Non-small-cell lung cancer (NSCLC) is the leading cause of cancer death worldwide. Before 1980, radiotherapy was considered the only real recourse in advanced disease. In 1995, a landmark meta-analysis of trials conducted in the 1980s and early 1990s demonstrated a survival benefit with platinum-based chemotherapy. Newer chemotherapy agents and improved supportive care measures have allowed more patients to benefit from chemotherapy with reduced toxicity. Concurrent platinum-based chemotherapy and radiotherapy has improved the survival in stage III disease, and recently chemotherapy has also demonstrated improved survival in resected early-stage disease. The majority of patients still present with advanced unresectable disease for whom the prognosis remains poor, but for key subpopulations the outlook has improved markedly since the emergence of targeted therapies directed against the epidermal growth factor receptor and vascular endothelial growth factor receptor pathways. Patient selection and the incorporation of targeted therapies with cytotoxic chemotherapy are the focus of many ongoing studies, and there is an abundance of new agents undergoing clinical trials. Together, these developments have moved us away from the nihilism of 20 years ago into an era of unprecedented optimism in taking on the many remaining challenges of managing NSCLC in the 21st century.

Lung cancer is the leading cause of cancer death worldwide, and it has been the most common cause of death from malignancy in the United States in men since the mid-1950s and in women since the mid-1980s.[1] While incidence and death rates from lung cancer peaked in men in 1990, the incidence and death rates in women continue to increase.[2] Approximately 85% of lung cancer cases are non-small-cell lung cancer (NSCLC), with the dominant histologic subtype in women drifting from squamous carcinoma to adenocarcinoma during the mid-1980s and the same drift occurring in men during the mid-1990s.[2] In the past 20 years, our methods of detecting, defining, and treating NSCLC have all undergone considerable change. This paper reviews the most significant of these changes and assesses their overall impact on the clinical management of NSCLC.

**Diagnosis: Screening, Staging, and Histologic Definition**

In those who are eligible, surgery has always offered the best chance of cure. A number of studies of screening in high-risk individuals by chest x-rays, sputum cytology, and computed tomography (CT) scanning have been reported since the mid-1980s, but the benefits and cost-effectiveness of routine screening for lung cancers have still not been definitively established.[3] The majority of patients with NSCLC continue to present with advanced inoperable disease. Apart from overt metastatic disease, the nodal status of NSCLC remains the most common determinant of operability. Up to approximately 70% of lymph nodes found to be positive at thoracotomy are in stations not accessible by standard mediastinoscopy.[4] Although the newest video-assisted thoracoscopic surgical (VATS) procedures potentially allow access to all lymph node stations, the real debate in recent years has become when and in whom should a mediastinoscopic assessment be performed. Because of the high false-negative rate and moderate false-positive rate for CT scanning alone in the mediastinum,[5] some have recommended preoperative mediastinoscopy in all potentially operable patients regardless of the CT scan results, while others routinely omit this procedure for small peripheral lesions without enlarged lymph nodes. Positron-emission tomography (PET) or PET/CT scanning is becoming commonplace and appears to be complementary to CT alone, with the primary role of the combination being in its high negative-predictive value. A negative PET/CT work-up may eventually preclude preoperative mediastinoscopy, with invasive preresection staging being restricted to confirming/denying suspicious lymph nodes, because of the moderate false-positive rate associated with both imaging modalities.[6]

The American Joint Committee for Cancer Staging (AJCC) originally adapted the
tumor-node-metastasis (TNM) system of Denoix into a staging system for NSCLC in 1974.[7] Since then, subgroups within the initial stages have been recognized (ie, with different outcomes or likely to benefit from different interventions), and two revisions of the AJCC system have been issued.[8,9] The World Health Organization system for histologic classification of lung cancers has also undergone a series of revisions since its first publication in 1967. Between 1981 and 1999, categories covering large-cell neuroendocrine carcinoma, spindle/giant cell carcinoma, and adenocarcinoma with mixed histologies were all added.[10,11] In 1999, bronchioalveolar carcinoma, listed as a subtype of adenocarcinoma since 1967, was more rigidly defined to include only tumors demonstrating pure lepidic, noninvasive growth.[11]

**Treatment of Potentially Operable Disease**

Improved preoperative work-up for predicting residual lung function, improved surgical techniques/equipment, and better supportive care have all made some previously inoperable patients operable. With additional improvements in imaging to fully delineate the extent of disease, minimalist surgery has also become more practical. VATS lobectomies have been reported as equivalent to conventional lobectomies, while wedge resections or segmentectomies have been associated with higher rates of local recurrence than lobectomies.[12,13] Probably the most significant change in the operative arena, however, has been in clarifying the roles of chemotherapy and radiotherapy as adjuncts to surgery, such that the standard management of any potentially operable NSCLC should now include a multidisciplinary team discussion.

**Adjuvant Radiotherapy**

Adjuvant radiotherapy, as a means to sterilize the resection margins, tumor bed, and regional lymph nodes postoperatively was demonstrated to dramatically reduce the risks of local recurrence from 41% to 3% for node-positive squamous carcinoma of the lung in the mid-1980s.[14] However, adjuvant radiotherapy was dealt a heavy blow in 1998 by the postoperative radiotherapy (PORT) meta-analysis. Not only did PORT not show any survival benefit in completely resected N2 disease, but survival in N0-1 disease was worsened,[15] with the survival curves separating after approximately 4 months postradiotherapy. This timing fits well with radiation-induced pneumonitis as the potential cause. Many believe that these results cannot be applied to radiotherapy using more modern planning techniques or, at the very least, that the question should be addressed for such techniques within more up-to-date trials of PORT.

**Adjuvant Chemotherapy**

In 1995, a comprehensive meta-analysis suggested that alkylating agents given in the adjuvant setting adversely affected survival (hazard ratio [HR] = 1.15, P < .005).[16] In contrast, cisplatin-based adjuvant trials showed a trend towards benefit (HR = 0.87, P = .08). As a consequence of this meta-analysis, a series of large randomized, controlled adjuvant trials focusing on platinum-based regimens were undertaken.

- **Key Trials**-The first such trial, the Adjuvant Lung Project Italy (ALPI), did not show a significant difference for adjuvant MIC chemotherapy (mitomycin, ifosfamide, cisplatin) in stage I-IIIA disease in terms of overall survival (HR = 0.96, 95% confidence interval [CI] = 0.81-1.13).[17] Soon afterwards, the positive results of the International Adjuvant Lung Cancer Trial (IALT), using a variety of more modern cisplatin-based doublets in stage I-III disease, were reported.[18] Overall survival favored adjuvant chemotherapy (HR = 0.86, 95% CI = 0.76-0.98), translating to a 4.1% increase in 5-year survival. Despite concerns about the impact of imbalances in PORT between the arms, and the lower-than-planned recruitment numbers, the result was hailed as a new standard of care. The study appeared to show more benefit for patients with higher-stage disease than for those with lower-stage disease, although the investigators were resistant to any formal subgroup analysis.

The following year, the positive results of the JBR.10 trial of cisplatin/vinorelbine in stage IB and II disease (HR = 0.69, 95% CI = 0.52-0.91) and the interim results at 34 months' follow-up of the CALGB 9633 trial of carboplatin/paclitaxel in stage IB disease (HR = 0.62, 95% CI = 0.41-0.95) were both announced at the 2004 American Society of Clinical Oncology (ASCO) meeting.[19,20] Subgroup analysis within JBR.10 showed that only patients with stage II (HR = 0.59, 95% CI = 0.42-0.85), and not stage IB disease, benefited from adjuvant chemotherapy.

At ASCO 2005, the results of yet another positive trial, in stage IB-IIIA disease were announced,[21] with subset analysis again suggesting benefit from chemotherapy in stages II-IIIA, but not stage IB. Some may initially have speculated that the cisplatin doublets used in these other trials were not as effective as the carboplatin/paclitaxel used for stage IB in CALGB 9633. However, at ASCO 2006, when the updated CALGB 9633 results at 54 months' median follow-up were announced, the trend toward improved survival was no longer statistically significant (HR = 0.80, 90% CI = 0.60-1.07).[22] Whether the negative result of CALGB 9633 reflects drug effects, stage effects, or simply the fact
that, due to slow accrual, only 344 patients were randomized (making it the smallest of these key adjuvant studies and therefore the lowest powered) continues to be debated.

**Conclusions** - We are left in a position where the evidence base does not support the widespread use of adjuvant chemotherapy for stage I disease. Stage IB patients certainly require further study in the context of a clinical trial. With regard to the optimal adjuvant chemotherapy regimen for resected higher-stage disease, the question remains open as to whether carboplatin/paclitaxel (the US standard in advanced disease) should be used in this setting in the absence of data, or whether the fact that more data are available for cisplatin in combination with vinorelbine or other agents should alter our practice.

It is now likely that we will have to follow a similar path to our colleagues in breast cancer, in painstakingly exploring the exact risks and benefits of different adjuvant treatments in different subgroups over the coming years. As an early indicator of some of the factors that may have to be considered, immunohistochemical profiling in the IALT study of the nucleotide excision repair gene product ERCC1—associated with platinum resistance through adduct repair—demonstrated that only ERCC1-negative tumors had significantly prolonged survival compared to observation (HR = 0.67, 95% CI = 0.51-0.89).[23]

**Neoadjuvant Chemotherapy and Chemoradiotherapy**

A number of theoretical advantages, as well as disadvantages, have become apparent for neoadjuvant chemotherapy vs adjuvant chemotherapy. In the early to mid-1990s, two small randomized trials of neoadjuvant cisplatin-based chemotherapy in stage IIIA disease were reported that changed many US oncologists' practice, at least for a time.

Both studies suggested that survival in stage IIIA disease (using the 1986 AJCC staging system, hence including some cases of T3, N0, M0) could be dramatically improved by treatment plans containing elements of neoadjuvant chemotherapy.[24,25] Although several comparably sized or larger studies across stages I-IIIA have subsequently shown similar benefits in terms of hazard ratios, none have proven statistically significant to date.[26-28] When the original Roth study was reanalyzed at 82 months' follow-up, the actual (no longer estimated) median and 3-year survivals were also no longer significantly different between the two arms.[29] In contrast, when the Rosell study was reanalyzed at 7 years' follow-up, the median survival was still 22 vs 10 months (P = .005).[30] The results of several large neoadjuvant chemotherapy trials, using more modern drug regimens and covering all stages of disease from IA to IIIA are awaited.

In 2003, the Intergroup 0139 study addressed the issue of trimodality neoadjuvant chemoradiotherapy vs bimodality definitive chemoradiotherapy in potentially resectable N2, IIIA disease (T1-3, N2, M0).[31] The investigators found no difference in overall survival but an excess of early deaths in the surgical arm, mostly from acute respiratory distress syndrome and mostly in patients undergoing right pneumonectomies. Median progression-free survival favored the surgical arm. While some surgeons may interpret this as showing a potential benefit for surgery, particularly if high-risk right pneumonectomies could be avoided, the trimodality approach currently cannot be recommended as standard. The only notable exception is in the treatment of T3-4, N0-1, M0 superior sulcus (Pancoast) tumors, for which trimodality therapy is currently accepted as the standard of care.[32]

Pragmatic, although not always data-driven, algorithms and case-by-case decision-making for the management of most stage IIIA and some IIIB disease are still needed: ie, neoadjuvant chemotherapy for all, chemotherapy or chemoradiotherapy only for those with anticipated difficult resections, and so forth. Given the large numbers required to show benefit in the adjuvant setting and the suggestion of risk-benefit ratios specific to molecular biology, disease stage, and possibly drug therapy, more randomized studies will be needed to truly tell us whether (or in whom) neoadjuvant chemotherapy or chemoradiotherapy, with or without targeted therapy, adds anything beyond what can be achieved with modern adjuvant regimens.

**Definitive Nonsurgical Therapy in Stage I-IIIB Disease**

It has always been the case that some patients with NSCLC do not want surgery, some are not fit enough for surgery, and some have locally advanced disease that is not amenable to surgery (bulky N2 IIIA, and IIIB disease). In the late 1990s, two large randomized trials demonstrated significant improvements in survival, from approximately 10 months to approximately 14 months for cisplatin/vinblastine chemotherapy followed by radiotherapy compared to radiotherapy alone.[33,34] Concurrent chemoradiotherapy was subsequently demonstrated to be superior to sequential treatments, with median survivals increasing from 12.9-14.6 months to 16.6-17 months.[35,36] The best radiosensitizer/systemic therapy and doses to use in this setting, as well as the optimal...
sequencing of additional chemotherapy cycles relative to the radiotherapy, continue to be explored. At about the same time that concurrent chemoradiotherapy was proving superior to sequential treatment, there was also considerable excitement in the NSCLC radiotherapy field: Continuous hyperfractionated accelerated radiotherapy (CHART), delivered at 54 Gy in 1.5-Gy fractions three times a day, 7 days a week, proved superior to conventional radiotherapy administered at 60 Gy in once-daily 2-Gy fractions, 5 days a week, in patients with stage I-IIIB disease. The logic of this approach, based on the reduction of tumor cell repopulation during treatment, was well validated with clear survival benefits.[37]

Unfortunately, the apparent benefit of simply administering radiotherapy more frequently during the day and on the weekends turns out to be relatively impractical in the real world, and as a consequence, 5-day-per-week regimens (variably called CHARTWEL [for "weekend-less"] or HART) and twice-daily regimens have been explored. It remains to be seen whether C/HART-like regimens offer additional benefit over the more convenient traditional radiotherapy regimens (when both are delivered concurrently with chemotherapy), or over a dose escalation of traditional fractionation regimens using more modern planning techniques.

**Advanced-Stage NSCLC: From Nihilism to Active Disease Control**

In 1995, the *British Medical Journal* meta-analysis established that platinum-based chemotherapy prolonged life in patients with advanced NSCLC. This was the first proof that any therapy could prolong survival for these patients. Still, the benefits were modest, with chemotherapy appearing to increase 1-year survival from 5% to 15% and only prolong median survival by 1.5 months.[16] The chemotherapy regimens used were quite toxic, and few supportive care measures were available at the time, so a general feeling of nihilism about anticancer treatment in advanced-stage NSCLC persisted. Randomized trials continued to include best supportive care arms.[38]

Cisplatin and carboplatin are the mainstays of therapy in unresectable stage III and IV NSCLC.[38] Early platinum combinations contained etoposide, ifosfamide, mitomycin, vindesine, and vinblastine in doublets or triplets and were associated with severe myelosuppression, nausea, and vomiting. Platinum doublets containing the so-called third-generation drugs (paclitaxel, vinorelbine, docetaxel [Taxotere], or gemcitabine [Gemzar]), introduced from the early 1990s onwards, consistently appear to be superior to single-agent platinum chemotherapy in the first-line setting (Table 1).[39-42] Comparisons with older cisplatin-containing multidrug regimens have not been exhaustive but have tended to show either equivalent or better efficacy with improved tolerability.[38,43,44]
Cytotoxic triplets containing third-generation drugs often produce small increases in response rate but coupled with considerable increases in toxicity, and without significant benefit in terms of survival.[45]

One of the largest phase III studies in NSCLC, the Eastern Cooperative Ongology Group (ECOG) 1594 trial, randomized patients to one of four modern platinum-containing doublet regimens, and 1- and 2-year survival rates were not significantly different between any of the arms.[46] The take-home message from this and related studies was that we had reached a plateau in terms of standard chemotherapy's anticancer efficacy, with modern doublets all being roughly equivalent—at least in the advanced-disease setting—and that the final choice of doublet could be based on cost.
convenience, and anticipated -toxicities. Similarly, randomized trials and meta-analyses of these trials showed that third-generation non-platinum-containing doublets do not differ significantly from platinum-based doublet therapy in terms of overall efficacy. These combinations tend to be more costly but may be considered appropriate when there are concerns over platinum-related toxicity.

**Second-Line Chemotherapy**

Initial work with docetaxel administered at 75 mg/m\(^2\) compared to best supportive care in the second-line setting showed a significant survival advantage, but this advantage was lost at a dose of 100 mg/m\(^2\) due to increased toxicity. Although overall survival was no different, docetaxel 75 mg/m\(^2\) was significantly better (in terms of 1-year survival) than vinorelbine or ifosfamide in the same setting and was associated with higher response rates. In 2004, pemetrexed (Alimta) was shown to be clinically equivalent (in terms of response rate, progression-free survival, and overall survival) to second-line docetaxel, but with significantly fewer neutropenia-related complications and less alopecia. Based on these data, the US Food and Drug Administration approved both agents for use in the second-line setting in the United States. Erlotinib (Tarceva) is also approved in the second- and third-line settings and is discussed further below.

**Duration of Chemotherapy**

The optimal duration of cytotoxic chemotherapy remains controversial. Between two and eight cycles of cisplatin-based treatment were used in the trials included in the 1995 meta-analysis, forming the basis for the 1997 ASCO recommendations of two to eight cycles of treatment in the first-line setting. Subsequently, there was shown to be no difference in time to progression or survival for three vs six cycles of mitomycin, ifosfamide, and cisplatin; or four cycles of carboplatin/paclitaxel vs treatment until disease progression. The current ASCO recommendations (from 2003) state that in stage IV disease, first-line chemotherapy should be stopped at four cycles in those who are not responding, and that no more than six cycles should be administered in total.

That said, no data inform the duration of therapy in the second-line setting. In the phase III trials of docetaxel, although treatment could be given until progression, the median number of cycles administered was still only three to four. In responders, however, the median number of cycles was much higher (median = 10, range = 4-28).

**Targeted Therapy for Advanced-Stage Disease**

To date, the two big targeted-therapy breakthroughs in NSCLC relate to agents that target the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) signalling pathways.

- **Gefitinib and Erlotinib**- Gefitinib (Iressa) exploded onto the scene in 2000 with reports of dramatic and rapid responses in some heavily pretreated NSCLC patients within the first phase I studies. Phase I results of erlotinib, another orally bioavailable small-molecule EGFR inhibitor, showed similar promise at the ASCO meeting the following year. It would be difficult to underemphasize the importance of what happened next—both to the ongoing management of NSCLC and to modern oncology drug development.

The maximum tolerated dose (MTD) of gefitinib, using a continuous daily dosing regimen, was 600 mg. As gefitinib demonstrated responses across the 150-700 mg range (unlike cytotoxic therapies, which have traditionally shown responses within 80% to 120% of the MTD), the possibility of effective dosing below the MTD—the so-called biologically effective dose—was championed. Continuous daily dosing with gefitinib at 250 mg was compared to 500 mg in two large randomized phase II studies (IDEAL 1 and 2). Response rates in the two trials ranged from 9% to 19%, with no discernible differences between the two doses, except in terms of toxicity. As a consequence, 250 mg was the dose of gefitinib put forward to use in combination with first line gemcitabine/cisplatin or paclitaxel/carboplatin in the first phase III studies (INTACT 1 and 2); and in the monotherapy vs best supportive care study (ISEL). In contrast, the MTD of erlotinib was 150 mg, and it was this dose, with its associated higher plasma area under the curve (AUC), that was used in the similarly designed phase III chemotherapy combination studies (TALENT and TRIBUTE) and in the study of monotherapy compared to best supportive care (BR.21).

Erlotinib and gefitinib initially seemed similar in terms of efficacy (or rather, lack of efficacy) in that continuous dosing with either agent did not add to the benefits of cytotoxic chemotherapy in the first-line NSCLC setting. However, while the monotherapy ISEL study showed only a small nonsignificant improvement in survival for gefitinib compared to placebo (HR = 0.89, 95% CI = 0.77-1.02), in BR.21, erlotinib monotherapy did prolong survival significantly (HR = 0.70, 95% CI =
Selection of patients for erlotinib and gefitinib remains a focus of attention. In the early studies, certain key histologic and demographic features (adenocarcinoma, female gender, never smoking, Asian ethnicity) were identified as predisposing toward responses. As we try to move from clinical to truly biologic selection factors, excitement continues over whether specific mutations in the cytoplasmic tail of the EGFR and/or EGFR gene amplification—partially overlapping with these other risk categories—will help identify not just responders, but those who will have survival benefit.[67] The identification of negative biologic factors such as k-ras mutations, which may help to actively weed out those who will not benefit, is also being actively pursued.[68] Of note, some evidence suggests that patients with EGFR mutation-bearing tumors do better than nonmutants regardless of EGFR inhibitor treatment. As such, the distinction between predictive and prognostic markers will become increasingly important over time, as well as the precise methods used for any molecular analyses.[67,69,70] Randomized studies of EGFR inhibitors in variously enriched NSCLC populations, from the first-line metastatic to the adjuvant setting, are already underway.

Whether imbalances in the arms of the ISEL and BR.21 studies in terms of these or other features contributed to the divergent fortunes of these two drugs, or whether it is all down to dose, with survival benefit requiring higher doses of drug than those required for responses (either because of off-target effects or simply heterogeneous sensitive cell populations) continues to be debated.[68,71,72] Either way, it is clear that a policy of choosing a better-tolerated dose of targeted therapy purely on the basis of equivalent response rate, assuming it to be a good surrogate for demonstrating later equivalent survival benefit, is unlikely to be adopted again. We owe gefitinib and erlotinib investigators a debt of gratitude for showing us the way on this early on. Why EGFR tyrosine kinase inhibitors do not add anything when given in combination with chemotherapy remains unclear. Clinical studies involving intermittent dosing regimens in combination with cytotoxics are ongoing.

- **Bevacizumab**-Bevacizumab (Avastin), a monoclonal antibody against the VEGF ligand, was the second targeted agent to show promising activity in NSCLC, although this time in combination with chemotherapy.[73] Bevacizumab at 15 mg/kg in conjunction with paclitaxel/carbo-platin proved superior to chemotherapy alone, in terms of longer time to progression. However, major hemoptysis/hematemesis, causing life-threatening bleeding, occurred in 9% of patients. All of these patients had centrally located tumors close to major blood vessels, and most of them had squamous cell carcinoma.

At ASCO 2005, an interim analysis of ECOG 4599, a larger randomized phase II/III trial, evaluating the role of bevacizumab in combination with paclitaxel/carboplatin in patients without a history of gross hemoptysis, squamous histology, or brain metastases, was reported. The combination regimen (PCB) was associated with significant improvement in response, progression-free survival, and median survival compared to chemotherapy alone, with major bleeding occurring in only 1.1% of patients.[74] On the basis of these results, PCB has been advocated as the new first-line standard of care in advanced NSCLC among those in whom the risks of bevacizumab are considered acceptable.

- **Looking Ahead**-These front-runners look set to be joined fairly soon by the next generation of targeting agents in NSCLC, with the small-molecule inhibitors of VEGFR taking center stage. Promising single-arm phase II results for sorafenib (Nexavar) and sunitinib (Sutent), and randomized phase II results for ZD6474 (Zactima) vs gefitinib, and for cetuximab (Erbitux), a monoclonal antibody against the EGFR, in combination with or following carboplatin/paclitaxel, were all reported at ASCO 2006.[75-78] Several phase II and III studies comparing chemotherapy alone to chemotherapy with these agents are in progress.

**In Summary: Where We've Come From, Where We Are Heading**

Twenty years ago, NSCLC was mostly squamous cell carcinoma in male smokers. Based on available imaging, if early-stage disease was suspected, then surgery was considered. However, many cases would have been understaged, and relapse rates were high. Radiotherapy was often given postoperatively. Locally advanced disease could be treated with radical radiotherapy, or as with widespread disease, radiotherapy could be reserved for symptom control.

While NSCLC remains an aggressive disease with poor average survival, adenocarcinoma now predominates, and overall management has changed dramatically. Improved imaging has allowed us to more accurately stage patients and, in those with early-stage disease, more appropriately determine the type of operation or preoperative invasive work-up required. Postoperative radiotherapy is now out of favor, and adjuvant chemotherapy is in favor. For locally advanced
disease, concurrent chemoradiotherapy has become the standard of care. Chemotherapy for advanced disease has been proven to prolong survival and improve quality of life, and we appear to be close to maximizing the efficacy and tolerability of combination cytotoxic regimens. We know that the addition of bevacizumab to standard first-line chemotherapy, for those in whom the risks are acceptable, improves outcome and that second-line chemotherapy is also worthwhile. With the advent of the EGFR inhibitors, we are starting to stratify NSCLC into several different diseases that respond better to some therapies than to others. Although there are still many challenges ahead, we have come a very long way and we should be optimistic, maybe for the first time in this field, in terms of our chances of really improving the lives of patients with this terrible disease in the coming years.

References:


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