Clin Cancer Res 17(5):1169–1180
58. Yu HA et al (2013) Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 19 (8):2240–2247
59. Kobayashi S et al (2005) EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 352(8):786–792

60. Pao W et al (2005) Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med 2(3):e73
61. Janjigian YY et al (2014) Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. Cancer Discov 4(9):1036–1045
62. Jackman D et al (2010) Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. J Clin Oncol 28(2):357–360
63. Katakami N et al (2013) LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J Clin Oncol 31(27):3335–3341
64. Janjigian YY (2014) Dual inhibition of EGFR with Afatinib and Cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. Cancer Dis 4:1036–1045
65. Sequist LV, Soria J-C, Gadgeel SM, Wakelee HA, Camidge DR, Varga A, Solomon BJ, Papadimitrakopoulou V, Jaw-Tsai SS, Caunt L, Kaur P, Rolfe L, Allen AR, Goldman JW (2014) First-in-human evaluation of CO-1686, an irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M). In: 2014 ASCO annual meeting on journal of clinical oncology, Chicago
66. Sequist LV et al (2015) Rociletinib in EGFR-mutated non-small-cell lung cancer. N Engl J Med 372(18):1700–1709
67. Sequist LV, Goldman JW, Wakelee HA et al (2015) Efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small cell lung cancer (NSCLC) patients (pts). In: 2015 ASCO annual meeting on journal of clinical oncology, Chicago
68. Janne PA, Ramalingam SS, Yang JC-H, Ahn M-J, Kim D-W, Kim S-W, Planchard D, Ohe Y, Felip E, Watkins C, Cantarini M, Ghiorghiu S, Ranson M (2014) Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor–resistant non-small cell lung cancer (NSCLC). J Clin Oncol (in ASCO. Chicago)
69. Jänne PA et al (2015) AZD9291 in EGFR inhibitor-resistant non–small-cell lung cancer. N Engl J Med 372(18):1689–1699
70. Tan D, Seto T, Leighl N et al (2015) First-in-human phase I stud; of EGF816, a third generation, mutant-selective EGFR tyrosine kinase inhibitor, in advanced non-small cell lung cancer (NSCLC) harboring T790M. In: 2015 ASCO annual meeting on journal of clinical oncology, Chicago
71. Goto Y, Nokihara H, Marakami H et al (2015) ASP8273, a mutant-selective irreversible EGFR inhibitor in patients (pts) with NSCLC harboring EGFR activating mutations: preliminary results of first-in-human phase I study in Japan. In: 2015 ASCO annual meeting on journal of clinical oncology, Chicago
72. Park K, Lee JS, Lee KH et al (2015) Updated safety and efficacy results from phase I/II study of HM61713 in patients (pts) with EGFR mutation positive non-small cell lung cancer (NSCLC) who failed previous EGFR-tyrosine kinase inhibitor (TKI). In: 2015 ASCO annual meeting on journal of clinical oncology, Chicago
73. Ercan D et al (2015) EGFR mutations and resistance to irreversible pyrimidine-based EGFR inhibitors. Clin Cancer Res 21(17):3913–3923
74. Morgillo F et al (2006) Heterodimerization of insulin-like growth factor receptor/epidermal growth factor receptor and induction of survivin expression counteract the antitumor action of erlotinib. Cancer Res 66(20):10100–10111
75. Bean J et al (2007) MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc Natl Acad Sci U S A 104(52):20932–20937
76. Cappuzzo F et al (2009) Increased MET gene copy number negatively affects survival of surgically resected non-small-cell lung cancer patients. J Clin Oncol 27(10):1667–1674
77. Engelman JA et al (2007) MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 316(5827):1039–1043

78. Scagliotti GV, Novello S, von Pawel J (2013) The emerging role of MET/HGF inhibitors in oncology. Cancer Treat Rev 39(7):793–801
79. Yano S et al (2008) Hepatocyte growth factor induces gefitinib resistance of lung adenocarcinoma with epidermal growth factor receptor-activating mutations. Cancer Res 68 (22):9479–9487
80. Yano S et al (2011) Hepatocyte growth factor expression in EGFR mutant lung cancer with intrinsic and acquired resistance to tyrosine kinase inhibitors in a Japanese cohort. J Thorac Oncol 6(12):2011–2017
81. Terai H et al (2013) Activation of the FGF2-FGFR1 autocrine pathway: a novel mechanism of acquired resistance to gefitinib in NSCLC. Mol Cancer Res 11(7):759–767
82. Zhang Z et al (2012) Activation of the AXL kinase causes resistance to EGFR-targeted therapy in lung cancer. Nat Genet 44(8):852–860
83. Harada D et al (2012) JAK2-related pathway induces acquired erlotinib resistance in lung cancer cells harboring an epidermal growth factor receptor-activating mutation. Cancer Sci 103(10):1795–1802
84. Sos ML et al (2009) PTEN loss contributes to erlotinib resistance in EGFR-mutant lung cancer by activation of Akt and EGFR. Cancer Res 69(8):3256–3261
85. Spigel D, Edelman M, O'Byrne K, Paz-Ares L, Shames DS, Yu W, Paton VE, Mok T (2014) Onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIb or IV NSCLC: results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial. In: 2014 ASCO annual meeting on journal of clinical oncology, Chicago
86. Eisert A, Scheffler M, Michels S et al (2015) Genetic variability and clinical presentation of patients with non-small cell lung cancer (NSCLC) harboring MET-amplifications. In: 2105 ASCO annual meeting on *journal of clinical oncology*, Chicago
87. Jones RL et al (2015) Phase I study of intermittent oral dosing of the insulin-like growth factor-1 and insulin receptors inhibitor OSI-906 in patients with advanced solid tumors. Clin Cancer Res 21(4):693–700
88. Puzanov I et al (2015) A phase I study of continuous oral dosing of OSI-906, a dual inhibitor of insulin-like growth factor-1 and insulin receptors, in patients with advanced solid tumors. Clin Cancer Res 21(4):701–711
89. Tan DS-W, Lim KH, Tai WM, Ahmad A, Pan S, Ng QS, Ang M-K, Gogna A, Ng YL, Tan BS, Lee HY, Krisna SS, Lau DPX, Zhong L, Iyer G, Chowbay B, Lim AST, Takano A, Lim W-T, Tan E-H (2013) A phase Ib safety and tolerability study of a pan class I PI3K inhibitor buparlisib (BKM120) and gefitinib (gef) in EGFR TKI-resistant NSCLC. In: 2013 ASCO annual meeting on journal of clinical oncology, Chicago
90. Wander SA, Hennessy BT, Slingerland JM (2011) Next-generation mTOR inhibitors in clinical oncology: how pathway complexity informs therapeutic strategy. J Clin Invest 121 (4):1231–1241
91. Peyton JD, Rodon Ahnert J, Burris H, Britten C, Chen LC, Tabernero J, Duval V, Rouyrre N, Silva AP, Quadt C, Baselga J (2011) A dose-escalation study with the novel formulation of the oral pan-class I PI3K inhibitor BEZ235, solid dispersion system (SDS) sachet, in patients with advanced solid tumors. In: 2011 ASCO annual meeting on journal of clinical oncology
92. Lara P, Longmate J, Mack PC, Kelly K, Socinski MA, Salgia R, Gitlitz BJ, Li T, Koczywas M, Reckamp KL, Gandara DR (2014) Phase II study of the AKT inhibitor MK-2206 plus erlotinib (E) in patients (pts) with advanced non-small cell lung cancer (NSCLC) who progressed on prior erlotinib: a California Cancer Consortium Phase II trial (NCI 8698). In: 2014 ASCO annual meeting on journal of clinical oncology
93. Nurwidya F et al (2012) Epithelial mesenchymal transition in drug resistance and metastasis of lung cancer. Cancer Res Treat 44(3):151–156
94. Batlle E et al (2000) The transcription factor snail is a repressor of E-cadherin gene expression in epithelial tumour cells. Nat Cell Biol 2(2):84–89

95. Cano A et al (2000) The transcription factor snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression. Nat Cell Biol 2(2):76–83
96. Smit MA et al (2009) A twist-snail axis critical for TrkB-induced epithelial-mesenchymal transition-like transformation, anoikis resistance, and metastasis. Mol Cell Biol 29(13): 3722–3737
97. Yang J et al (2004) Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis. Cell 117(7):927–939
98. Grunert S, Jechlinger M, Beug H (2003) Diverse cellular and molecular mechanisms contribute to epithelial plasticity and metastasis. Nat Rev Mol Cell Biol 4(8):657–665
99. Huber MA, Kraut N, Beug H (2005) Molecular requirements for epithelial-mesenchymal transition during tumor progression. Curr Opin Cell Biol 17(5):548–558
100. Savagner P (2001) Leaving the neighborhood: molecular mechanisms involved during epithelial-mesenchymal transition. BioEssays 23(10):912–923
101. Lee JM et al (2006) The epithelial-mesenchymal transition: new insights in signaling, development, and disease. J Cell Biol 172(7):973–981
102. Garofalo M et al (2012) EGFR and MET receptor tyrosine kinase-altered microRNA expression induces tumorigenesis and gefitinib resistance in lung cancers. Nat Med 18(1): 74–82
103. Yauch RL et al (2005) Epithelial versus mesenchymal phenotype determines in vitro sensitivity and predicts clinical activity of erlotinib in lung cancer patients. Clin Cancer Res 11(24 Pt 1):8686–8698
104. Reka AK et al (2010) Peroxisome proliferator-activated receptor-gamma activation inhibits tumor metastasis by antagonizing Smad3-mediated epithelial-mesenchymal transition. Mol Cancer Ther 9(12):3221–3232
105. Choi YL et al (2010) EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. N Engl J Med 363(18):1734–1739
106. Katayama R et al (2012) Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. Sci Transl Med 4(120):120ra17
107. Heuckmann JM et al (2011) ALK mutations conferring differential resistance to structurally diverse ALK inhibitors. Clin Cancer Res 17(23):7394–7401
108. Lovly CM, Pao W (2012) Escaping ALK inhibition: mechanisms of and strategies to overcome resistance. Sci Transl Med 4(120):120ps2
109. Sasaki T et al (2011) A novel ALK secondary mutation and EGFR signaling cause resistance to ALK kinase inhibitors. Cancer Res 71(18):6051–6060
110. Sun HY, Ji FQ (2012) A molecular dynamics investigation on the crizotinib resistance mechanism of C1156Y mutation in ALK. Biochem Biophys Res Commun 423(2):319–324
111. Awad MM et al (2013) Acquired resistance to crizotinib from a mutation in CD74-ROS1. N Engl J Med 368(25):2395–2401
112. Davies KD et al (2013) Resistance to ROS1 inhibition mediated by EGFR pathway activation in non-small cell lung cancer. PLoS ONE 8(12):e82236
113. Shaw AT et al (2014) Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 370(13):1189–1197
114. Friboulet L et al (2014) The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. Cancer Discov 4(6):662–673
115. Gadgeel SM et al (2014) Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol 15 (10):1119–1128
116. Ou SHI, Ahn JS, Petris LD et al (2015) Efficacy and safety of the ALK inhibitor alectinib in ALK+ non-small cell lung cancer (NSCLC) patients who have failed prior crizotinib: an open-label, single-arm, global phase 2 study (NP28673). In: 2015 ASCO annual meeting on journal of clinical oncology, Chicago

117. Gandhi L, Shaw A, Gadgeel SM et al (2015) A phase II, open-label, multicenter study of the ALK inhibitor alectinib in an ALK+ non-small-cell lung cancer (NSCLC) U.S./Canadian population who had progressed on crizotinib (NP28761). In: 2015 ASCO annual meeting on journal of clinical oncology, Chicago
118. Katayama R et al (2014) Two novel ALK mutations mediate acquired resistance to the next-generation ALK inhibitor Alectinib. Clin Cancer Res 20(22):5686–5696
119. Camidge DR, Bazhenova L, Salgia R et al (2015) Safety and efficacy of brigatinib (AP26113) in advanced malignancies, including ALK+ non-small cell lung cancer (NSCLC). In: 2015 ASCO annual meeting on journal of clinical oncology, Chicago
120. Arkenau HT, Sachdev JC, Mita MM et al (2015) Phase (Ph) 1/2a study of TSR-011, a potent inhibitor of ALK and TRK, in advanced solid tumors including crizotinib-resistant ALK positive non-small cell lung cancer. In: 2015 ASCO annual meeting on journal of clinical oncology, Chicago
121. Pall G (2015) The next-generation ALK inhibitors. Curr Opin Oncol 27(2):118–124
122. Yamaguchi N et al (2014) Dual ALK and EGFR inhibition targets a mechanism of acquired resistance to the tyrosine kinase inhibitor crizotinib in ALK rearranged lung cancer. Lung Cancer 83(1):37–43
123. Katayama R et al (2015) Cabozantinib overcomes Crizotinib resistance in ROS1 fusion-positive cancer. Clin Cancer Res 21(1):166–174
124. Zou HY et al (2015) PF-06463922 is a potent and selective next-generation ROS1/ALK inhibitor capable of blocking crizotinib-resistant ROS1 mutations. Proc Natl Acad Sci U S A 112:3493–3498
125. Shaw AT, Bauer TM, Felip E et al (2015) Clinical activity and safety of PF-06463922 from a dose escalation study in patients with advanced ALK+ or ROS1 + NSCLC. In: 2015 ASCO annual meeting on journal of clinical oncology, Chicago
126. Whitesell L, Lindquist SL (2005) HSP90 and the chaperoning of cancer. Nat Rev Cancer 5 (10):761–772
127. Shimamura T et al (2005) Epidermal growth factor receptors harboring kinase domain mutations associate with the heat shock protein 90 chaperone and are destabilized following exposure to geldanamycins. Cancer Res 65(14):6401–6408
128. Kobayashi N et al (2012) The anti-proliferative effect of heat shock protein 90 inhibitor, 17-DMAG, on non-small-cell lung cancers being resistant to EGFR tyrosine kinase inhibitor. Lung Cancer 75(2):161–166
129. Normant E et al (2011) The Hsp90 inhibitor IPI-504 rapidly lowers EML4-ALK levels and induces tumor regression in ALK-driven NSCLC models. Oncogene 30(22):2581–2586
130. Sang J et al (2013) Targeted inhibition of the molecular chaperone Hsp90 overcomes ALK inhibitor resistance in non-small cell lung cancer. Cancer Discov 3(4):430–443
131. Sequist LV et al (2010) Activity of IPI-504, a novel heat-shock protein 90 inhibitor, in patients with molecularly defined non-small-cell lung cancer. J Clin Oncol 28(33): 4953–4960
132. Piotrowska Z, Costa DB, Huberman M et al (2015) Activity of AUY922 in NSCLC patients with EGFR exon 20 insertions. In: 2015 ASCO annual meeting on journal of clinical oncology, Chicago
133. Schiller JH et al (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346(2):92–98
134. Scagliotti GV et al (2012) Rationale and design of MARQUEE: a phase III, randomized, double-blind study of tivantinib plus erlotinib versus placebo plus erlotinib in previously treated patients with locally advanced or metastatic, nonsquamous, non-small-cell lung cancer. Clin Lung Cancer 13(5):391–395
135. Ceppi P et al (2006) Squamous cell carcinoma of the lung compared with other histotypes shows higher messenger RNA and protein levels for thymidylate synthase. Cancer 107 (7):1589–1596

136. Shih C et al (1997) LY231514, a pyrrolo[2,3-d]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res 57(6):1116–1123
137. Takezawa K et al (2011) Thymidylate synthase as a determinant of pemetrexed sensitivity in non-small cell lung cancer. Br J Cancer 104(10):1594–1601
138. Gan PP, Pasquier E, Kavallaris M (2007) Class III beta-tubulin mediates sensitivity to chemotherapeutic drugs in non small cell lung cancer. Cancer Res 67(19):9356–9363
139. Olaussen KA et al (2006) DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 355(10):983–991
140. Wislez M et al (2014) Customized adjuvant phase II trial in patients with non-small-cell lung cancer: IFCT-0801 TASTE. J Clin Oncol 32(12):1256–1261
141. Friboulet L et al (2013) ERCC1 isoform expression and DNA repair in non–small-cell lung cancer. N Engl J Med 368(12):1101–1110
142. Hirano F et al (2005) Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 65(3):1089–1096
143. Ansell SM et al (2015) PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 372(4):311–319
144. Brahmer JR et al (2012) Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 366(26):2455–2465
145. Garon EB et al (2015) Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 372: 2018–2028
146. Patnaik A et al (2015) Phase I study of Pembrolizumab (MK-3475; Anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. Clin Cancer Res 21:4286–4293
147. Petrylak DP, Powles T, Bellmunt J, et al (2015) A phase Ia stu;y of MPDL3280A (anti-PDL1): Updated response and survival data in urothelial bladder cancer (UBC). In: 2015 ASCO annual meeting on journal of clinical oncology, Chicago
148. Rizvi NA et al (2015) Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol 16(3):257–265
149. Robert C et al (2015) Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 372(4):320–330
150. Segal NH, Ou S, Balmanoukian AS et al (2015) Safety; and efficacy of MEDI4736, an anti-PD-L1 antibody, in patient from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. In: 2015 ASCO annual meeting on journal of clinical oncology, Chicago
151. Sullivan RJ, Flaherty KT (2015) Pembrolizumab for treatment of patients with advanced or unresectable Melanoma. Clin Cancer Res 21:2892–2897
152. Akbay EA et al (2013) Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. Cancer Discov 3(12):1355–1363
153. Chen N et al (2015) Upregulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC: implication for optional immune targeted therapy for NSCLC patients with EGFR mutation. J Thorac Oncol 10(6):910–923
154. Tang Y et al (2015) The association between PD-L1 and EGFR status and the prognostic value of PD-L1 in advanced non-small cell lung cancer patients treated with EGFR-TKIs. Oncotarget 6(16):14209–14219

Immunotherapy in Lung Cancer

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Abstract

Lung cancer has not traditionally been viewed as an immune-responsive tumor. However, it is becoming evident that tumor-induced immune suppression is vital to malignant progression. Immunotherapies act by enhancing the patient's innate immune response and hold promise for inducing long-term responses in select patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Immune checkpoint inhibitors, in particular, inhibitors to cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) and programmed death receptor ligand 1 (PD-L1) have shown promise in early studies and are currently in clinical trials in both small cell lung cancer and non-small cell lung cancer patients. Two large randomized phase III trials recently demonstrated superior overall survival (OS) in patients treated with anti-PD-1 therapy compared to chemotherapy in the second-line setting.

Keywords

Immunotherapy · PD-1 · PD-L1 · CTLA-4

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Contents

1 Cancer and the Biology of Immune Evasion

The immune system provides the primary defense against the development and growth of cancer. Through immunosurveillance, the immune system is able to recognize and eradicate incipient tumor cells [61]. The ability to escape the immune response, therefore, is vital to cancer survival and malignant progression [25]. This evasion may occur through either tumor-directed processes, typically involving alteration in the tumor cells themselves or the tumor microenvironment, or immune system-directed processes in which the tumor induces innate regulatory mechanisms to suppress the immune response [17].

Immunosurveillance involves every aspect of both the innate and adaptive immune system [15]. The innate immune system initiates antitumor immunity when NK cells recognize tumor-specific antigens, leading to destruction of the malignant-transformed cells [13]. Lysed tumor cell fragments are adsorbed and processed by macrophages and dendritic cells. Activation of macrophages and dendritic cells leads to both expression of inflammatory cytokines and presentation of tumor-specific ligands to T and B cells, thereby instigating the adaptive immune response [43]. The adaptive immune response involves the generation and expansion of tumor-specific T cells and antibodies [16, 17, 41]. Ideally, these processes culminate in elimination of cancer cells and generation of long-term immune memory [16]. However, it is also possible that a state known as cancer equilibrium may occur, in which the immune system maintains the tumor in a state of functional dormancy [16, 43]. Under this state, tumor cells, exposed to persistent immune pressure, may undergo genetic and epigenetic changes that ultimately can result in the selection of less immunogenic phenotypes [41, 43, 63], thereby facilitating the possibility of immune escape [16].

Evasion of the antitumor immune response occurs both at the level of the tumor cell and the tumor microenvironment. Lung cancer cells may be protected from immune recognition by downregulating proteins involved in antigen presentation, such as the immunoproteasome subunits large multifunctional peptidases 2 and 7 (LMP2 and LMP7), antigen peptide transporters 1 and 2 (TAP1 and TAP2), and the major histocompatibility (MHC) molecules [7]. Additionally, the oncogenic process may lead to multiple genetic and epigenetic alterations, rendering potential lung cancer antigens unstable and allowing for passive immune escape [14]. Such immune escape mechanisms are thought to be particularly important in smoking- and pollution-associated lung cancers, which harbor a high density of somatic mutations and epigenetic dysregulation [23, 63]. The expression of immune inhibitory molecules is another mechanism of immune evasion that has therapeutic importance in lung cancer. Regulatory T cells, which are present at increased numbers in patients with NSCLC, can suppress T cell activation through the production of TGF-B and interleukin-10 [37, 77, 80], thereby inducing immune tolerance. Membrane-bound inhibitory ligands, also known as checkpoint ligands, have amplified expression in lung cancer and include programmed death receptor ligand 1 (PD-L1), PD-L2, B7-H3, and B7-H4 [7, 46]. PD-L1, which is the most studied checkpoint ligand to date, is thought to be expressed in approximately half of NSCLCs, with equal proportion in squamous and nonsquamous histologies [44]. Tumor-infiltrating CD8+ and CD4+ lymphocytes have been identified in resected NSCLC specimens at rate ranging from 25 to 83 % and are thought to have a favorable prognostic significance in resected early-stage disease [28, 34, 49, 58].

Disruption of tumor-induced immune suppression has been a goal of various immunotherapies under development. Tumor-specific antigens that theoretically should enable the immune system to distinguish between malignant and normal cells have been the focus of therapeutic vaccines, with limited success to date. More recently, immune checkpoint inhibitors have shown promising activity in patients with advanced small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). These agents were developed with the goal of overcoming tumor-induced immune suppression and generating potentially durable antitumor immune responses.

2 Immune Checkpoint Inhibitors

Immune checkpoint inhibitors liberate previously repressed antitumor immune responses by modulating the interaction of T cells with either antigen-presenting cells (APCs) or tumor cells. Because the released immune response is thought to encompass immune memory as well, some patients experience apparently durable remissions without evidence of tumor resistance or relapse. Agents targeting the cytotoxic T-lymphocyte antigen 4 (CTLA-4) and the programmed cell death receptor-1 (PD-1) and its ligand, PD-L1, are currently being evaluated in patients with advanced stage lung cancer.

2.1 Therapies Targeting CTLA-4

CTLA-4 inhibitors were the earliest checkpoint inhibitors to reach clinical development. Activation of cytotoxic T cells entails binding of the T cell receptor with an MHC molecule as well as co-stimulatory signals mediated through CD28 and B7 [41]. The CTLA-4 protein is expressed on the T cell surface and functions as a negative regulator of T cell activation by competing with CD28. Antibodies to CTLA-4 inhibit this crucial negative regulator of T cell activation with the goal of releasing suppressed antitumor immune responses [59, 76]. The resultant immune activation also causes a unique toxicity profile of immune-related adverse events including pneumonitis, colitis, dermatitis, hepatitis, endocrinopathies, and neuropathy.

Ipilimumab is a fully humanized monoclonal antibody directed at CTLA-4 and functions to prevent receptor binding to cognate ligands. It was approved for use in metastatic melanoma after showing significant improvement in overall survival compared to chemotherapy in pretreated patients with metastatic disease [30]. Ipilimumab has subsequently been evaluated at various doses and combinations in lung cancer. A phase II trial of paclitaxel (175 mg/m2) and carboplatin (AUC = 6) with ipilimumab (10 mg/kg) as either phased (two doses of placebo plus chemotherapy followed by four doses of ipilimumab plus chemotherapy) or concurrent (four doses of ipilimumab plus chemotherapy followed by two doses of placebo plus chemotherapy) administration, or placebo, in a treatment-naïve patients with advanced NSCLC resulted in immune-related progression-free survival (irPFS) of 5.7, 5.5, and 4.6 months, and median overall survival (OS) of 12.2, 9.7, and 8.3 months, respectively [42]. This resulted in a statistically significant improvement in irPFS with the phased dosing of ipilimumab as compared to placebo, but not the concurrent dosing schedule, and improvement in OS did not reach statistical significance. Under the phased dosing schedule, patients received two doses of placebo plus paclitaxel and carboplatin, followed by four doses of ipilimumab plus paclitaxel and carboplatin. An unplanned subset analysis of histologic subgroups revealed that both progression-free survival (PFS) and OS were improved in the phased ipilimumab group for patients with squamous histology (HR for progression 0.40 [95 % CI, 0.18–0.87], HR for death 0.48 [95 % CI, 0.22–1.03]) that was not seen in patients with nonsquamous cell histology. Grade 3 and 4 immune-related adverse events (irAEs) including colitis, hepatitis, and hypophysitis occurred at rates of 6, 20, and 15 % in the placebo, concurrent ipilimumab, and phased ipilimumab arms, respectively. A similar phase II trial of phased and concurrent ipilimumab (10 mg/kg) in combination with paclitaxel (175 mg/m^2) and carboplatin (AUC = 6) versus chemotherapy alone was performed in treatment-naïve patients with extensive stage SCLC [51]. Treatments were administered every 3 weeks for a maximum of 18 weeks, and followed by either maintenance ipilimumab or placebo every 12 weeks. This trial also found a statistically significant improvement in irPFS with phased ipilimumab (6.4 months) but not concurrent ipilimumab (5.7 months) as compared to placebo (5.3 months). Median OS was 12.9, 9.1, and 9.9 months with phased ipilimumab, concurrent

ipilimumab, and chemotherapy alone, respectively. Grade 3 and 4 irAEs including rash, colitis, and hepatitis occurred at rates of 9, 21, and 17 % in the placebo, concurrent ipilimumab, and phased ipilimumab arms, respectively. Further study of ipilimumab in lung cancer patients has moved forward with a phase III trial of ipilimumab (10 mg/kg) in combination with carboplatin (AUC = 6) and paclitaxel (175 mg/m2) versus carboplatin and paclitaxel alone in patients with advanced squamous NSCLC (NCT01285609). The combination of ipilimumab with carboplatin and etoposide as a first-line treatment in patients with extensive stage SCLC has completed enrollment and was recently reported as a negative trial (NCT01331525).

Tremelimumab is a fully humanized IgG2 monoclonal antibody to CTLA-4. In contrast to ipilimumab, a large phase III trial in treatment-naïve patients with advanced melanoma did not demonstrate improved PFS, OS, or objective response rate (ORR) compared to cytotoxic chemotherapy although some durable responses were observed and tremelimumab was given as maintenance rather than induction therapy [52]. Single agent tremelimumab in NSCLC has yielded similar results to date. In a phase II trial of 87 patients with advanced NSCLC, tremelimumab was administered as a maintenance therapy following 4 cycles of platinum-based chemotherapy [79]. There was no improvement in PFS in this study (20.9 vs. 14.3 % progression free at 3 months). Approximately 20 % of patients on the tremelimumab arm experienced a grade 3/4 adverse event the most common being colitis (9.1 %). Studies with tremelimumab in combination with anti-PD-L1 therapy and gefitinib in patients with NSCLC are ongoing (NCT02000947; NCT02040064).

2.2 Therapies Targeting PD-1

The PD-1 receptor and its two ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC), negatively regulate T cell activation [38]. The PD-1 receptor is a transmembrane protein that can be expressed on T cells, B cells, natural killer T cells, activated monocytes, and dendritic cells. PD-L1 is expressed by monocytes and lung tissue, as well as vascular endothelium, mesenchymal stem cells, keratinocytes, and activated T cells [38]. PD-L1 is also expressed in approximately half of NSCLCs (both adenocarcinoma and squamous cell histologies) and may be associated with a poor prognosis [44]. Binding of the PD-1 receptor by its ligands leads to inhibition of T cell receptor signaling, downregulation of the PI3 K pathway, and decreased induction of cytokines such as interferon-γ (IFN-γ) [38]. Therapies directed against PD-1 block the interaction of PD-1 with its ligands, thereby activating dormant T cell-mediated immune responses. PD-L1 is frequently found in combination with high levels of tumor-infiltrating lymphocytes, indicating that exhaustion of the antitumor T cell response may aid lung cancer progression and immune evasion [36]. However, this coupling of PD-L1 expression with tumor-infiltrating lymphocytes may help confine therapy-induced T cell activation to the tumor microenvironment, thereby limiting systemic immune-related toxicity [7]. Anti-PD-1 and anti-PD-L1 agents do not induce antibody-dependent cell-mediated

cytotoxicity (ADCC), an important consideration as ADCC could potentially deplete activated T cells and tumor-infiltrating immune cells [67]. Antibodies engineered against both PD-1 and PD-L1 are currently in development for use in lung cancer.

Nivolumab (BMS936558) is a human IgG4 monoclonal antibody to PD-1 and is the agent that is furthest in development in its class for NSCLC. Its utility in lung cancer patients was first explored in a large, phase I trial that included multiple expansion cohorts of patients including NSCLC, melanoma, and renal cell carcinoma (RCC) [69]. In this trial, 129 heavily pretreated patients with NSCLC received nivolumab (1, 3, or 10 mg/kg IV every 2 weeks). The ORR for patients with NSCLC across dosing levels was 17.1 %, with no significant difference between patients with squamous (16.7 %; 9 of 54) and nonsquamous histology (17.6 %; 13 of 74). Additionally, 5 % of patients had unconventional immune-pattern responses, and 10 % of patients had stable disease lasting at least 24 weeks. Median OS across doses was 9.9 months, and at the 3 mg/kg dose (which was chosen for use in subsequent trials) the 1-, 2-, and 3- year OS rates were 56, 42, and 27 %, respectively [20, 21]. Drug-related adverse events were seen in 53 % of patients, 6 % of which were grade 3/4 including gastrointestinal, pulmonary (pneumonitis), hepatitis, and infusion reactions. Durable responses were common with a median duration of response of 17 months (range 1.4–36.8 months). Eighteen responders discontinued nivolumab for reasons other than progressive disease, and 9 of these had responses for more than 9 months following therapy cessation [20, 21]. Subset analyses did not reveal any predictive value for EGFR or KRAS mutations as compared with wild-type (Brahmer JR [6]. However, there was predictive value for intratumoral PD-L1 expression (defined as 5 % expression threshold by immunohistochemistry). Of the 25 patients with known PD-L1-positive tumors, 36 % had an objective response versus no response among 17 patients with known PD-L1-negative tumors ($p = 0.006$) [69].

CheckMate 063 was a phase II single-arm trial of nivolumab (3 mg/kg) in patients with advanced, refractory squamous NSCLC[56]. Of the 117 patients enrolled, 17 (14.5, 95 % CI 8.7–22.2 %) had an objective response, and 77 % of those responses were ongoing at time of analysis. An additional 30 patients (26 %) had stable disease, with a median duration of 6.0 months (95 % CI 4.7–10.9 months). The most common grade 3/4 adverse events were fatigue (4 %), pneumonitis (3 %), and diarrhea (3 %). CheckMate-017 was a phase III open-label trial that enrolled 272 previously treated patients with advanced or metastatic squamous cell NSCLC [5]. Patients were randomized to receive either nivolumab (3 mg/kg every 2 weeks) or docetaxel (75 mg/m^2 every 3 weeks). The trial was stopped early when preliminary analyses indicated an overall survival advantage of 3.2 months favoring nivolumab over docetaxel (median OS 9.2 months versus 6.0 months for nivolumab and docetaxel, respectively; hazard ratio 0.59; $p < 0.001$). The median PFS was 3.5 months with nivolumab versus 2.8 months with docetaxel (HR for death or disease progression 0.62; $p < 0.001$), and the overall survival rate at one year was 42 % with nivolumab versus 24 % with docetaxel. At the time of study reporting, the median duration of response in the nivolumab arm had not been reached (range 2.9–20.5 + months), but

median duration of response was 8.4 months in the docetaxel arm. Grade 3 and 4 adverse events occurred in 7 % of patients receiving nivolumab, compared to 55 % of patients treated with docetaxel. PD-L1 expression was evaluated in 83 % of patients, but no prognostic or predictive association was found between PD-L1 expression and any efficacy endpoint. These findings led to FDA approval for nivolumab use in patients with refractory or recurrent advanced squamous NSCLC in March 2015. CheckMate-057, a phase III study of nivolumab (3 mg/kg every 2 weeks) versus docetaxel (75 mg/m^2 every 3 weeks) in previously treated patients with advanced or metastatic nonsquamous NSCLC, was also halted early when it was reported to meet its endpoint of improved overall survival [48]. As compared to docetaxel, nivolumab demonstrated superior OS (HR = 0.73, $p = 0.00155$) and ORR (19.2 vs. 12.4 %; $p = 0.0235$). The median response duration was 17.1 months (range: 8.4 months—not estimable) in the nivolumab arm, compared to 5.6 months (range: 4.4–7.0 months) in the docetaxel arm. Rates of grade 3–5 toxicity were substantially less in the nivolumab arm compared to docetaxel (10.5 vs. 53.7 %). Interestingly in this trial the median PFS with nivolumab (2.3 months) was inferior compared to chemotherapy (4.2 months), although the difference was not statistically significant (HR 0.92, 95 % CI: 0.77–1.11; $p = 0.393$). Positive expression of PD-L1 was not a prerequisite to study entry, but subset analysis was performed and higher levels of PD-L1 expression appeared to correlate with improved benefit. CheckMate 026 compared first platinum-based chemotherapy to nivolumab in patients with advanced stage NSCLC with *EGFR* and *ALK* wild-type status and showed tumors that are positive for expression of PD-L1 (NCT02041533).

Nivolumab is also being evaluated in combination with chemotherapy, as well as targeted agents such as erlotinib and bevacizumab. CheckMate-012 is a multi-arm phase 1b trial of nivolumab in combination with multiple agents including ipilimumab and several possible combinations of platinum-based doublet chemotherapy [2]. Patients were assigned to a chemotherapy regimen by histology: Squamous histology got nivolumab (10 mg/kg) plus gemcitabine (1250 mg/m^2) and cisplatin (75 mg/m^2); nonsquamous patients got nivolumab (10 mg/kg) plus pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2); and patients with any histology got either nivolumab 10 mg/kg or 5 mg/kg plus paclitaxel (200 mg/m^2) and carboplatin (AUC = 6). Early results reported at the 2014 Symposium in Thoracic Oncology demonstrated an ORR of 33, 47, and 47 % and 18-month OS rates of 33, 60, and 40 % for nivolumab 10 mg/kg when combined with gemcitabine/cisplatin, pemetrexed/cisplatin, and paclitaxel/carboplatin, respectively. Preliminary results from a separate study of 21 patients with *EGFR*-mutant NSCLC who received nivolumab plus erlotinib were reported at ASCO 2014 [55]. Of the twenty patients with acquired resistance to erlotinib, 3 patients experienced a PR (15 %) and 9 patients had stable disease (45 %). Grade 3/4 adverse events occurred in 4 patients including 3 with elevations in liver function tests.

Pembrolizumab (MK3475) is another humanized IgG4 anti-PD1 antibody that has shown promise for use in NSCLC patients. KEYNOTE-001 was a large phase I study of pembrolizumab at varying doses in 495 patients with advanced NSCLC [19]. This study also evaluated PD-L1 tumor expression as part of its eligibility

criteria; PD-L1 expression levels were assessed with the anti-PD-L1 antibody clone 22C3 and a prototype immunohistochemistry assay developed by Merck. A separate validation group of patients was selected to assess the efficacy of the prototype assay. For this group, PD-L1 expression cutoffs were defined as a proportion score of ≥50 % (strong), 1–49 % (weak), or <1 %. Of the 1143 patients initially screened for the study, 824 had evaluable samples and 23.2, 37.6, and 39.2 % had proportion scores of ≥50 %, 1–49 %, and <1 % by the prototype assay. The ORR was 19.5 %, with similar response rates among previously treated (18 %) and untreated (24.8 %) patients. An additional 21.8 % of patients exhibited stable disease. Responses were more frequent among current or former smokers as compared to never smokers, with ORR of 22.5 % vs 10.3 %, respectively. The median duration of response was 12.5 months (range 1.0–23.3 months). Median OS was 12.0 months, with better survival in treatment-naïve as compared to previously treated patients (median OS 16.2 months (95 % CI, 16.2 to not reached) and 9.3 months (95 % CI, 8.4–12.4), respectively). There was a positive relationship between PD-L1 expression and survival, as the median PFS (6.3 months) and OS (not reached) were better among patients with a PD-L1 proportion score of at least 50 % than patients with scores of 1–49 % or <1 %. However, duration of response was similar across all proportion scores: 12.5 months (range, 2.1–23.3) for a proportion score of at least 50 %, 7.2 months (range, 1.4–8.3) for a proportion score of 1–49 %, and not reached (range, 1.0–10.8) for a proportion score of less than 1 %. Grade 3/4 treatment-related toxicities were observed in only 9.5 % of patients and included pneumonitis, fatigue, asthenia, and anorexia. There were no significant differences in efficacy or adverse events in patients receiving doses of 10 mg/kg every 2 weeks compared to every 3 weeks; data regarding the lower 2 mg/kg dose were lacking at time of study publication. Although large trials of PD-1 agents generally exclude patients with active CNS disease, early data from a phase II study of NSCLC patients with untreated or progressive brain metastases (size range 5–20 mm) suggest that pembrolizumab has activity against CNS disease, with partial responses seen in 4 of 9 evaluable patients [22].

KEYNOTE-021 is a multi-arm phase II study evaluating the safety, tolerability, and efficacy of pembrolizumab combined with platinum doublet chemotherapy in patients with advanced NSCLC in the first-line setting [45]. Early results demonstrated promising response rates, particularly with the combination of pembrolizumab and carboplatin (AUC = 5) plus pemetrexed (500 mg/m2). Although numbers were small (n = 12 in each arm), patients who received this triplet combination demonstrated an ORR of 67 % and 50 % as well as a disease control rate of 100 and 92 % with this platinum doublet and pembrolizumab at doses of 10 and 2 mg/kg, respectively. As expected, the grade 3/4 toxicity rate of 38 % with this combination was higher than in studies of pembrolizumab monotherapy.

Several studies are ongoing or planned for pembrolizumab, including a single-arm monotherapy trial (NCT01295827), and a phase III trial comparing to docetaxel to pembrolizumab in previously treated patients (NCT01905657). Both of these trials require a biopsy prior to entry on study and are only enrolling patients with tumors that are positive for expression of PD-L1. A phase I/II trial in

unselected patients evaluated pembrolizumab in combination with chemotherapy, bevacizumab, tyrosine kinase inhibitors, or ipilimumab (NCT02039674). A first-line trial comparing pembrolizumab- to platinum-based chemotherapy in patients with newly diagnosed NSCLC is also ongoing (NCT02220894).

2.3 Therapies Targeting PD-L1

Several agents that target PD-L1, the ligand for PD-1, are also in development. These agents block the interaction of PD-L1 expressed on tumor cells and tumor-infiltrating immune cells with PD-1 and B7.1 expressed on T cells. The effects of these agents are predicted to be similar to anti-PD-1. It is theorized that this variation in mechanism may lead to different antitumor and toxicity profiles as compared to the anti-PD-1 agents. At this point, it is not clear which approach is superior.

BMS-936559 was the first PD-L1 antibody to be assessed in NSCLC patients. An ORR of 10 % was observed in 49 evaluable NSCLC patients enrolled in a phase I trial evaluating multiple different dose levels [9]. Clinical development of this agent has been suspended at this time. MEDI-4736 is an anti-PD-L1 antibody undergoing evaluation in a phase I study that includes a subgroup of NSCLC patients, in addition to other solid tumor malignancies. An early report described confirmed partial responses in 3 of 13 heavily pretreated NSCLC patients, with toxicities appearing similar to other anti-PD-L1 agents [8].

Atezolizumab (MPDL3280A) is a human IgG1 monoclonal antibody to PD-L1 that has shown the most promise in the class of agents in NSCLC to date. A phase I study conducted in advanced solid tumors found activity in NSCLC, melanoma, RCC, gastric cancer, and head and neck squamous cell carcinoma. Of the 85 patients with NSCLC included in the study, the ORR was 23 % per RECIST 1.1 criteria, with a higher ORR (83 %) in tumors that were IHC3 positive (defined as staining of 10 % of tumor for PD-L1 expression) [62]. Similar to anti-PD-1 agents, a higher ORR was seen in current/former smokers (26 %; $n = 43$) as compared to never smokers (10 %; $n = 10$). Most AEs were of low grade with only 11 % being grade 3/4, and no pneumonitis was observed. On the basis of these early results, the FDA granted atezolizumab Breakthrough Therapy Designation for NSCLC in February 2015. An interim analysis of FIR, a single-arm study of atezolizumab in patients with stage IIIB/IV NSCLC and high PD-L1 expression in either tumor cells or tumor-infiltrating immune cells, reported an ORR of 29 %, and 24 week PFS rate of 45 % [64]. Early results from POPLAR, a phase II study of atezolizumab (1200 mg IV every three weeks) versus docetaxel (75 mg/m2 every three weeks) in previously treated patients with NSCLC, were reported at ASCO 2015. Interim results indicated a nonstatistically significant improvement in median OS with atezolizumab as compared to docetaxel (11.4 vs. 9.5 months; HR 0.77, $p = 0.11$) in all comers, with greatest benefit seen in patients with high expression of PD-L1 in either tumor cells or tumor-infiltrating immune cells. Rates of grade 3–5 toxicity were lower in the atezolizumab group as compared to docetaxel (43 vs. 56 %,

respectively), and immune-mediated adverse events (any grade) included elevated AST (4 %), elevated ALT (4 %), pneumonitis (2 %), colitis (1 %), and hepatitis (1 %) [65]. Ongoing clinical trials include a single agent study in patients with PD-L1-positive tumors (NCT02031458) comparing MDPL3280A to chemotherapy (NCT02008227) and in combination with targeted therapy and bevacizumab in NSCLC patients (NCT02013219).

2.4 Combination Therapies

The promising outcomes and favorable toxicity profile of anti-PD-1/PD-L1 therapy have led to multiple ongoing studies combining these agents with CTLA-4-directed agents, targeted therapies, and chemotherapy. Early results of combination studies available at time of this publication are described below.

Anti-PD-1/PD-L1 and anti-CTLA-4 antibodies activate different aspects of the immune response, and it is thought that they may complement each other therapeutically. Anti-PD-1/PD-L1 therapies target the antigen-presenting cell–T cell interaction, whereas anti-CTLA-4 therapies act at the effector T cell–tumor cell interface [35]. A phase III trial comparing combined ipilimumab and nivolumab therapy to either nivolumab alone or ipilimumab alone in treatment-naïve patients with advanced melanoma found improved median PFS with the combination as compared to ipilimumab alone (11.5 vs. 2.9 months, HR 0.42, $p < 0.001$). Although patients with PD-L1-positive tumors showed improved PFS with the combination versus ipilimumab, in patients with PD-L1-negative tumors, the combination was superior to both agents as monotherapy [40]. Early results of a phase I study combining nivolumab and ipilimumab in 46 chemotherapy-naïve patients with NSCLC reported an ORR of 22 %, with an additional 33 % experiencing stable disease [4]. Responses were similar in patients with squamous and nonsquamous histologies (27 and 19 %), as well as in PD-L1-positive and PD-L1-negative tumors (19 and 14 %). Grade 3/4 treatment-related AEs occurred in 48 % of patients, and 3 patients dying of therapy-related complications (respiratory failure, bronchopulmonary hemorrhage, and toxic epidermal necrolysis). Early results of a phase 1 study evaluating pembrolizumab in combination with ipilimumab in patients with advanced, recurrent NSCLC found clinical responses in all doses groups among 11 evaluable patients [47]. A phase 1/2 trial (NCT01928394) of nivolumab both as monotherapy and in combination with ipilimumab in patients with SCLC, in addition to other solid tumors, is undergoing evaluation as well.

A phase I study evaluating the combination of MEDI-4736 and tremelimumab reported an overall response rate of 27 % and disease control rate of 48 % in 63 evaluable patients with PD-L1-negative tumors [3]. Toxicities included diarrhea, colitis, and elevated liver function tests. The dose combination selected for future studies (MEDI4736 20 mg every four weeks and tremelimumab 1 mg/kg every four weeks) was well tolerated, with grade 3/4 events in 4 of 22 patients at this dosing level.

2.5 Predictors of Response to Anti-PD-1 and Anti-PD-L1 Therapies

While agents targeting both PD-1 and PD-L1 have shown great promise in the treatment of NSCLC, only a subset of patients derives sustained clinical benefit, with response rates ranging from 16 to 23 % in unselected NSCLC patients across early trials [8, 9, 18, 20, 21, 57]. Thus, there is great interest in developing reliable predictors of response to therapy.

Tumor expression of PD-L1 by immunohistochemistry (IHC) has been studied as a potential biomarker of response to anti-PD-1/PD-L1. However, practical conclusions regarding the optimal use of PD-L1 as a predictive biomarker are complicated due to factors related to the assays and cell types used for measurement, as well as the biology of PD-L1 itself. Each of the major PD-1/PD-L1 antibodies in current trials has been developed with a unique companion diagnostic assay, each possessing individual performance specifications and thresholds for positivity. Definitions of PD-L1 "positivity" in various studies have ranged from $\geq$1 to $\geq$50 % of evaluated cells, which are generally tumor cells but in some cases may be tumor-infiltrating immune cells. By these various definitions, NSCLC specimens have been defined as PD-L1 "positive" in 13–70 % of samples; however, the degree of concordance across different testing platforms is unknown [39].

The clinical practicality of PD-L1 as a predictive biomarker is also unclear. Ideally, a biomarker should have either complete positive or negative value in predicting whether an individual will respond to therapy. However, not all patients with PD-L1 positivity, even at its most stringent definitions, will respond to therapy, with ORR ranging from 16 to 83 % in PD-L1-"positive" patients, depending upon the drug and assay used. Conversely, there are patients who are PD-L1 "negative" who still respond to therapy, with ORR ranging from 3 to 20 % in various studies [39]. The dynamic nature of PD-L1 expression also indicates that it may be an imperfect biomarker. PD-L1 expression is stimulated by factors expressed within the tumor microenvironment, such as IFN-γ [66, 70], and biopsy specimens taken from a remote point in time may not accurately reflect expression levels present at the start of therapy. Whether the predictive value of PD-L1 expression depends upon histology is also unknown. For example, in Checkmate 057, a phase III study of nivolumab versus docetaxel in nonsquamous NSCLC, PD-L1 expression (defined at cutoffs of 1, 5, and 10 %) appeared to correlate positively with response and survival [48]. However, Checkmate 017, a phase III trial comparing nivolumab and docetaxel in previously treated patients with squamous NSCLC, found no correlation with PD-L1 expression and clinical response or survival [5]. Additionally, the optimal pattern of expression for predicting response is undetermined. PD-L1 assays commonly evaluate tumor cells, but expression on tumor-infiltrating immune cells also appears to be predictive [27]. In studies of atezolizumab, a PD-L1-directed antibody, both tumor cells and tumor-infiltrating immune cell populations were assessed for PD-L1 expressions [20]. Interestingly, although expression of PD-L1 by tumor cells and tumor-infiltrating immune cells could be found concurrently at low-to-moderate levels of

expression, populations of tumor cells with high PD-L1 expression appeared to be exclusive of populations of tumor-infiltrating immune cells with high PD-L1 expression. Moreover, tumors with high PD-L1 expression in tumor cells (TC3) showed a dense desmoplastic and sclerotic tumor microenvironment with relatively scant immune infiltrates, while high PD-L1 expression in tumor-infiltrating immune cells (IC3) had an elevated frequency of immune infiltrates, as well a B- and NK-cell signatures. Although these two populations showed distinctive histopathologic characteristics, increased PD-L1 expression in either group was associated with an increased chance of response to atezolizumab therapy (OS HR, 0.47; PFS HR, 0.56 and ORR, 38 vs. 13 % in TC3 or IC3 patients) [65]. On the basis of these studies, PD-L1 expression appears to be a complicated, dynamic process, without a standard method of measurement at this point in time. Thus, while expression of PD-L1 may signify the general state of immune activity in the tumor microenvironment [62, 68] and is likely associated with clinical benefit of PD-1/PD-L1 directed therapy, its practical utility at this time remains to be determined.

Smoking status appears to have predictive value in several studies of PD-1 and PD-L1 agents. Response rates have been reported as higher among current or former smokers, as compared to nonsmokers [18, 26, 31]. It is thought that tumors related to a history of smoking may harbor a higher burden of somatic mutations [1, 11, 63], and a higher nonsynonymous mutation burden has been associated with improved responses, durable clinical benefit, and progression-free survival in NSCLC patients treated with pembrolizumab [54]. Measurement of various T cell-specific, antigen presentation-related, and IFN-γ signaling-related genes has been associated with response to pembrolizumab in melanoma, suggesting that responses are improved in the context of a preexisting interferon-mediated adaptive immune response [53].

2.6 Immune-Related Response Criteria

Immune checkpoint inhibitors have challenged traditional measures to evaluate clinical response. Early trials of ipilimumab in melanoma demonstrated that a subset of patients with apparent early progressive disease (increased tumor burden or appearance of new lesions) by traditional RECIST criteria ultimately showed clinical responses when followed over time. It was thus determined that confirmation of progression, as defined by an increased tumor burden of $\geq$25 % compared to nadir, must occur at two consecutive time points at least 4 weeks apart, in order for treatment to be determined a failure. These revised criteria for assessing therapeutic response have been termed immune-related response criteria [75] and are now commonly used in trials involving immune checkpoint inhibitors without chemotherapy.

2.7 Immune-Related Toxicities

Just as immunotherapies encompass a novel approach to tumor biology, the toxicities associated with these agents have created new challenges in the clinic. Unlike the toxicities of cytotoxic chemotherapy, side effects related to immune checkpoint inhibitors are autoimmune in nature. Generally, the incidence of immune-related toxicity is more frequent and more severe with ipilimumab as compared to anti-PD-1 and anti-PD-L1 agents; however, the immune-related toxicities can be life-threatening in either treatment class.

A pooled analysis of ipilimumab studies in melanoma found that approximately two-thirds of patients experienced an irAE, most of which were considered grade 1 and 2 [33]. Gastrointestinal and dermatologic toxicities were the most common class reported, but other significant immune-related toxicities included endocrine, hepatic, and neurological. Endocrine toxicity may be manifold and includes hypothyroidism, hyperthyroidism, hypophysitis, and adrenal insufficiency. Ipilimumab appears to have a relatively predictable kinetic profile with regard to toxicity, with timing of onset depending upon the organ system involved. Dermatologic irAEs tend to appear in the first 2–3 weeks of treatment, followed by gastrointestinal after 6–7 weeks, and endocrine occurring later, around 9 weeks [74]. Such guidelines are not absolute however, as late toxicity even after treatment discontinuation has been reported [12].

In contrast to anti-CTLA-4 therapy, toxicities related to anti-PD-1 and anti-PD-L1 agents are generally milder, but life-threatening presentations can occur. Commonly reported irAEs include dermatologic (rash, pruritus) and gastrointestinal (diarrhea, colitis), generally grade 1 or 2 in severity; other unique irAEs include hepatitis, hypophysitis, thyroiditis, and vitiligo [9, 56, 69]. Endocrine toxicity may be insidious, and monitoring of thyroid function during treatment may be helpful. Pneumonitis, while rare, is a unique toxicity of especial concern to lung cancer patients and may be associated more with anti-PD-1 agents than anti-PD-L1 therapies [36]. Most low-grade irAEs can be addressed with supportive measures and may not require therapy cessation. Management of grade 3/4 irAEs typically requires therapy discontinuation, as well as use of high dose intravenous steroids. A prolonged steroid taper after symptom resolution (up to 1 month) is generally advised [32].

3 Vaccine Therapy

Anticancer vaccines designed to elicit antigen-specific immune responses have been studied in lung cancer, albeit with less success than immune checkpoint inhibitors.

Melanoma-associated antigen-A3 (MAGE-A3) is an antigen expressed in approximately 35 % of NSCLCs, with higher levels of expression associated with more advanced disease and poor prognosis [24, 60]. The efficacy of the recombinant MAGE-A3 protein as a therapeutic vaccine was assessed in a phase II clinical trial of 182 resected early-stage NSCLC patients [73]. Patients were vaccinated with either the

MAGE-A3 protein or placebo every three weeks for five cycles, followed by eight vaccinations every three months. No statistically significant improvement in time to progression, disease-free survival, or overall survival was seen with the vaccine therapy as compared to placebo. The MAGRIT trial was a phase III clinical trial of resected NSCLC patients selected for tumor expression of the MAGE-A3 protein [71]. Although the vaccine was well tolerated, the trial failed to meet its primary endpoint of improved disease-free survival with the addition of the vaccine [72].

Tecemotide (L-BLP25) is a liposome-based vaccine derived from the tandem repeat region of MUC1, a peptide expressed in NSCLC. Preclinical studies found that MUC1-directed immunotherapy successful induced a cellular immune response characterized by T cell proliferation and production of IFN-γ in a mouse model of NSCLC [78]. Correlation was also found between overall survival at one year and the presence of endogenous MUC1 antibodies in NSCLC patients [29]. The START trial enrolled 1513 patients with unrespectable NSCLC who had achieved either stable disease or an objective response after treatment with either concurrent or sequential chemoradiation. Patients were assigned to either tecemotide or placebo in a 2:1 ratio, with treatments occurring weekly for 8 weeks, and then every 6 weeks thereafter until progression. Although the trial failed to meet its endpoint of improved overall survival, a subgroup analysis of patients who received concurrent chemoradiation found an improvement in overall survival with tecemotide as compared to placebo (median OS 30.8 vs. 20.6 months; HR 0.78; $p = 0.016$) [10]. START2, a confirmatory trial of tecemotide in patients with stage III NSCLC after concurrent chemoradiation, is currently underway (NCT02049151).

Immune tolerance to tumor-associated antigens has been identified as a significant hurdle in the development of therapeutic lung cancer vaccines [50]. Although studies of lung cancer vaccines have been relatively lackluster, there is interest in combining cancer vaccines with immune checkpoint inhibitors, with the goal of inducing a stronger tumor-specific immune response. Whether vaccines may be a useful adjunct therapy to immune checkpoint inhibitors in the future remains to be determined.

4 Future Directions

The advent of effective immunotherapies for lung cancer bears potential for a new generation of promising treatments with novel toxicities. Early studies of immune checkpoint inhibitors as single agent therapy in NSCLC patients and in combination with chemotherapy in both NSCLC and SCLC patients have been encouraging. In patients that respond to anti-PD-1 and PD-L1 therapy, responses appear to be both rapid and durable even beyond treatment discontinuation. However, many unanswered questions remain including the optimal patient population in which these agents will have benefit (PD-L1 positive or negative, specific molecular cohorts), the duration of therapy (one vs. two years), the sequence of therapy (prior to chemotherapy, in combination with chemotherapy or as maintenance therapy),

and the appropriate combinations (chemotherapy, targeted therapy or combining anti-PD1 and anti-CTLA antibodies).

The identification of biomarkers to predict benefit from immune checkpoint therapy, as well as possibly more active combination regimens, are needed as only a subset of patients currently obtain the sustained responses that are desired. Additionally, although the toxicity profile of these agents is relatively favorable, the associated immune-related side effects present unique challenges in clinical management as they differ significantly from chemotherapy. Many phase III trials comparing anti-PD-1 and anti-PD-L1 antibodies both as monotherapy and in combination to standard first- and second-line therapies are ongoing. Given the manageable toxicity profile and potential for rapid, durable responses, it is expected that these novel therapies will continue to play a major role in the future of lung cancer treatment.

The significant cost of these agents is worth noting, with the average cost per patient listed at $12,500 per month for both nivolumab and pembrolizumab in 2015. Given that the greatest toxicity of these agents appears to be financial in nature, it is likely that immunotherapy, while providing great clinical advances for patients with NSCLC, will unfortunately add to growing fiscal challenges within the healthcare system as well. Development of economically sound pricing for these agents will be important considerations to optimize the positive impact they may have on outcome of lung cancer patients.

References

1. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Borresen-Dale AL, Boyault S, Burkhardt B, Butler AP, Caldas C, Davies HR, Desmedt C, Eils R, Eyfjord JE, Foekens JA, Greaves M, Hosoda F, Hutter B, Ilicic T, Imbeaud S, Imielinski M, Jager N, Jones DT, Jones D, Knappskog S, Kool M, Lakhani SR, Lopez-Otin C, Martin S, Munshi NC, Nakamura H, Northcott PA, Pajic M, Papaemmanuil E, Paradiso A, Pearson JV, Puente XS, Raine K, Ramakrishna M, Richardson AL, Richter J, Rosenstiel P, Schlesner M, Schumacher TN, Span PN, Teague JW, Totoki Y, Tutt AN, Valdes-Mas R, van Buuren MM, van 't Veer L, Vincent-Salomon A, Waddell N, Yates LR, Australian Pancreatic Cancer Genome I, Consortium IBC, Consortium IM-S, PedBrain I, Zucman-Rossi J, Futreal PA, McDermott U, Lichter P, Meyerson M, Grimmond SM, Siebert R, Campo E, Shibata T, Pfister SM, Campbell PJ, Stratton MR (2013) Signatures of mutational processes in human cancer. Nature 500 (7463):415–421. doi:10.1038/nature12477
2. Antonia SJ, Brahmer JR, Gettinger S, Chow LQ, Juergens R, Shepherd FA, Laurie SA, Gerber DE, Goldman J, Shen R, Harbison C, Chen AC, Borghaei H, Rizvi NA (2014) Nivolumab (Anti-PD-1; BMS-936558, ONO-4538) in combination with platinum-based doublet chemotherapy (PT-DC) in advanced non-small cell lung cancer (NSCLC). In: Chicago multidisciplinary symposium in thoracic oncology, Chicago, IL (vol 5). International Jounral of Radiation Oncology, p S2
3. Antonia SJ GS, Balmanoukian A, Sanborn RE, Steele KE, Narwal R, Robbins PB, Gu Y, Karakunnel JJ, Rizvi N (2015) Phase 1b study of MEDI4736, a programmed cell death ligand-1 (PD-L1) antibody, in combination with tremelimumab, a cytotoxic T-lymphocyte-associated

protein-4 (CTLA-4) antibody, in patients with advanced non-small cell lung cancer (NSCLC). In: American Society of clinical oncology annual meeting, Chicago, IL
4. Antonia SJ GS, Chow LQM, Juergens RA, Borghaei H, et al (2014) Nivolumab (anti-PD-1; BMS-936558, ONO-4538) and ipilimumab in first-line NSCLC: Interim phase I results. In: ASCO annual meeting
5. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Aren Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR (2015) Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. The New England journal of medicine 373(2): 123–135. doi:10.1056/NEJMoa1504627
6. Brahmer JR Horn L, Antonia SJ, et al (2013) Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in patients with non-small cell lung cancer (NSCLC): overall survival and long-term safety in a phase 1 trial. In: World conference on lung cancer
7. Brahmer JR, Pardoll DM (2013) Immune checkpoint inhibitors: making immunotherapy a reality for the treatment of lung cancer. Cancer immunology research 1(2):85–91. doi:10.1158/2326-6066.CIR-13-0078
8. Brahmer JR Rizvi NA, Luzky J, Khleif S, Blake-Haskins A, et al (2014) Clinical activity and biomarkers of MEDI4736, an anti-PD-L1 antibody, in patients with NSCLC. In: ASCO annual meeting
9. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthy S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM (2012) Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. The New England journal of medicine 366(26):2455–2465. doi:10.1056/NEJMoa1200694
10. Butts C, Socinski MA, Mitchell PL, Thatcher N, Havel L, Krzakowski M, Nawrocki S, Ciuleanu TE, Bosquee L, Trigo JM, Spira A, Tremblay L, Nyman J, Ramlau R, Wickart-Johansson G, Ellis P, Gladkov O, Pereira JR, Eberhardt WE, Helwig C, Schroder A, Shepherd FA, team St (2014) Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. The Lancet Oncology 15(1):59-68. doi:10.1016/S1470-2045(13)70510-2
11. D'Incecco A, Andreozzi M, Ludovini V, Rossi E, Capodanno A, Landi L, Tibaldi C, Minuti G, Salvini J, Coppi E, Chella A, Fontanini G, Filice ME, Tornillo L, Incensati RM, Sani S, Crino L, Terracciano L, Cappuzzo F (2015) PD-1 and PD-L1 expression in molecularly selected non-small-cell lung cancer patients. Br J Cancer 112(1):95–102. doi:10.1038/bjc.2014.555
12. Di Giacomo AM, Biagioli M, Maio M (2010) The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. Semin Oncol 37(5):499–507. doi:10.1053/j.seminoncol.2010.09.007
13. Diefenbach A, Raulet DH (2002) The innate immune response to tumors and its role in the induction of T-cell immunity. Immunol Rev 188:9–21
14. Domagala-Kulawik J (2015) The role of the immune system in non-small cell lung carcinoma and potential for therapeutic intervention. Translational lung cancer research 4(2):177–190. doi:10.3978/j.issn.2218-6751.2015.01.11
15. Dranoff G (2004) Cytokines in cancer pathogenesis and cancer therapy. Nat Rev Cancer 4(1):11–22. doi:10.1038/nrc1252
16. Finn OJ (2008) Cancer immunology. The New England journal of medicine 358(25):2704–2715. doi:10.1056/NEJMra072739
17. Finn OJ (2012) Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. Annals of oncology: Official Journal of the European Society for Medical Oncology/ESMO 23(Suppl 8:viii6–viii9. doi:10.1093/annonc/mds256

18. Garon EB GL, Rizvi N, Hui R, Balmanoukian AS, Patnaik A, et al (2014) Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced non-small cell lung carcinoma (NSCLC). In: European Society for medical oncology 2014 congress, Madrid, Spain
19. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E, Ahn MJ, Felip E, Lee JS, Hellmann MD, Hamid O, Goldman JW, Soria JC, Dolled-Filhart M, Rutledge RZ, Zhang J, Lunceford JK, Rangwala R, Lubiniecki GM, Roach C, Emancipator K, Gandhi L, Investigators K- (2015) Pembrolizumab for the treatment of non-small-cell lung cancer. New Engl J Med 372(21):2018–2028. doi:10.1056/NEJMoa1501824
20. Gettinger SN, Kowanetz M, Koeppen H., Wistuba II, et al (2015) Molecular, immune and histopathological characterization of NSCLC based on PDL1 expression on tumor and immune cells and association with response to the anti-PDL1 antibody MPDL3280A. In: American Society of clinical oncology annual meeting, Chicago, IL. J Clin Oncol
21. Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, Powderly JD, Heist RS, Carvajal RD, Jackman DM, Sequist LV, Smith DC, Leming P, Carbone DP, Pinder-Schenck MC, Topalian SL, Hodi FS, Sosman JA, Sznol M, McDermott DF, Pardoll DM, Sankar V, Ahlers CM, Salvati M, Wigginton JM, Hellmann MD, Kollia GD, Gupta AK, Brahmer JR (2015) Overall survival and long-term safety of nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol: Official J Am Soc Clin Oncol 33(18):2004–2012. doi:10.1200/JCO.2014.58.3708
22. Goldberg SM, Gettinger SN, Mahajan A, et al (2015) Activity and safety of pembrolizumab in patients with metastatic non-small cell lung cancer with untreated brain metastases. In: American society of clinical oncology annual meeting, Chicago, IL. J Clin Oncol
23. Govindan R, Ding L, Griffith M, Subramanian J, Dees ND, Kanchi KL, Maher CA, Fulton R, Fulton L, Wallis J, Chen K, Walker J, McDonald S, Bose R, Ornitz D, Xiong D, You M, Dooling DJ, Watson M, Mardis ER, Wilson RK (2012) Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell 150(6):1121–1134. doi:10.1016/j.cell.2012.08.024
24. Gure AO, Chua R, Williamson B, Gonen M, Ferrera CA, Gnjatic S, Ritter G, Simpson AJ, Chen YT, Old LJ, Altorki NK (2005) Cancer-testis genes are coordinately expressed and are markers of poor outcome in non-small cell lung cancer. Clin Cancer Res: Official J Am Assoc Cancer Res 11(22):8055–8062. doi:10.1158/1078-0432.CCR-05-1203
25. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–674. doi:10.1016/j.cell.2011.02.013
26. Hellmann MD, Creelan BC, Sima CS, Iams WT, Antonia SJ, Horn L, Brahmer JR, Gettinger S, Harbison C, Rizvi N (2014) Smoking history and response to nivolumab in patients with advanced NSCLCs. In: Annals of Oncology (Supplement 4, pp iv426–iv470)
27. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, Kohrt HE, Horn L, Lawrence DP, Rost S, Leabman M, Xiao Y, Mokatrin A, Koeppen H, Hegde PS, Mellman I, Chen DS, Hodi FS (2014) Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 515(7528):563–567. doi:10.1038/nature14011
28. Hiraoka K, Miyamoto M, Cho Y, Suzuoki M, Oshikiri T, Nakakubo Y, Itoh T, Ohbuchi T, Kondo S, Katoh H (2006) Concurrent infiltration by CD8+T cells and CD4+T cells is a favourable prognostic factor in non-small-cell lung carcinoma. Br J Cancer 94(2):275–280. doi:10.1038/sj.bjc.6602934
29. Hirasawa Y, Kohno N, Yokoyama A, Kondo K, Hiwada K, Miyake M (2000) Natural autoantibody to MUC1 is a prognostic indicator for non-small cell lung cancer. Am J Respir Crit Care Med 161(2 Pt 1):589–594. doi:10.1164/ajrccm.161.2.9905028

30. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbe C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ (2010) Improved survival with ipilimumab in patients with metastatic melanoma. New England J Med 363 (8):711–723. doi:10.1056/NEJMoa1003466
31. Horn L Horn R, Spigel DR, et al (2013) An analysis of the relationship of clinical activity to baseline EGFR status, PD-L1 expression and prior treatment history in patients with non-small cell lung cancer (NSCLC) following PD-L1 blockade with MPDL3280A (anti-PDL1). In: World conference on lung cancer
32. Howell M, Lee R, Bowyer S, Fusi A, Lorigan P (2015) Optimal management of immune-related toxicities associated with checkpoint inhibitors in lung cancer. Lung Cancer 88(2):117–123. doi:10.1016/j.lungcan.2015.02.007
33. Ibrahim R, Berman D, DePril V, Humphrey R, Chen T (2011) Ipilimumab safety profile: summary of findings from completed trials in advanced melanoma. In: American society of clinical oncology annual meeting
34. Ikeda S, Funakoshi N, Inagaki M, Shibata T (2006) Clinicopathologic roles of tumor-infiltrating lymphocytes and CD8-positive lymphocytes in lung cancer imprint smears in squamous cell carcinoma and adenocarcinoma. Acta Cytol 50(4):423–429
35. Johnson DB, Peng C, Sosman JA (2015) Nivolumab in melanoma: latest evidence and clinical potential. Ther Adv Med Oncol 7(2):97–106. doi:10.1177/1758834014567469
36. Johnson DB, Rioth MJ, Horn L (2014) Immune checkpoint inhibitors in NSCLC. Curr Treat Options Oncol 15(4):658–669. doi:10.1007/s11864-014-0305-5
37. Ju S, Qiu H, Zhou X, Zhu B, Lv X, Huang X, Li J, Zhang Y, Liu L, Ge Y, Johnson DE, Ju S, Shu Y (2009) CD13 + CD4 + CD25hi regulatory T cells exhibit higher suppressive function and increase with tumor stage in non-small cell lung cancer patients. Cell Cycle 8(16):2578–2585
38. Keir ME, Butte MJ, Freeman GJ, Sharpe AH (2008) PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 26:677–704. doi:10.1146/annurev.immunol.26.021607.090331
39. Kerr KM, Tsao M-S, Nicholson A, Yasushi Y, Wistuba II, Hirsch FR (2015) Programmed death-ligand 1 immunohistochemistry in lung cancer: in what state is this art? J Thoracic Oncol 10(7):985–989
40. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD (2015) Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. New England J Med. doi:10.1056/NEJMoa1504030
41. Lesokhin AM, Callahan MK, Postow MA, Wolchok JD (2015) On being less tolerant: enhanced cancer immunosurveillance enabled by targeting checkpoints and agonists of T cell activation. Sci Trans Med 7(280):280sr281. doi:10.1126/scitranslmed.3010274
42. Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, Sebastian M, Neal J, Lu H, Cuillerot JM, Reck M (2012) Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol: Official J Am Soc Clin Oncol 30(17):2046–2054. doi:10.1200/JCO.2011.38.4032
43. Mittal D, Gubin MM, Schreiber RD, Smyth MJ (2014) New insights into cancer immunoediting and its three component phases–elimination, equilibrium and escape. Curr Opin Immunol 27:16–25. doi:10.1016/j.coi.2014.01.004
44. Mu CY, Huang JA, Chen Y, Chen C, Zhang XG (2011) High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol 28(3):682–688. doi:10.1007/s12032-010-9515-2

45. Papadimitrakopoulou V, Patnaik A, Borghaei H, et al (2015). Pembrolizumab (pembro; MK-3475) plus platinum doublet chemotherapy (PDC) as front-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 Cohorts A and C. In: American society of clinical oncology annual meeting, Chicago, IL. J Clin Oncol
46. Pardoll DM (2012) The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 12(4):252–264. doi:10.1038/nrc3239
47. Patnaik A, Socinski MA, Gubens MA, et al (2015) Phase 1 study of pembrolizumab (pembro; MK-3475) plus ipilimumab (IPI) as second-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 cohort D. In: American society of clinical oncology annual meeting, Chicago, IL. J Clin Oncol
48. Paz-Ares L Horn L, Borghaei H, Spigel DR, et al (2015) Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). In: American society of clinical oncology annual meeting, Chicago, IL, 2015. J Clin Oncol
49. Petersen RP, Campa MJ, Sperlazza J, Conlon D, Joshi MB, Harpole DH Jr, Patz EF Jr (2006) Tumor infiltrating Foxp3 + regulatory T-cells are associated with recurrence in pathologic stage I NSCLC patients. Cancer 107(12):2866–2872. doi:10.1002/cncr.22282
50. Ramlogan-Steel CA, Steel JC, Morris JC (2014) Lung cancer vaccines: current status and future prospects. Trans Lung Cancer Res 3(1):46–52. doi:10.3978/j.issn.2218-6751.2013.12.01
51. Reck M, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, Sebastian M, Lu H, Cuillerot JM, Lynch TJ (2013) Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Annals Oncol: Official J Eur Soc Med Oncol/ESMO 24 (1):75–83. doi:10.1093/annonc/mds213
52. Ribas A, Kefford R, Marshall MA, Punt CJ, Haanen JB, Marmol M, Garbe C, Gogas H, Schachter J, Linette G, Lorigan P, Kendra KL, Maio M, Trefzer U, Smylie M, McArthur GA, Dreno B, Nathan PD, Mackiewicz J, Kirkwood JM, Gomez-Navarro J, Huang B, Pavlov D, Hauschild A (2013) Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol: Official J Am Soc Clin Oncol 31(5):616–622. doi:10.1200/JCO.2012.44.6112
53. Ribas A, Robert C, Hodi FS, Wolchok JD, et al. printer-friendly version. Association of response to programmed death receptor 1 (PD-1) blockade with pembrolizumab (MK-3475) with an interferon-inflammatory immune gene signature. In: American society of clinical oncology annual meeting, Chicago, IL, 2015. J Clin Oncol
54. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN, Chan TA (2015a) Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 348(6230):124–128. doi:10.1126/science.aaa1348
55. Rizvi NA, Man Chow LQ, Borghaei H, Shen Y, Harbison C, Alaparthy S, Chen AC, Gettinger S (2014) Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC (vol 5s). In: American society of clinical oncology annual meeting, Chicago, IL. J Clin ONcol
56. Rizvi NA, Mazieres J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, Horn L, Lena H, Minenza E, Mennecier B, Otterson GA, Campos LT, Gandara DR, Levy BP, Nair SG, Zalcman G, Wolf J, Souquet PJ, Baldini E, Cappuzzo F, Chouaid C, Dowlati A, Sanborn R, Lopez-Chavez A, Grohe C, Huber RM, Harbison CT, Baudelet C, Lestini BJ, Ramalingam SS (2015b) Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. The Lancet Oncology 16 (3):257-265. doi:10.1016/S1470-2045(15)70054-9

57. Rizvi NA Shepherd FA, Antonia SJ, Brahmer JR, Chow LQ, Goldman J, et al (2014) First-line monotherapy with nivolumab (anti-PD-1; BMS-936558, ONO-4538) in advanced non-small cell lung cancer (NSCLC): safety, efficacy and correlation of outcomes with PD-L1 status. Int J Radiat Oncol
58. Ruffini E, Asioli S, Filosso PL, Lyberis P, Bruna MC, Macri L, Daniele L, Oliaro A (2009) Clinical significance of tumor-infiltrating lymphocytes in lung neoplasms. Annals Thorac Surgery 87(2):365–371; discussion 371–362. doi:10.1016/j.athoracsur.2008.10.067
59. Selby MJ, Engelhardt JJ, Quigley M, Henning KA, Chen T, Srinivasan M, Korman AJ (2013) Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. Cancer immunology research 1(1):32–42. doi:10.1158/2326-6066.CIR-13-0013
60. Sienel W, Varwerk C, Linder A, Kaiser D, Teschner M, Delire M, Stamatis G, Passlick B (2004) Melanoma associated antigen (MAGE)-A3 expression in Stages I and II non-small cell lung cancer: results of a multi-center study. Eur J Cardiothorac Surg 25(1):131–134
61. Smyth MJ, Dunn GP, Schreiber RD (2006) Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. Adv Immunol 90:1–50. doi:10.1016/S0065-2776(06)90001-7
62. Soria JC et al (2013) Clinical activity, safety and biomarkers of PD-L1 blockade in non-small cell lung cancer (NSCLC): additional analyses from a clinical study of the engineered antibody MPDL3280A (anti-PDL1). In: ECCO annual congress
63. Soria JC, Marabelle A, Brahmer JR, Gettinger S (2015) Immune checkpoint modulation for non-small cell lung cancer. Clinical Cancer Res: Official J Am Assoc Cancer Res 21 (10):2256–2262. doi:10.1158/1078-0432.CCR-14-2959
64. Spigel DR Chart JE, Gettinger SN, Chao BH, et al (2015) Clinical activity and safety from a phase II study (FIR) of MPDL3280A (anti-PDL1) in PD-L1–selected patients with non-small cell lung cancer (NSCLC). In: American society of clinical oncology annual meeting, Chicago, IL. J Clin Oncol
65. Spira A.I. Park K, Mazieres J, Vansteenkiste JF, et al (2015) Efficacy, safety and predictive biomarker results from a randomized phase II study comparing MPDL3280A vs docetaxel in 2L/3L NSCLC (POPLAR). In: American society of clinical oncology annual meeting, Chicago, IL. J Clin Oncol
66. Spranger S, Spaapen RM, Zha Y, Williams J, Meng Y, Ha TT, Gajewski TF (2013) Up-regulation of PD-L1, IDO, and T(regs) in the melanoma tumor microenvironment is driven by CD8(+) T cells. Sci Transl Med 5(200):200ra116. doi:10.1126/scitranslmed.3006504
67. Sundar R, Cho BC, Brahmer JR, Soo RA (2015) Nivolumab in NSCLC: latest evidence and clinical potential. Therapeutic advances in medical oncology 7(2):85–96. doi:10.1177/1758834014567470
68. Taube JM, Klein A, Brahmer JR, Xu H, Pan X, Kim JH, Chen L, Pardoll DM, Topalian SL, Anders RA (2014) Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res: Official J Am Assoc Cancer Res 20(19):5064–5074. doi:10.1158/1078-0432.CCR-13-3271
69. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharfman WH, Anders RA, Taube JM, McMiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. New England J Med 366(26):2443–2454. doi:10.1056/NEJMoa1200690
70. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, Chmielowski B, Spasic M, Henry G, Ciobanu V, West AN, Carmona M, Kivork C, Seja E, Cherry G, Gutierrez AJ, Grogan TR, Mateus C, Tomasic G, Glaspy JA, Emerson RO, Robins H, Pierce RH, Elashoff DA, Robert C, Ribas A (2014) PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 515(7528):568–571. doi:10.1038/nature13954

71. Tyagi P, Mirakhur B (2009) MAGRIT: the largest-ever phase III lung cancer trial aims to establish a novel tumor-specific approach to therapy. Clin Lung Cancer 10(5):371–374. doi:10.3816/CLC.2009.n.052
72. Vansteenkiste J, Cho B, Vanakesa T, De Pase T, et al (2014) MAGRIT, a double-blind, randomized, placebo-controlled Phase III study to assess the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC). In: European society of medical oncology, Madrid, Spain
73. Vansteenkiste J, Zielinski M, Linder A, Dahabreh J, Gonzalez EE, Malinowski W, Lopez-Brea M, Vanakesa T, Jassem J, Kalofonos H, Perdeus J, Bonnet R, Basko J, Janilionis R, Passlick B, Treasure T, Gillet M, Lehmann FF, Brichard VG (2013) Adjuvant MAGE-A3 immunotherapy in resected non-small-cell lung cancer: phase II randomized study results. J Clin Oncol: Official J Am Soc Clin Oncol 31(19):2396–2403. doi:10.1200/JCO.2012.43.7103
74. Weber JS, Kahler KC, Hauschild A (2012) Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol: Official J Am Soc Clin Oncol 30 (21):2691–2697. doi:10.1200/JCO.2012.41.6750
75. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS (2009) Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res: Official J Am Assoc Cancer Res 15(23):7412–7420. doi:10.1158/1078-0432.CCR-09-1624
76. Wolchok JD, Saenger Y (2008) The mechanism of anti-CTLA-4 activity and the negative regulation of T-cell activation. Oncologist 13(Suppl 4):2–9. doi:10.1634/theoncologist.13-S4-2
77. Woo EY, Chu CS, Goletz TJ, Schlienger K, Yeh H, Coukos G, Rubin SC, Kaiser LR, June CH (2001) Regulatory CD4(+)CD25(+) T cells in tumors from patients with early-stage non-small cell lung cancer and late-stage ovarian cancer. Cancer Res 61(12):4766–4772
78. Xia W, Wang J, Xu Y, Jiang F, Xu L (2014) L-BLP25 as a peptide vaccine therapy in non-small cell lung cancer: a review. J Thorac Dis 6(10):1513–1520. doi:10.3978/j.issn.2072-1439.2014.08.17
79. Zatloukal P, Heo DS, Park K, Kang J, Butts C, Bradford D, Graziano S, Huang B, Healey D (2009) Randomized phase II clinical trial comparing tremelimumab (CP-675,206) with best supportive care (BSC) following first-line platinum-based therapy in patients (pts) with advanced non-small cell lung cancer (NSCLC). In: American society of clinical oncology annual meeting, Chicago, IL. J Clin Oncol
80. Zou W (2006) Regulatory T cells, tumour immunity and immunotherapy. Nat Rev Immunol 6 (4):295–307. doi:10.1038/nri1806

Palliative Care in Lung Cancer

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Abstract

Lung cancer is the most common cancer worldwide and is the leading cause of cancer death for both men and women in the USA. Symptom burden in patients with advanced lung cancer is very high and has a negative impact on their quality of life (QOL). Palliative care with its focus on the management of symptoms and addressing physical, psychosocial, spiritual, and existential suffering, as well as medically appropriate goal setting and open communication with patients and families, significantly adds to the quality of care received by advanced lung cancer patients. The Provisional Clinical Opinion (PCO) of American Society of Clinical Oncology (ASCO) as well as the National Cancer Care Network's (NCCN) clinical practice guidelines recommends early integration of palliative care into routine cancer care. In this chapter, we will provide an overview of palliative care in lung cancer and will examine the evidence and recommendations with regard to a comprehensive and interdisciplinary approach to symptom management, as well as discussions of goals of care, advance care planning, and care preferences.

Keywords

Lung cancer · Palliative care · Symptom management · Goals of care · Advanced care planning

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Contents

1 Introduction

Lung cancer represents 13.5 % of all new cancer cases in the USA and per the National Cancer Institute (NCI) estimate was the cause of death in approximately 159,260 people in 2014. While the five-year survival for localized lung and bronchus cancer is 54 %, it decreases to only 4 % in patients with distant metastases [1]. Symptom burden in patients with advanced lung cancer is very high and has a negative impact on the quality of life (QOL) [2]. While comprehensive oncologic care aims at improving patients' QOL, palliative care with its focus on the management of symptoms and addressing physical, psychosocial, spiritual, and existential suffering [3], as well as medically appropriate goal setting and open communication with patients and families, has been proven to significantly add to the quality of care received by advanced lung cancer patients [4].

1.1 Definition of Palliative Care

The definition of palliative care has evolved over time. In the 1960s, when the only method of palliative care delivery was via hospice care at the very end of life, it was seen as care limited to people who were no longer receiving cancer-directed therapy. Today, it is widely recognized that palliative care principles are applicable at the time of diagnosis of any serious illness, and this care should be continued throughout the course of treatment, cure, or until death [5].

The World Health Organization (WHO) defines palliative care as "an approach that improves the QOL of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual" [3]. As the goal of palliative care is to anticipate, prevent, and reduce suffering and to support the best possible QOL for patients, its delivery to cancer patients should begin at the time of diagnosis, concurrent with cancer-directed life-prolonging therapies [6].

It is with this intent and in review of substantial evidence demonstrating palliative care leading to better patient outcomes [4], that the Provisional Clinical Opinion (PCO) of American Society of Clinical Oncology (ASCO) [7] as well as the National Comprehensive Cancer Network's (NCCN) clinical practice guidelines [6], recommend early integration of palliative care into routine cancer care, both as part of usual oncology assessment as well as specialty palliative care evaluations. In this chapter, we will provide an overview of palliative care in lung cancer and will examine the evidence and recommendations with regard to a comprehensive and interdisciplinary approach to symptom management, as well as discussions of goals of care, advance care planning, and care preferences.

1.2 Palliative Care in Lung Cancer

Over the past few decades, studies have been conducted to determine the effect of early integration of palliative care in the care of cancer patients. Perhaps, the strongest evidence comes from a 2010 randomized clinical trial study conducted by Temel et al., examining the effect of early palliative care integration into routine cancer care in a cohort of metastatic non-small cell lung cancer patients. Compared to the patients receiving standard oncologic care alone, patients who received concurrent palliative care with standard cancer care had better QOL, less depressive symptoms, and interestingly had longer median survival despite having received less aggressive care at end of life [4].

1.3 Palliative Care Domains

The National Consensus Project for Quality Palliative Care (NCP) is a collaborative and groundbreaking initiative with participation of six major Palliative Care organizations to "further define and underscore the value of palliative care and to improve upon the delivery of palliative care in the USA" [8]. The clinical practice guidelines developed by NCP incorporate important quality assessment and improvement initiatives into palliative care with the goal of improving the quality of palliative care delivery in the USA.

The 2013 updated National Consensus Project Clinical Practice Guidelines for Quality Palliative Care define eight major domains in comprehensive palliative care assessment: (1) structure and process of care, (2) physical, (3) psychological and

psychiatric, (4) social, (5) spiritual, religious, and existential, (6) cultural aspects of care, (7) care of the patient at end of life, and (8) ethical and legal aspects of care.

For the purpose of this chapter, we will review these domains in two broader sections:

Symptom assessment and management
Goals of care, treatment preferences, and advance care planning

2 Symptom Assessment and Management

Patients with lung cancer experience a significant symptom burden. In a recent nationally representative cohort study of 2411 patients with lung cancer, greater than 98 % of patients experienced at least one symptom within the 4 weeks prior to the survey and 73 % patients reported at least one moderate-to-severe symptom [2]. Common symptoms include respiratory and gastrointestinal symptoms, fatigue, sleep disturbances, and depression. Management of symptoms requires frequent and accurate assessment as well as documentation of the symptoms. A thorough history and physical is the next critical step in determining the etiology of the symptom and developing a treatment strategy. As the method(s) employed to ameliorate the symptom may involve the possibility of additional burdens and risk, it is essential to understand an individual's prognosis and goals of care. Once treatments are attempted, frequent re-assessment for efficacy and adjustments to optimize symptom relief are important, as the character and intensity of symptoms can fluctuate throughout the illness trajectory.

2.1 Pain

Pain, as defined by International Association for Study of Pain (IASP), is an unpleasant, multidimensional, ***sensory,*** and ***emotional*** experience associated with actual or potential tissue damage, or described in relation to such damage [9]. A meta-analysis of more than 50 studies has revealed that more than 50 % of patients with cancer in the USA experience pain, and that pain is most prevalent among the patients with higher disease burden [10]. One recent study collecting data from a nationally representative cohort has reported the prevalence of pain in lung cancer patients for both early and late stages to be greater than 50 %. Furthermore, the prevalence of moderate-to-severe pain was reported at 17 and 20 % for early versus late stages of lung cancer, respectively [2].

Unfortunately, despite the availability of established and effective guidelines [11, 12] for the treatment of cancer pain in the past few decades, adequate pain control still remains a serious issue for cancer patients and under-treatment of pain is widely reported in various studies across the continuum [13, 14]. Concurrently, there is growing evidence in oncology that survival is linked to symptom control and that pain management contributes to broad QOL improvement [4, 12].

Uncontrolled pain leads to unnecessary suffering and can additionally adversely impact patients' functional status, sleep, appetite, and treatment compliance [15]. Effective pain management can help maximize patient outcomes and is an essential component of oncologic care.

While pharmacologic and other non-pharmacologic palliative measures such as radiation are being used to address the physical aspect of cancer pain, it is important to recognize that pain is not a purely physical experience and that many psychological, spiritual, existential, and social factors also play a role in the experience of pain in cancer patients [16, 17]. This is particularly important as efforts solely directed at managing the physical aspect of pain might not be adequate to effectively control the pain and to improve a patient's QOL. Therefore, a whole-person interdisciplinary approach is recommended to address the multilayer complexities of the cancer pain experience.

2.1.1 Pain Assessment

The most important initial step in addressing cancer pain is a comprehensive pain assessment. It is crucial to determine the cause, extent of the disease, and presence of other comorbidities through routine history taking, physical examination as well as use of laboratory and imaging studies as indicated [16]. This step will guide the treatment strategy which, in addition to analgesic medications, can include disease modifying therapy and incorporation of other non-pharmacologic approaches to optimize pain control. Furthermore, characterization of multiple dimensions of pain, such as intensity, quality, location, radiation, and temporal features, is important for determining the cause and type of pain and in establishing an appropriate treatment plan.

2.1.2 Pain Scales

All patients should be screened for pain at every encounter. Pain intensity must be quantified with an appropriate rating scale. At minimum, patients should be asked about "current" pain, "usual" pain, "worst" pain, and "least" pain in the past 24 h. For a comprehensive pain assessment, "worst pain in the last week," and "pain at rest" and "pain with movement" should also be included. Some of the most commonly used standardized scales are the *Numerical verbal or written scale* (numbers from 0 for no pain to 10 for the most severe pain imaginable), the *Categorical scale* (what word best describes pain: none, mild, moderate or severe), as well as the *Visual Faces Pain Rating scale* [12]. In the nonverbal patient, and in the absence of self-report, observation of behavior is a valid approach to assessment of pain, with the caveat that any such behavioral changes could also reflect other sources of distress (such as delirium or dyspnea). Response to pain medicines in such cases can be a clue as whether there are other distressing symptoms complicating the picture [12].

2.1.3 Pathophysiology and Type of Pain

An understanding of the cause and pathophysiologic type of pain can additionally guide decision making in regard to pharmacologic choice and analgesic plan of

care. A conventionally accepted, yet somewhat simplified, clinical classification of cancer pain, describes two broad categories:

Nociceptive pain:
Nociceptive pain is an inflammatory pain that is caused by direct activation of nociceptors by tumor infiltration into tissue or by tissue damage as a result of cancer treatment. It signals an ongoing tissue injury and is further categorized as either somatic or visceral [18].

- *Somatic* pain results from involvement of bone and muscle structures. Metastatic bone disease is the most common type of somatic cancer pain.
- *Visceral* pain is also very common and results from stretching or distension of internal organs (such as liver capsular pain). This type of pain is hard to localize and is often referred to cutaneous sites which can mislead the examiner [18]. One of the other characteristics of this type of pain is its association with motor and autonomic reflexes such as nausea and vomiting [19].

Neuropathic pain:

Neuropathic pain may be a complication of injury to the peripheral or central nervous system. This type of pain is often poorly tolerated and difficult to control. As a result of this injury, the typical stimuli which normally would not result in the sensation of pain, now causes pain (allodynia). Furthermore, a painful stimulus results in an exaggerated experience of pain (hyperalgesia). It is often described as paroxysms of burning, tingling, and electric-like bouts of pain. Chemotherapy-induced peripheral neuropathy, malignant or radiation-induced brachial plexopathy, and a subset of chronic post-thoracotomy pain syndrome are some examples of neuropathic pain in lung cancer patients [18].

2.1.4 Pharmacologic Management of Cancer Pain

In an effort to improve cancer pain management, the WHO developed and presented the three-step analgesic ladder as a framework for physicians in 1986. This guideline recommended a three-step approach to managing pain based on severity:

Step 1: non-opioids such as acetaminophen or nonsteroidal anti-inflammatory (NSAIDs) drugs for mild pain;
Step 2: addition of weak opioids (Tramadol, codeine or low dose of stronger opioids such as morphine) to non-opioids for moderate pain; and
Step 3: to proceed with using stronger opioids (morphine, hydromorphone, etc.) for severe pain.

It is noteworthy, however, that some recent studies have suggested modifications to the WHO analgesic ladder or even elimination of the step 2 altogether. Despite this, the use of opioids for cancer pain, as first proposed by this guideline, has now been supported by almost 30 years of clinical experience and is the cornerstone of pharmacologic management of cancer pain [20].

2.1.5 Opioid Selection

The pure μ-agonist opioids are conventionally selected for cancer pain. When it comes to the choice of one particular opioid versus another, studies have suggested

that there are individual differences in response to different types of opioids which cannot necessarily be predicted unless an agent has been tried before. Any pure μ-agonist opioid, such as morphine or oxycodone, can be prescribed for management of moderate-to-severe cancer pain [20], though factors such as kidney or liver disease can limit the choice, dose, and frequency of use [21, 22].

2.1.6 Opioid Pharmacokinetics

Perhaps, one of the most important factors to consider before prescribing opioids for cancer pain is their pharmacokinetic. The liver is the major site of biotransformation of most opioids [21], and the majority of the opioid metabolites are excreted through the kidneys [22]. Therefore, in liver disease, lower doses of opioids or longer administration intervals are needed to mitigate the risk of accumulation in the body. Additionally, in renal failure, specific metabolites (especially morphine's metabolite morphine-3-glucuronide) can accumulate resulting in significant neurotoxicity [18]. It is important to note that equianalgesic doses of a particular opioid can be delivered via intravenous (IV), subcutaneous (SC), or oral routes, despite the variable potencies of such preparations (see Table 1) [23]. However, differences exist in the time-to-peak effect.

Time-to-Peak Effect for Opioids:
For most commonly used opioids, time-to-peak effect is between 6 and 10 min after an IV administration, 30 min after subcutaneous (SQ) injection, and about 60–90 min after oral use [23]. This is particularly important, as re-dosing of opioids after the expected peak effect has been reached (IV 10–15 min, SQ 30 min and oral 2 h) is a safe and reliable method of pain control. Given the shortest time-to-peak effect occurs with IV administration, parenteral administration of opiates is considered to be the route of choice during a cancer pain crisis.

Route of Administration of Opioids:

The oral route is usually preferred, owing to its convenience and flexibility. Several of the immediate release opioids, such as morphine, hydromorphone, and oxycodone, are also available in liquid formulations which may be useful for patients with dysphagia and swallowing problems, or those who can only receive medications through feeding tubes. For patients who are unable to tolerate oral medications or need faster pain relief, subcutaneous and intravenous formulations are available. Subcutaneous injections are a reliable and effective method for delivery of pain medications and are widely used in management of cancer pain. Intramuscular injections are not recommended as they are painful and provide no pharmacologic advantage [16]. Occasionally, patients are treated with rectal administration of an opioid [24]. The potency of rectally administered opioids is believed to approximate oral dosing, but absorption is variable and relative potency may be higher or lower than expected.

Table 1 Equanalgesia among common opioid medications

Opioid	IV/SQ	Oral (mg)
Morphine	10 mg	30
Oxycodone	N/A	20
Hydromorphone	1.5 mg	7.5
Hydrocodone	N/A	30
Codeine	N/A	200

2.1.7 Short Acting Oral Opioids

The most commonly available short acting or immediate release opioids in the market include morphine, hydromorphone, oxycodone, and hydrocodone (usually combined with acetaminophen). Short acting opioids are particularly useful for acute intermittent, incidental, or breakthrough pain and for dose finding for chronic cancer pain. A reasonable starting dose for opioid naïve patients is 5 mg of oral morphine equivalent every four hours as needed; however, doses as low as 2.5 mg oral morphine equivalent have been proven safe and effective for treating pain in elderly patients, and in patients with underlying liver disease. Clinical response and side effects should be monitored closely and frequently, and doses should be adjusted to maintain the desired pain control. For patients with uncontrolled pain, for whom the initial dose is ineffective, dose titration involves increasing subsequent doses of opioid by 30–100 % based upon the severity of pain in response to the previous dose, and waiting until at least one time-to-peak effect has passed before providing an additional dose [16]. As a general rule, the dose of an opioid can be increased until a favorable balance between analgesia and side effects is obtained, or the patient develops intolerable and unmanageable side effects.

2.1.8 Long Acting Opioids

Long acting or sustained release preparations are effective in providing a basal level of analgesia in chronic persistent cancer pain [12]. It has been suggested that these formulations provide a more consistent pain control and improve patient's adherence and overall QOL, while reducing the risk of abuse and diversion [16]. Some of the readily available formulations include morphine sulfate sustained action, oxycontin, fentanyl patch, and methadone. These formulations are prescribed as standing or fixed schedule doses, usually combined with "as needed" rescue dose of short acting formulations for breakthrough pain.

2.1.9 Management of Opioid Side Effects

Effective management of opioid side effects increases patient's compliance and ultimately results in better pain control. Opioid-induced constipation is a very common side effect. Factors, including advanced age, immobility, poor diet, hypercalcemia, and concurrent constipating medications, can worsen constipation and additionally cause nausea, poor appetite, and abdominal pain. Tolerance develops very slowly if at all, and most patients continue to need laxatives for the duration of opioid use. All opioids cause constipation, although there have been some suggestions that fentanyl and methadone might be less constipating than morphine and other similar opioids [18]. Prevention should be a priority when prescribing opioids and laxatives should be used consistently to prevent constipation. Hydration, electrolyte correction, and discontinuation of other nonessential and potentially constipating medications can assist in management of opioid-induced constipation. For severe cases where combination of laxatives, suppositories, and enemas are insufficient in relieving constipation, the FDA approved subcutaneous methylnaltrexone, which is a peripherally acting opioid antagonist that can be effective in treating constipation without affecting analgesia

or causing withdrawal [18]. Nausea and vomiting are common with initiation or increase in the dose of opioids and usually respond well to antiemetics, such as antidopaminergics, and often resolve spontaneously within three to four days. Sedation, opioid-induced neurotoxicity, urinary retention, and pruritus are also some of the other well-recognized side effects of the opioids [18].

2.1.10 Adjuvant Drugs

Adjuvant medications are drugs with a primary indication other than analgesia, that when administered along with analgesics can enhance pain relief, address the pain that has not responded to the opioid regimen, or allow reduction of opioid dose; hence, they reduce opioid-induced side effects. Numerous classes of these drugs with different primary indications are available and have been proven effective for certain pain syndromes such as neuropathic or bone pain. Antidepressants, steroids, anticonvulsants, neuroleptics, NMDA-receptor antagonists, bisphosphonates, and anticholinergics are some of the widely used classes of adjuvants prescribed for cancer pain relief. Steroids, bisphosphonates, calcitonin, and radiopharmaceuticals are a few of the effective agents for bone pain. Gabapentinoids (gabapentin or pregabalin), the analgesic antidepressants (tricyclics or serotonin-noradrenaline reuptake inhibitors), and topical lidocaine are commonly used for neuropathic pain [18].

2.1.11 Other Treatments

Although most cancer patients gain significant pain relief from systemic pharmacologic analgesia, other modalities often can be used to optimize pain control. Interventional nerve blocks, neuroaxial analgesia, and palliative radiation are effective modalities for cancer pain relief. Additionally, psychological, integrative, and rehabilitative strategies such as relaxation training, guided imagery, hypnosis, and biofeedback are adjunctive treatments intended to reduce pain and anxiety and improve coping. These therapies highlight the concept that cancer pain is not a pure physical experience and that cognition and emotion play important roles as mediators of symptom distress and QOL [16].

2.2 Respiratory Symptoms—Dyspnea, Cough, and Hemoptysis

Patients with lung cancer frequently report respiratory symptoms. Common respiratory symptoms include dyspnea, cough, wheezing, and hemoptysis. Published prevalence rates of these symptoms vary and can be as high as 95 % for dyspnea, 93 % for cough, 31 % for wheezing, and 63 % for hemoptysis [25–27]. These symptoms can be present at diagnosis or develop over the course of the illness, due to progression of disease or as a direct result of treatment [28]. Furthermore, many individuals with lung cancer have comorbid conditions, which can result in the development of these symptoms prior to diagnosis of lung cancer. The prevalence of these symptoms varies with tumor type and location, stage of disease, age,

gender, and comorbid conditions [15]. Difficulties with breathing have frequently been ranked as the most distressing symptom in patients with lung cancer. Furthermore, they can significantly impact an individuals' ability to perform activities of daily living and result in a diminished QOL [26, 29]. Therefore, aggressive management to palliate these symptoms can have a dramatic impact upon the quality of a patient's life.

2.2.1 Dyspnea

Dyspnea has been described as "breathlessness," and/or "a subjective experience of breathing discomfort that consists of qualitatively different sensations that vary in intensity." It is important to note that the sensation of dyspnea is independent of the level oxygen saturation [30]. Dyspnea has been further classified as chronic dyspnea, and a more temporary break through dyspnea, which can last for minutes. Dyspnea can be present at diagnosis and has increasing prevalence and intensity with progression of disease. The symptoms are more common in older patients, and men, and are often more severe in patients with high levels of pain and anxiety [15]. The etiology for the sensation of dyspnea is often multifactorial. Dyspnea may be caused by direct involvement of the lung by cancer, by indirect respiratory complications caused by lung cancer (i.e., post-obstructive pneumonia, pleural effusions), as a result of specific cancer-directed therapies (i.e., radiation or chemotherapy-induced lung toxicity), as a result of respiratory complications that occur more frequently in patients with lung cancer (i.e., pulmonary embolism, lung infections), or as a result of comorbid conditions [i.e., chronic obstructive pulmonary disease (COPD), cardiac disease, previous lung resection, malnutrition]. These physiological factors interact with psychological, social, and environmental factors, to create the distressing experience of dyspnea which may in turn induce secondary physiological and behavioral responses [30].

Given the multifaceted dimensions of dyspnea and the complex interplay between experience and response to the experience, the symptom of dyspnea often requires a multi-modality, stepwise approach to its palliation. Therapies for the palliation of dyspnea can be broadly categorized into invasive interventions, pharmacologic therapies, and behavioral therapies. Determining which therapies are appropriate begins with identifying the cause(s) of dyspnea. Next, one should address reversible causes of dyspnea, in the context of the individual's goals and clinical condition. When causes are not identified, or irreversible conditions are present, or attempts at reversal are not consistent with a person's clinical condition or stated goals, non-etiology specific therapies should be employed.

Invasive Interventions for Respiratory Symptoms

Common clinical conditions causing dyspnea in patients with lung cancer that may benefit from invasive interventions include airway obstruction, pleural effusions, and hemoptysis. Airway obstruction may be caused by disease within the airway, external to the airway causing compression of the airway, or within the walls of the airway [31]. Significant hemoptysis may result from tumor bleeding, or erosion of a

blood vessel into the airway. Progressive symptoms of dyspnea, progressive or large volume hemoptysis, or stridor should lead the clinician to consider bronchoscopic evaluation. Bronchoscopy can be effective as a palliative modality for the treatment of respiratory symptoms. Associated bronchoscopic therapies include tumor debulking, laser therapy, balloon dilation, airway stent placement, electrocautery, argon plasma coagulation, photodynamic therapy, and cryotherapy. Furthermore, if it is consistent with the patient's goals, short-term endotracheal intubation can also be performed to allow for more definitive therapies [15, 32].

Malignant pleural effusions are a common cause of dyspnea in patients with lung cancer. When pleural effusions are present, a thoracentesis can be both diagnostic and therapeutic. Patients who experience improvement in dyspnea with removal of the effusion may benefit from additional procedures to address expected re-accumulation of the effusion [33]. For patients who are planning to undergo further cancer-directed therapies which are expected to result in improvement of tumor burden and decreased production of the malignant effusion, it is reasonable to repeat a thoracentesis as needed if the effusion recurs. Similarly, in patients with a short life expectancy, for whom the goal is short-term relief from dyspnea over a period of weeks, as-needed therapeutic thoracentesis are appropriate if it is consistent with the patient's goals. For patients with a prognosis of weeks to months and a demonstrated or expected re-accumulation of malignant pleural effusion, pleurodesis or placement of a tunneled catheter may be appropriate. Chemical pleurodesis, which can be done at bedside, has a success rate of 50–90 %, but requires hospitalization for observation and treatment of associated post-procedural inflammatory pain. Surgical pleurodesis may be more successful, but requires that a patient to be more fit to undergo a surgical intervention [34]. Alternatively, a relatively inexpensive indwelling tunneled pleural catheter (IPC) can be placed allowing care providers to drain the pleural fluid at home upon re-accumulation. IPCs placed for malignant pleural effusions have been demonstrated to have a low rate of infectious complications, and remain effective for months until a patient's death. Furthermore, when compared to pleurodesis, placement of IPCs requires significantly fewer days in hospital and is associated with fewer additional pleural procedures, with a similar safety and symptom relief profile [35, 36]. The choice of methods to address the dyspnea associated with malignant effusions should be based upon patient preference, and with consideration of prognosis, acceptable burdens of therapy, and maximization of QOL.

Small volume hemoptysis is common in lung cancer and can be emotionally distressing to patients and family, though it generally does not require aggressive interventions. However, large volume hemoptysis, characterized as greater than 200 mL of blood in a 24-h period, can cause significant dyspnea and be life-threatening. Although hemoptysis can be managed with surgical resection, most patients with lung cancer and significant hemoptysis have advanced disease and are not candidates for aggressive surgical interventions. For these patients, less aggressive invasive interventions such as angiography with arterial embolization, or therapeutic bronchoscopy with balloon tamponade, electrocautery, laser coagulation, or injection of vasoconstrictive agents under direct visualization can be helpful

to control hemoptysis [15]. Alternatively, for patients who do not desire or are not candidates for invasive therapies, external beam radiation therapy can be an effective modality for controlling hemoptysis [37].

Pharmacologic Interventions

Pharmacologic management of dyspnea involves the use of bronchodilators, corticosteroids, diuretics, opioids, anxiolytics, and oxygen. Furthermore, use of chemotherapy, when associated with tumor response, can provide relief from dyspnea. Addressing and optimizing therapy for comorbid conditions such as COPD and congestive heart failure which are contributing to the dyspnea should be attempted. Bronchospasms and inflammation can be treated with inhaled bronchodilators (B2-agonists, anticholinergics) and aerosolized or oral corticosteroids, and pulmonary edema can be treated with diuretics. Dyspnea-associated hypoxia should be treated with oxygen supplementation. For patients who are not hypoxemic, a trial of oxygen therapy can be considered to improve exercise tolerance, though room air delivered via nasal cannula may be effective at relieving dyspnea [38].

Opioids are recommended for symptomatic treatment of dyspnea in lung cancer. A meta-analysis of eighteen randomized clinical trials demonstrated a benefit of opiates in the treatment of dyspnea [39]. Opiates can be delivered orally, subcutaneously, parenterally, or aerosolized, though the latter has not demonstrated consistent results in clinical studies [40]. For patients who are opiate naïve, a low dose of sustained release oral formulation has been demonstrated to provide significant improvement in dyspnea in patients with lung cancer [41]. Furthermore, dyspnea can be more severe in patients with severe pain, and opiates can be effective in treating both symptoms. Opioids exert their action on opioid receptors within the central respiratory centers in the medulla, as well as peripherally in the airways and lung parenchyma. It is postulated that their mechanism of action in the palliation of dyspnea is multifold: (1) decreased metabolic rate and ventilatory demand, (2) blunted medullary sensitivity to hypercarbia/hypoxia, (3) suppression of respiratory awareness within the medullary respiratory center and cortex, (4) reduction of pain-induced respiratory drive, (5) anxiolytic effects, (6) blunted afferent transmission from pulmonary mechanoreceptors to the central nervous system (CNS), and (7) vasodilation resulting in improved cardiac function [30, 42]. Importantly, and contrary to prevailing myths, while opiates can affect the respiratory drive, no study has demonstrated increased mortality from respiratory depression with the appropriate use of opiates to treat dyspnea [43]. In cases where reversal of the underlying cause of dyspnea is not possible, or is insufficient to relieve the symptom burden, opiate therapy should be initiated to treat dyspnea.

For patients in whom dyspnea is not adequately managed with opiate therapy, and there is a suspected component of anxiety contributing to the dyspnea, a trial of low dose scheduled benzodiazepines can be initiated. It should be noted, however, that studies of the use anxiolytics alone in the treatment of dyspnea have not demonstrated a consistent benefit over placebo [15]. Furthermore, combination of

an opiate and benzodiazepine may result in respiratory depression at lower opiate doses.

Behavioral Interventions

A multidisciplinary approach is necessary to evaluate and address not only the pathophysiology but also the perception and psychosocial burden of dyspnea.

Behavioral interventions address the complex interplay of factors that result in the sensation of dyspnea and therefore can be effective for the management of dyspnea [44]. Interventions offered should be appropriate to the individual and take into account motivational factors, physical conditioning, disease trajectory, and prognosis. Behavioral interventions for dyspnea can be divided into direct and indirect interventions. Direct interventions are those that are designed to reduce the feeling of breathlessness. Indirect interventions are aimed at factors which can help to reduce the impact or severity of dyspnea and are generally part of a more complex multifactorial intervention to manage dyspnea. Interventions such as exercise and physical rehabilitation can be both direct and indirect by improving physical fitness and thereby increasing the level of activity at which dyspnea is experienced, as well as to desensitize the individual to the sensation of breathlessness. Activity, as tolerated and rehabilitation where appropriate, can be helpful to maintain health, serve as a distraction technique, and minimize breathlessness. Therapy focusing on teaching appropriate positioning, activity pacing and energy conservation, anxiety reduction (i.e., cognitive behavioral therapy, relaxation methods), and breathing techniques has all been demonstrated to reduce dyspnea. Mobility aids, such as rollators, can help to minimize breathlessness in the mobile patients. Furthermore, facial cooling with the use of fans can be helpful in decreasing the sensation of dyspnea and is appropriate for all patients [45]. Given the specialized training necessary for these techniques, and the higher level of support required to implement the education, early involvement of allied health professionals (occupational therapists, physiotherapists) in the management of patients with dyspnea is critical [44].

2.2.2 Cough

Cough is a sudden, often repetitive reflex which results in the forceful expiration of air which helps to clear the airways of irritants, secretions, and foreign particles. It can present as nonproductive ("dry") or productive and is a common symptom in patients with lung cancer. As an initial symptom, it is a present in 81 and 84 % of patients with early and late stage lung cancer, respectively [2], and can be productive in 49 % of cases [46]. It is often under recognized by healthcare professionals, even though it can exacerbate the sensation of dyspnea, and significantly affect QOL [47]. Therefore, its prompt recognition and treatment is important. Cough may be caused by involvement of the respiratory tract by tumor (i.e., impingement or obstruction of the airway, lymphangitic spread, pleural disease with effusions or masses), as a result of therapies directed against the malignancy (i.e., radiation or chemotherapy-induced pneumonitis, postoperative changes), by

infection, by comorbidities (i.e., commonly coexisting COPD, heart failure, gastroesophageal reflux, postnasal drip), or by concomitant smoking. However, often the underlying etiology of cough in a patient with lung cancer is multifactorial. Much as with dyspnea, management of cough begins with identifying the underlying cause of cough, and then addressing reversible causes of the cough, in the context of an individual's goals and clinical condition [48].

There is limited data from a number of small studies to guide the treatment of cough in lung cancer. Nonetheless, recommendations have been developed based upon these studies and expert consensus [48, 49]. Therapies for cough can be divided into pharmacologic agents and non-pharmacologic treatments.

Pharmacologic Interventions

Pharmacologic treatments of comorbid conditions, when present, can provide cough relief. For example, when bronchospasm is contributing to cough, particularly in the setting of coexisting COPD, or the post-infectious setting, bronchodilators may be helpful. Patients with lung cancer are at increased risk of pulmonary infections with bacteria, viruses, and opportunistic fungi. This risk may be exacerbated in the setting of immunosuppressive therapies directed against the malignancies. Therefore, clinicians should be cognizant of this risk and be prepared to provide appropriate antibiotic therapy when indicated. In situations where cough results from chemotherapy or radiation-induced pneumonitis, or airway edema secondary to malignant airway involvement, corticosteroid therapy may be helpful. When cough is secondary to the tumor, appropriate chemotherapy regimens have also demonstrated improvement in responders in the first and second line setting and should be considered.

Opioids, including codeine, dextromethorphan, hydrocodone and morphine, are centrally acting antitussives and have demonstrated efficacy as cough suppressants in patients with lung cancer. Opioids can be administered to treat cough in settings where the underlying condition is unknown, partially reversible or non-reversible, or an individual's clinical condition or goals are not consistent with therapies directed against the underlying etiology of the cough. Furthermore, opioid therapy should be considered in conjunction with more targeted therapies, until the cough has resolved [49, 50]. Hydrocodone 5 mg (equivalent to 5 mg of oral morphine) given orally every four hours as needed for cough is a reasonable starting dose.

Benzonatate, a peripherally acting antitussive, has demonstrated an antitussive benefit in patients with lung cancer and cough, particularly when combined with opiates [51]. For patients with secretions and the ability to generate a sufficient cough, the addition of mucolytics, such as acetylcysteine, and expectorants, such as guaifenesin, may be helpful.

Non-pharmacologic Interventions

Non-pharmacologic interventions for cough include smoking cessation, surgical resection, radiation therapy, and endobronchial therapies. Concurrent smoking may

contribute to cough in a patient with lung cancer. Patients should be encouraged to quit smoking and offered assistance in the form of counseling, behavioral therapy, group sessions, nicotine replacement and other pharmacologic aides as appropriate [49]. In patients with stage I or II non-small cell lung cancer, resection of the tumor will generally resolve the cough, though cough may persist for greater than a year after surgery [52]. Palliative radiation delivered in a few fractions can be considered for relief of cough and has been demonstrated to result in durable relief of cough in randomized clinical trials [53]. Obstruction of central airways can cause cough, along with symptoms of dyspnea and hemoptysis. While relief of cough is rarely an indication for endoscopic intervention, treatment of airway obstruction, dyspnea or hemoptysis with endobronchial therapy has demonstrated to improve cough in the majority of patients [50]. Although it may not be possible to achieve complete cessation of cough, it is important to recognize that decreasing the severity of cough can substantially improve a patient's QOL [49, 50].

2.3 Gastrointestinal Symptoms

Common gastrointestinal symptoms experienced by patients with cancer include nausea, vomiting, diarrhea, and constipation. While these symptoms are less prevalent in lung cancer when compared to gynecologic and gastrointestinal cancers, their presence can have a significant negative impact on QOL. The assessment and management of specific chemotherapy associated gastrointestinal symptoms are well described in various clinical guidelines and are outside the scope of this review. However, the approach to these symptoms in patients with any malignancy is similar and involves assessing for possible causes, addressing reversible causes if it is consistent with a patient's goals of care, and tailoring further therapies to the putative etiology of the symptom. In reality, many of these symptoms have a multifactorial etiology and therefore are often treated in an empirical manner.

2.3.1 Nausea and Vomiting

The prevalence of nausea and vomiting among patients with lung cancer is poorly understood in part due to lack of a standard research definition, and exclusion from a number of symptom assessment tools in cancer [54]. However, the palliative care literature characterizes these symptoms as common, affecting the majority of patients, and undertreated [55]. Understanding the etiology can be helpful in developing a treatment plan. The etiology of nausea and vomiting can be divided into 4 broad categories: due to the cancer (i.e., liver metastasis, peritoneal carcinomatosis, hypercalcemia), as a side effect of the therapy (i.e., chemotherapy, radiation, or opioid-induced nausea), secondary to debility (i.e., esophageal candida, cachexia), or caused by a comorbid condition (i.e., diabetic gastroparesis) [54].

The brain and the gut possess complex neural networks that trigger nausea in response to stimuli. While not completely understood, it is recognized that these pathways utilize specific neurotransmitter signals to relay signals to the central

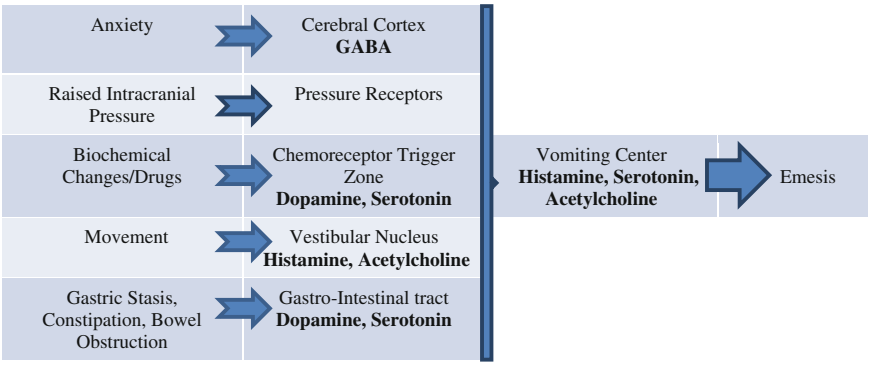

Fig. 1 Nausea and emesis pathways

nervous system. Specifically, the gastrointestinal tract may signal pathologic mucosal irritation, distention/obstruction, stasis, and inflammation, utilizing various substances including serotonin, dopamine, cannabinoids, acetylcholine, and substance P. Vestibular networks may signal motion sickness, CNS lesions, and opioid-induced vertigo via histamine and cholinergic neurotransmission. The chemoreceptor trigger zone (CTZ), located in the floor of the fourth ventricle, senses toxins and noxious agents within the blood and in the cerebral spinal fluid (CSF), and transmits this information utilizing dopaminergic, serotonergic, and neurokinin-1 receptor systems. The cortex integrates sensory input, higher thought processes such as memory and anxiety which can modulate nausea, as well as meningeal irritation and increased intracranial pressure and contributes to nausea. Signals from these systems converge upon the emetic complex in the medulla, which generates the series of actions resulting in emesis (Fig. 1). The palliative care literature emphasizes the targeting of specific neurotransmitter receptors within these networks to palliate nausea. While there is little evidence that this method is superior to empiric selection of antiemetics, it does provide a foundation upon which to develop a treatment strategy [54, 56].

A proper history and physical exam is crucial in determining the etiology of nausea and vomiting, and to develop a plan for the palliation of the system. Characteristics such as appearance of emesis, frequency and timing of emesis, relationship to oral intake, medications, and chemotherapy, as well as physical signs such evidence of bowel sounds can assist in understanding the etiology. Associated symptoms of abdominal pain and distension, constipation, vertigo can support specific etiologies. These characteristics can point to specific points of stimulation for nausea within the gut, liver, CTZ, cortex, and vestibular apparatus. Antiemetics can be selected to target specific associated stimulated systems. For example, 5-HT3 receptor antagonists such as ondansetron, or dopamine antagonists such as haloperidol or metoclopramide can be utilized to target nausea associated with toxins, such as drug-associated nausea. Medications which target muscarinic receptors in the vestibular apparatus, such as scopolamine, can be used in cases of

Table 2 Antiemetic neurotransmitter receptor affinity

Drug	Dopamine antagonist	Histamine antagonist	Acetylcholine antagonist	Serotonin antagonist
Chlorpromazine	++	++	+	
Haloperidol	+++			
Hyoscine			+++	
Metoclopramide	++			+/++
Ondansetron				+++
Prochlorperazine	++	+		
Promethazine	+	+++	++	
Olanzapine	+++	++	+	++/+++

High Affinity: +++
Moderate Affinity: ++
Low Affinity: +

vertigo associated nausea. Glucocorticoids and benzodiazepines which target the cortex can be utilized for cortex-mediated nausea such as mass effect and anticipatory nausea, respectively. While this approach can be useful, it is important to recognize that the etiology for nausea is often multifactorial and may require targeting of more than one neural system. Therefore, antiemetics with affinity at multiple receptor sites may be helpful (Table 2). Olanzapine, which antagonizes multiple dopamine and serotonin sub-receptor types, as well as cholinergic, and histamine receptors, has demonstrated superior breakthrough antiemetic efficacy in patients undergoing emetogenic chemotherapy and who received appropriate chemotherapy-induced nausea prophylaxis [57, 58].

2.3.2 Constipation

Constipation is a common symptom experienced by patients with cancer [59]. The etiology is often multifactorial and includes drug-induced constipation (i.e., opiates, 5HT3 antagonists, anticholinergics, and chemotherapy), immobility, dehydration, metabolic abnormalities, and autonomic/neurologic dysfunction. Constipation can result in many secondary complications which contribute to a diminished QOL including nausea and emesis, poor nutrition, abdominal distension and pain, and overflow incontinence from impaction. A proper history and physical is crucial to determining the underlying etiology. Specifically, abdominal, rectal, and targeted neurologic exam are important, as is information gained from history such as medications, associated symptoms, and duration of constipation. Laboratory evaluation of electrolytes (i.e., calcium) and thyroid function, as well as plain film imaging of the abdomen may be helpful in certain circumstances. Management of constipation involves reversing underlying etiologies if possible, and then providing adequate prophylaxis for future constipation. Prevention includes encouraging activity, regular toileting, adequate hydration, and avoidance of contributing drugs, when possible. However, the majority of patients with advanced illness will require regular use of laxatives to prevent constipation. The use of a scheduled stimulant at

night such as senna, along with a stool softener is recommended. Osmotic laxatives such as polyethylene glycol or lactulose can be safely used multiple times per day in the well-hydrated patient when scheduled laxative is not sufficient. While not preferred by patients, stimulant suppositories and enemas are also effective for treating constipation. Patients should be instructed to aggressively manage symptoms of constipation, if they are not stooling daily, as it is easier to treat constipation earlier than later. Given that patients with advanced stages of disease are unlikely to experience resolution of the underlying factors predisposing to constipation (i.e., opiates, immobility), they should be encouraged to continue with a daily regimen. For patients, with lose stools as a result of laxatives, the laxatives should be held for one day, and then restarted at a lower dose, or with one less agent.

2.3.3 Diarrhea

Diarrhea is defined as greater than three unformed stools in a 24-h period and is a prevalent symptom in patients with cancer. It can significantly impact a person's QOL and result in social isolation, as patients limit their time away from their home. Furthermore, when left untreated, diarrhea can result in malnutrition and dehydration. Causes include treatment-related side effects (chemotherapy or radiation-induced, antibiotic-related), infection (i.e., clostridium difficile), malabsorption, and obstruction (tumor, stool impaction). Furthermore, diarrhea can be the result of aggressive laxative use. Palliating the symptom of diarrhea begins with an appropriate history and physical exam, as well as focused laboratory testing. Reversible causes should be identified and addressed. If infection is not suspected, therapies can be utilized to slow gastrointestinal transit. Loperamide, diphenoxylate/atropine, and tincture of opium can be effective in decreasing the number of stools. Bulk-forming agents may assist in patients with history of bowel resection. Digestive enzymes may be effective for cases of malabsorption. In severe cases, octreotide may be helpful to decrease gastrointestinal secretions and transit [60, 61].

2.4 Cancer-Related Fatigue

Cancer-related fatigue (CRF) has been described by the NCCN as "a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [62]. More than three in four patients with lung cancer experience CRF, with 43 % of patients with late stage disease characterizing CRF as moderate to severe, second only to cough and dyspnea in this population [2]. In fact, patients with cancer have characterized fatigue as the most distressing symptom associated with cancer and cancer-related treatment [63]. CRF can significantly impact a person's QOL, as it limits their ability to participate in meaningful life activities. Despite its prevalence and impact, CRF is underreported. Fatigue assessment should be part of serial oncologic evaluations, focusing on its impact on daily functioning. While there is limited understanding of the underlying pathophysiology of CRF, and specific interventions have not proven to be effective to mitigate

the drivers of CRF, there are specific interventions to treat comorbid conditions that can significantly impact the experience of fatigue. Studies have demonstrated that fatigue rarely exists by itself. Oftentimes, fatigue exists in combination with sleep difficulties, pain, anxiety, and depression. Aggressive management of these associated symptoms can result in improvement in fatigue [64, 65]. Poor nutrition and electrolyte abnormalities can also contribute to fatigue and should be appropriately addressed. Medications can contribute to fatigue, and therefore, a thorough review of medications and side effects should be part of the evaluation for CRF. Optimizing management of comorbidities, such as hypothyroidism, heart disease, and COPD, can also alleviate fatigue. Depending on the prognosis of the patient, and specific clinical condition, general strategies for management of CRF may be appropriate. Energy conservation (i.e., pacing, prioritizing activities, postponing nonessential activities, setting realistic expectations) and distraction have been demonstrated to be helpful to minimize CRF. Short afternoon naps may be encouraged if nighttime sleep is not affected. Furthermore, moderate physical activity during and after active cancer treatment has been associated with improvement in fatigue and should be encouraged in the appropriate patient. In small studies, complementary therapies such as yoga and acupuncture have also demonstrated benefit in CRF and may be appropriate for the motivated individual. Results of studies assessing the benefit of pharmacologic interventions such as methylphenidate and modafinil for the alleviation of CRF are mixed and are not recommended as standard therapy. For patients with advanced disease, there is evidence for the effectiveness of corticosteroids in providing short-term benefit for CRF and overall QOL. Therefore, corticosteroids can be considered in the advanced disease population when the benefits of therapy outweigh the risks associated with long-term therapy [65, 66].

2.5 Sleep Disturbances

Sleep disturbances, including insomnia and daytime somnolence, are common in patients with cancer [67]. Furthermore, studies have demonstrated that sleep patterns are often disrupted in patients with cancer, resulting in less restful sleep [68]. Management of sleep disorders begins with appropriate evaluation of history and daily behaviors. Further evaluation with polysomnography should be considered for patients with sleep-disordered breathing, or history of malignancy involving the upper airways. Primary sleep disorders, such as obstructive sleep apnea and restless leg syndrome should be addressed with breathing assist devices and medications, respectively. Patients should undergo evaluation and treatment for concomitant conditions such as depression, and anxiety which can affect sleep. Specific behaviors, such as late night consumption of caffeine or alcohol, late night TV watching and cell phone use, should be assessed with patients and discouraged. Positive sleep hygiene habits should be discussed with patients and promoted. Medications which may be interfering with nighttime sleep, or causing daytime somnolence should be reviewed and adjusted when possible. For patients with

persistent insomnia, a trial of sedating antidepressants such as trazadone or mirtazapine may be helpful, particularly if there is coexisting depression. Cautious use of benzodiazepines such as lorazepam or non-benzodiazepine hypnotics such as zolpidem can be considered for insomnia, though these medications should be avoided in the elderly. For patients with persistent daytime somnolence, a trial of methylphenidate, modafinil or caffeine can be considered, though they should not be given in the evening as they are likely to affect nighttime sleep.

2.6 Depression

Depressive symptoms are common in advanced cancer patients and may arise as a "final common pathway of distress in response to psychosocial vulnerabilities, physical suffering, and proximity to death" [69]. Patients with lung cancer have an especially high prevalence of major depression and depressive symptoms. Studies have found a prevalence range of 17–25 % for major depression and clinically significant depressive symptoms in patients with metastatic non-small cell lung cancer [4], and one recent study reported a 79 and 83 % overall prevalence of depressive symptoms in a cohort of both early and late stage lung cancer patients, respectively [2]. While high symptom burden in lung cancer is considered to contribute to high prevalence of depression, depression itself can also adversely impact patients' experience of symptoms, their functionality, QOL [70] and even survival [71].

The management of depression, especially among poor prognosis cancers, is particularly challenging as the treatment needs to be both rapidly effective and deliverable in the setting of progressive physical decline [72]. Although currently there is little evidence to guide the management of depression in cancer patients, two randomized clinical trials [72, 73] have demonstrated that a multimodality and collaborative approach, including antidepressants, along with psychological support from a nurse case manager, a primary care physician, a psychiatrists, and a liaison with the patient's oncologist, can be successful in improving depressive symptom burden in cancer patients. This approach would allow a comprehensive assessment and management of not only the depressive symptoms but also the disease-related symptom burden and psychosocial factors contributing to development of depression in these patients.

Psychotherapy may be the only modality required in mild-to-moderate depression. However, antidepressant medication may also be tried in such cases when depressive symptoms fail to respond to psychological treatment [74]. No particular antidepressant class has been shown to be most effective for treating depression although prior response to treatment in patients or their family members and the side effect profile of the antidepressant can influence the choice of medication used in cancer patients. Among the selective serotonin reuptake inhibitors (SSRIs), sertraline, citalopram, and escitalopram are considered to have the fewest drug–drug interactions and are relatively well tolerated. The choice of antidepressants can also be influenced by the additional effect of some of these medications on

improving other cancer-related symptoms such as anorexia, insomnia, fatigue, and neuropathic pain (i.e., mirtazapine, duloxetine, venlafaxine) [74]. Most antidepressants take 3–6 weeks to achieve their therapeutic effect. Therefore, where there is need for a more rapid onset of action, particularly in the setting of a shorter prognosis, psychostimulants such as methylphenidate have been used to improve depressive symptoms [75], though the evidence for their use is limited [74, 76].

3 Goals of Care

Patients with advanced cancer face the emotional impact of a serious and life-limiting illness, coupled with the need to make treatment decisions that are often complex. In addition, they face the challenge of simultaneously maintaining hope and having realistic goals. Effective communication between patients and their clinicians can positively affect a patient's understanding and experience of the disease, impact their treatment decisions, and facilitate their journey throughout the disease trajectory. When done well, patient-centered communication can result in better alignment of the care plan with patients' goals, values, and preferences.

The NCI's framework for patient-centered communication processes and outcomes in cancer care is organized around six core functions of patient–clinician communication: Exchanging information, making decisions, fostering healing relationships, enabling patient self-management, managing uncertainty and responding to emotions [77]. Clinicians must build a trusting and therapeutic relationship with patients from diverse personal, social, cultural, spiritual, and religious backgrounds. Awareness of patients' unique characteristics and backgrounds will allow the clinician to meet their patients "where they are" and to be able to support them in every stage of their illness. Additionally, having a distinct set of communication skills will empower the clinicians to have a more honest and empathic discussion with their patients. Over the past two decades, communication tools and modules have been developed to enable physicians to build the skillset necessary for more effective communication with their patients. The **SPIKES** protocol for delivery of bad news (**S**etting up the interview, assessing the patient's **P**erception, obtaining the patient's **I**nvitation, giving **K**nowledge and information, addressing the patient's **E**motion with empathic responses, **S**trategy and **S**ummary) [78], ***Ask-tell-ask*** to respond to informational concerns, **NURSE** verbal empathic response to emotional concerns (**N**ame the emotion, **U**nderstand the emotion, **R**espect the emotion, **S**upport patients and families by sharing resources and relevant reassurance, **E**xplore the patient's feelings and concerns) [79] are just a few of the available tools to improve clinicians' communication skills.

Assessing goals of care, at its heart, is an ongoing conversation about a patient's hopes, priorities, and acceptable and unacceptable burdens of therapy in achieving their desired outcomes at any stage of the disease. In advanced stages of cancer, the challenge for clinicians is to support the patient's hopes while acknowledging the severity of the patient's disease. Offering an opportunity to discuss a patient's concerns as well as their personal and non-medical goals is essential and can often

inform the development of the patient-centered medical care plan. In cancer care, a "turning point" [80] is reached when chemotherapy is no longer an option. While there is consensus for honest and open communication [7], learned communication and self-awareness skills [81] can tremendously aid the clinicians to perform this difficult task effectively and with empathy.

3.1 Advanced Care Planning

Advanced care planning (ACP) is a communication process between individuals and their healthcare agents to understand, discuss, and plan for future healthcare decisions for a time when individuals are no longer able to make their own healthcare decisions [82]. While ACP is appropriate for any adult, at any age, it has increased importance and urgency in patients with life-threatening or life-limiting illness. The Institute of Medicine's report *Dying in America* has recommended advance care planning discussions as an essential part of patient–physician communication to ensure patients receive care reflecting their values, goals, and preferences [83]. As the long-term prognosis is poor for many patients with lung cancer, ACP is an integral part of patient-centered care delivery in this patient population. Timely completion of ACP such as durable power of attorney, living wills, and documents outlining goals of care and preferences surrounding life-sustaining therapies is important. Patients should be directed to resources available for completion of these documents [84]. Medical teams should incorporate this information regarding care preferences into the patient's medical record.

3.2 Transitions in Care

When cancer-directed therapy is no longer effective in meeting a patient's goals, whether to prolong and/or to improve QOL, the focus of the care should transition from such treatments to pure palliation of symptoms to optimize the quality of patient's remaining life. Ideally with the early integration of palliative care into routine cancer care, this transition can be achieved smoothly and effectively. As patient's prognosis worsens to an estimated six months or less, hospice care should be considered to ensure optimum symptom management and comprehensive support for the patient and family. While historically hospice care has been offered and reimbursed after cancer-directed therapy has been discontinued, some of the newer models of hospice have developed a more balanced "open access" approach to care, allowing for concurrent cancer-directed palliative therapy and modalities such as total parenteral nutrition, chest tubes, palliative radiation etc., to help individuals avoid the "terrible decision" between tumor directed therapy and comfort focused care [85]. This approach allows patients to receive the most comprehensive support focused on optimizing their QOL.

4 Conclusion

Lung cancer is the most common cancer globally and is the leading cause of cancer death in both men and women in the USA. Additionally, and specifically in advanced stages, its significant symptom burden can adversely affect a patient's QOL, adding more to the constellation of physical, emotional, psychosocial and existential suffering so prevalent in the setting of any advanced illness. Effective and timely assessment and management of symptoms in an interdisciplinary manner, along with open communication and dynamic goal setting, can positively impact QOL, patient and family's overall experience of the disease, meaning finding and maintaining hope even in the midst of ongoing clinical decline. Therefore, Palliative Care delivered by oncologists and via specialty Palliative Care when needed should be an integral part of routine cancer care for these patients.

References

1. SEER stat fact sheets: lung and bronchus cancer. Available from: http://seer.cancer.gov/statfacts/html/lungb.html
2. Walling AM et al (2015) Symptom prevalence in lung and colorectal cancer patients. J Pain Symptom Manage 49(2):192–202
3. WHO definition of palliative care. Available from: http://www.who.int/cancer/palliative/definition/en/
4. Temel JS et al (2010) Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363(8):733–742
5. Hennessy JE et al (2013) Practical issues in palliative and quality-of-life care. J Oncol Pract 9 (2):78–80
6. Palliative Care (Version 1.2014) (2015) NCCN clinical practice guidelines in oncology. Available from: http://www.nccn.org/professionals/physician_gls/pdf/palliative.pdf. 5 Jan 2015
7. Smith TJ et al (2012) American society of clinical oncology provisional clinical opinion: the integration of palliative care into standard oncology care. J Clin Oncol 30(8):880–887
8. Clinical practice guidelines for quality palliative care 3rd edition 2013. Available from: http://www.nationalconsensusproject.org. 5 Jan 2015
9. Merskey H, Bogduk N (1994) Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms, 2nd edn. IASP Press, Seattle
10. van den Beuken-van Everdingen MH et al (2007) Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol 18(9):1437–1449
11. Stjernsward J (1988) WHO cancer pain relief programme. Cancer Surv 7(1):195–208
12. Adult Cancer Pain (Version 2.2014) (2015) NCCN clinical practice guidelines in oncology. Available from: http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf. 5 Jan 2015
13. Fisch MJ et al (2012) Prospective, observational study of pain and analgesic prescribing in medical oncology outpatients with breast, colorectal, lung, or prostate cancer. J Clin Oncol 30 (16):1980–1988
14. Deandrea S et al (2008) Prevalence of undertreatment in cancer pain. A review of published literature. Ann Oncol 19(12):1985–1991
15. Kvale PA et al (2007) Palliative care in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edn). Chest 132(3 Suppl):368S–403S
16. Portenoy RK (2011) Treatment of cancer pain. Lancet 377(9784):2236–2247

17. Total Cancer Pain (2015) Global year against cancer pain. Available from: https://www.iasp-pain.org/files/Content/ContentFolders/GlobalYearAgainstPain2/CancerPainFactSheets/TotalCancerPain_Final.pdf. 5 Jan 2015
18. Bruera E et al (2006) Textbook of palliative medicine. Oxford University Press, New York
19. Cervero F, Laird JM (1999) Visceral pain. Lancet 353(9170):2145–2148
20. Vargas-Schaffer G, Cogan J (2014) Patient therapeutic education: placing the patient at the centre of the WHO analgesic ladder. Can Fam Physician 60(3):235–241
21. Tegeder I, Lotsch J, Geisslinger G (1999) Pharmacokinetics of opioids in liver disease. Clin Pharmacokinet 37(1):17–40
22. Davies G, Kingswood C, Street M (1996) Pharmacokinetics of opioids in renal dysfunction. Clin Pharmacokinet 31(6):410–422
23. McPherson ML (2010) Demystifying opioid conversion calculations: a guide for effective dosing. American Society of Health-System Pharmacists, Bethesda
24. Bruera E et al (1995) Clinical efficacy and safety of a novel controlled-release morphine suppository and subcutaneous morphine in cancer pain: a randomized evaluation. J Clin Oncol 13(6):1520–1527
25. Cooley ME (2000) Symptoms in adults with lung cancer. A systematic research review. J Pain Symptom Manage 19(2):137–153
26. Tishelman C et al (2007) Symptom prevalence, intensity, and distress in patients with inoperable lung cancer in relation to time of death. J Clin Oncol 25(34):5381–5389
27. Iyer S et al (2014) The symptom burden of non-small cell lung cancer in the USA: a real-world cross-sectional study. Support Care Cancer 22(1):181–187
28. Cooley ME, Short TH, Moriarty HJ (2003) Symptom prevalence, distress, and change over time in adults receiving treatment for lung cancer. Psychooncology 12(7):694–708
29. Gupta D, Lis CG, Grutsch JF (2007) The relationship between dyspnea and patient satisfaction with quality of life in advanced cancer. Support Care Cancer 15(5):533–538
30. Parshall MB et al (2012) An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med 185 (4):435–452
31. Ernst A et al (2004) Central airway obstruction. Am J Respir Crit Care Med 169(12):1278–1297
32. Prakash UB (2005) Bronchoscopy. In: Murray and Nadel's textbook of respiratory medicine. Philadelphia, Saunders, pp 1617–1650
33. Antony VB et al (2001) Management of malignant pleural effusions. Eur Respir J 18(2):402–419
34. Shaw P, Agarwal R (2004) Pleurodesis for malignant pleural effusions. Cochrane Database Syst Rev (1):CD002916
35. Fysh ET et al (2014) Predictors of clinical use of pleurodesis and/or indwelling pleural catheter therapy for malignant pleural effusion. Chest
36. Fysh ET et al (2012) Indwelling pleural catheters reduce inpatient days over pleurodesis for malignant pleural effusion. Chest 142(2):394–400
37. Kwok Y et al (2006) Radiation oncology emergencies. Hematol Oncol Clin North Am 20 (2):505–522
38. Abernethy AP et al (2010) Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. Lancet 376(9743):784–793
39. Jennings AL et al (2002) A systematic review of the use of opioids in the management of dyspnoea. Thorax 57(11):939–944
40. Zeppetella G (1997) Nebulized morphine in the palliation of dyspnoea. Palliat Med 11(4): 267–275
41. Abernethy AP et al (2003) Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. BMJ 327(7414): 523–528

42. Mahler DA, O'Donnell DE (2015) Recent advances in dyspnea. Chest 147(1):232–241
43. Mahler DA et al (2010) American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. Chest 137 (3):674–691
44. Booth S et al (2011) Nonpharmacological interventions for breathlessness. Curr Opin Support Palliat Care 5(2):77–86
45. Galbraith S et al (2010) Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. J Pain Symptom Manage 39(5):831–838
46. Selim AJ et al (1997) A symptom-based measure of the severity of chronic lung disease: results from the Veterans Health Study. Chest 111(6):1607–1614
47. Harle AS et al (2012) Understanding cough and its management in lung cancer. Curr Opin Support Palliat Care 6(2):153–162
48. Molassiotis A et al (2010) Clinical expert guidelines for the management of cough in lung cancer: report of a UK task group on cough. Cough 6:9
49. Simoff MJ et al (2013) Symptom management in patients with lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 143(5 Suppl):e455S–e497S
50. Kvale PA (2006) Chronic cough due to lung tumors: ACCP evidence-based clinical practice guidelines. Chest 129(1 Suppl):147S–153S
51. Doona M, Walsh D (1998) Benzonatate for opioid-resistant cough in advanced cancer. Palliat Med 12(1):55–58
52. Sawabata N et al (2005) Persistent cough following pulmonary resection: observational and empiric study of possible causes. Ann Thorac Surg 79(1):289–293
53. Medical A (1992) Research Council (MRC) randomised trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non-small-cell lung cancer (NSCLC) and poor performance status. Medical Research Council Lung Cancer Working Party. Br J Cancer 65(6):934–941
54. Glare P et al (2011) Treating nausea and vomiting in palliative care: a review. Clin Interv Aging 6:243–259
55. von Gunten CF, Gafford E (2013) Treatment of non-pain-related symptoms. Cancer J 19 (5):397–404
56. Harris DG (2010) Nausea and vomiting in advanced cancer. Br Med Bull 96:175–185
57. Navari RM, Nagy CK, Gray SE (2013) The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer 21(6):1655–1663
58. Prommer E (2013) Olanzapine: palliative medicine update. Am J Hosp Palliat Care 30(1): 75–82
59. Mancini I, Bruera E (1998) Constipation in advanced cancer patients. Support Care Cancer 6 (4):356–364
60. Rangwala F, Zafar SY, Abernethy AP (2012) Gastrointestinal symptoms in cancer patients with advanced disease: new methodologies, insights, and a proposed approach. Curr Opin Support Palliat Care 6(1):69–76
61. Fallon M, O'Neill B (1997) ABC of palliative care. Constipation and diarrhoea. BMJ 315 (7118):1293–1296
62. Cancer-Related Fatigue (Version 2.2015). NCCN Clinical Practice Guidelines in Oncology; Available from: http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf. 25 Jan 2015
63. Hinds PS et al (2000) An evaluation of the impact of a self-care coping intervention on psychological and clinical outcomes in adolescents with newly diagnosed cancer. Eur J Oncol Nurs 4(1): 6–17; discussion 18–19
64. de Raaf PJ et al (2013) Systematic monitoring and treatment of physical symptoms to alleviate fatigue in patients with advanced cancer: a randomized controlled trial. J Clin Oncol 31 (6):716–723

65. Bower JE et al (2014) Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. J Clin Oncol 32(17):1840–1850
66. Mock V et al (2000) NCCN practice guidelines for cancer-related fatigue. Oncology (Williston Park) 14(11A):151–161
67. Palesh OG et al (2010) Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-Community Clinical Oncology Program. J Clin Oncol 28(2):292–298
68. Roscoe JA et al (2007) Cancer-related fatigue and sleep disorders. Oncologist 12(Suppl 1): 35–42
69. Lo C et al (2010) Longitudinal study of depressive symptoms in patients with metastatic gastrointestinal and lung cancer. J Clin Oncol 28(18):3084–3089
70. Kroenke K et al (2010) The association of depression and pain with health-related quality of life, disability, and health care use in cancer patients. J Pain Symptom Manage 40(3):327–341
71. Pirl WF et al (2012) Depression and survival in metastatic non-small-cell lung cancer: effects of early palliative care. J Clin Oncol 30(12):1310–1315
72. Walker J et al (2014) Integrated collaborative care for major depression comorbid with a poor prognosis cancer (SMaRT Oncology-3): a multicentre randomised controlled trial in patients with lung cancer. Lancet Oncol 15(10):1168–1176
73. Sharpe M et al (2014) Integrated collaborative care for comorbid major depression in patients with cancer (SMaRT Oncology-2): a multicentre randomised controlled effectiveness trial. Lancet 384(9948):1099–1108
74. Li M, Fitzgerald P, Rodin G (2012) Evidence-based treatment of depression in patients with cancer. J Clin Oncol 30(11):1187–1196
75. Chochinov HM (2001) Depression in cancer patients. Lancet Oncol 2(8):499–505
76. Ng CG et al (2011) The prevalence and pharmacotherapy of depression in cancer patients. J Affect Disord 131(1–3):1–7
77. Patient-Centered Care and Communication. Available from: http://appliedresearch.cancer.gov/areas/pcc/. 5 Jan 2015
78. Baile WF et al (2000) SPIKES-A six-step protocol for delivering bad news: application to the patient with cancer. Oncologist 5(4):302–311
79. Back AL et al (2008) Communication about cancer near the end of life. Cancer 113(7 Suppl):1897–1910
80. Back AL et al (2014) Reframing the goals of care conversation: “we’re in a different place”. J Palliat Med 17(9):1019–1024
81. Sanders J (2015) Finding the right words at the right time-high-value advance care planning. N Engl J Med 372(7):598–599
82. ACP Definition. Available from: http://acpelsociety.com/acpdefinition.php. 5 Jan 2015
83. Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life (2014). Available from: http://www.iom.edu/Reports/2014/Dying-In-America-Improving-Quality-and-Honoring-Individual-Preferences-Near-the-End-of-Life.aspx. 5 Feb 2015
84. Advanced Care Planning. Available from: http://www.cancer.net/navigating-cancer-care/advanced-cancer/advanced-cancer-care-planning. 5 Jan 2015
85. The debate in hospice care. J Oncol Pract 4(3):153–157 (2008)

Management of Lung Cancer in the Elderly

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Abstract

Lung cancer is the leading cause of cancer-associated mortality in the USA. The median age at diagnosis of lung cancer is 70 years, and thus, about one-half of patients with lung cancer fall into the elderly subgroup. There is dearth of high level of evidence regarding the management of lung cancer in the elderly in the three broad stages of the disease including early-stage, locally advanced, and metastatic disease. A major reason for the lack of evidence is the underrepresentation of elderly in prospective randomized clinical trials. Due to the typical decline in physical and physiologic function associated with aging, most elderly do not meet the stringent eligibility criteria set forth in age-unselected clinical trials. In addition to performance status, ideally, comorbidity, cognitive, and psychological function, polypharmacy, social support, and patient preferences should be taken into account before applying prevailing treatment paradigms often derived in younger, healthier patients to the care of the elderly patient with lung cancer. The purpose of this chapter was to review the existing evidence of management of early-stage, locally advanced disease, and metastatic lung cancer in the elderly.

Keywords

Lung cancer · Elderly · Geriatric assessment

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Contents

Lung Cancer in the Elderly

Lung cancer is the leading cause of cancer-related mortality and accounts for more than one-quarter of all cancer-related deaths in both males and females in the USA. It is estimated that in 2016, there will be 221,200 new diagnoses and 158, 040 deaths attributable to lung cancer [1]. The median age for diagnosis of lung cancer in the USA is 70 years with two-thirds of cases in patients aged 65 years or older [2]. The incidence of lung cancer increases with age, and in a recent report, the incidence of lung cancer was highest among those aged ≥ 75 years and decreased with decreasing age [3]. While the World Health Organization (WHO) defines elderly as age 65 and older, in the US and other industrialized nations, age 70 years is considered a more appropriate definition. The absolute numbers as well as the proportion of elderly individuals are expected to rise dramatically over the next 15 years. By one estimate, the number of adults over the age of 65 years in the USA will have doubled by the year 2030. This will lead to a dramatic rise in the incidence of diseases such as lung cancer [4]. It is therefore critical to study and streamline the management of this disease in the elderly population, which has been largely understudied. This chapter will focus on non-small cell lung cancer (NSCLC) given that it is the predominant histology (85 %). We will consider the issues specific to the management of lung cancer in the elderly with early stage (role of surgery, radiation, and adjuvant chemotherapy), locally advanced disease (role of concurrent chemoradiation) and advanced disease (chemotherapy use with a focus

on toxicity). In addition, the emerging role of the geriatric assessment as well as integrating palliative care into the management of lung cancer will be reviewed.

1 Management of Early-Stage Disease

1.1 The Role of Surgery

The surgical management of elderly patients with lung cancer remains an area under investigation. There is no age "cutoff" as such to determine the eligibility for surgery in the elderly population. Retrospective trials have shown that there is no difference in overall survival (OS) in elderly ($\geq$ 70 years) or younger patients undergoing surgery for lung cancer [5, 6]. Published data on postoperative morbidity and mortality in the elderly versus the younger population are currently conflicting [7–9]. Age alone does not seem to be an independent risk factor to determine postoperative morbidity and mortality [10]. Hence, there is a need to assess other factors on an individual basis prior to surgery in the elderly. The five-year survival in the elderly decreases with the increasing stage of cancer (Table 1). Given that the elderly population is at a higher risk of other synchronous or metachronous malignancies, it is vital to determine the etiology of lung masses and nodules to confirm that they represent a lung primary and not metastatic disease, especially if there is a history of prior cancer. A diagnostic mediastinoscopy or bronchoscopy with endobronchial ultrasound (EBUS) guided nodal sampling should be used when feasible before subjecting them to general anesthesia or thoracotomy. In patients who are being evaluated for lung resection, it is important to obtain PET/CT or mediastinoscopy to determine accurate staging prior to surgery. Studies have shown that elderly patients who have N2 and N3 disease have poor outcomes after surgery and they should preferably undergo non-surgical

Table 1 Five-year overall survival (%) in patients with lung cancer by stage between 1998 and 2003

Lung cancer stage	Age <70 years	Age 70–79 years	Age >80 years	*P* value
Stage I	60.6	50.3	41.2	<0.0001
Stage II	38	26.4	21.8	<0.0001†‡; 0.001§
Stage III	13.4	7.7	5.1	<0.0001*
Stage IV	2.2	1.6 _	0.8	<0.0001*

**P* for comparison of age groups <70 years versus 70–79 years, of <70 years versus >/=80 years, and of 70–79 years versus >/=80 years
†*P* for comparison of age groups <70 years versus 70–79 years
‡*P* for comparison of age groups <70 years versus >/=80 years
§*P* for comparison of age groups 70–79 years versus >/=80 years

management [11–17]. This is particularly true for octogenarians with either T3N0 or node positive stage IIIA disease [17].

1.1.1 Role of Minimally Invasive Surgery/Video-Assisted Thoracic Surgery (VATS) in the Elderly

Yan et al. conducted a systematic review and meta-analysis looking at safety and efficacy of VATS for early-stage NSCLC. It was not elderly specific. It showed no significant statistical differences between VATS and open lobectomy in terms of postoperative prolonged air leak ($P = 0.71$), arrhythmia ($P = 0.86$), pneumonia ($P = 0.09$), and mortality ($P = 0.49$). VATS did not demonstrate any significant difference in locoregional recurrence (P 0.24), as compared with the open lobectomy arm, but the data suggested a reduced systemic recurrence rate (P 0.03) and an improved 5-year mortality rate of VATS ($P = 0.04$) [18]. There are retrospective studies looking at advantages of VATS over lobectomy in the elderly population. Jaklitsch et al. showed that the 30-day operative mortality was superior and length of hospital stay was decreased in patients >65 years of age in those undergoing VATS as compared to open thoracotomy [19]. A retrospective study by Koizumi et al. in patients >80 years of age showed better 5 survival and lower mortality rates with VATS as compared to open thoracotomy [20]. A retrospective review by Mun et al. in octogenarians with stage I NSCLC found morbidity, mortality, and 5-year survival rates of 26, 3.6, and 66 %, respectively [21]. A retrospective study in 338 patients older than 70 years by the Duke group showed that 30-day mortality and morbidity were 4.3 and 52 %, respectively. VATS lobectomy and age were statistically significant predictors of morbidity at multivariable logistic regression analysis [22]. A review of 1100 VATS lobectomies with either lymph node sampling or dissection for patients with a mean age of 71.2 years demonstrated low rates of mortality (<1 %) and morbidity, with 84.7 % of patients exhibiting no significant complications [23]. Studies have shown that in patients greater than 75 years of age, segmentectomy and wedge resections could be feasible alternatives to lobectomy with comparable survival and local and distant recurrence rates as compared to younger patients [24, 25]. Thus, VATS lobectomy could be a reasonable alternative to open thoracotomy with lower morbidity and mortality rates.

1.1.2 Preoperative Assessment

Pagni et al. outlined criteria that must be taken into account before determining eligibility for surgery in the elderly [25]. These include the following: (1) The tumor should not outlive patient's life expectancy if left untreated; (2) the life expectancy gained as a result of the surgery should justify the surgery and the recuperation time; (3) the operative mortality should be low enough to warrant the operation; and (4) the morbidity of the procedure should not be excessive or chronic to preserve the patient's quality of life (QOL). In addition to these factors, consideration must be given to cardiopulmonary status and nutritional status as well as social issues in the elderly. Geriatric assessment may be helpful in some cases, and this will be further discussed later in this chapter.

1.1.3 Intraoperative Management

Monitoring temperature, EKG, end-tidal CO_2, and placement of an arterial line are vital during the intraoperative management of an older adult with lung cancer. It is important to assess the intraoperative volume status and end-organ perfusion by looking the urine output [26]. Lymph node sampling is preferred to radical mediastinal lymphadenectomy especially in the elderly to avoid potential complications such as damage to the esophagus, vagus or phrenic nerve, tracheobronchial tree, chyle leak, or recurrent laryngeal nerve palsy [14]. More importantly, lymph node sampling reduces operative time, thereby reducing times for single-lung ventilation and complications of anesthesia [27].

1.1.4 Postoperative Management

Elderly patients are at a significant risk of developing supraventricular tachycardia in the postoperative period and need to be monitored in a telemetry unit. Postoperative pain management can often be challenging in the elderly. They are more sensitive to narcotics, and hence, the medications need to be used judiciously to optimize pain management while minimizing the side effects. This is usually achieved with an epidural catheter or an intravenous patient-controlled analgesia. Nonsteroidal anti-inflammatory drugs (NSAIDS) can be used as adjuvant agents in pain control. Delirium in the elderly is another common problem seen in up to 15–53 % of patients postoperatively [26]. It is important to recognize delirium early on and evaluate potential reversible causes such as polypharmacy, electrolyte disturbances, or underlying infections that could be contributory. Small doses of haloperidol or risperidol may be helpful in symptom management. It is important to avoid the use of benzodiazepines as they could potentially worsen delirium in the elderly. It is important to re-orient the patients periodically and make sure they are in possession of their hearing aids or eye glasses , in addition to early mobilization, adequate physical therapy, and pulmonary toileting to improve postoperative outcomes.

1.1.5 Postoperative Outcomes

Large randomized controlled trials have shown that the postoperative mortality associated with lobectomy is 1.4 %, and this does not change with advanced age [28, 29]. However, there was no clear criterion for selecting elderly patients for lung surgery in these studies. Ginsberg et al. reported a marginal survival advantage with lobectomy as compared to a more limited resection such as segmentectomy or wedge resection in unselected population which became apparent after 3 years of surgery [30]. However, no such advantage was seen in the elderly population over 70 years of age. A study which looked at the factors affecting long-term survival in octogenarians post-resection showed that survival in octogenarians correlates with pathological stage, extent of resection, and gender (female survival was better), but histological subtype or comorbidities were not significantly associated with differences in 5-year survival [31]. A few studies have looked at the QOL in elderly patients after thoracic surgery. These studies indicate that there is an initial decline in the QOL postoperatively followed by improvement similar to that of younger patients [32, 33]. Preoperative QOL is an important predictor of long-term survival

after thoracic surgery in elderly patients [34]. The data on pneumonectomy and postoperative mortality are mixed. Some studies show a higher rate of morbidity and mortality in the elderly versus younger patients, whereas others reveal no difference in outcomes between the young and elderly [15, 35, 36]. Despite these mixed data, the general consensus is to opt for lung conservation surgery where possible with adequate surgical margins as compared to pneumonectomy in the elderly. Cardiopulmonary complications such as arrhythmias, pneumonias, and heart failure are more common in the elderly. Osaki et al. found a higher rate of cardiopulmonary complications in the elderly as compared to younger patients. However, the sample size in the study was small (n = 33) [37]. Morandi et al. also showed similar results; however, the rate of all complications was similar between the young and the elderly [38]. Minimally invasive thoracoscopic procedures may be preferable to thoracotomy in the elderly when feasible [39, 40]. Ishida et al. showed no difference in the postoperative complication rate or perioperative mortality between elderly (>70 years) and younger (29–69 years) patients [41].

In conclusion, age alone is not a determining factor in the long-term survival in lung cancer patients. Standard surgical resection should be offered to elderly patients with early-stage lung cancer after careful patient selection and operative planning. A preoperative geriatric assessment may assist in patient selection and better risk stratification of these patients in the future.

1.2 Role of Radiation Therapy in Early-Stage Lung Cancer

Radiation therapy is a reasonable alternative for early-stage lung cancer in the elderly population when patients are not surgical candidates or when surgery is declined. Untreated patients with early-stage lung cancer do poorly and 21 % of them die from lung cancer within 90 days [42]. Survival can be improved by opting for less invasive techniques such as stereotactic body radiation therapy (SBRT) [43, 44]. SBRT, a technique that requires advanced technology, consists in the delivery of the whole treatment either in a single session (radiosurgery) or in a limited number of fractions. Louie et al. compared outcomes of SBRT versus best supportive care (BSC) in elderly COPD patients with stage I lung cancer [45]. Survival and quality-adjusted survival favored SBRT over BSC for all groups although the benefit was the least for larger tumors and higher grades of COPD. The two prospective studies which studied the role of SBRT in early-stage lung cancer have shown promising results. The multicentre Radiation Therapy Oncology Group study (RTOG 0236) included 59 patients with biopsy-proven peripheral T1-T2N0M0 tumors treated with 54 Gy in three fractions. The 3-year disease-free and OS rates were 48 and 56 %, respectively [46]. The Nordic Cooperative Group study was a phase II study which included 57 patients with T1-T2N0M0 tumors, and they were treated with 45 Gy in 3 fractions. The overall- and cancer-specific survivals at 3 years were 60 and 88 %, respectively [47].

There are no randomized controlled trials comparing SBRT to surgery in the elderly population for early-stage lung cancer. SBRT versus wedge resection was

being studied in a multi-institutional phase III study for high-risk surgical patients with stage I lung cancer (ACOSOG Z4099, NCT01336894), but the study was closed due to slow accrual. Shirvani et al. conducted a population-based study using the SEER database linked to Medicare to determine the baseline characteristics and outcomes of 9093 patients with early-stage, node-negative NSCLC who underwent definitive treatment consisting of lobectomy (59 %), sublobar resection(11.7 %), conventional radiation(14.8 %), observation (12.6 %), or stereotactic ablative radiotherapy (SABR) (1.1 %) from January 1, 2003, through December 31, 2009 [42]. Conventional radiotherapy had worse survival outcomes compared to SABR with a hazard ratio (HR) of 2. A propensity score-matching analysis of well-matched SABR and lobectomy cohorts demonstrated similar OS in both groups. Haasbeek et al. looked at 193 patients 75 years or older with stage I lung cancer. They reported 89 % local control, 86 % 1-year OS and 45 % 3-year OS [44]. Retrospective studies have compared SBRT with wedge resection in patients greater than or equal to 70 years and have shown excellent outcomes and comparable toxicity in both groups [48]. In summary, surgery should be offered as a treatment option when possible. But for those patients, who do not undergo surgery, SBRT should be offered as a reasonable alternative.

1.3 Role of Adjuvant Chemotherapy in Early-Stage Lung Cancer

Given the improvements in surgical techniques and advances in perioperative care, surgery is being increasingly offered in the elderly population for early-stage lung cancer. However, both local and distant relapse is common and 5-year survival with surgery alone is <50 % [49]. Data from randomized controlled trials and meta-analyses have shown that cisplatin-based adjuvant chemotherapy is the standard of care for patients with stage II–stage IIIA lung cancer [50–54, Table 2]. There are currently no published randomized phase III trials in lung cancer comparing the efficacy of adjuvant chemotherapy specifically in the elderly. The Adjuvant Navelbine International Trialist Association 02 (ANITA-02) study looked at single-agent vinorelbine at a dose of 30 mg/m square weekly for 16 weeks in the adjuvant setting in the elderly, but has not been reported yet due to slow accrual. Data on adjuvant chemotherapy in the elderly mainly come from subgroup analyses of the older population in the previously conducted trials in age-unselected populations [50–52]. However, these trials essentially used cisplatin-based regimens, which often pose a challenge in the elderly due to the high risk of nephrotoxicity, ototoxicity, and neuropathy. The representation of elderly patients is limited in these trials, and thus, extrapolating the results of these trials to the elderly population may not be accurate. On the other hand, potentially curative chemotherapy may be underutilized by physicians treating elderly patients due to a lack of referral to medical oncology in early-stage lung cancer [55, 56].

Pepe et al. performed a subgroup analysis in the elderly population of the JBR.10, a study of cisplatin and vinorelbine in 482 patients with resected NSCLC

Table 2 Summary of positive adjuvant trials in non-small-cell lung cancer

Trial [Ref]	ANITA [52]	IALT [50]	JBR.10 [51]	All Cis [53]
Total (n)	840	1867	482	4584
Age >65–69 (%)	170 (20)	328 (18)	84 (17)	901 (20)
Age >70 (%)	64 (8)	168 (9)	71 (15)	414 (9)
Stage inclusion	IB-IIIA	I-III	IB-II	I-IIIA
PS inclusion	0–2	0–2	0,1	NA
Cisplatin dose in mg/sqm	400	300–400	400	150–400
OS increase at 5 years (%)	8.6	4.1	15	5.4

Table 3 Summary of first-line phase III trials in elderly patients with advanced NSCLC

Study, year of publication [Ref]	Total n	Regimen	Median OS, mo	Median PFS, mo	ORR, %
ELVIS, 1999 [72]	161	Vin versus	6.5	NR	19.7
		Control	4.9		–
Frasci et al. [74]	120	Gem + Vin versus	6.7	NR	22
		Vin	4.2		15
WJTOG 9904 [73]	182	Doc versus	14.3	5.5	23
		Vin	9.9	3.1	10
WJCOG0803/WJOG4307L [76]	276	Doc versus	17.3	NR	NR
		Doc + Cis	13.3		
IFCT-0501 [77]	451	Pac + Carbo versus	10.3	6.0	27
		Vin or Gem	6.2	2.8	10

Carbo, carboplatin; *Cis,* cisplatin; *Doc,* docetaxel; *Gem,* gemcitabine; *ORR,* overall response rate; *Pac,* paclitaxel; *PFS,* progression-free survival; *Vin,* vinorelbine

[57]. A total of 155 of the 482 patients were $\geq$65 years of age. They found that chemotherapy prolonged survival for elderly patients. The HR was 0.61 (95 % CI: 0.38–0.98; $p = 0.04$), and the survival advantage was similar to the younger population. There were no significant differences in toxicities, hospitalization, or treatment-related death by age group. Elderly patients received fewer doses of cisplatin compared with young patients (fewer than five doses, 49 % vs. 27 %; five to seven doses, 19 % vs. 21 %; all eight doses, 32 % vs. 51 %; $P = 0.006$). Similarly, elderly patients received fewer doses of vinorelbine (<10 doses, 71 % vs. 51 %; 10–15 doses, 29 % vs. 47 %; all 16 doses, 0 % vs. 3 %; $P = 0.014$). More elderly patients discontinued chemotherapy treatment due to refusal compared with younger patients (40 % vs. 23 %; $P = 0.01$) (Tables 3 and 4).

A pooled analysis by the Lung Adjuvant Cisplatin Evaluation (LACE) group looked at age as one of the factors and found that age did not influence survival [53]. With a median follow-up of 5.2 years, this study found a 5-year absolute benefit from chemotherapy of 5.4 %. Fruh et al. also used the LACE project but

Table 4 Outcomes in patients with advanced NSCLC: age-based subanalysis of phase III trials comparing patients ≥70 years of age versus <70 years of age

Study and year [Ref]	Chemotherapy regimen	Patient age	Median OS (months)	Median PFS (months)	ORR %
ECOG 5592 [80]	Etop + Cis	≥70 years (86)	6.3	2.7	18
	Pac + Cis ± G-CSF		9.2	5.3	25
	Etop + Cis	<70 years (488)	NR	NR	12
	Pac + Cis ± G-CSF		NR	NR	27
ECOG 1594[a] [79]	Plat-based doublet	≥70 years (227)	8.3	3.8	25
	Plat-based doublet	<70 years (912)	8.2	2.7	22
ECOG 4599 [87]	Pac + bev + carbo	≥70 years (224)	11.3	5.9	29
	Pac + carbo		12.4	4.9	17
	Pac + bev + carbo	<70 years (626)	NR	NR	NR
	Pac + carbo		NR	NR	NR
Socinski et al. [84]	*nab*-P + carbo	≥70 years (156)	19.9	8	34
	Pac + carbo		10.4	6.8	24
	nab-P + carbo	<70 years (896)	11.4	6.0	32
	Pac + carbo		11.3	5.8	25
Rodrigues Pereira et al. [83]	Pem + carbo	≥70 years (37)	15.1	6.1	41
	Doc + carbo		12.6	5.8	15
	Pem + carbo	<70 years (174)	14.8	5.8	33
	Doc + carbo		14.9	6.0	25

Bev, bevacizumab; *Carbo,* carboplatin; *Cis,* cisplatin; *ECOG PS,* Eastern Cooperative Oncology Group performance status; *G-CSF,* granulocyte colony-stimulating factor; *nab-P,* nab-paclitaxel; *NR,* not reported; *ORR,* overall response rate; *OS,* overall survival; *Pac,* paclitaxel; *Pem,* pemetrexed; *PFS,* progression-free survival; *Plat,* platinum

[a]This analysis examined outcomes in elderly patients with an ECOG PS of 0 or 1 (i.e., fit elderly patients)

focused on an age-based analysis [58]. Patients were stratified into three groups: <65 years of age, 65–70 years of age, and greater than 70 years of age. However, those >70 years of age were a minority and 41 % of them came from the ALPI trial, which did not reveal a survival advantage for adjuvant chemotherapy [59]. The HR of death were not statistically significant between age groups ($p = 0.29$). More elderly patients died from non-lung cancer-related causes (12 % young, 19 % mid-category, 22 % elderly; $P < 0.0001$). No differences in severe toxicity rates were observed. Elderly patients received significantly lower first and total cisplatin doses, and fewer chemotherapy cycles (χ^2 $P < 0.0001$). Thus, older patients can get cisplatin-based chemotherapy safely and even lower total doses may offer benefit in the elderly.

Two population-based studies have looked at the role of adjuvant chemotherapy in the elderly for early-stage lung cancer [60, 61]. Cuffe et al. identified 6304

patients with NSCLC using the Ontario Cancer Registry who were treated with surgical resection from 2001 to 2006 [60]. Adoption of chemotherapy was compared across age groups: younger than 70, 70–74, 75–79, and over 80 years. In all, 2763 (43.8 %) of 6304 surgical patients were elderly (age $\geq$ 70 years). Utilization of adjuvant chemotherapy in the elderly increased from 3.3 % (2001–2003) to 16.2 % (2004–2006). Among evaluable elderly patients, 70 % received cisplatin and 28 % received carboplatin-based regimens. Requirements for dose adjustments or drug substitutions were similar across age groups. Hospitalization rates, within 6–24 weeks of surgery, used as a surrogate for toxicity, were similar across age groups. Four-year survival of elderly patients increased significantly (47.1 % for patients diagnosed from 2001 to 2003; 49.9 % for patients diagnosed from 2004 to 2006; $P < 0.01$). Survival improved in all subgroups except in patients age over 80 years. In a recent retrospective study from the Veterans Administration, the patterns of adjuvant chemotherapy were studies in over 7500 patients with stage IB-III disease of who 38 % were at the age of 70 years or older [61]. The percentage of older patients who received adjuvant chemotherapy was approximately one-half that of younger patients who did so (15.3 % vs. 31.6 %; $P < 0.0001$). Carboplatin-based doublets were used most often in all patients (64.6 %). Both younger patients (hazard ratio, 0.79; 95 % confidence interval, 0.72–0.86) and older patients (hazard ratio, 0.81; 95 % confidence interval, 0.71–0.92) were found to have a lower risk of death with receipt of adjuvant chemotherapy. These population-based studies provide a "real-world" view that might be better than the post hoc analyses conducted on prospective trials, which typically enroll younger patients with good performance status. It is noteworthy that the use of carboplatin-based regimens in adjuvant therapy has been reported in CALGB 9633 [62], a randomized study evaluating the role of carboplatin and paclitaxel or observation in patients with resected T2N0M0 NSCLC. After a median follow-up of 74 months, overall survival was not significantly different [hazard ratio (HR), 0.83; CI, 0.64–1.08; $P = 0.12$]. However, exploratory analysis demonstrated a significant survival difference in favor of adjuvant chemotherapy for patients who had tumors > or = 4 cm in diameter (HR, 0.69; CI, 0.48–0.99; $P = 0.043$). Thus, while this regimen has not been studied extensively in higher stage disease post-resection, it is often used in clinical practice especially when contraindications to cisplatin exist, a common occurrence in the elderly.

In conclusion, there is currently insufficient high-level evidence to make recommendations for adjuvant chemotherapy in patients >75 years of age. Data from post hoc analyses and population studies suggest that elderly fit patients who receive adjuvant chemotherapy do derive a survival advantage and toxicities are comparable to those seen in younger patients in this population. Cisplatin-based chemotherapy remains the standard of care even in the elderly population. However, similar conclusions cannot be drawn in patients >80 years of age and further studies are warranted in this population.

Carboplatin-based regimens appear to confer a survival advantage based on observational studies and should be considered if there are contraindications to cisplatin. Efforts should be directed toward looking at reasons for this, so that older

patients are not denied potentially curative chemotherapy only on the basis of age. The role of neoadjuvant chemotherapy in the elderly is uncertain, and studies have shown no difference in morbidity and mortality in elderly patients [25].

2 Management of Locally Advanced Non-small Cell Lung Cancer (LA-NSCLC)

Concurrent chemoradiotherapy (CRT) is the most common treatment modality used in unresectable, locally advanced NSCLC (LA-NSCLC). However, in this group, the elderly are again underrepresented in clinical trials. There are no large, prospective clinical trials limited to the elderly with LA-NSCLC in the USA with a single study from Japan. Consequently, much of the information in the elderly is derived from subset analyses of age-unspecified trials. Such an analysis of a phase III trial from the Hoosier Oncology Group (HOG) and US Oncology, which included 64 patients ≥ 70 years of age, concluded that age did not have a major impact on efficacy outcomes with similar median OS and PFS in both older (≥ 70 years) and younger LA-NSCLC patients treated with concurrent chemoradiation [63]. However, older adults did experience higher rates of hospitalization, grade 3–4 toxicity, and treatment discontinuation due to toxicity. Similarly, combined analysis of 2 phase 3 trials showed that older patients gain survival benefit with concurrent chemoradiation (CRT) as compared to radiation alone, but they also experience higher rates of toxicities [64]. The median OS in this analysis was 10.5 months in the RT arm and 13.7 months in the RT plus chemotherapy group, and the 5-year survival rates were 5.4 % versus 14.7 %. Grade 3 or more toxicities were seen in 89.9 % of adults in the combined treatment arm as compared to 32.4 % in the RT alone arm ($P < 0.01$). A secondary analysis of 104 patients (≥ 70 years) on the RTOG 9401 trial showed that concurrent chemotherapy with once daily RT had better survival than those getting concurrent chemotherapy with twice daily RT or those getting sequential chemotherapy followed by RT (median survival 22.4 months vs. 16.4 months vs. 10.8 months, $P = 0.069$). Again, toxicity risk was increased in the elderly as compared to younger patient [65]. A retrospective analysis of 2 Cancer and Leukemia Group B trials (CALGB 8931 and 9130) also found that patients aged 70 years or above tolerated treatment as well as younger patients and no significant negative impact of older age on response to treatment or OS was noted [66]. However, age-related increases in grade 3+ neutropenia and renal toxicity were seen in the elderly. Since age-unspecified trials only include the "fit elderly" the findings may not be representative of the elderly population who tend to have greater comorbid disease burden and poorer PS when compared to trial enrollees. Retrospective studies can provide insight into the treatment of the elderly with LA-NSCLC not treated on a clinical trial. In a retrospective analysis of data from the Cancer Registry at Mayo Clinic Arizona, 389 patients with newly diagnosed stage III NSCLC were followed from 1998 to 2006 [67]. Of these, 62 % of the patients were <75 years of age and 38 % were ≥ 75 years of age. The rate of patients getting CRT was 45 % versus 21 % ($P < 0.0001$).

The median survival in the <75 years of age group was 15 months in patients who received CRT versus 14.1 months without CRT ($P = 0.02$). In the elderly group, it was 19.9 months in the CRT group versus 7.8 months without CRT ($P = 0.0048$). Thus, even though CRT improved outcome in elderly, they were less likely to get combined modality treatment. In another single-institution retrospective study, data from 189 patients [86 elderly (aged 70 years or above) and 103 younger (aged <70 years)] with stage III A or B NSCLC treated between 1998 and 2010 were analyzed [68]. Elderly patients were less likely to receive definitive RT (71 % vs. 87 %; $P < 0.05$) and had less utilization of concurrent CRT (49 % vs. 86 %; $P < 0.05$). On multivariate analysis for all elderly patients, Eastern Cooperative Oncology Group (ECOG) PS > 2 was associated with risk of death but age (>70 years old) had no significant effect on risk of death. On univariate analysis, factors associated with improved survival were definitive RT ($P < 0.05$), ECOG PS 0–1 (<0.05), and concurrent chemotherapy if receiving definitive RT ($P < 0.05$). In a phase 3 trial by the Japan Clinical Oncology Group (JCOG), patients >70 years of age with unresectable LA-NSCLC were randomized to either CRT [60 Gy plus concurrent low-dose carboplatin (30 mg/m^2 per day, 5 days a week for 20 days)] or radiotherapy alone [69]. The primary end point was OS. Median OS was 22.4 months for the combined modality arm and 16.9 months for the radiotherapy alone arm (HR 0.68; 95 % CI 0.47–0.98; $P = 0.0179$). Grade 3–4 hematological toxicities and grade 3 infection rates were higher in the CRT arm. However, there was no difference in the grade 3–4 pneumonitis and late lung toxicity between the two groups. There were three treatment-related deaths in the combined arm and four in the radiotherapy alone arm. Thus, combined modality therapy improved survival in the elderly but with increased toxicities.

As discussed in the above studies, combined modality therapy with chemotherapy and RT improves outcomes in elderly but is also associated with increased toxicities and possible treatment discontinuation. Thus, it is essential to select patients who would be able to tolerate the treatment. A study conducted by Lee et al. assessed the prognostic effect of different comorbidities on treatment in elderly patients with stage III NSCLC [70]. In this study, 125 patients, aged 70 years or more with stage III NSCLC, were followed between 1990 and 2010, 82 received RT alone and 43 patients underwent CRT. General comorbidity status was assessed using a simplified comorbidity score (SCS) which included seven comorbidities, namely tobacco consumption, diabetes mellitus, renal insufficiency, respiratory comorbidity, cardiovascular comorbidity, neoplastic comorbidity, and alcoholism. Patients were divided into a fit elderly group (SCS $\geq$ 10) and a frail elderly group (SCS < 10). OS and PFS following CRT were significantly superior to RT in the fit elderly subgroup, while in the frail elderly subgroup, there was a significant difference in PFS, but not in OS with CRT. Also, the incidence of severe pulmonary toxicities was significantly higher in the frail than the fit elderly subgroup. This study highlights the fact that the elderly population is not homogenous, and response and tolerance to cancer treatment also depend on other factors.

As per the recommendations by the European Organization for Research and Treatment of Cancer EORTC Elderly Task Force, Lung Cancer Group, and International Society for Geriatric Oncology, combined modality treatment either sequentially or concurrently can be considered as an option in selected, fit elderly patients [71]. Data are limited in the elderly and should be considered with caution. Treatment decisions should take into account the patient's life expectancy, the presence of comorbidities, functional limitations, and patient preferences.

3 Management of Advanced Metastatic Lung Cancer in the Elderly

3.1 Single-Agent Therapy

The important issue regarding the role of chemotherapy in metastatic disease is the ability to prolong survival without compromising the QOL, and this is especially true for older adults. The ELVIS trial (The Elderly Lung Cancer Vinorelbine Italian Study) was the first multicenter randomized controlled trial in older adults and assigned 191 patients randomly to single-agent vinorelbine versus BSC alone [72]. Patients 70 years or older with stage IIIB or IV NSCLC with an ECOG PS of ≤ 2 were selected. Most (73 %) had stage IV disease. Chemotherapy was associated with an improvement in median OS of 7 weeks (28 weeks vs. 21 weeks) as compared to BSC alone ($P = 0.03$, HR = 0.65; 95 % CI, 0.45–0.93). Improvement in QOL was also noted. However, the trial recruited only 191 out of planned 350 subjects due to slow accrual; hence, it was not clear from the study if the OS would be maintained at full accrual. Moreover, the primary end point of the study was QOL and not OS. But to date, it is the only prospective study demonstrating an OS advantage with chemotherapy over BSC in the elderly with advanced NSCLC. The support for taxane-based chemotherapy in the elderly comes from the phase III West Japan Thoracic Oncology group trial (WJTOG 9904) which assessed outcomes in 180 elderly patients with single-agent vinorelbine versus single-agent docetaxel [73]. Docetaxel significantly improved PFS (5.5 months vs. 3.1 months) and ORR (22.7 % vs. 9.9 %) compared with vinorelbine ($P < 0.05$), but no significant difference was observed in OS (14.9 months vs. 9.9 months, $P = 0.138$). Significant neutropenia, mucositis, and vomiting occurred in the docetaxel arm versus vinorelbine arm.

3.2 Doublet Chemotherapy

Frasci et al. looked at efficacy of non-platinum doublet chemotherapy versus single-agent therapy in the elderly in a phase III Southern Italy Cooperative Oncology Group study [74]. This trial showed that the combination of gemcitabine and vinorelbine significantly improved survival outcomes over vinorelbine alone in elderly patients with advanced NSCLC, 6.7 months versus 4.2 months ($P < 0.01$).

The median age of patients in this trial was 75 years (range: 71–83 years), and 59 % had stage IV disease. The ORR was not significantly different between the arms, but the time to symptom deterioration was significantly longer for those who received the combination regimen versus single-agent vinorelbine (4.9 months vs. 3.0 months; $P < 0.002$). Neutropenia, thrombocytopenia, and vomiting were higher in the combination arm as compared to vinorelbine alone. The Multicenter Italian Lung Cancer in the Elderly Study (MILES) trial compared vinorelbine plus gemcitabine versus vinorelbine versus gemcitabine in 698 patients who were 70 years or older [75]. This study did not show a survival advantage for doublet chemotherapy versus single-agent chemotherapy and was associated with a higher incidence of side effects. However, this study did not include a platinum-based doublet. A phase III intergroup trial, JCOG0803/WJOG4307L, compared first-line docetaxel plus cisplatin with single-agent docetaxel in 276 patients greater than or equal to 70 years of age with advanced NSCLC [76]. The median OS in the doublet versus monotherapy arm was 13.3 months versus 17.3 months and was not statistically significant. The trial was terminated early since at the time of first interim analysis, the predictive probability that the doublet would be superior to single agent at the time of final analysis was 0.996 %. There were 3 treatment-related deaths in the doublet arm, and the proportion of patients with an improved QOL score after 3 courses of treatment was higher in the single-agent arm. A phase III multicenter randomized trial was conducted by Quiox et al. comparing doublet versus monotherapy which consisted of either gemcitabine or vinorelbine in patients ($n = 451$) 70 years of age or older with a PS of 2 or better [77]. Median OS was 10.3 months with platinum-based doublet therapy versus 6.2 months with monotherapy (HR, 0.64; 95 % CI, 0.52–0.78; $P = 0.001$). Doublet therapy caused more severe myelosuppression and myasthenia, but the treatment was tolerable. However, this trial has established the role of carboplatin-based doublet as a standard of care in the fit elderly. A recent meta-analysis of ten studies included more than 2600 elderly patients with advanced NSCLC showed that doublets containing a platinum agent and a third-generation chemotherapy agent significantly improved ORR but not OS and was associated with higher rates of myelosuppression [78].

3.3 Age-Based Subset Analyses from Phase III Trials

In a subset analysis of ECOG 5592 trial, a phase III study of cisplatin and etoposide versus cisplatin and paclitaxel, the response rate, toxicity, and survival among fit elderly were similar to those in younger patients. However, older patients had more comorbidity and suffered more leukopenia and neuropsychiatric toxicity [79]. Similarly, a subanalysis of the phase III ECOG 1594 study showed no significant differences between outcomes in patients less than 70 years of age and those in fit elderly patients (≥ 70 years and ECOG PS 0–1) [80]. This was especially relevant considering that the elderly population had significantly higher comorbidities as

compared to those who were <70 years of age, suggesting that fit elderly patients do gain benefit from carboplatin-based doublet akin to younger patients.

Pemetrexed-based regimens are increasingly used in patients with non-squamous histology. A retrospective age-based subanalysis of phase III trial comparing cisplatin plus pemetrexed versus gemcitabine plus pemetrexed showed pemetrexed plus cisplatin improved OS in patients greater than 65 years of age (HR: 0.75, 95 % CI: 0.59–0.94) but not in those greater than 70 years of age (HR: 0.85, 95 % CI: 0.59–1.22) [81]. Results from a subset analysis of elderly patients (age $\geq$70 years) of a phase III trial of single-agent pemetrexed versus pemetrexed plus carboplatin demonstrated that in elderly patients (age $\geq$70 years) with advanced NSCLC and an ECOG PS of 2, median survival times were 5.3 and 9.9 months, respectively (HR, 0.49; 95 % CI, 0.29–0.82; $P = 0.006$) compared with 5.9 and 2.8 months in younger patients (HR, 0.49; 95 % CI, 0.34–0.70; $P = 0.001$) [82]. A subset analysis by Pereira et al. of a randomized phase III study comparing pemetrexed plus carboplatin with docetaxel plus carboplatin as first-line treatment for patients with locally advanced or metastatic NSCLC showed that the median OS for patients greater than or equal to 65 years of age treated with docetaxel plus carboplatin was higher than that for patients greater than or equal to 70 years of age and those less than 70 years of age (17.9 months vs. 12.6 months vs. 14.9 months), whereas the median OS was similar (≈15 months) across age groups for patients receiving pemetrexed plus carboplatin [83]. Patients greater than 70 years of age had the highest rate or ORR as compared to other age groups.

There are studies which have looked platinum-based doublet regimens with taxanes including nab-paclitaxel. A subanalysis of a phase III trial of first-line nab-paclitaxel plus carboplatin versus paclitaxel plus carboplatin in 156 patients aged greater than or equal to 70 years with advanced NSCLC was reported by Socinski et al. [84]. Nab-paclitaxel was associated with 10-month improvement in OS as compared to paclitaxel (19.9 months vs. 10.4 months; $p = 0.009$). There was a nonsignificant improvement in ORR and PFS and significantly lower rates of neutropenia and neuropathy but a higher rate of anemia in the nab-paclitaxel group. There are no clear reasons that can explain this finding from the study. There is an ongoing phase IV ABOUND.70+ trial which may will provide more definitive answers regarding the benefit of nab-paclitaxel plus carboplatin in the elderly population.

3.4 Population-Based Studies in Elderly

A recent population-based study looking at SEER-Medicare linked data gives us a real-world perspective of survival data for 3 first-line regimens in elderly patients with advanced NSCLC [85]. More than 10,000 patients with advanced NSCLC aged greater than or equal to 65 years who had received first-line therapy with carboplatin in combination with paclitaxel, gemcitabine, or docetaxel were analyzed. Paclitaxel plus carboplatin was the most commonly used first-line regimen in this study. The median OS for the paclitaxel, gemcitabine, and docetaxel groups

were 8.0, 7.3, and 7.5 months, respectively. Patients who received the gemcitabine and docetaxel regimens had a slightly higher risk of death compared with those who received the paclitaxel regimen [HR: 1.10 (95 % CI: 1.05–1.16) and 1.09 (95 % CI: 1.03–1.06), respectively] based on multivariate COX-proportion hazards model.

To summarize, there is evidence to say that chemotherapy improves survival as compared to BSC in the elderly. While it is the standard to offer platinum-based doublet chemotherapy to the "fit elderly," the management of less than fit elderly remains controversial. Decisions regarding chemotherapy in metastatic disease should be undertaken on an individual basis after careful assessment of risk factors and using tools such as comprehensive geriatric assessment (CGA), which will be discussed, along with PS.

3.5 Geriatric Assessment-Based Study in the Elderly

In a recently reported multicenter, open-label, phase III trial, patients ≥ 70 years of age ($n = 494$) with stage IV NSCLC and PS of 0–2 were randomized to chemotherapy based on PS and age (standard arm: carboplatin-based doublet if PS $\leq$ 1 and age ≤ 75 years; docetaxel if PS = 2 or age >75 years) or treatment based on a CGA (CGA arm: carboplatin-based doublet for fit patients, docetaxel for vulnerable patients, and BSC for frail patients) [86]. The primary end point was treatment failure-free survival (TFFS) with secondary end of OS, PFS, tolerability, and QOL. More patients received carboplatin-based doublet in the CGA arm (46 % vs. 35 %) and 23.0 % received BSC in the CGA arm. In the standard and CGA arms, median TFFS times were 3.2 and 3.1 months (H.R. 0.91; 95 % CI, 0.76–1.1), and median OS times were 6.4 and 6.1 months, respectively (H.R. 0.92; 95 % CI, 0.79–1.1). Patients in the CGA arm, compared with standard arm patients, experienced significantly less all grade toxicity (85.6 % vs. 93.4 %, respectively, $P = 0.015$) and fewer treatment failures as a result of toxicity (4.8 % vs. 11.8 %, respectively; $P = 0.007$). This study suggests that CGA may limit treatment-associated toxicity and appropriately select patients for doublet therapy. Data regarding subset analysis (outcomes in doublet-treated patients) are not reported, nor the impact on healthcare utilization.

3.6 Role of Targeted Therapy in the Treatment of Metastatic Lung Cancer in the Elderly

3.6.1 Role of Bevacizumab

Sandier et al. showed that bevacizumab improves OS from 10.3 to 12.3 months (HR, 0.79; $P = 0.003$) in patients with metastatic non-squamous NSCLC in combination with paclitaxel and carboplatin [87]. However, subanalyses in the elderly population conducted by four studies have not confirmed these benefits. Higher response rates (29 % vs. 17 %, $P = 0.067$) and improved progression-free survival (5.9 months vs. 4.9 months, $p = 0.063$) were reported by Ramalingam et al. in a

post hoc subset analysis of patients >/=70 years of age [88]. There was no difference in the OS (11.3 months and 12.1 months, respectively; $P = 0.4$). Grade 3 or worse adverse effects were higher in elderly patients treated with bevacizumab as compared to those who did not receive bevacizumab (87 % vs. 61 %). Avastin in Lung cancer (AVAiL) was a phase III trial looking at chemotherapy with cisplatin and gemcitabine with or without bevacizumab [89]. A subgroup analysis of patients >65 years of age in this trial showed that bevacizumab at lower doses of 7.5 mg/kg every 3 weeks was associated with an improvement in the progression-free survival (HR = 0.71, $P = 0.023$), but this was not seen with higher doses of bevacizumab at 15 mg/kg every 3 weeks (HR = 0.84, $P = 0.25$). OS was similar for each bevacizumab arm versus placebo (7.5 mg/kg bevacizumab: HR = 0.84, $P = 0.31$; 15 mg/kg bevacizumab: HR = 0.88, $P = 0.44$), and adverse events were comparable between the two groups. The results of a subgroup analysis from the safety of Avastin in lung trial in 623 patients >65 years of age showed that the incidence of adverse events (AEs) of special interest was similar for elderly and younger patients (any grade bleeding 38.2 % vs. 38.3 %; any grade hypertension 33.1 % vs. 30.6 %; any grade proteinuria 33.4 % vs. 29.3 %) [90]. Most AEs were grade less than or equal to 2. Serious AEs were reported in 45.3 and 34.7 % of elderly and younger patients, respectively. Median OS was similar in elderly and younger patients (14.6 months in both age groups), as were TTP (8.2 months vs. 7.6 months), response rate (49.3 % vs. 52.4 %), and disease control rate (89.3 % vs. 88.4 %). In a pooled, age-based analysis from two large prospective age-unspecified studies evaluating chemotherapy with or without bevacizumab, no benefit was noted with the addition of bevacizumab in patients 75 years or above (HR, 1.05; 95 % CI, 0.70–1.57) [91]. Increased incidence of grade ≥ 3 AEs was reported within the bevacizumab arms versus chemotherapy alone in patients 65–74 years (63 % vs. 48 %; $P < 0.05$) as well as those 75 years or above (81 % vs. 56 %; $P < 0.05$) in E4599. Some other prospective randomized controlled trials evaluating the role of maintenance therapy with bevacizumab and/or pemetrexed have not specifically reported on the outcome in the elderly subset [92, 93]. A SEER-based study which provides a "real-world" view of the use of bevacizumab compared survival in older patients with the addition of bevacizumab versus carboplatin and paclitaxel alone [94]. Addition of bevacizumab to paclitaxel plus carboplatin was not associated with an improved survival among elderly patients with advanced NSCLC. These findings were similar to the subanalysis of elderly in the ECOG 4599 trial.

In conclusion, the use of bevacizumab in the elderly population is not associated with a definite survival advantage. AEs are usually worse in the elderly. Hence, it is important to exercise caution while using this drug in the elderly population with advanced NSCLC.

3.6.2 Role of Ramucirumab

Ramucirumab is a human IgG1 monoclonal antibody that targets the extracellular domain of VEGFR-2. The REVEL trial was a phase III randomized controlled trial which randomized patients with squamous and non-squamous lung cancer NSCLC who had progressed during or after a first-line platinum-based chemotherapy

regimen to docetaxel plus placebo or docetaxel plus ramucirumab [95]. Out of 1253 patients, 455 patients were $\geq$65 years of age. The median OS was 10.5 months for 628 patients allocated ramucirumab plus docetaxel and 9.1 months for 625 patients who received placebo plus docetaxel (HR: 0.86, 95 % CI 0.75–0.98; $P = 0.023$). The median progression-free survival was 4.5 months (IQR 2.3–8.3) for the ramucirumab group compared with 3.0 months (1.4–6.9) for the control group (0.76, 0.68–0.86; $P < 0.0001$). The study was not powered for a subgroup analysis based on age. However, both the OS (HR: 1.07; 95 % CI: 0.8–1.43) and progression-free survival (HR: 0.94; 95 % CI: 0.73–1.22) were not statistically significant for patients $\geq$70 years across the two arms. Thus, based on this study alone, there is insufficient evidence to recommend ramucirumab in combination with docetaxel in second-line setting for metastatic NSCLC in the elderly.

3.6.3 Role of Targeted Agents–Actionable Mutations

Nearly 10 % of North American population with NSCLC has somatic mutation in the gene encoding for epidermal growth factor receptor (EGFR). Approximately 70 % of patients whose lung cancers harbor somatic mutations in exons encoding the tyrosine kinase domain of EGFR experience significant tumor regressions when treated with the EGFR tyrosine kinase inhibitors (TKIs) [96–98]. Targeted therapy with EGFR TKIs as initial therapy for advanced NSCLC in the elderly population was originally studied in unselected populations [99, 100]. These studies failed to show a survival advantage as compared to conventional chemotherapy in the elderly. In those patients with *EGFR*-mutated tumors, no specific prospective trials have been conducted in older adults. A retrospective age-based analysis (< or $\geq$70 years of age) of the BR.21 study showed that the PFS, OS, and response rates were similar in the younger and older age groups [101]. However, the older population suffered higher incidence of rash, diarrhea, and dehydration as well as more severe (grade 3 or higher) side effects and were more likely to discontinue treatment as a result of treatment-related toxicity. An age-based subanalysis of the phase IV Tarceva Lung Cancer Survival Treatment (TRUST) in unselected patients with unresectable stage IIIB/stage IV NSCLC reported a median OS and PFS of 7.29 and 4.57 months, respectively, in patients greater than or equal to 70 years of age treated with first-line erlotinib [102]. The one-year survival was 36.6 %, and dose reductions were required in 27 % population and treatment discontinuation in 10 %. The EURTAC (European Randomised Trial of Tarceva vs. Chemotherapy) trial accrued an older cohort (median age 65 years) of patients with *EGFR*-mutated tumors [103]. This trial showed that erlotinib yielded a longer progression-free survival than chemotherapy. Median PFS was 9.7 months (95 % CI: 8.4–12.3) in the erlotinib group, compared with 5.2 months (4.5–5.8) in the standard chemotherapy group (HR: 0.37, 95 % CI 0.25–0.54; $P < 0.0001$).

Other available EGFR TKIs include gefitinib and afatinib. Both these drugs have been shown to improve progression-free survival as compared to chemotherapy in metastatic NSCLC patients with activating EGFR mutations. However, data specific to elderly are lacking [105–107]. Based on prescribing information for gefitinib, no overall safety differences were observed between patients <65 or >/

=65 years of age. There is insufficient information to assess differences in efficacy between the two groups. In the phase IV, open-label, single-arm gefitinib trial, objective response rates (ORR) for the age subgroups (patients ≤ 65 years; patients >65 and <75 years; and >/=75 years) were consistent with overall population [108].

In conclusion, EGFR TKI is the preferred agent for first-line treatment of metastatic NSCLC in the elderly with *EGFR*-mutated tumors. However, patients should be selected carefully based on side effect profile.

Cetuximab is another chimeric antibody which acts on the EGFR. The FLEX phase III trial studied whether chemotherapy plus cetuximab was superior to chemotherapy alone in patients with advanced EGFR-expressing NSCLC [104]. An age-based subanalysis showed that the HR for death in patients ≥ 65 years of age was not statistically significant in the chemotherapy plus cetuximab group but was significant for the younger sub group.

In patients with *anaplastic lymphoma kinase* (*ALK*) fusion oncogene tumors, crizotinib which is a specific inhibitor of ALK; is the preferred treatment [109, 110]. The enrollment of elderly in these trials was limited but is still considered the preferred treatment option in this subset of patients. Newer generation ALK inhibitors such as ceritinib and alectinib, now available in the USA, are active in patients who have resistant mutations to crizotinib and offer better CNS penetration [111, 112].

3.6.4 Role of Checkpoint Inhibitors

There has been much interest recently in the role of checkpoint inhibitors which have been studied mainly in melanoma and lung cancer and gradually finding their way in other cancers as well. Checkpoint molecules include cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), T-cell immunoglobulin- and mucin domain-3-containing molecule 3 (TIM3), lymphocyte- activation gene 3 (LAG3), and killer cell immunoglobulin-like receptor (KIR) [113]. These checkpoints protect against autoimmunity in a normal physiological state. When there is tumorigenesis, there can be dysfunction of these checkpoint proteins leading to tumor tolerance and escape from the immune system.

One such checkpoint molecule PD-1 is expressed by T and B lymphocytes as well as NK cells [114]. Ligands of PD-1 include PD-L1 and PD-L2, which are upregulated in solid tumors such as NSCLC [115]. PDL1 binds to PD-1 and evades immune surveillance and death. Nivolumab is a genetically engineered, fully human immunoglobulinG4 (IgG4) monoclonal antibody specific for human PD-1. Brahmer et al. showed that among patients with advanced, previously treated squamous-cell NSCLC, OS, response rate, and progression-free survival were significantly better with nivolumab than with docetaxel, regardless of PD-L1 expression level [116]. In the phase III trial, 44 % of patients were ≥ 65 years of age and 11 % were ≥ 75 years of age. Age-based subset analysis showed that OS and PFS remained statistically significant for age group between 65 and 75 years but was not significant for >/=75 years. Fatigue (16 %), decreased appetite (11 %), and asthenia (10 %) were the most common side effects in the nivolumab group. Overall, adverse effects were less in the nivolumab group as compared to the

docetaxel group (age-unspecified). Nephritis, colitis, and pneumonitis are other serious side effects of nivolumab. Pneumonitis, which occurs in about 6 % of cases, is especially of concern in the elderly who may have compromised lung function at baseline due to age, smoking, and lung cancer [117]. Paz-Ares et al. conducted a randomized open-label phase III study (checkmate 057) of nivolumab *v*ersus docetaxel in the previously treated patients with advanced or metastatic non-squamous NSCLC. It showed that in patients with advanced nonsquamous NSCLC that had progressed during or after platinum-based chemotherapy, overall survival was longer (12.2 months vs. 9.4 months hazard ratio for death, 0.73; 96 % CI, 0.59–0.89; $P = 0.002$) with nivolumab than with docetaxel [118]. However, OS was not statistically significant in the predefined subset based on age among those <65 and ≥ 75 years of age. Research is still ongoing to answer questions regarding optimal duration, retreatment, and long-term toxicities of nivolumab. There are trials looking at combination of immunotherapy with chemotherapy or molecular-targeted therapy. Elderly specific data with these checkpoint inhibitors are still lacking. It can be considered in the elderly population with good performance status pending further studies.

4 Issues Specific to the Elderly

4.1 Geriatric Syndromes

Unique clinical conditions found in older adults that do not fit into any specific disease category can have a significant impact on functionality and QOL [119]. Common geriatric syndromes include vision and hearing impairment, urinary incontinence, falls, depression, cognitive disorders (dementia and delirium), osteoporosis, and poor nutrition. Older adults with cancer are at higher risk of developing geriatric syndromes; for example, in elderly patients with lung cancer, visual or hearing impairment along with poor nutrition is very common [120]. Additionally, chemotherapy can lead to worsening of these geriatric syndromes. The presence of geriatric syndromes by itself can complicate cancer therapy and increase patient morbidity, thereby triggering the infinite loop [121].

Vision impairment: The most common causes of visual impairment in the elderly are presbyopia, cataracts, age-related macular degeneration, primary open angle glaucoma, and diabetic retinopathy. Visual impairment can increase the risk of falls, depression, and physical handicap [122]. It can also lead to poor compliance as patients may not be able to read the medication labels properly [123]. Underlying malignancy and subsequent chemotherapy can cause peripheral neuropathy, fatigue, and dizziness which can further increase the risk of falls [121].

Hearing impairment: Disabling hearing loss is seen in nearly 25 % of people aged 65–74 and in 50 % of adults who are 75 years of age or above [124]. Hearing loss is the most common sensory deficit in elderly and can affect the QOL by impairing communication [125]. It is also associated with depression, social isolation, and functional disability [126]. Assessment of hearing is particularly

important in elderly cancer patients as some of the chemotherapeutic drugs are particularly ototoxic (e.g., cisplatin) commonly used in lung cancer causes dose-dependent, high-frequency sensorineural hearing loss [127]. Hearing loss also leads to cognitive decline and has been independently associated with incident all-cause dementia [128]. Thus, these patients can have difficulty in understanding their disease which also affects their ability to give informed consent.

Urinary incontinence: It is involuntary leakage of urine and can be of four different types: stress, urge, mixed, and overflow incontinence [129]. It is an underreported and underdiagnosed problem and seen in >50 % of patients in long-term facilities [130]. Fluids and diuretics used during chemotherapy can further exacerbate underlying urinary incontinence [131]. Urinary tract infection can sometimes manifest as urinary incontinence and can also lead to further sepsis in neutropenic patients.

Falls: Impairments in multiple domains increase the risk of falls in elderly [132]. It can lead to significant morbidity and mortality and affect their independence. As per a study by Carol et al., 50 % of patients with advanced cancer experience a fall irrespective of the age, with a higher risk in patients with primary brain neoplasm or metastases. Various factors contributing to increased fall risk were cognitive deficits, corticosteroid-related proximal myopathy, presence of cancer-related pain, depression, and past history of falls [133]. As mentioned above, underlying malignancy can cause fatigue and dizziness which can increase the risk of falls [121]. Assessment of falls is particularly important in patients with cancers involving the bone as bone disease is associated with increased risk of fractures [134]. Older patients are particularly prone to suffering functional deficits from chemotherapy-induced peripheral neuropathy which is usually seen with taxane derivatives (paclitaxel and docetaxel), vinca alkaloids (vincristine), and platinum complexes (cisplatin and oxaliplatin) [135].

Depression: Major depression is seen in 1–5 % of community-dwelling older adults aged 65 years or above [136]. Risk factors for late life depression include female gender, social isolation, widowed/divorced/separated individuals, lower socioeconomic conditions, comorbidities, uncontrolled pain, insomnia, functional, and cognitive impairment [137]. In elderly cancer patients, there is a strong association between pain, depression, and cancer. Aging patients with depression are more sensitive to pain due to cancer, and pain can by itself leads to depression in cancer patients. Fatigue is another symptom which is related to pain and depression in cancer patients. Many somatic symptoms of depression such as fatigue, anorexia, weight loss, and insomnia are also manifestations of underlying cancer, thus making it difficult to make a diagnosis of depression [138].

Cognitive disorders: Elderly are more prone to getting dementia and delirium. Dementia is decline in cognition involving one or more cognitive domains [139]. Alzheimer's disease is the most common dementia followed by vascular and mixed dementia. Other types are Lewy body dementia, frontal–temporal dementia, dementia associated with Parkinson's disease, and pseudodementia [140]. Delirium is an acute confusional state characterized by an alteration of consciousness with decreased ability to focus. It is seen in 14–56 % of hospitalized older patients with

mortality ranging from 25 to 33 %. It is associated with increased morbidity/mortality, functional decline, increased healthcare costs, prolonged hospital stay, and increased nursing home placement [141]. Brain tumors have been known to impair cognitive function and impair QOL [142]. Cancer-related cognitive impairment (CRCI) also known as chemobrain or chemofog is usually due to chemotherapy-associated neurotoxicity, but it has also been seen in non-CNS cancers in the absence of chemotherapy mainly in breast cancer [143]

Osteoporosis: Osteoporosis is seen in 2 % of men and 10 % of women above 50 years of age [144]. It decreases bone mass and increases risk of fractures which can impair QOL. Fractures are associated with chronic pain and cause functional disability. Osteoporosis is a long-term complication of cancer treatment. The various mechanisms of chemotherapy-induced osteoporosis are hypogonadism, osteopathy, malnutrition, and growth hormone deficiency. Assessment of osteoporosis by measuring bone mineral density is very important and should be done before the first fracture occurs [145].

Malnutrition: The nutritional status of elderly individuals is a predictor of QOL, morbidity, and mortality. Aging is associated with changes in normal physiologic functions of the body which can impair the nutritional status. Other factors contributing to malnutrition in the elderly are functional immobility, depression, use of multiple medications, prolonged hospitalization, social isolation, and increased frailty. The prevalence of malnutrition in the elderly ranges from 5 to 10 % in independently living individuals to around 85 % in nursing home patients [146]. In a study by Dewys et al., weight loss before chemotherapy was associated with shorter median survival, lower chemotherapy response rate, and poor performance status. Further, patients with higher burden of disease had higher incidence of weight loss [147].

4.2 Comprehensive Geriatric Assessment (CGA)

CGA refers to a multidimensional, multidisciplinary approach used to identify medical, psychosocial, and functional limitations of an elderly individual. It includes assessment of their functional status (including gait), social support, polypharmacy, and advance directives as well as evaluation for geriatric syndromes including vision and hearing impairment, urinary incontinence, falls, depression, cognitive disorders, osteoporosis, and poor nutrition [148]. There are various versions of the CGA, many of which are abbreviated to facilitate application in the busy cancer clinic. Thus, in this section, it will simply be referred to as geriatric assessment (GA).

4.2.1 CGA and Elderly Patients with Cancer

The elderly are underrepresented in the clinical trials and sometimes are not treated with standard chemotherapy because of age [149]. We have sufficient data that chemotherapy provides similar benefit in older and younger patients, but older people are also at risk of chemotherapy toxicity. In a prospective multicenter study by Hurria et al., impairment in functional status was one of the factors that predicted the risk of chemotherapy in elderly patients [150]. A recent study in breast cancer patients

showed that functional status and comorbid conditions had significant effect on the prognosis and survival and advanced age was not found to be a contraindication for chemotherapy [135]. Assessment of functional status by ECOG performance status is not sufficient in the elderly because of the presence of multiple comorbidities [151, 152]. As per the NCCN and SIOG guidelines, CGA should be used in elderly cancer patients to assess their health issues and functional status [153]. Various studies have shown that incorporation of CGA can predict morbidity and mortality in elderly patients with cancer, provide information on impact of chemotherapy on their functional status and other geriatric conditions, and also improve QOL and survival in both inpatient and outpatient settings. Functional status by itself predicts survival, chemotherapy toxicity, postoperative morbidity, and mortality [154]. The ELCAPA study, in which 375 patients with cancer were prospectively followed and assessed using the CGA, showed that functional impairment and malnutrition were independently associated with changes in the initial cancer treatment plan [155]. In another study, poor nutritional status and impaired mobility were associated with early death in elderly cancer patients [156]. Various factors that affect treatment decision in elderly include their life expectancy, risk of complications from cancer or chemotherapy, and whether the patient would be able to tolerate the treatment. It is important to distinguish patients who would benefit from chemotherapy from those who are at higher risk of complications and adverse effects [157]. Three groups of aging patients can be identified with the help of CGA. Group 1 patients (fit) are functionally independent and without serious comorbidity; group 2 patients (vulnerable) may be dependent on one or more instrumental activities of daily living (IADLs) and/or may present one or two comorbid conditions; group 3 patients (frail) represent the frail patients. Fit patients should get standard treatment, and frail patients are mostly suitable for symptomatic management; treatment should be adjusted in vulnerable patients [158, 159]. More recently, the SIOG international society of geriatric oncology updated their recommendations on the use of geriatric assessment in older patients with cancer, and the various domains tested are functional status, comorbidity, cognition, mental health status, nutrition, social status and support, fatigue, assessment for polypharmacy, and presence of geriatric syndromes [160]. Since a CGA can be time-consuming and not possible to perform in general oncology practice, various screening tools have been tested to identify patients who need more extensive assessment with a CGA. A cancer-specific geriatric assessment was used in 43 patients in a prospective study and was found to be feasible in the outpatient setting [161]. A self-administered screening tool, the vulnerable elders survey-13 (VES-13), was able to stratify patients to healthy, vulnerable, and frail and thus identify those who would benefit from a more comprehensive assessment, CGA. Thus, a 2-step approach of utilizing a screening tool followed by CGA in patients who are identified to be high risk is more feasible and has also been recommended in the recommended in the National Comprehensive Cancer Network (NCCN), the European Organization for Research and Treatment of Cancer (EORTC), and the International Society of Geriatric Oncology (SIOG) guidelines [162].

4.2.2 Use of GA in Patients with Lung Cancer

The use of GA in lung cancer patients can provide additional clinical information that can have prognostic implications which are usually undetected by an oncological evaluation. In a single center prospective study by Girones et al., CGA was conducted in 83 patients diagnosed with lung cancer (76 % NSCLC) at any stage. About 48.2 % of patients were found to be dependent for activities of daily living (ADLs) and 69.9 % for IADLs; the geriatric depression scale was positive in almost 1/3rd of the patients; weight loss was identified in 55.4, 48.2 % of the patients were found to have one of the geriatric syndromes; and 72.3 % patients were diagnosed as being frail. Various GA domains associated with poor survival were ECOG PS, IADL dependency, dementia, depression, weight loss, albumin level, and frailty [163]. GA variables can also predict the effect of chemotherapy on elderly people. A secondary analysis of the MILES study showed that pretreatment QOL and functional assessment predicted the prognosis and thus can help in selection of elderly NSCLC patients for chemotherapy [164]. Elderly patients with localized lung cancer are treated with surgery, but the risk of postoperative morbidity and mortality after lung resection also increases with age. Geriatric assessment done preoperatively can predict postoperative morbidity and mortality. In a prospective study by Fujinaga et al., CGA was conducted preoperatively in elderly patients with lung cancer appropriate for resection. Preoperative cognitive dysfunction increased the risk of postoperative complications and delirium, and dependency for ADLs was found to be more predictive of postoperative complications than PS alone [165]. A geriatric assessment, especially assessment of cognition and IADLs, can change decision making in elderly lung cancer patients, and it mainly affects patients who are found to be vulnerable as compared to fit and frail patients. In one study, it changed therapeutic decisions in half of the vulnerable patients with lung cancer [166].

Thus, CGA adds substantial information to functional assessment of elderly lung cancer patients. It can help in predicting their survival, effect of chemotherapy, and risk of postoperative complications and in identifying the vulnerable patients in whom treatment needs to be changed.

4.3 Preferences and Perceptions of the Elderly

With an increase in life expectancy globally, the aging population is more susceptible to developing cancer. Cancer treatment in the elderly has changed significantly over the years, and there has been an effort toward tailoring treatments that are better tolerated in the elderly. The elderly population is heterogeneous with respect to physical, emotional, social, financial, and psychological factors. Cardiopulmonary status and renal function also play an important role in the decision to give chemotherapy. All these factors have led to wide variations in offering chemotherapy in this population among oncologists [167, 168].

Older patients may have goals or expectations that are different from those of younger patients especially in the setting of advanced cancer. In a study of patients with advanced NSCLC treated with at least one cycle of chemotherapy, patients

elected a median survival threshold of 4.5 months for mild toxicity and 9 months for severe toxicity to accept chemotherapy. When given the choice between supportive care and chemotherapy, only 22 % of patients chose chemotherapy for a survival benefit of 3 months; 68 % of patients chose chemotherapy if it substantially reduced symptoms without prolonging life. Older patients tended to demand greater benefit before accepting chemotherapy and were more likely to accept supportive care instead of chemotherapy than younger patients [169]. A prospective, observational cohort study evaluated 710 patients with advanced NSCLC treated with palliative intent chemotherapy to characterize the prevalence of the expectation that chemotherapy might be curative in these patients [170]. A majority (69 %) gave answers that were not consistent with understanding that chemotherapy was very unlikely to cure their cancer. In multivariable logistic regression, factors that were associated with a greater likelihood of this apparent misunderstanding were non-white race or ethnic group compared with white race (OR for Hispanic patients, 2.82; 95 % CI, 1.51–5.27; OR for black patients, 2.93; 95 % CI, 1.80–4.78). Educational level, functional status, and the patient's role in decision making were not associated with inaccurate beliefs about chemotherapy. There was a strong trend of worse understanding with age (OR 1.68 for patients in the age group 70–79 years; 95 % CI, 1.10–2.59). Further, the lack of understanding about chemotherapy was worse in patients who rated their communication with their physician very favorably, as compared with less favorably (O.R. 1.90; 95 % CI, 1.33–2.72).

4.4 The Role of Palliative Care in Advanced Lung Cancer

A prospective randomized controlled study evaluated the effect of early palliative care (EPC) after the diagnosis of metastatic NSCLC on patient-reported outcomes and end-of-life care among ambulatory patients with newly diagnosed disease. Of the 151 patients who underwent randomization, 27 died by 12 weeks and 107 (86 % of the remaining patients) completed assessments [171]. Patients assigned to EPC had a better QoL than the patients assigned to standard care based on the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale, in which scores range from 0 to 136, with higher scores indicating better QoL, (mean score 98.0 vs. 91.5; *P* 0.03). In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms (16 % vs. 38 %; *P* 0.01). Despite there being fewer patients in the EPC group than in the standard care group receiving aggressive end-of-life care (33 % vs. 54 %; *P* 0.05), median survival was longer among patients receiving EPC (11.6 months vs. 8.9 months; *P* 0.02). An age- and gender-based subset analysis of this study has revealed that the EPC intervention affects the patients' QoL and mood differentially based on their age and gender. Specifically, males and younger patients receiving EPC experienced better QOL and mood than those receiving oncology care alone. Conversely, females and older patients did not experience this treatment effect [172]. Such an EPC intervention is now being tested in a large multicenter study, and the findings especially as they pertain to the elderly patients with NSCC will be instructive.

The medical oncologist plays a pivotal role in assisting the older patients regarding the role and purpose of chemotherapy. Thus, goals of chemotherapy need to be conveyed clearly to patients given the high prevalence of misconceptions about the role of chemotherapy, with minority ethnic groups and older patients being at the greatest risk of such misunderstanding.

References

1. American Cancer Society, Cancer Facts & Figures 2015. Accessed 1 Feb 2016
2. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) (2014). SEER Cancer Statistics Review, 1975–2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014; Accessed 1 Feb 2016
3. Henley SJ, Richards TB, Underwood JM, Eheman CR, Plescia M, McAfee TA (2014) Centers for disease control and prevention (CDC). Lung cancer incidence trends among men and women—United States, 2005–2009. MMWR Morb Mortal Wkly Rep 63(1):1–5
4. Federal Interagency Forum on Aging-Related Statistics: Older Americans 2010: Key Indicators of WellBeing. http://www.agingstats.gov/agingstatsdotnet/ Main_Site/Data/2010_Documents/Docs/OA_2010.pdf
5. Sterlacci W, Stockinger R, Schmid T et al (2012) The elderly patient with surgically resected non-small cell lung cancer—a distinct situation. Exp Gerontol 47:237–242
6. Rivera C, Falcoz PE, Bernard A, Thomas PA, Dahan M (2011) Surgical management and outcomes of elderly patients with early stage non-small cell lung cancer. Chest 140:874–880
7. Chambersa A, Routledge T, Pilling J, Scarci M (2010) In elderly patients with lung cancer is resection justified in terms of morbidity, mortality and quality of life? Interact Cardiovasc Thorac Surg 10:1015–1021
8. Rivera C, Falcoz PE, Bernard A, Thomas PA, Dahan M (2011) Surgical management and outcomes of elderly patients with early stage non-small cell lung cancer. Chest 140:874–880
9. Port JL, KentM, Krost RJ, Lee PC, Levin MA, Flieder D et al (2004) Surgical resection for lung cancer in the octogenarian. Chest 126
10. Olivia F, Marcello CA, Paolo D, Marco L, Franca M, Federico D et al (2011) Surgical treatment of non-small cell lung cancer in octogenarians. Interact CardioVasc Thorac Surg 12:749–753
11. Nugent WC, Edney MT, Hammerness PG, Dain BJ, Maurer LH, Rigas JR (1997) Non-small cell lung cancer at the extremes of age: impact on diagnosis and treatment. Ann Thorac Surg 63:193–197
12. Bernet F, Brodbeck R, Guenin M et al (2000) Age does not influence early and late tumor-related outcome for bronchogenic carcinoma. Ann Thorac Surg 69:913–918
13. Sherman S, Guidot CE (1987) The feasibility of thoracotomy for lung cancer in the elderly. JAMA 258:927–930
14. Thomas P, Piraux M, Jacques LF, Gregoire J, Bedard P, Deslauriers J (1998) Clinical patterns and trends of outcome of elderly patients with bronchogenic carcinoma. Eur J Cardiothorac Surg 13:266–274
15. Mizushima Y, Hirofumi N, Sugiyama S et al (1997) Survival and prognosis after pneumonectomy for lung cancer in the elderly. Ann Thorac Surg 64:193–198
16. Ciriaco P, Zannini P, Carretta A et al (1998) Surgical treatment of non-small cell lung cancer in patients 70 years of age or older. Int Surg 83:4–7
17. Pagni S, Federicon JA, Ponn RB (1997) Pulmonary resection for lung cancer in octogenarians. Ann Thorac Surg 63:785–789

18. Yan T, Black D et al (2009) Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. J Clin Oncol 27:2553–2562
19. Jaklitsch MT, DeCamp MM, Liptay MJ et al (1996) Video-assisted thoracic surgery in the elderly: a review of 307 cases. Chest 110:751–758
20. Koizumi K, Haraguchi S et al (2003) Lobectomy by video-assisted thoracic surgery for lung cancer patients aged 80 years or more. Ann Thorac Cardiovasc Surg 9(1):14–21
21. McKenna RJ Jr, Houck W, Fuller CB (2006) Video-assisted thoracic surgery lobectomy: experience with 1100 cases. Ann Thorac Surg 81:421–425; discussion 425–426
22. Mun M, Kohno T (2008) Video-assisted thoracic surgery for clinical stage I lung cancer in octogenarians. Ann Thorac Surg 85:406–411
23. Berry MF, Hanna J et al (2009) Risk factors for morbidity after lobectomy for lung cancer in elderly patients. Ann Thorac Surg 88:1093–1099
24. Okami J, Ito Y, Higashiyama M et al (2010) Sublobar resection provides an equivalent survival after lobectomy in elderly patients with early lung cancer. Ann Thorac Surg 90:1651–6
25. Pagni S et al (1998) Pulmonary resection for malignancy in the elderly: is age still a risk factor? Eur J Cardiothorac Surg 14(1):40–4; discussion 44–45
26. Agostini JV, Inouye SK (2003) Delirium. In: Hazzard WR, Blass JP, Halter JB, Ouslander JG, Tinetti ME (eds) Principles of geriatric medicine and gerontology, 5th edn. McGraw-Hill, New York, pp 1503–1515
27. Dexter E, Jahangir N et al (2004) Resection for lung cancer in the elderly patient. Thorac Surg Clin 14:163–171
28. Schuchert MJ, Pettiford BL, Luketich JD et al (2008) Parenchymal-sparing resections: why, when, and how. Thorac Surg Clin 18:93–105
29. Allen MS, Darling GE, Pechet TT et al (2006) Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg 81:1013–1019
30. Ginsberg RJ, Rubinstein LV (1995) Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer: Lung Cancer Study Group. Ann Thorac Surg 60: 615–622
31. Doninguez-Ventura A, Cassini SD et al (2007) Lung cancer in octogenerians: factors affecting long term survival after resection. Eur J cardiothorac surg 32:370–374
32. Brunelli A, Socci L, Refai M et al (2007) Quality of life before and after major lung resection for lung cancer: a prospective follow-up analysis. Ann Thorac Surg 84:410–416
33. Salati M, Brunelli A, Xiumè F et al (2009) Quality of life in the elderly after major lung resection for lung cancer. Interact CardioVasc Thorac Surg 8:79–83
34. Montazeri A, Milroy R, Hole D et al (2003) How quality of life data contribute to our understanding of cancer patients' experiences? A study of patients with lung cancer. Qual Life Res 12:157–166
35. Yamamoto K, Padilla Alarcon J, Calvo Medina V et al (2003) Surgical results of stage I non-small cell lung cancer:comparison between elderly and younger patients. Eur J Cardiothorac Surg 23:21–25
36. Naunheim KS, Kesler KA, D'Orazio SA, Fiore AC, Judd DR (1994) Lung cancer surgery in the octogenarian. Eur J Cardiothorac Surg 8(9):453–456
37. Osaki T, Shirakusa T et al (1994) Surgical treatment of lung cancer in the octogenarian. Ann Thorac Surg 57(1):188–192
38. Morandi U, Stefani A et al (1997) Results of surgical resection in patients over the age of 70 years with non small cell lung cancer. Eur J Cardiothorac Surg 11:432–439
39. Mikami I, Koizumi K, Tanaka S (2001) Changes in right ventricular performance in elderly patients who underwent lobectomy using video-assisted thoracic surgery for primary lung cancer. Jpn J Thorac Cardiovasc Surg 49(3):153–159

40. Koizumi K, Haraguchi S, Hirata T, Hirai K et al (2003) Video-assisted lobectomy for a lung cancer patient with chronic obstructive pulmonary disease. Jpn J Thorac Cardiovasc Surg 51 (11):569–576
41. Ishida T, Yokoyama H, Kaneko S, Sugio K, Sugimachi K (1990) Long-term results of operation for non-small cell lung cancer in the elderly. Ann Thorac Surg 50(6):919–922
42. Shirvani S, Jiang J, Chang J et al (2012) Comparative effectiveness of five treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys 84(5):1060–1070
43. Palma D, Visser O, Lagerwaard FJ et al (2010) Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I nonsmall-cell lung cancer: a population-based time-trend analysis. J Clin Oncol 28:5153–5159
44. Haasbeek C, Palma D, Visser O et al (2012) Early-stage lung cancer in elderly patients: a population-based study of changes in treatment patterns and survival in the Netherlands. doi:10.1093/annonc/mds081[e-pubaheadofprint]. Ann Oncol
45. Louie AV, Rodrigues G, Hannouf M et al (2011) Withholding stereotactic radiation therapy in elderly patients with stage I non-small cell lung cancer and coexisting COPD is not justified: outcomes of a Markov model analysis. Radiother Oncol 99:161–165
46. Timmerman R, Paulus R, Galvin J et al (2010) Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 303(11):1070–1076
47. Baumann P, Nyman J, Hoyer M et al (2009) Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 10;27(20):3290–3296. doi:10.1200/JCO.2008.21.5681. Epub 4 May 2009
48. Parashar B, Patel P, Singh P et al (2011) Management of single malignant lung nodules in elderly patients (70 years or older) who are not candidates for lobectomy. Am J Clin Oncol 35(5):480–485
49. Hanagiri T, Muranaka H, Hashimoto M et al (1999) Results of surgical treatment of lung cancer in octogenarians. Lung Cancer 23:129–133
50. Arriagada R, Bergman B, Dunant A et al (2004) Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 350:351–360
51. Winton T, Livingston R, Johnson D et al (2005) Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 352:2589–2597
52. Douillard JY, Rosell R, De Lena M et al (2006) Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA nonsmall-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomized controlled trial. Lancet Oncol 7:719–727
53. Pignon JP, Tribodet H, Scagliotti GV et al (2008) Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 26:3552–3559
54. NSCLC Meta-Analyses Collaborative Group, Arriagada R, Auperin A et al (2010) Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two metaanalyses of individual patient data. Lancet 375:1267–1277
55. Winget M, Stanger J, Gao Z et al (2009) Predictors of surgery and consult with an oncologist for adjuvant chemotherapy in early stage NSCLC patients in Alberta, Canada. J Thorac Oncol 4:629–634
56. Kassam F, Shepherd FA, Johnston M et al (2007) Referral patterns for adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. J Thorac Oncol 2:39–43
57. Pepe C, Hasan B, Winton TL et al (2007) Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. J Clin Oncol 25:1553–1561 (This important secondary analysis was one of the first to investigate the question of whether adjuvant chemotherapy should be prescribed to older patients)

58. Fruh M, Rolland E, Pignon J-P et al (2008) Pooled analysis of the effect of age on adjuvant cisplatin based chemotherapy for completely resected non-small cell lung cancer. J Clin Oncol 26:3573–3581
59. Scagliotti GV, Fossati R, Torri V et al (2003) Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small cell lung cancer. J Natl Cancer Inst 95:1453–1461
60. Cuffe S, Booth CM, Peng Y et al (2012) Adjuvant chemotherapy for non-small-cell lung cancer in the elderly: a population-based study in Ontario, Canada. J Clin Oncol 30 (15):1813–1821
61. Ganti AK, Williams CD, Gajra A, Kelley MJ (2015) Effect of age on the efficacy of adjuvant chemotherapy for resected non-small cell lung cancer. Cancer 121(15):2578–2585
62. Strauss GM, Herndon JE 2nd, Maddaus MA et al (2008) Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 26(31):5043–5051
63. Jalal SI, Riggs HD, Melnyk A et al (2012) Updated survival and outcomes for older adults with inoperable stage III non-small-cell lung cancer treated with cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel: analysis of a phase III trial from the Hoosier Oncology Group (HOG) and US Oncology. Ann Oncol 23:1730–1738
64. Schild Steven E et al (2007) The value of combined-modality therapy in elderly patients with stage III nonsmall cell lung cancer. Cancer 110(2):363–8
65. Langer C, Hsu C, Curran W et al (2002) Elderly patients (pts) with locally advanced nonsmall cell lung cancer (LA-NSCLC) benefit from combined modality therapy: secondary analysis of radiation therapy oncology group (RTOG) 94–10. Proc Am Soc Clin Oncol 21: 299a (Abstr 1193)
66. Rocha Lima C, Herndon J, Kosty M et al (2002) Therapy choices among older patients with lung carcinoma: an evaluation of two trials of the Cancer and Leukemia Group B. Cancer 94:181–187
67. Paripatia HR, Karlina NJ, Schild SE, Vorab SA, Dueckc AC, Rossa HJ (2012) Multimodality therapy improves survival in elderly patients with locally advanced non-small cell lung cancer—a retrospective analysis. J Geriatric Oncol 3(2):104–110
68. Aridgides PD, Janik A, Bogart JA et al (2013) Radiotherapy for stage III non-small-cell lung carcinoma in the elderly (age $\geq$ 70 years). Clin Lung Cancer 14:674–679
69. Atagi S, Kawahara M, Yokoyama A et al (2012) Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301). Lancet Oncol 13:671–678
70. Lee JH, Wu HG, Kim HJ, Kim DW, Lee SH, Kim TM, Kim YW, Heo DS (2012) Influence of comorbidities on the efficacy of radiotherapy with or without chemotherapy in elderly stage III non-small cell lung cancer patients. Cancer Res Treat 44:242–250
71. Pallis AG, Gridelli C, Wedding U, Faivre-Finn C, Veronesi G, Jaklitsch M, Luciani A, O'Brien M (2014) Management of elderly patients with NSCLC; updated expert's opinion paper: EORTC elderly task force, lung cancer group and international society for geriatric oncology. Ann Oncol 25(7):1270–83. doi:10.1093/annonc/mdu022. Epub 16 Mar 2014
72. The Elderly Lung Cancer Vinorelbine Italian Study Group (1999) Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 91:66–72
73. Kudoh S, Takeda K, Nakagawa K et al (2006) Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 24(22):3657–3663
74. Frasci G, Lorusso V, Panza N et al (2000) Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 18 (13):2529–2536

75. Gridelli C, Perrone F, Gallo C et al (2003) Chemotherapy for elderly patients with advanced nonsmall-cell lung cancer: the multicenter italian lung cancer in the elderly study (MILES) phase III randomized trial. J Natl Cancer Inst 95:362–372
76. Abe T, Yokoyama A, Takeda K, Ohe Y (2011) Randomized phase III trial comparing weekly docetaxel (D)-cisplatin (P) combination with triweekly D alone in elderly patients (pts) with advanced non-small cell lung cancer (NSCLC): an intergroup trial of JCOG0803/WJOG4307L. J Clin Oncol 29(Suppl. 15), [Abstract 7509]
77. Quoix E, Zalcman G, Oster JP et al (2011) Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 378:1079–1088
78. Des Guetz G, Uzzan B, Nicolas P, Valeyre D, Sebbane G, Morere JF (2012) Comparison of the efficacy and safety of single-agent and doublet chemotherapy in advanced non-small cell lung cancer in the elderly: a meta-analysis. Crit Rev Oncol Hematol 84(3):340–349
79. Langer CJ, Manola J, Bernardo P et al (2002) Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592: a randomized trial. J Natl Cancer Inst 94(3):173–181
80. Langer CJ, Vangel M, Schiller J et al (2003) Age-specific subanalysis of ECOG 1594: fit elderly patients (70–80 years) with NSCLC do as well as younger pts (<70). Proc Am Soc Clin Oncol 22:639 [Abstract 2571]
81. Gridelli C, Brodowicz T, Langer CJ et al (2012) Pemetrexed therapy in elderly patients with good performance status: analysis of two Phase III trials of patients with nonsquamous non-small-cell lung cancer. Clin Lung Cancer 13(5):340–346
82. Zukin M, Barrios CH, Pereira JR et al (2013) Randomized Phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. J Clin Oncol 31 (23):2849–2853
83. Pereira JR, Cheng R, Orlando M, Kim JH, Barraclough H (2013) Elderly subset analysis of randomized Phase III study comparing pemetrexed plus carboplatin with docetaxel plus carboplatin as first-line treatment for patients with locally advanced or metastatic non-small cell lung cancer. Drugs R D 13(4):289–296
84. Socinski MA, Langer CJ, Okamoto I et al (2013) Safety and efficacy of weekly *nab*®-paclitaxel in combination with carboplatin as first-line therapy in elderly patients with advanced non-small-cell lung cancer. Ann Oncol 24(2):314–321
85. Zhu J, Sharma DB, Chen AB, Johnson BE, Weeks JC, Schrag D (2013) Comparative effectiveness of three platinum-doublet chemotherapy regimens in elderly patients with advanced non-small cell lung cancer. Cancer 119(11):2048–2060
86. Corre R, Greillier L, Le Caër H et al (2016) Use of a comprehensive geriatric assessment for the management of elderly patients with advanced non-small-cell lung cancer: the Phase III randomized ESOGIA-GFPC-GECP 08-02 Study. J Clin Oncol. pii: JCO635839. [Epub ahead of print]
87. Sandler A, Gray R, Perry MC et al (2006) Paclitaxel carboplatin alone or with bevacizumab in non-small cell lung cancer. N Engl J Med 355:2542–2550
88. Ramalingam SS, Dahlberg SE, Langer CJ et al (2008) Outcomes for elderly, advanced-stage non small cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. J Clin Oncol 26:60–65
89. Leighl NB, Zatloukal P, Mezger J et al (2010) Efficacy and safety of bevacizumab-based therapy in elderly patients with advanced or recurrent nonsquamous non small cell lung cancer in the phase III BO17704 study (AVAiL). J Thorac Oncol 5:1970–1976
90. Laskin J, Crinò L, Felip E et al (2012) Safety and efficacy of first-line bevacizumab plus chemotherapy in elderly patients with advanced or recurrent nonsquamous non small cell lung cancer: safety of avastin in lung trial (MO19390). J Thorac Oncol 7:203–211

91. Langer CJ, Socinski MA, Patel JD, Sandler AB, Schiller JH, Leon L, Hazard SJ, Ramalingam SS (2015) Isolating the role of bevacizumab in elderly patients with previously untreated nonsquamous non-small cell lung cancer: secondary analyses of the ECOG 4599 and PointBreak trials. Am J Clin Oncol
92. Barlesi F, Scherpereel A, Rittmeyer A et al (2013) Randomized Phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). J Clin Oncol 31(24):3004–3011
93. Patel JD, Socinski MA, Garon EB et al (2013) PointBreak: a randomized Phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIb or IV nonsquamous non-small-cell lung cancer. J Clin Oncol 31(34):4349–4357
94. Zhu J, Sharma DB, Gray SW, Chen AB, Weeks JC, Schrag D (2012) Carboplatin and paclitaxel with vs. without bevacizumab in older patients with advanced non-small cell lung cancer. JAMA 307(15):1593–1601
95. Garon EB, Ciuleanu TE, Arrieta O et al (2014) Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 384(9944):665–673
96. Costa DB, Kobayashi S, Tenen DG et al (2007) Pooled analysis of the prospective trials of gefitinib monotherapy for EGFR-mutant non-small cell lung cancers. Lung Cancer 58: 95–103
97. Miller VA, Riely GJ, Zakowski MF et al (2008) Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. J Clin Oncol 26:1472–1478 (Abstract/FREE Full Text)
98. Jackman DM, Miller VA, Cioffredi LA et al (2009) Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: results of an online tumor registry of clinical trials. Clin Cancer Res 15:5267–5273
99. Crinò L, Cappuzzo F, Zatloukal P et al (2008) Gefitinib versus vinorelbine in chemotherapy-naive elderly patients with advanced non-small-cell lung cancer (INVITE): a randomized, phase II study. J Clin Oncol 26(26):4253
100. Jackman DM, Yeap BY, Lindeman NI et al (2007) Phase II clinical trial of chemotherapy-naive patients > or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. J Clin Oncol 25(7):760
101. Wheatley-Price P, Ding K, Seymour L et al (2008) Erlotinib for advanced non-small-cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 26:2350–2357
102. Merimsky O, Cheng CK, Au JS, von Pawel J, Reck M (2012) Efficacy and safety of first-line erlotinib in elderly patients with advanced non-small cell lung cancer. Oncol Rep 28(2): 721–727
103. Rosell R, Carcereny E, Gervais R et al (2012) Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomized phase 3 trial. Lancet Oncol 13:239–246
104. Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R (2009) Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised Phase III trial. Lancet 373(9674):1525–1531
105. Maemondo M, Inoue A, Kobayashi K et al (2010) Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362:2380–2388

106. Sequist LV, Yang JCH, Yamamoto N et al (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. JCO 31 (27):3327–3334
107. Wu YL, Zhou C, Hu CP et al (2014) Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 15(2):213–22. doi:10.1016/S1470-2045(13)70604-1. Epub 2014 Jan 15
108. Douillard J-Y, Ostoros G, Cobo M et al (2014) First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. Br J Cancer 110:55–62
109. Shaw AT, Kim DW, Nakagawa K et al (2013) Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 368(25):2385
110. Solomon BJ, Mok T, Kim DW et al (2014) First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 371(23):2167–2177
111. Shaw AT, Kim DW, Mehra R et al (2014) Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 370:1189–1197
112. Santarpia M, Altavilla G, Rosell R (2015) Alectinib: a selective, next-generation ALK inhibitor for treatment of ALK-rearranged non-small-cell lung cancer. Expert Rev Respir Med 9(3):255–68. doi:10.1586/17476348.2015.1009040
113. Pardoll DM (2012) The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer Nat Rev Cancer 12(4):252–264
114. Keir ME, Butte MJ, Freeman GJ et al (2008) PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 26(1):677–704
115. Dong H, Strome SE, Salomao DR et al (2002) Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 8(9):1039
116. Brahmer J, Reckamp KL, Baas P et al (2015) Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373(2):123–135
117. Brahmer JR (2013) Harnessing the immune system for the treatment of non-small-cell lung cancer. J Clin Oncol 31(8):1021–1028
118. Borghaei H, Paz-Ares L, Horn L et al (2015) Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373(17):1627–1639
119. Inouye SK, Studenski S, Tinetti ME et al (2007) Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc 55(5):780–791
120. Mohile SG, Fan L, Reeve E et al (2011) Association of cancer with geriatric syndromes in older medicare beneficiaries. J Clin Oncol 29(11):1458–1464
121. http://www.cancernetwork.com/review-article/geriatric-syndromes-and-assessment-older-cancer-patients/page/0/1. Accessed 2 Feb 2016
122. Loh KY, Ogle J (2004) Age related visual impairment in the elderly. Med J Malaysia 59 (4):562–8, quiz 569
123. Kelly M (1996) Medications and the visually impaired elderly. Geriatric Nursing 17(2):60–62
124. http://www.nidcd.nih.gov/health/statistics/pages/quick.aspx
125. Ciorba A, Bianchini C, Pelucchi S et al (2012) The impact of hearing loss on the quality of life of elderly adults. CIA, Clin Interv Aging 159
126. Yueh B, Shekelle P (2007) Quality indicators for the care of hearing loss in vulnerable elders. J Am Geriatr Soc 55
127. Rademaker-Lakhai JM, Crul M, Zuur L et al (2006) Relationship between cisplatin administration and the development of ototoxicity. J Clin Oncol 24(6):918–924
128. Lin FR, Metter EJ, O'Brien RJ et al (2011). Hearing Loss and Incident Dementia. Arch Neurol Arch Neurol 68(2)
129. Holroyd-Leduc JM, Tannenbaum C, Thorpe KE et al (2008) What type of urinary incontinence does this woman have? JAMA 299(12):1446–1456. doi:10.1001/jama.299.12.1446

130. Erdem N, Chu FM (2006) Management of overactive bladder and urge urinary incontinence in the elderly patient. Am J Med 119(3):29–36
131. Diokno AC, Brown MB, Herzog AR (1991) Relationship between use of diuretics and continence status in the elderly. Urology 38(1):39–42
132. Tinetti ME (1995) Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. J Am Med Assoc 273(17):1348–1353
133. Stone CA, Lawlor PG, Savva GM et al (2012) Prospective study of falls and risk factors for falls in adults with advanced cancer. J Clin Oncol 30(17):2128–2133
134. Vestergaard P, Rejnmark L, Mosekilde L (2009) Fracture risk in patients with different types of cancer. Acta Oncol 48(1):105–115
135. Hile ES, Fitzgerald GK, Studenski SA (2010) Persistent mobility disability after neurotoxic chemotherapy. Phys Ther 90(11):1649–1657
136. Fiske A, Wetherell JL, Gatz M (2009) Depression in older adults. Annu Rev Clin Psychol 5 (1):363–389
137. Cole MG, Dendukuri N (2003) Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. Am J Psychiatry AJP 160(6):1147–1156
138. Spoletini I, Gianni W, Repetto L et al (2008) Depression and cancer: an unexplored and unresolved emergent issue in elderly patients. Crit Rev Oncol/Hematol 65(2):143–155
139. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5). American Psychiatric Association, Arlington, VA
140. Small GW (1998) Differential diagnosis and early detection of dementia. Am J Geriatr Psychiatry 6(2)
141. Leslie DL, Inouye SK (2011) The importance of delirium: economic and societal costs. J Am Geriatr Soc 59
142. Shen C, Bao WM, Yang BJ et al (2012) Cognitive deficits in patients with brain tumor. Chin Med J (Engl) 125(14):2610–2617
143. Wefel JS, Kesler SR, Noll KR et al (2014) Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. CA Cancer J Clin 65(2):123–138
144. http://www.cdc.gov/nchs/fastats/osteoporosis.htm
145. Pfeilschifter J, Diel IJ (2000) Osteoporosis due to cancer treatment: pathogenesis and management. J Clin Oncol 18(7):1570–1593
146. Brownie S (2006) Why are elderly individuals at risk of nutritional deficiency? Int J Nurs Pract 12(2):110–118
147. Dewys WD, Begg C, Lavin PT et al (1980) Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern cooperative oncology group. Am J Med 69(4): 491–497
148. Devons CA (2002) Comprehensive geriatric assessment: making the most of the aging years. Curr Opin Clin Nutr Metab Care 5(1):19–24
149. Talarico L (2004) Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-Year experience by the us food and drug administration. J Clin Oncol 22(22):4626–4631
150. Hurria A, Togawa K, Mohile SG et al (2011) Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 29(25):3457–3465
151. Sonmez OU, Arslan UY, Esbah O et al (2014) Effects of comorbidities and functional living activities on survival in geriatric breast cancer patients. Wo Współczesna Onkologia 3: 204–210
152. Repetto L (2002) Comprehensive geriatric assessment adds information to eastern cooperative oncology group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol 20(2):494–502
153. Extermann M, Aapro M, Bernabei R et al (2005) Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol 55(3):241–252

154. Extermann M, Hurria A (2007) Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 25(14):1824–1831
155. Caillet P, Canoui-Poitrine F, Vouriot J et al (2011) Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. J Clin Oncol 29 (27):3636–3642
156. Soubeyran P, Fonck M, Blanc-Bisson C et al (2012) Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. J Clin Oncol 30(15):1829–1834
157. Balducci L (2000) Management of cancer in the older person: a practical approach. Oncologist 5(3):224–237
158. Balducci L (2000) Management of cancer in the older person: a practical approach. Oncologist 5(3):224–237
159. Balducci L, Stanta G (2000) Cancer in the frail patient. Hematol Oncol Clin North Am 14 (1):235–250
160. Wildiers H, Heeren P, Puts M et al (2014) International society of geriatric oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 32(24): 2595–2603
161. Hurria A, Supriya G, Marjorie Z et al (2005) Developing a cancer-specific geriatric assessment. Cancer 104(9):1998–2005
162. Wildiers H, Cindy K (2012) Comprehensive geriatric assessment (cga) in older oncological patients: why and how? J Geriatr Oncol 3(2):174–176
163. Gironés R, Dolores T, Inma M et al (2012) Comprehensive geriatric assessment (CGA) of elderly lung cancer patients: a single-center experience. J Geriatr Oncol 3(2):98–103
164. Maione P (2005) Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter italian lung cancer in the elderly study. J Clin Oncol 23(28):6865–6872
165. Fukuse T, Naoki S, Kyoko H, Fujinaga T (2005) Importance of a comprehensive geriatric assessment in prediction of complications following thoracic surgery in elderly patients. Chest 127(3):886–891
166. Aliamus V, Adam C, Druet-Cabanac M et al (2011) Geriatric assessment contribution to treatment decision-making in thoracic oncology. Rev Lung Dis 28(9):1124–1130
167. Puts MTE, Girre V, Monette J, Wolfson C, Monette M, Batist G et al (2010) Clinical experience of cancer specialists and geriatricians involved in cancer care of older patients: a qualitative study. Crit Rev Oncol Hematol 74:87–96
168. Wan-Chow-Wah D, Monette J, Monette M, Sourial N, Retornaz F, Batist G et al (2011) Difficulties in decision making regarding chemotherapy for older cancer patients: a census of cancer physicians. Crit Rev Oncol Hematol 78:45–58
169. Silvestri G, Pritchard R, Welch HG (1998) Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. BMJ 317:771-775
170. Weeks JC, Catalano PJ, Cronin A et al (2012) Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med 367(17):1616–1625
171. Temel J, Greer J et al (2010) Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363:733–742
172. Nipp RD, Greer JA, El-Jawahri A et al (2016) Age and gender moderate the impact of early palliative care in metastatic non-small cell lung cancer. Oncologist 21(1):119–126

Multidisciplinary Care

Megan E. Daly and Jonathan W. Riess

Abstract

Optimal multidisciplinary care of the lung cancer patient at all stages should encompass integration of the key relevant medical specialties, including not only medical, surgical, and radiation oncology, but also pulmonology, interventional and diagnostic radiology, pathology, palliative care, and supportive services such as physical therapy, case management, smoking cessation, and nutrition. Multidisciplinary management starts at staging and tissue diagnosis with pathologic and molecular phenotyping, extends through selection of a treatment modality or modalities, management of treatment and cancer-related symptoms, and to survivorship and end-of-life care. Well-integrated multidisciplinary care may reduce treatment delays, improve cancer-specific outcomes, and enhance quality of life. We address key topics and areas of ongoing investigation in multidisciplinary decision making at each stage of the lung cancer treatment course for early-stage, locally advanced, and metastatic lung cancer patients.

Keywords

Multidisciplinary care · Non-small cell lung cancer · Multimodality treatment · Integrated care

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Contents

1 Tumor Boards: Conventional and Molecular

A tumor conference or multidisciplinary tumor board (MTB) allows review of imaging, pathology, and clinical information to provide consensus staging and treatment recommendations [1]. Both the Commission on Cancer and the American College of Surgeons require implementation of MTB as a standard for accreditation [2]. Typical participants in a thoracic tumor board or conference include medical, surgical, and radiation oncologists, radiologists, pathologists, and pulmonologists, but additional participation from social workers, nutritionists, oncology nurses, physicians in training, clinical research coordinators, pain management, and palliative care specialists may also be of benefit [3]. Depending on the setting, MTB may be general (covering all tumor types), or site specific.

A systematic review published in 2007 found that MTB enhanced cancer diagnosis, treatment planning, outcomes, and patient satisfaction [4]. A recent prospective single institution cohort study found that MTB review impacted the treatment plan for 40 % of lung cancer patients [5]. A second institutional cohort study similarly found that multidisciplinary team meetings impacted consensus treatment plans for 58 % of patients [6]. For smaller community centers, the availability of teleconferencing or "virtual" tumor boards extends access to multidisciplinary care to patients in healthcare systems without a formal MTB process [7, 8]. A single tertiary care center analysis of 1222 patients with non-small cell lung cancer treated before ($n = 535$) or after ($n = 687$) the implementation of a MTB identified a marked increase in the percentage of patients undergoing a complete staging evaluation (79 vs. 93 %, $p < 0.0001$), multidisciplinary evaluation prior to therapy (62 vs. 96 %, $p < 0.0001$), adherence to guidelines from the National Comprehensive Cancer Network (NCCN) (81 vs. 97 %; $p < 0.0001$), with

a reduction in the interval from diagnosis to treatment of 27–17 days after tumor board implementation ($p < 0.0001$) [9].

Despite these documented benefits of MTB implementation in single institution studies, few studies have specifically correlated tumor board implementation and cancer-specific survival. A large retrospective multi-institution cohort study using the Scottish cancer registry identified improvement in overall survival among women with symptomatic breast cancer following implementation of a multidisciplinary team care model for breast cancer in one Scottish health board area, compared to health board areas not adopting the multidisciplinary care team model [10]. However, such studies specific to lung cancer are lacking. A large analysis evaluating the correlation between MTB and measures of cancer care quality and use for lung, prostate, breast, lymphoma, multiple myeloma, and colon cancer patients in the VA system using the Department of Veterans Affairs Central Cancer Registry, including receipt of stage-specific recommended care, failed to identify a clear correlation between tumor board implementation and measures of cancer care use, quality, or survival [11]. The one measure of quality care that remained statistically significant after adjusting for repeated measures, however, was receipt of concurrent chemoradiation for limited stage small cell lung cancer, with an association between uses of concurrent chemoradiation for unresectable stage III non-small cell lung cancer that did not remain statistically significant after correction for multiple comparisons. No survival correlation for either non-small cell or small cell lung cancer was identified with tumor board availability. The authors of both the study and multiple accompanying editorials [12–14] address many of the potential reasons for the failure to identify a clear association between quality of care or survival and tumor board access, noting that specifics of tumor board structure such as physician participation, format, and frequency were not documented, nor was the percentage of each VA's cancer patients discussed at the MTB. It was also not determined whether the included tumor boards discussed cases prospectively or retrospectively. The results, however, suggest that merely instituting a MTB is insufficient to broadly impact cancer care quality and outcomes, and that more nuanced specifics of multidisciplinary management that may not consistently have been included in the studied VA tumor boards may be responsible for the benefits identified in single institution studies.

Multiple efforts to improve the quality and efficacy of MTB have been described. Lamb and colleagues outline a novel multicomponent quality improvement intervention consisting of team training with a lecture, interactive workshop, and discussion; a quality improvement checklist designed to support clinical decision making; physician resident training on the preparation and structuring of MTB cases; and written guidance to MTB members outlining clinical information required for decision making [15]. The study was structured as a pre- and post-intervention analysis, and the authors found post-intervention improvements in the MTB's ability to reach a clinical decision, quality of information presented, and quality of teamwork. The barriers to reaching a consensus clinical decision identified in the study included inadequate radiologic and pathologic information and inappropriate patient referrals. In aggregate, while single institution studies suggest

MTB may result in more complete staging and multidisciplinary evaluation, alter patient management, and reduce treatment delays, quality improvement processes are necessary to realize systematic improvements in cancer outcomes from MTB.

With the discovery of effective targeted treatments in lung cancer and other tumors coupled with the exponentially decreasing costs of next-generation sequencing, many cancer centers are instituting molecular tumor boards. The purpose of these tumor boards is to match the molecular aberrations driving the patient's tumor to appropriate therapies. In addition to standard tumor board participants (such as clinicians, pathologists and radiologists), molecular tumor boards may also include basic scientists, geneticists, and bioinformatics specialists.

In a single institution review, a substantial subset of patients presented at a molecular tumor board that had treatment directed by molecular diagnostics had a response to therapy (3/11 = 27 %) [16]. An important component of these molecular tumor boards is determining what genomic aberrations are most likely to drive the tumor versus bystander or non-functional mutations that are unlikely to impact tumor growth. A second equally important component is matching potentially actionable molecular alterations to appropriate treatment whether they are for FDA-approved indications such as crizotinib in *ALK*-rearranged NSCLC or clinical trials. Increasingly, clinical trials are matching treatment based on molecular testing results such as the Lung MAP (Master Protocol) in squamous cell lung cancer [17] or the NCI MATCH trial [18].

2 Multidisciplinary Tissue Diagnosis and Staging

Management of the lung cancer patient begins with tissue diagnosis and staging, aspects of care in which multidisciplinary input is often crucial. Tumor tissue is obtained to confirm a malignant diagnosis, establish a histologic sub-type, and with increasing frequency to allow genetic sequencing to identify activating mutations that may predict response to available biologic agents such as tyrosine kinase inhibitors. An up-front multidisciplinary discussion establishing the staging and tissue needs tailored to the individual patient's anatomy, radiographic stage, and potential treatment options may reduce redundant procedures, ensure adequate tissue and staging information, and allow expedient initiation of cancer-directed therapy. Decision points include whether tissue should be obtained from the primary tumor, a node, or a metastatic deposit; whether pathologic staging or simple tissue diagnosis is required; and whether a needle aspirate, core biopsy, or more extensive tumor tissue is needed to establish a diagnosis and perform any planned molecular diagnostics. Early multidisciplinary discussion should reduce the need for multiple procedures by avoiding an initial biopsy approach that provides insufficient tissue or inadequate staging information.

An early decision point in the work-up of localized disease is whether comprehensive pathologic mediastinal staging is warranted. Comprehensive pathologic nodal staging with systematic tissue sampling of multiple mediastinal nodal stations

is generally recommended for tumor localized to the chest, particularly when surgery is being considered. However, the need for systematic nodal staging or simple tissue confirmation will depend on the radiographic disease burden and the planned therapy. Patients with convincing, bulky, infiltrative mediastinal adenopathy rarely undergo systematic pathologic staging and will generally be managed with non-surgical therapies, whereas those with radiographically negative or equivocal nodes should be pathologically assessed whether surgery is being considered. Biopsy of radiographically equivocal lymph nodes may also have substantial impact on radiation therapy target volumes for non-surgical patients planned for definitive chemoradiation. Ultimately, input from all physicians who will be diagnosing and treating the patient will streamline the process of biopsy and pathologic staging.

Pathologic mediastinal staging can be performed via systematic staging endobronchial ultrasound (EBUS) or surgically with mediastinoscopy/mediastinotomy. Randomized trials comparing staging EBUS to surgical staging suggest that combined approach with up-front endosonography followed by surgical staging only when EBUS is pathologically negative results in superior sensitivity, lower costs, and fewer unnecessary thoracotomies [19, 20]. Selection of a technique should balance available institutional expertise, potential complications of the selected approach, needed tissue specimen type and volume in the context of planned systemic and molecular therapies, timeframe for planned treatment initiation, and anatomic limitations of the planned biopsy site.

For patients who do not require comprehensive pathologic mediastinal staging, selection of an appropriate biopsy technique and target includes an evaluation of tumor location and suitability for percutaneous or endobronchial access, as well as a comprehensive assessment of diagnostic tissue needs in light of planned therapies. The primary tumor may be accessed surgically or percutaneously under computed tomography (CT) guidance. Mediastinal and hilar nodes may be accessed surgically, via the bronchus with or without EBUS guidance, or less commonly via trans-esophageal ultrasound or percutaneously under CT guidance [21]. Fine needle aspirate (FNA) may be suitable for simple cytologic confirmation of malignancy, but is frequently insufficient for molecular testing, and may provide insufficient tissue when extensive immunohistochemistry (IHC) is planned. Core specimens are generally necessary to distinguish between certain histologic sub-types, such as small cell carcinoma and atypical carcinoid tumors, and are also frequently required for molecular testing. Surgical biopsy, performed via mediastinoscopy/mediastinotomy, video-assisted thoracoscopic surgery (VATS), or thoracotomy, obtains more tumor tissue and permits access to tumors and nodes inaccessible by percutaneous CT guidance or EBUS. Patients considering enrollment on specific clinical trials may also require more robust tissue specimens for specific pathologic testing required for eligibility [22]. Occasionally, other surgical specialists may be involved in the process of tissue confirmation from metastatic deposits, including resection of solitary or symptomatic brain metastases or surgical biopsy of other extrathoracic sites.

Ensuring adequacy of tissue samples with tumor is critical for molecular testing, particularly for *EGFR* mutations and *ALK* rearrangements where FDA-approved therapies such as erlotinib and crizotinib can substantially alter the patient's clinical course and lead to dramatic tumor regression. Current guidelines recommend results for *EGFR* and *ALK* within 2 weeks or 10 business days [23].

3 Timeliness of Care

Multidisciplinary integration is also critical for ensuring timely, coordinated care. Some, but not all, studies suggest a correlation between treatment delays and inferior survival for lung cancer patients. A recently large analysis using Medicare claims data identified selective improvements in survival among patients with localized disease, and those with metastatic disease who survive >1 year who had prompt initiation of cancer-directed therapy, but no specific correlation between treatment delays and survival for locally advanced disease, and a decrement in survival among metastatic patients who initiated treatment quickly but died within one year [24]. The authors postulate that the need for sicker, more urgently ill patients to initiate treatment more rapidly may confound results for certain subpopulations. Other studies have similarly identified an inverse correlation between clinical expediency and survival [25]. Despite only an incomplete understanding of the relationship between survival and rapid initiation of treatment, avoiding treatment delays is widely considered good practice given the typically rapid growth of lung cancer and potential for upstaging with delays. Several small retrospective studies also suggest that disease progression while awaiting initiation of chemoradiation is a substantial problem, resulting in larger tumor volumes and metastatic progression in a subset of patients [26, 27].

4 Multidisciplinary Management of Early-stage Disease

Once a diagnosis of lung cancer is confirmed, multidisciplinary management of the patients moves into the treatment phase. For early-stage non-small cell lung cancer (NSCLC), treatment may involve a thoracic surgeon, radiation, and/or medical oncologist. The standard of care for stage I NSCLC remains lobectomy or pneumonectomy with mediastinal nodal sampling, with consideration of adjuvant systemic therapy, depending on pathologic features. However, many patients are medically unable to tolerate lobectomy secondary to cardiac, pulmonary, or other comorbidities. Medically inoperable patients may be candidates for sub-lobar resection, which in randomized trials carries a higher risk of local failure [28]. Stereotactic body radiotherapy (SBRT), an ablative, non-invasive, and precise radiation technique delivered over 1-5 fractions, is an attractive alternatives for poor surgical candidates. In prospective clinical trials, SBRT consistently offers 5-year in-field control exceeding 80 %, with 5-year survival of approximately 45–50 % [29, 30]. SBRT has also been studied in the medically operable population.

Radiation Therapy Oncology Group (RTOG) 0618 enrolled 33 medically operable patients with early-stage NSCLC treatment with SBRT to 54 Gy over 3 fractions, and identified 2-year estimates of in-lobe, regional, and distant failure of 19.2, 11.7, and 15.4 %. Two-year progression-free survival was 65.4 %.

Several groups have attempted and failed to accrue medically operable or marginally patients to prospective, randomized comparisons between SBRT and either lobectomy [31, 32] or sub-lobar resection [33]. The STARS trial was an international, industry sponsored randomized phase III comparison of lobectomy to SBRT using the CyberKnife system. The study closed to accrual in 2013 after accruing only 36 patients over a 4-year period [31]. The ROSEL trial, a similar randomized comparison sponsored by the VU University Medical Center in Amsterdam, similarly closed early secondary to poor accrual. The American College of Surgeons Oncology Group (ACOSOG) Z4099/Radiation Therapy Oncology Group (RTOG) 1021 was a large intergroup collaboration randomizing high-risk operable early-stage NSCLC patients between sub-lobar resection (with or without brachytherapy) and SBRT. It too closed early after failure to accrue. The 58 patients accrued to the STARS and ROSEL trials were recently pooled and analyzed. Three-year overall survival was 95 % for SBRT and 79 % for the surgical cohort (HR 0.14; CI = 0.017–1.190], $p = 0.037$) [34]. The authors conclude that SBRT may be an option for medically operable patients, but that given the low patient accrual and short follow-up that additional, randomized trials are needed. A large single institution retrospective comparison identified identical cause-specific survival for SBRT and wedge resection [33].

For high-risk patients, early consultation with both a surgeon and a radiation oncologist prior to treatment allows an informed discussion as to the suitability of each therapy for a given patient and provides patients with all treatment options. Comprehensive review at a tumor board or other multidisciplinary setting allows a thorough review of all imaging studies, ensures a complete staging evaluation, and permits a collaborative discussion of any potential patient-specific or anatomic impediments to either surgical resection or SBRT for marginally resectable patients. As many surgically resected patients are potential candidates for adjuvant systemic therapy, early involvement of a multidisciplinary team, including a medical oncologist, also facilitates expedient adjuvant therapy and ensures evaluation for potential clinical trials. Finally, early multidisciplinary input allows integration with during and post-treatment supportive care services including pulmonary rehabilitation, smoking cessation, social work, and nutrition support.

5 Multidisciplinary Management of Locally Advanced Disease

Perhaps no treatment setting is multidisciplinary integration more crucial than that of locally advanced, non-metastatic lung cancer. The potential benefit of incorporating surgical resection into the management of stage III disease remains unclear, and patient selection appears to be crucial. The European Organization for the

Research and Treatment of Cancer (EORTC) 08941 was a randomized phase III trial enrolling stage IIIA (N2) NSCLC patients to a comparison of induction chemotherapy followed by either surgical resection or thoracic radiation for responding patients [35]. No difference in median survival (16.4 vs. 17.5 months) or 5-year overall survival (15.7 vs. 14 %; HR 1.06, 95 % CI = 0.84–1.35) was identified. Contemporaneously, Albain and colleagues randomized stage III (N2) NSCLC patients to concurrent chemoradiation to 45 Gy followed by either surgery and consolidation chemotherapy or completion of definitive chemoradiation to 61 Gy [36]. Progression-free survival was superior in the surgical arm, with a median PFS of 12.8 months as compared to 10.5 months (HR 0.77 (0.62–0.96; $p = 0.017$)). Median overall survival was similar between groups (23.6 vs. 22.2 months; HR 0.87, CI 0.70–1.10). However, an exploratory analysis suggested a median survival benefit to surgery among matched cohorts of patients undergoing lobectomy (33.6 vs. 21.7 months) with a non-significant trend toward worse median survival following pneumonectomy (18.9 vs. 29.4 months). Current consensus guidelines, including those of the American Association of Chest Physicians (AACP), support concurrent chemoradiation as the therapy of choice for prospectively identified N2/N3 NSCLC [37]. However, for low volume, particularly non-bulky single-station N2 disease, surgery is still incorporated at many centers [38]. Integrated multidisciplinary decision making and management is crucial for stage III disease, both for patients considered for surgical resection and those treated with non-surgically with chemoradiation. As outlined previously, pathologic mediastinal staging, either surgical or endosonographic, provides crucial information on nodal disease burden for patients with inconclusive imaging, may prevent major resections when inappropriate, or alternatively downstage patients with non-malignant causes for lymphadenopathy, allowing curative intent surgical resection.

When trimodality therapy is considered, delivery of each treatment impacts the potential delivery of other therapies. Preoperative chemoradiation is occasionally used in select low volume N2 patients prior to surgical resection, and pathologic response to therapy is a major predictor of survival [39]. However, selection of the preoperative radiation dose has implications for subsequent safety and success of resection. Early studies suggested increased risk of surgical mortality with surgical resection following full-dose chemoradiation, particularly when pneumonectomy is required [36, 40, 41]. However, refinements in both radiation and surgical techniques, such use of vascularized muscle flaps to cover bronchial stumps and limitation of intraoperative fluids, have resulted in acceptable morbidity and mortality for trimodality therapy incorporating full-dose (60–61 Gy) chemoradiation in select reports [42, 43]. Clear communication and integration between specialties in the planning and execution of trimodality therapy allows discussion of the intended radiation dose and planned timing of and technique of the intended surgery. When lower dose ($\sim$45 Gy) chemoradiation is planned, integration between specialties is also crucial in ensuring that patients do not complete a non-definitive radiation dose and then fail to move forward with surgical resection.

6 Multidisciplinary Care in the Metastatic Setting

Frontline therapy for metastatic lung cancer is systemic, whether chemotherapy or targeted agents. However, other specialists' input and treatment may offer valuable benefit in quality of life and symptom control. Bony metastases may lead to debilitating pain, high opioid requirements, and loss of function. Palliative radiotherapy is an excellent approach to reduce or eliminate pain from bone metastases. Prospective trials suggest equal efficacy from single and multifraction regimens [44, 45]. A Cochran meta-analysis identified rates of complete pain relief of 32–34 %, with lower rates of retreatment (21.5 vs. 7.4 %) with multifraction regimens [44]. Other interventional approaches of potential benefit for pain control include radioisotopes such as samarium 153 and strontium 89, typically delivered by a nuclear medicine specialist [46, 47]. Percutaneous vertebroplasty is also a potentially beneficial maneuver for painful pathologic vertebral compression fractures [48]. For refractory pain, interventional nerve blocks can also be considered and in small case series provide excellent pain relief, although systematic prospective studies are lacking [49].

Malignant airway obstruction and tumor-related hemoptysis may also benefit from multidisciplinary involvement. Bronchoscopy and stenting are effective in a substantial proportion of patients. Palliative external beam radiotherapy has also been demonstrated to provide effective palliation of obstructive symptoms and hemoptysis in a substantial proportion of patients [50, 51], and endobronchial brachytherapy is occasionally used for endobronchial lesions, particularly in the setting of prior thoracic radiotherapy [52, 53]. Palliative radiotherapy in the setting of intubation is controversial, but does result in extubation in a minority of patients [54].

Early integration of palliative care specialists has been demonstrated to improve not only quality of life, but also duration of survival. A landmark paper by Temel and colleagues studied the impact of early palliative care (meeting with a board-certified palliative care specialist and advanced practice nurses within 3 weeks of enrollment and at least monthly until death in an outpatient setting) integrated with standard oncologic care, compared to standard oncologic therapy alone for patients with newly diagnosed metastatic NSCLC, and found that early palliative care improved quality of life, reduced depressive symptoms, and improved median survival (11.6 vs. 8.9 months, $p = 0.02$) [55].

7 Supportive and Ancillary Care

Several specific supportive care services are of demonstrated benefit to lung cancer patients both during and after treatment, including nutritional support, smoking cessation, pulmonary rehabilitation, and physical therapy/structured exercise programs, among others. Poor nutritional status, including such factors as low body mass index (BMI), weight loss, and low albumin, are well-established risk factors

for increased surgical complications and perioperative death [56–58], poor tolerance to multimodal therapy [59], and poor response to therapy [60] in lung cancer patients. However, one completed prospective trial randomizing older (≥ 70 years) patients with cancer undergoing chemotherapy for a solid tumor (including 10.4 % lung cancer) to face-to-face dietary counseling versus standard care and identified no effect of mortality or nutritional status. The authors suggest cancer cachexia may have played a role in the lack of benefit [61]. Similarly, an older trial published in 1993 randomized 105 patients undergoing chemotherapy for lung, breast, or ovarian cancer to nutritional counseling versus standard care. Despite increasing caloric and protein intake, subjects randomized to receive nutritional counseling did not increase response rates to chemotherapy, overall survival, or quality of life [62].

Retrospective studies suggest patients with poor exercise tolerance fare poorly following lung cancer surgery [63, 64], and structured exercise interventions have been suggested to improve functional outcomes and quality of life during and following treatment for lung cancer [65]. A Cochrane database systematic review published in 2012 assessed the impact of exercise interventions on health-related quality of life (HR-QOL) for cancer patients. The authors evaluated 56 trials with 4826 participants randomized to an exercise or comparison group, and found that exercise interventions may have a positive impact on HR-QOL domains including physical functional, social functioning, fatigue, and role function [66]. A more focused Cochrane systematic review published in 2013 compiled the randomized controlled trials looking at the impact of exercise training on patients treated with resection for NSCLC [67]. The authors identified 3 such trials enrolling 178 patients, one of which has been published only in abstract form [68–70]. The review suggests exercise training may increase exercise capacity (as assessed by the 6 min walk test), but did not clearly impact qualify of life measures. Given the disparate approaches of the three studies, limited conclusions could be drawn and a need for larger randomized trials systematically evaluating the impact of a structured exercise intervention on exercise tolerance and quality of life in lung cancer patients was stressed.

Smoking cessation and maintenance is also a crucial component of post-treatment care for the lung cancer patient [71]. Current smoking increases overall and disease-specific mortality as compared to former and never smokers with cancer [72]. Smoking consistently predicts for higher surgical risks and postoperative mortality following lung resection [57, 58]. Despite these well-known risks, population-based investigations suggest cancer survivors smoke at rates comparable to non-cancer patients, with higher rates of smoking among young cancer survivors [73]. More than half of currently smoking lung cancer patients will try to quit smoking at diagnosis [74], but one study suggests nearly half will return to smoking within 12 months [75]. Integrated, supportive systems to identify and assist current and former lung cancer patients with smoking cessation are clearly an area of great need. The MD Anderson Cancer Center Tobacco Treatment Program (TTP) is one such model program based on the Public Health Service tobacco treatment guidelines and tailored to the individual patient. The TTP combines in-person interviews, comprehensive self-assessments of depression, sleep

problems, nicotine dependence, smoking withdrawal, and alcohol use with individually tailored behavioral and pharmacologic treatment and frequent behavioral counseling. With this aggressive approach, 6-month abstinence rates are 34 %, comparing favorably to other treatment approaches in non-cancer populations [71].

8 Survivorship

Approximately 54 % of patients with stage I NSCLC will survive 5 years, and 27 % of patients with locally advanced disease will survive 5 years [76]. Historical 5-year survival with stage IV disease is only 4 %, but with increasing molecular targeted therapies, select patients with metastatic disease with tyrosine kinase mutations amenable to targeted therapeutics may have extended survival of several years or more [77].

However, long-term sequelae of treatment may substantially impact quality and duration of life. Anatomic lung resection reduces pulmonary function from preoperative levels. Postoperative forced expiratory volume in 1 s (FEV_1) and exercise capacity are expected to diminish by approximately 15 and 16 % after lobectomy and by 35 and 23 % after pneumonectomy [78], and chronic chest wall pain is a potential complication of both video-assisted and open thoracotomy [79]. Potential long-term complications of thoracic radiation include parenchymal lung scarring and fibrosis, rib fractures [80], cardiac valve disease [81], increased risk of myocardial infarction, chronic chest wall pain [82], esophageal strictures, and secondary malignancies. Complications of chemotherapy can result in neuropathy, renal insufficiency, and other permanent sequelae. Psychiatric comorbidities including depression and anxiety are also common among lung cancer survivors [83]. Studies have identified reduced HR-QOL among long-term survivors of lung cancer as compared to age- and gender-matched controls [84]. A Surveillance, Epidemiology, and End Results (SEER) Program database analysis identified durable elevated risks of second malignancy among survivors of stage I lung cancer, including second primary NSCLC, laryngeal, esophageal, colon, gastric, and bladder cancers [85]. In addition to regular surveillance visits with their treating physician(s) and primary care physician, depending on post-treatment sequelae, lung cancer survivors may benefit from additional multidisciplinary input from a nutritionist, psychiatrist, gastroenterologist, pulmonologist, or cardiologist, depending on individualized assessment of comorbidities, expected side effects, and ongoing cancer risk.

The Institute of Medicine first recommended provision of a "survivorship care plan" in 2005 [86], but widespread implementation has been slow. Recently, the Commission on Cancer established provision of a survivorship care plan to all patients completing definitive-intent cancer therapy as a standard for accreditation [87]. The guidelines outline details of the survivorship care plan that should be provided to each cancer patient at the completion of therapy, which should include treatment received, expected and possible short- and long-term side effects, plans for cancer surveillance and for follow-up care. The specific benefits of this approach

to formalized survivorship care have not yet been rigorously studied in lung cancer patients, however. Two randomized trials in breast cancer patients failed to identify a specific benefit to the formalized survivorship care plan in patient satisfaction, adherence to guidelines for post-treatment care, or health-related quality of life [88, 89]. Clearly, additional research both assessing and refining the optimal use and implementation of formalized survivorship for lung cancer patients is needed.

9 Conclusions

Multidisciplinary care of the lung cancer patient starts and diagnosis and staging, and continues through surveillance and survivorship. Integration of surgical, medical, and radiation oncology with other medical specialists and supportive services is encouraged at all disease stages and may reduce treatment delays, improve health-related quality of life, and enhance survival in select circumstances. Studies suggest integration of nutritional support, psychotherapy, exercise training, and smoking cessation is warranted, but well-designed prospective studies validating specific integrated approaches are an ongoing area of need. Well-designed prospective studies are necessary to refine the optimal implementation of multidisciplinary care forums such as the MTB and tools such as the survivorship care plan.

References

1. http://www.cancer.gov/dictionary?cdrid=322893. Cited 25 May 2015
2. Cancer, A.C.o.S.C.o (2012) Cancer program standards 2012: ensuring patient-centered care V1.0, in American College of Surgeons, Chicago
3. El Saghir N et al (2014) Tumor boards: optimizing the structure and improving efficiency of multidisciplinary management of patients with cancer worldwide, in ASCO Educational Book
4. Wright FC et al (2007) Multidisciplinary cancer conferences: a systematic review and development of practice standards. Eur J Cancer 43(6):1002–1010
5. Schmidt HM et al (2015) Thoracic multidisciplinary tumor board routinely impacts therapeutic plans in patients with lung and esophageal cancer: a prospective cohort study. Ann Thorac Surg 99(5):1719–1724
6. Ung, KA et al (2014) Impact of the lung oncology multidisciplinary team meetings on the management of patients with cancer. Asia Pac J Clin Oncol
7. Hazin R, Qaddoumi I (2010) Teleoncology: current and future applications for improving cancer care globally. Lancet Oncol 11(2):204–210
8. Heifetz LJ et al (2011) A model for rural oncology. J Oncol Pract 7(3):168–171
9. Freeman RK et al (2010) The effect of a multidisciplinary thoracic malignancy conference on the treatment of patients with lung cancer. Eur J Cardiothorac Surg 38(1):1–5
10. Kesson EM et al (2012) Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women. BMJ 344:e2718
11. Keating NL et al (2013) Tumor boards and the quality of cancer care. J Natl Cancer Inst 105 (2):113–121
12. Blayney DW (2013) Tumor boards (team huddles) aren't enough to reach the goal. J Natl Cancer Inst 105(2):82–84

13. Devitt B, Philip J, McLachlan SA (2013) Re: tumor boards and the quality of cancer care. J Natl Cancer Inst 105(23):1838
14. Krasna M, Freeman RK, Petrelli NJ (2013) Re: tumor boards and the quality of cancer care. J Natl Cancer Inst 105(23):1839–1840
15. Lamb BW et al (2013) Improving decision making in multidisciplinary tumor boards: prospective longitudinal evaluation of a multicomponent intervention for 1421 patients. J Am Coll Surg 217(3):412–420
16. Schwaederle M et al (2014) Molecular tumor board: The University of California San Diego Moores Cancer Center experience. Oncologist 19(6):631–636
17. www.clinicaltrials.gov Lung-MAP: S1400 biomarker-targeted second-line therapy in treating patients with recurrent stage IIIB-IV squamous cell lung cancer. Cited 9 June 2015
18. www.clinicaltrials.gov NCI-MATCH: targeted therapy directed by genetic testing in treating patients with advanced refractory solid tumors or lymphomas. cited 9 June 2015
19. Annema JT et al (2010) Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. JAMA 304(20):2245–2252
20. Sharples LD et al (2012) Clinical effectiveness and cost-effectiveness of endobronchial and endoscopic ultrasound relative to surgical staging in potentially resectable lung cancer: results from the ASTER randomised controlled trial. Health Technol Assess 16(18):1–75, iii–iv
21. Silvestri GA et al (2013) Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 143(5 Suppl):e211S–50S
22. Cooke DT et al (2014) Outcomes and efficacy of thoracic surgery biopsy for tumor molecular profiling in patients with advanced lung cancer. J Thorac Cardiovasc Surg 148(1):36–40
23. Lindeman NI et al (2013) Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the study of lung cancer, and association for molecular pathology. J Thorac Oncol 8(7):823–859
24. Gomez DR et al (2015) Time to treatment as a quality metric in lung cancer: Staging studies, time to treatment, and patient survival. Radiother Oncol
25. Diaconescu R, Lafond C, Whittom R (2011) Treatment delays in non-small cell lung cancer and their prognostic implications. J Thorac Oncol 6(7):1254–1259
26. Everitt S et al (2013) The impact of time between staging PET/CT and definitive chemo-radiation on target volumes and survival in patients with non-small cell lung cancer. Radiother Oncol 106(3):288–291
27. Kishan AU et al (2014) Quantification of gross tumour volume changes between simulation and first day of radiotherapy for patients with locally advanced malignancies of the lung and head/neck. J Med Imaging Radiat Oncol 58(5):618–624
28. Ginsberg RJ, Rubinstein LV (1995) Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 60 (3):615–622; discussion 622–623
29. Chi A et al (2010) Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: clinical implications. Radiother Oncol 94(1):1–11
30. Timmerman R et al (2010) Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 303(11):1070–1076
31. www.clinicaltrials.gov (2015) Randomized Study to compare cyber knife to surgical resection in stage I non-small cell lung cancer (STARS). Cited 26 May 2015
32. www.clinicaltrials.gov (2015) Trial of either surgery or stereotactic radiotherapy for early stage (IA) lung cancer (ROSEL). Cited 26 May 2015
33. www.clinicaltrials.gov (2015) Surgery with or without internal radiation therapy compared with stereotactic body radiation therapy in treating patients with high-risk stage I non-small cell lung cancer. Cited 26 May 2015

34. Chang JY et al (2015) Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol 16 (6):630–637
35. van Meerbeeck JP et al (2007) Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 99(6):442–450
36. Albain KS et al (2009) Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 374 (9687):379–386
37. Robinson LA et al (2007) Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 132(3 Suppl):243S–265S
38. Tanner NT et al (2012) Physician preferences for management of patients with stage IIIA NSCLC: impact of bulk of nodal disease on therapy selection. J Thorac Oncol 7(2):365–369
39. Albain KS et al (1995) Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol 13(8):1880–1892
40. Deutsch M et al (1994) Phase II study of neoadjuvant chemotherapy and radiation therapy with thoracotomy in the treatment of clinically staged IIIA non-small cell lung cancer. Cancer 74(4):1243–1252
41. Fowler WC et al (1993) Postoperative complications after combined neoadjuvant treatment of lung cancer. Ann Thorac Surg 55(4):986–989
42. Suntharalingam M et al (2012) Radiation therapy oncology group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. Int J Radiat Oncol Biol Phys 84(2):456–463
43. Sonett JR et al (1999) Safe pulmonary resection after chemotherapy and high-dose thoracic radiation. Ann Thorac Surg 68(2):316–320
44. Sze WM et al (2004) Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy—a systematic review of the randomised trials. Cochrane Database Syst Rev 15 (2): CD004721
45. Tong D, Gillick L, Hendrickson FR (1982) The palliation of symptomatic osseous metastases: final results of the study by the radiation therapy oncology group. Cancer 50(5):893–899
46. Serafini AN et al (1998) Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. J Clin Oncol 16 (4):1574–1581
47. Robinson RG et al (1995) Strontium 89 therapy for the palliation of pain due to osseous metastases. JAMA 274(5):420–424
48. Cheung G et al (2006) Percutaneous vertebroplasty in patients with intractable pain from osteoporotic or metastatic fractures: a prospective study using quality-of-life assessment. Can Assoc Radiol J 57(1):13–21
49. Klepstad P et al (2014) The evidence of peripheral nerve blocks for cancer-related pain: a systematic review. Minerva Anestesiol
50. Lee JW et al (2015) The efficacy of external beam radiotherapy for airway obstruction in lung cancer patients. Cancer Res Treat 47(2):189–196
51. Stevens R et al (2015) Palliative radiotherapy regimens for patients with thoracic symptoms from non-small cell lung cancer. Cochrane Database Syst Rev 1: CD002143
52. Manali ED et al (2010) High dose-rate endobronchial radiotherapy for proximal airway obstruction due to lung cancer: 8-year experience of a referral center. Cancer Biother Radiopharm 25(2):207–213
53. de Aquino Gorayeb MM et al (2013) High-dose-rate brachytherapy in symptom palliation due to malignant endobronchial obstruction: a quantitative assessment. Brachytherapy 12(5): 471–478

54. Louie AV et al (2013) Radiotherapy for intubated patients with malignant airway obstruction: futile or facilitating extubation? J Thorac Oncol 8(11):1365–1370
55. Temel JS et al (2010) Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363(8):733–742
56. Thomas PA et al (2014) National perioperative outcomes of pulmonary lobectomy for cancer: the influence of nutritional status. Eur J Cardiothorac Surg 45(4):652–659; discussion 659
57. Bagan P et al (2013) Nutritional status and postoperative outcome after pneumonectomy for lung cancer. Ann Thorac Surg 95(2):392–396
58. Harpole DH Jr et al (1999) Prognostic models of thirty-day mortality and morbidity after major pulmonary resection. J Thorac Cardiovasc Surg 117(5):969–979
59. van der Meij BS et al (2011) Nutrition during trimodality treatment in stage III non-small cell lung cancer: not only important for underweight patients. J Thorac Oncol 6(9):1563–1568
60. Illa P, Tomiskova M, Skrickova J (2015) Nutritional risk screening predicts tumor response in lung cancer patients. J Am Coll Nutr 1–5
61. Bourdel-Marchasson I et al (2014) Nutritional advice in older patients at risk of malnutrition during treatment for chemotherapy: a two-year randomized controlled trial. PLoS ONE 9(9): e108687
62. Ovesen L et al (1993) Effect of dietary counseling on food intake, body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy: a prospective, randomized study. J Clin Oncol 11(10):2043–2049
63. Holden DA et al (1992) Exercise testing, 6-min walk, and stair climb in the evaluation of patients at high risk for pulmonary resection. Chest 102(6):1774–1779
64. Marjanski T et al (2015) Patients who do not reach a distance of 500 m during the 6-min walk test have an increased risk of postoperative complications and prolonged hospital stay after lobectomydagger. Eur J Cardiothorac Surg 47(5):e213–e219
65. Bade BC et al (2015) Increasing physical activity and exercise in lung cancer: reviewing safety, benefits, and application. J Thorac Oncol 10(6):861–871
66. Mishra SI et al (2012) Exercise interventions on health-related quality of life for people with cancer during active treatment. Cochrane Database Syst Rev 8:CD008465
67. Cavalheri V et al (2013) Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer. Cochrane Database Syst Rev 7: CD009955
68. Arbane G et al (2011) Evaluation of an early exercise intervention after thoracotomy for non-small cell lung cancer (NSCLC), effects on quality of life, muscle strength and exercise tolerance: randomised controlled trial. Lung Cancer 71(2):229–234
69. Brocki B et al (2010) Rehabilitation after lung cancer operation—a randomised controlled study. In: Annals ERS Annual Congress 2010
70. Stigt JA et al (2013) A randomized controlled trial of postthoracotomy pulmonary rehabilitation in patients with resectable lung cancer. J Thorac Oncol 8(2):214–221
71. Karam-Hage M, Cinciripini PM, Gritz ER (2014) Tobacco use and cessation for cancer survivors: an overview for clinicians. CA Cancer J Clin 64(4):272–290
72. Warren GW et al (2013) Smoking at diagnosis and survival in cancer patients. Int J Cancer 132(2):401–410
73. Bellizzi KM et al (2005) Health behaviors of cancer survivors: examining opportunities for cancer control intervention. J Clin Oncol 23(34):8884–8893
74. Cooley ME et al (2012) Factors associated with smoking abstinence among smokers and recent-quitters with lung and head and neck cancer. Lung Cancer 76(2):144–149
75. Walker MS et al (2006) Smoking relapse during the first year after treatment for early-stage non-small-cell lung cancer. Cancer Epidemiol Biomarkers Prev 15(12):2370–2377
76. Surveillance, Epidemiology, and End Results Program (2015) SEER stat fact sheets: lung and bronchus cancer. cited 31 May 2015
77. Riely GJ et al (2006) Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib. Clin Cancer Res 12(3 Pt 1):839–844

78. Win T et al (2007) The effect of lung resection on pulmonary function and exercise capacity in lung cancer patients. Respir Care 52(6):720–726
79. Kirby TJ et al (1995) Lobectomy–video-assisted thoracic surgery versus muscle-sparing thoracotomy. A randomized trial. J Thorac Cardiovasc Surg 109(5): 997–1001; discussion 1001–1002
80. Stanic S et al (2011) Rib fracture following stereotactic body radiotherapy: a potential pitfall. Clin Nucl Med 36(11):e168–e170
81. Cella L et al (2014) Complication probability models for radiation-induced heart valvular dysfunction: do heart-lung interactions play a role? PLoS ONE 9(10):e111753
82. Dunlap NE et al (2010) Chest wall volume receiving >30 Gy predicts risk of severe pain and/or rib fracture after lung stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 76 (3):796–801
83. Yun YH et al (2013) Needs regarding care and factors associated with unmet needs in disease-free survivors of surgically treated lung cancer. Ann Oncol 24(6):1552–1559
84. Rauma V et al (2015) Long-term lung cancer survivors have permanently decreased quality of life after surgery. Clin Lung Cancer 16(1):40–45
85. Surapaneni R et al (2012) Stage I lung cancer survivorship: risk of second malignancies and need for individualized care plan. J Thorac Oncol 7(8):1252–1256
86. Hewitt M, Greenfield S, Stovall E (eds) (2005) From cancer patient to cancer survivor: lost in transition. National Academies Press, Washington, DC
87. Cancer, C.o. (2012) Cancer program standards 2012: Ensuring Patient-Centered Care
88. Boekhout AH et al (2015) A survivorship care plan for breast cancer survivors: extended results of a randomized clinical trial. J Cancer Surviv
89. Hershman DL et al (2013) Randomized controlled trial of a clinic-based survivorship intervention following adjuvant therapy in breast cancer survivors. Breast Cancer Res Treat 138(3):795–806

Small Cell Lung Cancer

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Abstract

Small cell lung cancer (SCLC) is an aggressive cancer of neuroendocrine origin, which is strongly associated with cigarette smoking. Patients typically present with a short duration of symptoms and frequently (60–65 %) with metastatic disease. SCLC is a heterogeneous disease including extremely chemosensitive and chemoresistant clones. For this reason, a high percentage of patients respond to first-line chemotherapy but rapidly succumb to the disease. SCLC is generally divided into two stages, limited and extensive. Standard treatment of limited stage disease includes combination chemotherapy with cisplatin and etoposide for four cycles, thoracic radiation initiated early with the first cycle of chemotherapy, and consideration of prophylactic cranial irradiation (PCI) in the subset of patients with good response. Surgery may play a role in TNM stages I and II. In extensive disease, platinum agents and etoposide, used in combination, are again the first-line standard of care in the USA. However, thoracic radiation therapy is used predominately in patients where local control is important and PCI is of uncertain benefit. Despite these treatments, prognosis remains poor and novel therapies are needed to improve survival in this disease.

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Contents

1 Introduction

1.1 Epidemiology and Risk Factors

Small cell lung cancer (SCLC) comprises 13 % of all lung cancers and leads to approximately 30,000 deaths annually in the USA [1]. It is strongly associated with cigarette smoking with 95 % of all patients having a history of heavy tobacco exposure. This strong association is further highlighted by the decreasing incidence of SCLC with the decline of smoking rates, changes in smoking habits, and increased use of filtered cigarettes in the USA [2]. The decline in rate could also be related to changes in the World Health Organization classification of lung tumors which made the diagnosis of SCLC more restrictive. Other risk factors for the development of SCLC include exposures to radon, halogenated ethers, arsenic, asbestos, chromium, polyaromatic hydrocarbons, and vinyl chloride. Women smokers are more likely to develop SCLC when compared to their male counterparts due to factors that are not clearly defined [2].

1.2 Presentation

Patients typically presented with a short duration of symptoms, on average three months. Endobronchial tumors may manifest with symptoms of cough, wheezing, dyspnea, or post-obstructive pneumonia. Patients with regional extension of disease may experience vocal hoarseness, chest or throat pain, dysphagia, or superior vena cava syndrome due to the central nature of these tumors. Patients with metastatic disease may present with abdominal pain, bone pain, nausea, vomiting, anorexia, weight loss, or focal neurologic deficits. Patients of any stage may present with paraneoplastic syndromes. The majority of SCLC cells are extremely sensitive to chemotherapy. In fact, patients with a large tumor burden may develop tumor lysis syndrome when exposed to potent chemotherapy. Unfortunately, these tumor cells are heterogeneous with chemoresistant clones ultimately surviving, proliferating, and causing disease recurrence and death.

1.3 Histology

SCLC histology reveals dense sheets of cells with neuroendocrine differentiation that are small, round, and blue (Fig. 1) [3]. Light microscopy shows monotonous undifferentiated morphology with finely granular nuclear chromatin, faint or absent nucleoli, a high nuclear to cytoplasmic ratio and frequent mitoses [3]. These cells divide quickly are highly metastatic, invasive, and angiogenic. In fact, 60–65 % of patients present with extensive metastatic disease [2]. Occasionally, SCLC may occur in conjunction with non-small cell lung cancer (NSCLC) [3]. When assessed using the immunoperoxidase antibody panel, cells are typically keratin positive and

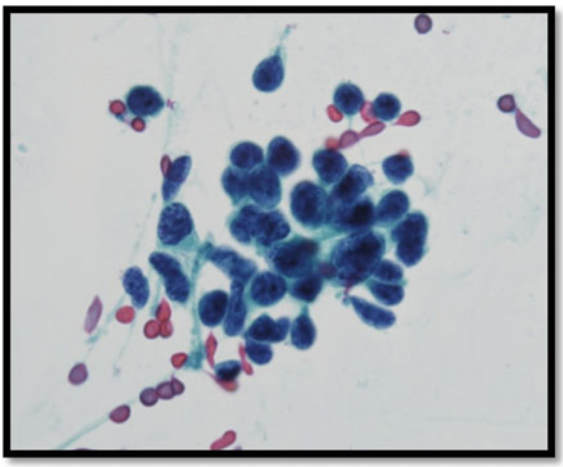

Fig. 1 Papanicolaou-stained cytology smear, at 400x magnification, demonstrating malignant epithelium tumor consisting of small cells with scan cytoplasm and ill-defined boarders classic for small cell lung cancer. Photograph provided courtesy of Dr. Chen Zhang, Indiana University School of Medicine Department of Pathology

CD45/leukocyte common antigen (LCA) negative. Neuroendocrine markers such as synaptophysin and chromogranin, and thyroid transcription factor are usually positive [4].

2 Paraneoplastic Syndromes

2.1 Endocrine Paraneoplastic Syndromes

Given its ability to produce multiple hormones, SCLC is associated with several paraneoplastic syndromes. These include hyponatremia associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH), Cushing's syndrome associated with adrenocorticotropic hormone secretion, and acromegaly associated with growth hormone secretion by tumor cells [5]. In fact, symptoms of paraneoplastic syndromes may precede the discovery of the underlying cancer. Likewise, they may be the first sign of relapse after a remission has been achieved. Therefore, typical signs of paraneoplastic disorder should prompt a swift search for the underlying cancer. In fact, the only definitive treatment for these disorders is chemotherapy (± radiation if limited stage) to target the cancer itself.

2.2 Neurologic Paraneoplastic Syndromes

More rarely, SCLC is associated with neurologic paraneoplastic disorders that include sensory, sensorimotor, and autoimmune neuropathies as well as encephalomyelitis. These syndromes are thought to occur through autoimmune mechanisms when antibodies bind to both the SCLC and the central nervous system. In patients with SCLC, the most common neurologic paraneoplastic disorders are subacute sensory neuropathy and/or paraneoplastic encephalomyelitis [5]. These disorders are associated with anti-Hu antibodies and are sometimes referred to as "anti-Hu syndromes." Anti-Hu-associated subacute sensory neuropathy usually presents with numbness in the distal extremities including hands and feet. Anti-Hu-associated encephalomyelitis may present with an array of central neurologic symptoms including but not limited to memory loss, confusion, seizure, muscle weakness, aphasia, dysarthria, facial numbness, or neuropsychiatric disturbance including anxiety or depression. Serum and cerebral spine fluid (CSF) are tested for paraneoplastic antibodies and, when elevated, are diagnostic of this condition. Lambert–Eaton syndrome is less commonly associated with SCLC and is caused by autoantibody impairment of voltage-gated calcium channels on the muscle cell membrane [5]. Patients presented with proximal leg weakness that improves with repetition. Electromyography is used for definitive diagnosis. Rare neurologic disorders seen in SCLC include cerebellar degeneration, opsoclonus, retinal blindness, and Stiff Person Syndrome [5].

2.3 Treatment and Prognosis of Paraneoplastic Syndromes

Treatment of the underlying cancer will improve symptoms and often times reverse the course of associated paraneoplastic syndromes. This is especially true to SIADH, Cushing's syndrome, and acromegaly, as the associated hormone secretion is dramatically reduced along with the decreased tumor burden. However, neurologic paraneoplastic disorders typically involve irreversible destruction of neurons secondary to inflammation and immune activation of autoantibodies. Therefore, manifestations of neurologic disease may persist even after treating the underlying malignancy [5].

3 Staging

Given the rapid doubling time of SCLC, prompt workup and treatment is essential. In fact, given the highly metastatic potential of SCLC cells, workup should not delay definitive treatment with chemoradiation. Given its correlation with multiple

paraneoplastic syndromes, a thorough history, physical examination, and laboratory investigation should be completed. We also recommend computed tomography (CT) of the chest, abdomen, and pelvis along with magnetic resonance imaging (MRI) of the head for standard staging. If the patient is suspected to have limited disease by preliminary imaging, then position emission tomography (PET) and possible endobronchial ultrasound with biopsy may be indicated to exclude or confirm mediastinal disease. In a study on the use of PET in clinical staging, 11 % of patients classified as limited stage by CT were upgraded to extensive disease while 18 % of patients originally thought to have extensive disease were downgraded to limited disease after scanning [6]. Therefore, when staging by CT and MRI is in question, PET may be of utility in establishing a definitive stage.

3.1 Limited Versus Extensive Disease

Limited disease (LD) is defined as tumor that is confined to one hemithorax and associated regional lymph nodes. This constitutes approximately 35–40 % of patients and includes tumor node metastasis (TNM) stages I through III [2]. Tumor must be encompassed by a tolerable radiation port and exclude pleural or pericardial involvement with malignant effusion. Extensive disease (ED) is defined as tumor outside the confines of limited stage disease including patients with malignant pericardial and pleural effusion. ED includes patients of TNM IV.

3.2 Tumor, Node, Metastasis Staging

TNM staging has gained popularity in recent years, particularly since the International Association for the Study of Lung Cancer (IASLC) lung cancer staging project revealed significant variability in survival based on stage [7]. TNM staging system seems more accurate than the Veterans Administration Lung Study Group staging of limited versus extensive stage in determining prognosis. This is especially true in the earlier stages of the disease [7]. T1 is defined as tumor less than or equal to 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion, more proximal than the lobar bronchus; or superficial spreading of tumor in the central airways confined to the bronchial wall [8]. T1 is then further subdivided into stage T1a (tumor less than 2 cm in greatest dimension) and stage T1b (tumor greater than 2 cm but less than 3 cm in greatest dimension). T2 is generally defined as tumor greater than 3 cm but less than or equal to 7 cm [8]. However, smaller tumors that are 3 cm or less may be upstaged to T2 if they involve the main bronchus but are greater than 2 cm distal to the carina, involve atelectasis or obstructive pneumonitis extending into the hilar region but not the entire lung, and/or invade the visceral pleura of the lung. Additionally, T2 is also subdivided by size. Tumors greater than 3 cm and less than or equal to 5 cm are classified as T2a. Tumors that are greater than 5 cm but are lesser than or equal to 7 cm are classified as T2b. T3 is defined as any tumor greater than 7 cm in

size or one that directly invades any of the following: chest wall, parietal pleural, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium [8]. Additionally, if the tumor is less than 7 cm but involves the main bronchus and is less than 2 cm distal to the carina but without involvement of the carina, it is also upstaged to a T3 lesion. If the tumor is less than 7 cm in size but is associated with atelectasis or obstructive pneumonitis of the entire lung, it is upstaged to a T3 lesion. Finally, if the primary lesion is less than 7 cm but there is at least one separate tumor nodule in the same lobe, then the patient is upstaged to T3. T4 is defined as a tumor of any size that invades any of the following: heart, mediastinum, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or a separate tumor lesion(s) in the ipsilateral lobe [8]. N0 is defined as no regional lymph node metastasis. N1 is defined as metastasis to the ipsilateral peribronchial, hilar, or intrapulmonary nodes. N2 is defined as metastasis to the ipsilateral mediastinal or subcarinal nodes. N3 is defined as metastasis to the contralateral mediastinal, or hilar nodes, and/or any scalene or supraclavicular lymph nodes. Metastasis is defined as absent (M0) or present (M1). Staging and prognosis is then completed using the following chart (Table 1) [8].

Table 1 Staging as established by the TNM system and associated median survival with optimal chemoradiation or chemotherapy

Stage	Tumor	Node	Metastasis	Median survival
(Limited)				
Ia	T1a	N0	M0	60 months
	T1b	N0	M0	
Ib	T2a	N0	M0	43 months
IIa	T1a	N1	M0	34 months
	T1b	N1	M0	
	T2a	N1	M0	
	T2b	N0	M0	
IIb	T2b	N1	M0	18 months
	T3	N0	M0	
IIIa	T1	N2	M0	14 months
	T2	N2	M0	
	T3	N1	M0	
	T3	N2	M0	
	T4	N0	M0	
	T4	N1	M0	
IIIb	T4	N2	M0	10 months
	T1	N3	M0	
	T2	N3	M0	
	T3	N3	M0	
	T4	N3	M0	
IV (*Extensive*)	T Any	N Any	M1	6 months

3.3 Pleural Effusions

Of the patients in the IASLC database, 68 had pleural effusion with associated cytologic examination. Interestingly, in patients with LD, the presence of cytologically negative pleural effusion conferred an intermediate prognosis, which was worse than LD but better than ED [7]. Also, the survival of patients with positive effusions and otherwise LD was superior to that of patients with ED [7]. Other poor prognostic factors associated with ED include multiple metastatic sites, performance score (PS) 3–4, cachexia, older age, and increased levels lactate dehydrogenase (LDH) in the serum [9]. Favorable prognostic factors include a single metastatic site, PS 0–2, younger age, and a normal serum LDH [9]. Though the initial response rate to chemotherapy is as high as 70 %, the disease universally recurs in patients with ED and the majority of patients with LD, leading to the poor prognosis associated with SCLC.

4 Treatment of Limited Stage Disease

4.1 Surgery

A prospective randomized trial was conducted and published in 1994 to assess the role of surgical resection in limited stage disease [10]. Patients first received chemotherapy with cyclophosphamide, doxorubicin, and vincristine for a total of five cycles. Patients that achieved at least partial response and were fit for surgery were randomized to thoracotomy versus no surgery. There was no difference in survival between the arms of the study. This was the only phase III trial evaluating the role of surgical resection of residual disease after chemotherapy in limited stage SCLC. In 2009, the IASLC published their lung cancer study project [7]. Of the 8000 cases of SCLC in the IASLC database, 349 cases included SCLC that had been resected and pathologically staged. The data revealed a statistically significant survival advantage for stage I and stage II patients when surgically staged and resected: stage IA, 60 months versus 119 months; stage IB, 43 versus 81 months; stage IIA, 34 versus 49 months; and stage IIB, 18 versus 34 months. Surgery alone is not the treatment of choice in SCLC as it is a disease characterized by rapid early hematogenous spread. We believe surgery might have a role in a small group of patients with peripheral T1N0 SCLC tumors. Given the IASLC data, resection followed by adjuvant chemotherapy is reasonable in these patients.

4.2 Evolution of Chemotherapy Regimens

Given the early metastatic potential of SCLC, most patients with LD are initially treated with concurrent chemoradiation. This includes four cycles of etoposide and cisplatin (EP) combined with chest radiotherapy. Though EP is the current standard,

cyclophosphamide was the first drug to show activity against SCLC. Anthracyclines and vincristine were later combined with cyclophosphamide resulting in the CAV regimen. Until the late 1980s, CAV was the standard chemotherapy for limited stage SCLC. At that time, data began to suggest that EP may be superior in the treatment LD SCLC. A study published in 1988 by Einhorn et al. [11] revealed that patients who were treated with EP consolidation, after response to CAV initial therapy, remained in remission and ultimately survived longer. This led to a 1993 phase III study by Johnson, et al. [12] which compared response rates and survival in patients treated with CAV versus CAV plus radiation therapy who, after response, were then again randomized to either observation or consolidation chemotherapy with EP. The study did not show a statistically significant response rate or survival advantage in the chemotherapy alone versus chemoradiation groups; however, patients who received consolidation chemotherapy did have superior median and two-year survival when compared to the observation group [12]. A larger 1999 study by Turrisi et al. [13] did find superior survival when combining EP with chest radiotherapy. A 2002 phase III trial also confirmed that EP was superior to carboplatin, epirubicin, and vincristine (CEV) in LD SCLC. This study followed patients for five years and revealed that the two- and five-year survival rates were significantly increased in the EP versus CEV groups (14 and 5 % vs. 6 and 2 %, $P = 0.0004$) [14]. However, for the group of ED SCLC patients, there was no significant survival advantage for EP over CEV. Finally, two meta-analyses revealed a small but significant survival benefit with regimens including cisplatin and etoposide [15, 16]. These data led to cisplatin and etoposide becoming the preferred chemotherapy regimen to be administered concurrently with chest radiation in patients with LD SCLC. Although the study by Einhorn et al. suggested benefit of EP in the context of consolidation, later studies failed to show benefit with induction or consolidation chemotherapy in the context of standard treatment with EP and radiation therapy (XRT) (Table 2).

Table 2 Studies evaluating induction and consolidation chemotherapy

Author	Induction	Standard	Consolidation	Number of patients	Median survival (months)	*P* value
Thomas [54]	None	Cis, etop, vincris + XRT	Etoposide	114	24.2	NS
Edelman [55]	None	EP + XRT	Carbo, paclitax	87	17	NS
Maranzano [56]	CAV	EP + XRT	Vincris, MTX, etop, doxorub, cyclophos	55	17	NS
Bogart [57]	Topotecan, paclitaxel	EP + XRT	None	63	22.4	NS

Legend: *XRT,* radiation therapy; *NS,* not significant *p* value

4.3 Chemotherapy Versus Chemoradiation

In the early 1980s, investigators began to study the possible synergetic effects of chemoradiation. SCLC was found to be both a chemosensitive and a radiosensitive disease. Theories suggested that radiotherapy controlled bulky chest disease while also conferring increased chemosensitivity of the primary tumor. During this period, smaller studies investigating the addition of XRT to chemotherapeutic regimens revealed mixed results. Finally, two meta-analyses explored the benefit of radiation therapy in conjunction with chemotherapy for limited stage SCLC. The first, published by Pignon in the New England Journal of Medicine in 1992, pooled data from 13 trials including 2140 patients with limited disease and 433 patients with extensive disease [17]. The results revealed a 14 % reduction in mortality and a 5.4 % increase in survival at three years when patients were treated with combination chemoradiation. A second study by Warde and Payne [18], during the same year, confirmed a small but significant increase in two-year survival of 5.4 % in patients treated with concurrent chemoradiation.

4.4 Concurrent Versus Sequential Chemoradiation

The timing of chest radiation therapy has also been evaluated. A phase III study in Japan randomized 231 patients with limited stage SCLC to either sequential or concurrent thoracic radiotherapy [19]. The results revealed a significant survival advantage with concurrent chemoradiation. Patients in the sequential group were treated with four cycles of chemotherapy with EP every three weeks. Chemotherapy was followed by 45 Gray of radiation therapy over three weeks. The concurrent arm was treated with four cycles of EP every three weeks with radiation starting on day two of the first chemotherapy cycle. The median survival time was 19.7 months in the sequential group versus 27.2 months in the concurrent group although not statistically significant. The question of concurrent versus sequential radiation therapy was also evaluated by a randomized trial published in the New England Journal of Medicine in 1987 [20]. This study revealed a slight survival advantage when radiation therapy was given sequentially but this was not statistically significant (Table 3). Concurrent chemoradiotherapy is currently the standard of care

Table 3 Summary of studies exploring benefits of concurrent versus sequential chemoradiation

Author	Regimen	Number of patients	Median survival (months)	*P* value
Perry [20]	CAV + concurrent XRT	125	13.1	NS
	CAV + sequential XRT	145	14.6	
Takada [19]	EP + concurrent XRT	114	27.2	0.097
	EP + sequential XRT	114	19.7	

Legend: *XRT,* radiation therapy; *NS,* not significant *p* value

in patients with LD SCLC who are healthy enough for the combination. The benefit in survival is modest at 5 % improvement in five-year survival and many confounding patient variables can enhance or eliminate this benefit.

4.5 Early Versus Late Chemoradiation

The benefits of early versus late radiation therapy have been explored in three landmark studies: Murray et al. [21], Work et al. [22], and Jeremic et al. [23]. Two of these studies favored survival benefit when radiation therapy was given early with the first two cycles of chemotherapy (Table 4). The benefits of early versus late radiation therapy were then verified by systematic review solidifying early chemoradiation as the standard of care [24].

4.6 Standard Versus Hyperfractionated Radiation

Standard versus hyperfractionated radiotherapy has been the subject of multiple studies in SCLC. Two phase III trials compared standard to hyperfractionated chest radiotherapy in combination with chemotherapy in patients with LD SCLC. The first by Bonner et al. in 1999 enrolled 311 patients to receive late chemoradiation therapy [25]. All patients received three cycles of EP up-front. Patients who did not progress on this regimen were then randomized to receive either twice-daily thoracic radiation or once-daily thoracic radiation with two additional cycles of EP. There was no difference in progression rates or overall survival; however, the twice-daily group did experience a greater rate of grade ≥3 or higher esophagitis [25]. In the Turrisi et al.'s trial, 417 patients with limited stage disease were randomized to receive 45 Gy of early radiation therapy (concurrently with EP chemotherapy) either twice-daily over a three-week period or once-daily over a

Table 4 Summary of studies exploring benefits of early versus late chemoradiation

Author	Regimen	Number of patients	Median survival (months)	*P* value
Murray [21]	CAV + EP with early XRT	155	21.2	0.008
	CAV + EP with late XRT	153	16	
Work [22]	EP followed by early CAV +XRT	99	10.5	NS
	EP followed by later CAV + XRT	100	12	
Jeremic [23]	EP + early hyperfractionated XRT	52	34	0.027
	EP + late hyperfractionated XRT	51	26	

Legend: *XRT,* radiation therapy; *NS,* not significant *p* value

Table 5 Summary of studies evaluating standard versus hyperfractionated radiotherapy

Author	Regimen	Number of patients	Median survival	*P* value
Bonner [25]	EP (3 cycles) followed by EP (2 cycles) + daily XRT	132	24.6 months	NS
	EP (3 cycles) followed by EP (2 cycles) + twice-daily XRT	130	23 months	
Turrisi [13]	EP + daily XRT (over 5 weeks)	185	19	0.04
	EP + twice-daily XRT (over 3 weeks)	196	23	

Legend: *XRT,* radiation therapy; *NS,* not significant *p* value

period of five weeks. Hyperfractionated radiotherapy was associated with a small but significantly increased survival (23 vs. 19 months, $P = 0.04$) [13]. However, twice-daily treatment was again associated with increased rates of radiation-induced side effects including an increased incidence of grade 3 esophagitis. The toxicity and the inconvenience of twice-daily radiation for patients have precluded hyperfractionated radiation from being considered standard of care in the USA (Table 5).

4.7 Prophylactic Cranial Irradiation (PCI)

After remission is achieved, the brain unfortunately remains an area of frequent recurrence for SCLC and is a sanctuary site. Although no single trial showed a statistically significant survival benefit with PCI, when examined by meta-analysis the results were practice changing. This meta-analysis, by Auperin et al. [26], published in the New England Journal of medicine in 1999, reviewed seven trials and included a total of 987 patients. The results revealed a 5.4 % increased rate of survival at three years when patients with limited disease who were in complete remission were prophylactically irradiated. Unfortunately, whole brain radiation is not without risk. Patients may experience acute or delayed neurotoxicity including ataxia, confusion, memory loss, and dementia associated with the reduced quality of life [27].

4.8 Summary

To summarize, the standard of care in limited stage SCLC continues to be cisplatin and etoposide for four cycles concurrently with chest radiation. Surgical resection can be considered with adjuvant chemotherapy in a small group of patients with peripheral T1N0 disease. PCI should be considered in patients who achieve a good response to chemoradiotherapy.

5 Treatment of Extensive Stage Disease

5.1 Choice of Chemotherapeutic Regimen

In the USA, platinum combined with etoposide is the standard first-line chemotherapy for extensive stage SCLC [28]. However, as discussed under the treatment of LD, CAV was the regimen of choice until the late 1980s. A 1991 study comparing CAV with EP for initial therapy revealed improved response rates as well as reduced toxicity with EP [28]. The study treated 288 patients who were randomized into three groups: CAV, EP, and a third group alternating CAV and EP (CAV/EP). The response rates for EP were significantly higher (78 %) while the CAV/PE and CAV response rates were 76 and 55 %, respectively. Complete response rates were similar among all three groups (EP 14 %, CAV/EP 16 %, and CAV 15 %). Interestingly, 23 % of the patients who failed to respond to the initial CAV treatment responded to EP at the time of crossover. Conversely, 8 % of patients who failed to respond to EP responded to CAV suggesting the two regimens were non-cross-resistant. CAV is still considered occasionally as a second-line chemotherapy in a small group of patients that are highly fit after progressing on EP. A year later, a similar study was completed by Roth et al. comparing 12 weeks of EP with 18 weeks of CAV, and 18 weeks of alternating treatment with CAV and EP. Results revealed no significant difference in response rate (61, 51, and 59 %), complete response rates (10, 7, and 7 %), or median survival (8.6, 8.3, and 8.1 months, respectively). The Norwegian Lung Cancer Study Group compared CEV with EP and showed no survival difference in the ED setting [14]. Therefore, EP for a total of four cycles became the standard of care for both LD and ED SCLC. Studies from Japan indicate that platinum combined with Irinotecan is more effective than EP in that population [29]. These data, however, could not be replicated in the USA [30].

5.2 Substitution of Carboplatin for Cisplatin

In 1994, a randomized study from the Hellenic Co-operative Oncology Group revealed that carboplatin can be effectively substituted for cisplatin [31]. This study enrolled 143 patients randomized to receive either EP or etoposide and carboplatin (EC) in combination with chest radiation. The results revealed similar response rates and median survival, 12.5 months for EP and 11.8 months for EC, respectively [31]. In addition, the study also reported decreased adverse events such as neutropenia, nausea, vomiting, and neurotoxicity in the EC group. A randomized phase III study from Japan confirmed these results in a group of elderly or poor-risk patients exclusively with ED [32]. Again, similar response rates (73 % to 73 %) and survival (median 10.6 months versus 9.9 months) with less toxicity were observed in patients treated with EC [32]. Therefore, carboplatin is often substituted for cisplatin in older patients or those who may not tolerate standard cisplatin therapy.

5.3 Strategies for Improving Current Chemotherapy

Multiple other strategies have been studied in ED SCLC with hopes of improving outcomes in this chemosensitive disease. These included increased dose intensity, three drug combinations rather than two, and maintenance chemotherapy. These studies showed higher response rates with no improvement in overall survival at the consequence of increased toxicity [33, 34]. With regard to maintenance chemotherapy, one meta-analysis suggested a small overall survival advantage; however, many randomized trials have given negative results [35–37]. In particular, most studies revealed an increased time to progression at the consequence of increased toxicity and no overall improvement in survival [35, 36].

5.4 Radiation Therapy for Extensive Disease

Recent data have suggested thoracic radiation might have a role not only in LD, but also in ED. Thoracic radiation therapy has been shown to increase overall survival in select patients with ED SCLC. A European multicenter trial assessed overall survival and progression-free survival in patients treated with chest radiation therapy versus observation after at least a partial response to systemic chemotherapy [38]. As a caveat, all patients were treated with PCI as initial PCI studies suggested improved OS in ED setting. The overall survival at one year was only minimally increased; however, two-year survival and progression-free survival were significantly increased, 13 % versus 3 % ($p = 0.004$) and 24 % versus 7 % ($p = 0.001$), respectively. Another study assessed radiation therapy versus further chemotherapy [39]. To be included in the study, ED SCLC patients were required to show complete response at distant sites of metastasis with at least a partial response in the original lung lesion. When compared to additional cycles of chemotherapy, thoracic radiation increased the overall survival and the five-year survival rate, 11 months versus 17 months and 4 % versus 9 %, respectively. We believe thoracic radiation might have a place in a subset of patients with ED SCLC, particularly those with bulky mediastinal disease where local control is important.

5.5 Prophylactic Cranial Irradiation for Extensive Disease

PCI was previously thought to reduce the risk of brain metastases and prolong survival in patients with extensive stage SCLC [40]. However, this study was not associated with the standard of care platinum-based chemotherapy nor did it require baseline MRI to rule out the presence of brain metastasis prior to study enrollment. Recently, a 2014 randomized phase III trial from Japan revealed that while PCI did reduce brain metastases (32.4 % vs. 58 % at 12 months) it reduced overall survival when compared to observation (10.1 months vs. 15.1 months) [41]. This study included 330 SCLC patients with extensive disease who were randomized to PCI versus observation after any response to first-line platinum-based chemotherapy.

Patients were only allowed on the study after baseline MRI revealed the absence of brain metastases. Given this conflicting evidence, more studies are needed to determine the role of PCI in ED SCLC and we do not routinely recommend that to patients with ED SCLC

5.6 Summary

To summarize, standard of care first-line chemotherapy for ED SCLC includes combination chemotherapy with etoposide and a platinum agent (cisplatin or carboplatin). Similarly to LD SCLC, four cycles are considered optimal while increased dose intensity and maintenance therapies have not proven beneficial. For elderly or debilitated patients, chemotherapeutic modifications with attenuated EP or oral etoposide alone can be considered. Thoracic radiation may help a select group of patients while the role of PCI is undetermined. Enrollment in clinical trials remains a valuable option in patients with ED SCLC.

6 Second-Line Chemotherapy

Most patients will respond to first-line chemotherapy with EP but the majority will relapse with the emergence of chemoresistant clones. Unfortunately, response to second-line chemotherapy is poor. A patient's response to second-line chemotherapy can be predicted based on the interval from the completion of initial therapy to relapse. If this interval is less than three months, then the patient is thought to have chemoresistant disease. In these individuals, response to second-line agents is typically poor and is estimated to be less than 10 % [9]. If the interval is greater than three months since completion of initial chemotherapy, then the patient is deemed chemosensitive. These patients have a predicted response rate of approximately 25 % [9]. Regardless, relapsed disease is difficult to treat as evidenced by a reduced median survival of 4–5 months even with second-line chemotherapy [9].

Multiple agents have shown activity in relapsed SCLC including: platinum agents (cisplatin and carboplatin), podophyllotoxins (etoposide and teniposide), camptothecins (irinotecan and topotecan), alkylating agents (cyclophosphamide and ifosfamide), anthracycline (amrubicin, doxorubicin, epirubicin), taxanes (docetaxel and paclitaxel), vinca alkaloids (vincristine and vinorelbine), the folate antimetabolite methotrexate, and the pyrimidine analog gemcitabine [9]. Unfortunately, topotecan is the only FDA approved agent for the treatment of relapsed disease. This was based on a British study in 2006, which randomly assigned relapsed SCLC patients to oral Topotecan as compared to best supportive care alone (BSC) [42]. Survival was increased from 13.9 weeks in the BSC group to 25.9 weeks in the topotecan group. Partial response rate to topotecan was 7 % while 44 % of patients exhibited stable disease. The most common toxicities

included grade 4 neutropenia (33 %), grade 3–4 anemia (25 %), and grade 4 thrombocytopenia (7 %).

A German study in 1999 studied the efficacy of intravenous (IV) topotecan versus CAV in relapsed SCLC patients [43]. Patients were eligible for the study if they had relapsed at least 60 days after the completion of first-line chemotherapy and displayed adequate marrow, liver, and renal function with an ECOG performance status of 2 or less. Response rates and median time to progression were both improved with topotecan over CAV, 24.3 % versus 18.3 % and 13.3 weeks versus 12.3 weeks, respectively. For these reasons, topotecan IV or oral is typically used first in relapsed disease.

7 Targeted Therapy

Multiple genetic abnormalities have been discovered in the tumors of patients with SCLC. In 2010, a SCLC cell line (NCI-H209) was sequenced for genomic mutations. The results revealed 22,910 mutations associated with the carcinogens present in tobacco smoke [44]. By dividing the number of mutations by the average smoking history in SCLC patients, this paper estimated that on average one new mutation is acquired for every 15 cigarettes consumed. Over a lifetime of heavy smoking, these mutations lead to an aggressive and highly complex cancer. The most notable mutations involve inactivation of tumor suppressor genes including P53 (80–90 %), RB1 (60–90 %), and PTEN loss of heterozygosity (13 % of all tumors) [41]. Chromosomal deletions have been reported in the regions of 3p, 4p, 5q, 16q, 13q, and 17p though the significance of these is not well understood. Infrequently, tumor cells carry activating mutations of proto-oncogenes including *KRAS*, *EGFR*, *C-myc*, and *C-KIT* [41]. These mutations have led to experimentation with several targeted therapies such as sorafenib, gefitinib, imatinib, and others (Table 6). Unfortunately, the vast majority of these targeted agents have failed to increase survival. SCLC tumors also exhibit increased levels of vascular endothelial growth factor, which likely enables their invasive and angiogenic potential; however, treatment with bevacizumab has not been shown to increase survival. Despite the multiple failures of many targeted agents, early in vitro studies suggest that poly (ADP-ribose) polymerase (PARP) inhibitors may show some activity against SCLC [45, 46]. More clinical trials are needed to support these positive preliminary findings. Finally, a study recently published in 2015 revealed a statistically significant increase in progression-free survival from 2.1 months to 3.7 months when sunitinib (a multiple receptor tyrosine kinase inhibitor) was used as maintenance therapy for extensive stage SCLC [47]. SCLC research has clearly demonstrated that SCLC has distinct biology from NSCLC and targeted agents that have activity in NSCLC do not show similar results in SCLC.

Cigarette smoking is the strongest risk factor for the development of SCLC and continued smoking after diagnosis is also associated with a poorer prognosis. Research has shown that nicotine enhances tumor growth, angiogenesis, metastatic

Table 6 Targeted agents that have been studied in the treatment of SCLC

Agent	Mechanism of action	Result
Sorafenib	Inhibits intracellular Raf kinases, most notably BRAF, and cell surface kinase receptors most notably, vascular endothelial growth factor (VEGFR)	No benefit
Thalidomide	Immunomodulatory and antiangiogenic effects vary given targeted cancer	No benefit
Bevacizumab	Monoclonal antibody which binds VEGFR	No benefit
Marimastat	Matrix metalloproteinase inhibitor	No benefit
Vandetanib	Tyrosine kinase inhibitor (TKI) of epidermal growth factor reception (EGFR) and VEGF	No benefit
Gefitinib	TKI inhibits multiple cell surface receptors including EGFR	No benefit
Imatinib	Inhibits Bcr-Able tyrosine kinase produced by the Philadelphia chromosome	No benefit
Bortezomib	Proteasome inhibitor	No benefit
Oblimersen	Antisense oligodeoxyribonucleotide directed at blocking production of Bcl-2	No benefit
Temsirolimus	Mechanistic target of rapamycin (mTOR) inhibitor	No benefit
AT 101	Inhibitor of the anti-apoptotic Bcl proteins (Bcl-2, Bcl-XL, Bcl-W, and Mcl-1) and an inducer of the pro-apoptotic proteins noxa and puma	No benefit
Romidepsin	Histone deacetylase inhibitor	No benefit
Dasatinib	Second generation BCR-ABL TKI	No benefit
Cediranib	TKI targeting VEGFR-1, 2, and 3, PDGFR-alpha/beta, FGFR-1, and c-kit	No benefit
Sunitinib	TKI targeting PDGFR, VEGFR1-3, FLT3, CSF-R1, and RET	Benefit [47]

potential, and chemoresistance [48]. Tumor growth and increased metastatic potential are thought to occur by nicotine-induced increased migration of malignant cells through collagen matrices. Nicotine also protects cells from apoptosis, thereby conferring chemoresistance. Interestingly, these effects are reversible with the withdrawal of nicotine during in vitro studies [48]. These data highlight the importance of smoking cessation even after the diagnosis of SCLC is made.

8 Immune Therapy

As discussed in treatment of ED SCLC, chest radiotherapy to the original small cell tumor confers a survival benefit in the face of metastatic disease [38]. Similar benefit has been shown in other solid organ malignancies, most notably renal cell carcinoma where resection of the primary tumor leads to improvement in survival [49]. The mechanism behind this observation has not been well defined. One theory suggests that the primary tumor may act as an immunologic sink, thereby diverting circulating antibodies and lymphocytes away from the sites of distant metastasis [50]. Another theory suggests that the bulk of the primary tumor may suppress the body's natural antitumor response through potentiating tolerance to the mass [49].

These observations along with others have led to testing a variety of immune therapies in SCLC. In a 2013 phase II study, SCLC patients were randomized to receive chemotherapy alone versus chemotherapy combined with interferon alpha. A small but statistically significant survival benefit was found in patients with LD [51]. Furthermore, improvement in immune markers accompanied clinical improvement, whereas decline in the same markers was associated with disease progression. Tumor vaccines have also been studied in the treatment of SCLC. Up to 90 % of patients have accumulation of altered p53 in their cancer cells, and targeting p53 by vaccine has been evaluated by phase II clinical trials. The overall immune response rate was low with anti-p53 immunity developing in only 41.8 % of patients in one study and 51.1 % in the second [4]. However, within the subset of patients developing immunity, response rates were significantly higher. Also of note, the ganglioside antigen N-glycolyl-GM3 is highly expressed in SCLC cells. This has led to phase I, II, and III studies to evaluate benefit from the vaccination of its anti-idiotypic antibody, 1E10 [4]. Unfortunately, the phase III trial did not improve survival, possibly because only a third of patients developed a detectable antibody response after vaccination.

More recently, ipilimumab (an anti-CTLA4 monoclonal antibody) has been studied in combination with carboplatin and paclitaxel in first-line ED SCLC [52]. The study yielded some useful hints at possible successful strategies harnessing the immune system including the importance of timing of immune therapies. Phased ipilimumab (ipilimumab given after chemotherapy) improved immune-related progression-free survival while concurrent ipilimumab (ipilimumab given with chemotherapy) did not [52]. However, there was no improvement in overall survival while immune-related adverse events were significant [52]. Pembrolizumab has shown some single agent activity in PD L1 positive SCLC patients and the activity of nivolumab in combination with ipilimumab seems promising. Further studies are needed to demonstrate whether immune therapies will have a place in treatment of SCLC.

9 Conclusion

In 2012, Congress passed the Recalcitrant Cancer Act, thereby requiring the National Cancer Institute (NCI) to develop scientific frameworks that will promote scientific and therapeutic progress against recalcitrant or deadly cancers [53]. SCLC was identified as one of these cancers given a five-year survival rate of less than 7 % with the loss of approximately 30,000 lives per year. The scientific framework put forth included building better research tools for the study of SCLC by increasing the collection of tumor tissue specimens, developing new tumor models including genetically engineered mouse models, expanding genomic profiling in hopes of developing new targeted therapies, and examining the underlying mechanisms contributing to the high rate of initial chemotherapeutic response yet rapid resistance following primary treatment. Given the lack of progress in the treatment of SCLC over the last 30 years, the hope is that this new scientific framework will lead to better treatment options for this deadly cancer.

References

1. Siegel R, Ma J, Zou Z (2014) Cancer statistics, 2014. CA Cancer J Clin 64(1):9–29
2. Govindan R, Page N, Morgensztern D et al (2006) Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 24:4539–4544
3. Oberg K, Hellman P, Kwekkeboom D, Jelic S (2010) Neuroendocrine bronchial and thymic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 21(Suppl 5):v220–v222
4. Bridle BW (2011) Neuroendocrine cancer vaccines in clinical trials. Expert Rev Vaccines 10 (6):811–823
5. Kanaji N, Watanabe N, Kita N (2014) Paraneoplastic syndromes associated with lung cancer. World J Clin Oncol 5(3):197–223
6. Brink I, Schumacher T, Mix M et al (2004) Impact of [18F]FDG-PET on the primary staging of small-cell lung cancer. Eur J Nucl Med Mol Imaging 31:1614
7. Vallières E, Shepherd FA, Crowley J et al (2009) The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol 4:1049
8. Shepherd FA, Crowley J, Van Houtte P et al (2007) The international association for the study of lung cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. J Thorac Oncol 2(12):1067–1077
9. Kalemkerian GP, Akerley W, Bogner P et al (2013) Small cell lung cancer. J Natl Compr Canc Netw 11:78–98
10. Lad T, Piantadosi S, Thomas P et al (1994) A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. Chest 106(6):320S–323S
11. Einhorn LH, Crawford J, Birch R et al (1988) Cisplatin plus etoposide consolidation following cyclophosphamide, doxorubicin, and vincristine in limited small-cell lung cancer. J Clin Oncol 6(3):451–456

12. Johnson DH, Bass D, Einhorn LH et al (1993) Combination chemotherapy with or without thoracic radiotherapy in limited-stage small-cell lung cancer: a randomized trial of the Southeastern Cancer Study Group. J Clin Oncl 11(7):1223–1229
13. Turrisi AT, Kyungmann K, Blum R et al (1999) Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 340:265–271
14. Sundstrom S, Bremnes RM, Aasebo U et al (2002) Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. J Clin Oncol 20(24):4665–4672
15. Pujol JL, Carestia L, Dauries JP (2000) Is there a case for cisplatin in the treatment of small cell lung cancer? A meta-analysis of randomized trials of a cisplatin-containing regimen versus a regimen without this alkylating agent. Br J Cancer 83(1):8–15
16. Mascaux C, Paesmans M, Berghmans T et al (2000) A systematic review of the role of etoposide and cisplatin in the chemotherapy of small cell lung cancer with methodology assessment and meta-analysis. Lung Cancer 30(1):23–36
17. Pignon JP, Arriagada R, Ihde DC et al (1992) A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 237:1618–1624
18. Warde P, Payne D (1992) Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol 10(6):890–895
19. Takada M, Fukuoka M, Kawahara M et al (2002) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 20(14):3054–3060
20. Perry MC, Eaton WL, Propert KJ et al (1987) Chemotherapy with or without radiation therapy in limited small-cell carcinoma of the lung. N Engl J Med 316(15):912–918
21. Murray N, Coy P, Pater JL et al (1993) Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 11(2):336–344
22. Work E, Nielson OS, Bentzen SM, Fode K, Palshof T (1997) Randomized study of initial versus late chest irradiation combined with chemotherapy in limited-stage small-cell lung cancer. Aarhus Lung Cancer Group. J Clin Oncol 15(9):3030–3037
23. Jeremic B, Shibamotot Y, Acimovic L, Milisavljevic S (1997) Initial versus delayed accelerated hyperfractionated radiation therapy and concurrent chemotherapy in limited small-cell lung cancer: a randomized study. J Clin Oncol 15(3):893–900
24. Fried DB, Morris DE, Poole C et al (2004) Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol 22(23):4837–4845
25. Bonner JA, Sloan JA, Shanahan TG et al (1999) Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small- cell lung carcinoma. J Clin Oncol 17:2681
26. Auperin A, Arriagada R, Pignon JP et al (1999) Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. N Engl J Med 341:476–484
27. DeAngelis LM, Delattre JY, Posner JB (1989) Radiation-induced dementia in patients cured of brain metastases. Neurology 39:789
28. Fukuoka M, Furuse K, Saijo N et al (1991) Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. J Natl Cancer Inst 83:855
29. Noda K, Nishiwaki Y, Kawahara M et al (2002) Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346:85–91
30. Lara PN Jr, Natale R, Crowley J, Lenz HJ, Redman MW, Carleton JE, Jett J, Langer CJ, Kuebler JP, Dakhil SR, Chansky K, Gandara DR (2009) Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 27:2530–2535

31. Skarlos DV, Samantas E, Kosmidis P et al (1994) Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group Study. Ann Oncol 5(7):601–607
32. Okamoto H, Watanabe K, Kunikane H et al (2007) Randomized phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer. Br J Cancer 97:162–169
33. Johnson DH, Einhorn LH, Birch R et al (1987) A randomized comparison of high-dose versus conventional-dose cyclophosphamide, doxorubicin, and vincristine for extensive-stage small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 5(11):1731
34. Ihde DC, Mulshine JL, Kramer BS et al (1994) Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. J Clin Oncol 12(10):2022
35. Bozcuk H, Artac M, Ozdogan M, Savas B (2005) Does maintenance/consolidation chemotherapy have a role in the management of small cell lung cancer (SCLC)? A meta-analysis of the published controlled trials. Cancer 104(12):2650
36. Hanna NH, Sandier AB, Loehrer PJ et al (2002) Maintenance daily oral etoposide versus no further therapy following induction chemotherapy with etoposide plus ifosfamide plus cisplatin in extensive small-cell lung cancer: a Hoosier Oncology Group randomized study. Ann Oncol 13(1):95
37. Bleehan NM, Girling DJ, Stephens RJ (1993) A randomised trial of three or six courses of etoposide cyclophosphamide methotrexate and vincristine or six courses of etoposide and ifosfamide in small cell lung cancer (SCLC). Br J Cancer 68(6):1157–1166
38. Slotman BJ, van Tinteren H, Praag JO et al (2014) Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 9962(385):36–42
39. Jeremic B, Shibamoto Y, Nikolic N et al (1999) Role of radiation therapy in the combine-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. J Clin Oncol 17(7):2092–2099
40. Slotman BJ, Faivre-Finn C, Kramer G et al (2007) Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 357:664–672
41. Seto T, Takahashi T, Yamanaka T et al (2014) Prophylactic cranial irradiation (PCI) has a detrimental effect on the overall survival (OS) of patients (pts) with extensive disease small cell lung cancer (ED-SCLC): results of a Japanese randomized phase III trial. J Clin Oncol 32:5s (suppl; abstr 7503)
42. O'Brien ME, Ciuleanu TE, Tsekov H et al (2006) Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol 24(34):5441–5447
43. von Pawel J, Schiller JH, Shepherd FA et al (1999) Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 17:658–667
44. Pleasance ED, Stephens PJ, O'Meara J et al (2001) A small cell lung cancer genome reports complex tobacco exposure signatures. Nature 463(7278):184–190
45. Cardnell RJ, Feng Y, Diao L et al (2013) Proteomic markers of DNA repair and PI3K pathway activation predict response to the PARP inhibitor BMN 673 in small cell lung cancer. Clin Cancer Res 19:6322
46. Byers LA, Wang J, Nilsson MB et al (2012) Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. Cancer Discov 2:798
47. Ready NE, Pang HH, Gu L et al (2015) Chemotherapy with or without maintenance sunitinib for untreated extensive-stage small-cell-lung cancer: a randomized, double-blind, placebo-controlled phase II study. J Clin Oncol. Advanced online publication. doi:10.1200/JCO.2014.57.3105

48. Martinez-Garcia E, Irigoyen M, Gonzalez-Moreno O et al (2010) Repetitive nicotine exposure leads to a more malignant and metastasis-prone phentotype of SCLC: a molecular insight into the importance of quitting smoking during treatment. Toxicol Sci 116(2):467–476
49. Freed SZ (1977) Nephrectomy for renal cell carcinoma with metastases. Urology 9(6):613–616
50. Robertson CN, Linehan WM, Pass HI et al (1990) Preparative cytoreductive surgery in patients with metastatic renal cell carcinoma treated with adoptive immunotherapy with interleukin-2 or interleukin-2 plus lymphokine activated killer cells. J Urol 144:614–618
51. Zarogoulidis K, Boutsikou E, Zarogoulidis P et al (2013) Immunomodifiers in combination with conventional chemotherapy in small cell lung cancer: a phase II, randomized study. Drug Des Dev Ther. 7:611–617
52. Reck M, Bondarenko I, Luft A et al (2013) Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol 24(1):75–83
53. United States (2012) Recalcitrant Cancer Research Act of 2012. Subpart 1 of part C of title IV of the Public Health Service Act (42 U.S.C. 285 et seq.) amended and passed by the House of Representatives, 19 Sept 2012
54. Thomas CR, Giroux DJ, Janaki LM et al (2001) Ten-year follow-up of Southwest Oncology Group 8269: a phase II trial of concomitant cisplatin-etoposide and daily thoracic radiotherapy in limited small-cell lung cancer. Lung Cancer 33(2–3):213–219
55. Edelman MJ, Chansky K, Gaspar LE et al (2004) Phase II trial of cisplatin/etoposide and concurrent radiotherapy followed by paclitaxel/carboplatin consolidation for limited small-cell lung cancer: Southwest Oncology Group 9713. J Clin Oncol 22(1):127–132
56. Maranzano E, Crino L, Piro F et al (2002) Long-term results of induction chemotherapy followed by concurrent chemotherapy and thoracic irradiation in limited small cell lung cancer. Lung Cancer 37(1):79–85
57. Bogart JA, Herndon JE, Lyss AP et al (2004) 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B Study 39808. Int J Radiat Oncol Biophys 59(2):460–468

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