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Ajmal Khan
Navneet Singh
Department of Pulmonary Medicine,
PGIMER, Chandigarh

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MANAGEMENT OF RESECTABLE NON SMALL CELL LUNG CANCER

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality. Non-small cell lung cancer (NSCLC) represents 85% of cases of lung cancer, and 5-year survival rates are poor in comparison to cancers at other body sites. Approximately one third of NSCLC patients present with early-stage disease that is amenable to potentially curative resection and multimodality therapy. Over 40% of the patients present with advanced and metastatic disease and can only be considered for palliative chemotherapeutic treatment. Approximately 30–35% belong to the locally advanced stages IIIA and IIIB and are best treated within combined modality protocols depending on the initial performance status and the existing comorbidity profile.

The high mortality associated with lung cancer can be attributed to multiple factors: lack of effective screening tools for early detection, failure of local therapy in a majority of patients with early stage disease due to presence of micrometastasis, and lack of curative potential with available systemic therapy.

Improvements to therapy for lung cancer have come in steady, albeit small, increments over the recent years. Better understanding of the biology of the disease, availability of novel chemotherapeutic agents, progress in radiotherapy delivery, and improvements in supportive care measures have all contributed to "growing" optimism in the treatment of lung cancer. Local therapy for patients with early-stage NSCLC, combined-modality therapy with radiation and chemotherapy for locally advanced NSCLC, and systemic chemotherapy for advanced/metastatic NSCLC constitute the current standard of care for NSCLC.

With disease confined to the thorax, surgery is an important, and possibly the most effective, treatment modality. Unfortunately, only 15–20% of these tumors can be radically resected, and, overall, surgically-treated patient survival is only around 40% at 5 years. For advanced disease, palliation and improving patients' quality of life are still the primary goals of therapy, with total cure remaining elusive.

The diagnosis and staging of NSCLC are usually undertaken together, because the approach to achieving a diagnosis usually depends on the presumed stage of the disease. The clinical evaluation remains the most important starting point in the workup of a patient who is suspected of having lung cancer. The initial symptoms, as well as chest imaging, often can be used to establish a presumptive diagnosis and

stage. The staging algorithm for NSCLC should proceed in a sequential fashion with the goal of identifying patients who can be treated with curative intent as quickly and efficiently as possible, while minimizing expensive and invasive testing. This evaluation also needs to identify patients who have incurable disease accurately to minimize the risk of exposing these patients to the morbidity of surgery or combined-modality approaches.

Table 1 : TNM staging of lung cancer

Stage	Tumor	Nodes	Meta-stasis	Definition
IA	T1	N0	M0	T1 tumor: ≤ 3 cm, surrounded by lung or pleura; no tumor more proximal than lobe bronchus
IB	T2	N0	M0	T2 tumor : >3cm, involving main bronchus ≥ 2 cm distal to carina, invading pleura; atelectasis or pneumonitis extending to hilum but not entire lung
IIA	T1	N1	M0	N1: Involvement of ipsilateral peribronchial or hilar nodes and intra, pulmonary nodes by direct extension
IIB	T2 T3	N1 N0	M0 M0	T3 tumor : Invasion of chest wall, diaphragm, mediastinal pleura, pericardium, main bronchus <2 cm distal to carina; atelectasis or pneumonitis of entire lung.
IIIA	T1 T2 T3 T3	N2 N2 N1 N2	M0 M0 M0 M0	N2 : Involvement ipsilateral mediastinal or subcarinal nodes.
IIIB	Any T	N3	M0	N3 : Involvement of contralateral (lung) nodes or any supraclavicular node.
IIIB	T4	Any N	M0	T4 tumor: invasion of mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; separate tumor nodules; malignant pleural effusion
IV	Any T	Any N	M1	Distant metastasis

If the diagnosis of NSCLC is suspected based on the clinical presentation or confirmed by a tissue diagnosis, the TNM system (Table 1) serves as the basis for the staging evaluation. Accurate staging is essential to make estimates of prognosis and to choose the best combination of treatment modalities such as surgery, radiotherapy, and chemotherapy in an attempt to improve survival. The staging system defines the TNM category of each patient who has non-small cell lung cancer (NSCLC). T describes the primary tumor by size and invasiveness, ranging from T1 (< 3 cm and entirely surrounded by lung tissue) to T4 (invading critical organs such as the aorta). N describes the loco-regional lymph node (LN) spread, either no metastatic nodes (N0), to intrapulmonary or hilar nodes only (N1), to ipsilateral mediastinal nodes (N2), or to contralateral mediastinal or supraclavicular nodes (N3). M denotes absence (M0) or presence (M1) of distant metastasis.

The pattern of LN spread; depends, on the site of the primary tumor. Right upper- and middle-lobe tumors often spread to the right hilar and right superior mediastinal nodes, right lower-lobe tumors often spread to the right hilar and inferior mediastinal stations. Left upper-lobe tumors have a predilection for left hilar, aortic, and left paratracheal nodes; left lower-lobe tumors spread to the left hilar nodes and the inferior mediastinal nodes, with a high tendency to cross the midline.

TREATMENT OF EARLY STAGE NON SMALL CELL LUNG CANCER

The most effective treatment for early stages (IA–IIIA) NSCLC is surgical resection. However, up to 60% of patients with IB to IIIA NSCLC relapse after surgery and die. The presence of micrometastatic disease at the time of resection is the most likely cause of recurrence occurring even after complete surgical removal of all macroscopically recognizable disease. The potential for distant relapse increases with advancing disease stage and is the primary cause of lung cancer associated mortality. Micrometastases in patients with radiologically localized lung cancer can be detected by immunohistochemistry and polymerase chain resection assays. If micrometastases are indeed responsible for disease recurrence, adjuvant chemotherapy would be a rational treatment, and this hypothesis has led to attempts to reduce the risk of relapse and death from lung cancer by giving adjuvant chemotherapy to patients with complete surgical resection. Adjuvant chemotherapy for resected

early-stage NSCLC was still a research question until just a few years ago, but has now become the standard of care for patients with resected stage II and IIIA disease.

Full anatomic resection is defined as a resection of either a complete lobe of the lung (lobectomy) or the entire lung (pneumonectomy). Either of these procedures requires dissection and division of hilar, vascular and bronchial structures. Virtually all shared vascular, lymphatic, and vascular divisions are removed as a unit.

Wedge resection refers to the removal of a non-anatomic portion of the lung, usually performed as removal of a “wedge” of parenchymal with tumor near the pleural surface. A segmentectomy is an anatomic resection of a bronchopulmonary segment; however, hilar dissection is not usually required. Both of these lesser operations require division of the lung parenchyma across shared lobar vasculature, lymphatics and bronchi, theoretically increasing the risk of local recurrence.

Treatment of Stage I NSCLC

Complete surgical resection of stage I lung cancer offers the best chance for cure. At present, surgical resection remains the recommended treatment approach for patients with stage I NSCLC. Lobectomy or greater forms of resection are recommended rather than sub-lobar resections (wedge resection or segmentectomy). One group of patients in whom limited resection has been advocated includes those with poor pulmonary function. Lobectomy performed with video assisted thoracoscopic surgery (VATS) can achieve cure rates similar to those performed via thoracotomy. Thus, VATS is recommended in patients who are considered appropriate candidates for thoracoscopic anatomic lung resection (lobectomy or segmentectomy).

For patients with completely resected stage IA NSCLC, postoperative chemotherapy is not recommended. There is very little data available on this subset of patients because most randomized trials on adjuvant chemotherapy have excluded patients with stage IA disease. In the lung adjuvant cisplatin evaluation (LACE) meta-analysis, there was no benefit for postoperative adjuvant cisplatin-based chemotherapy among 347 stage IA NSCLC patients.

For patients with stage IB NSCLC, the majority of recent trials have not found a statistically significant survival benefit for this subset of patients for postoperative adjuvant chemotherapy. The LACE meta-analysis found a trend

toward improvement in survival in 1371 stage IB patients randomized to postoperative cisplatin-based chemotherapy over surgery alone, with an 8% reduction in the risk of death associated with chemotherapy, but this difference was not statistically significant.

However, somewhat different results have been shown in studies from Japan where the use of oral uracil/tegafur (UFT) as an adjuvant therapy to surgery in early stage NSCLC was evaluated. The largest single study of UFT in the adjuvant setting was a multicenter randomized trial conducted by the Japan Lung Cancer Research Group. Patients with completely resected stage I NSCLC were randomized to either observation or treatment with UFT for 2 years. Therapy was well tolerated, with only a 2% incidence of grade 3 toxicities. With the median follow-up time approaching 6 years, a statistically significant difference in overall survival (OS) favoring UFT was observed, with 5-year OS rates of 88% and 85% for UFT and observation, respectively. Subgroup analyses showed that patients with T2 disease significantly benefited from UFT therapy, with a 5-year survival rate of 85% versus 74% in the observation group.

Findings of the above study were further supported by a meta-analysis conducted by the Adjuvant Chemotherapy for Lung Cancer Study Group in Japan. They included data of 2003 patients from 6 randomized controlled trials and showed adjuvant therapy with UFT was associated with a significant improvement in OS compared with surgery alone [hazard ratio (HR) = 0.74; 95% confidence interval (CI) 0.61-0.88; p = 0.001]. But there is no data on the use of adjuvant oral UFT outside Japan that could help to confirm the above findings and therefore its routine use is not recommended.

Treatment of Stage II NSCLC

Like in stage IA, at present, surgical resection remains the recommended treatment approach for patients with stage II NSCLC.

Data for the use of adjuvant cisplatin-based chemotherapy in stage II NSCLC are strong. The International Adjuvant Lung Trial (IALT), National Cancer Institute of Canada JBR.10, and Adjuvant Navelbine International Trialist Association (ANITA) studies all found significant benefit for the use of adjuvant chemotherapy in the general population of NSCLC studied, as well as in the subset of patients with stage II disease. In the LACE meta-analysis, a 27% reduction in the risk of death

(HR = 0.83; 95% CI 0.73-0.95) was found in the 1616 stage II patient subset.

Long-term survival after surgical treatment for T3 (chest wall) NSCLC is highly dependent on the completeness of resection. Thus, for T3 tumors that extend beyond the parietal pleura, *en bloc* resection of T3 (chest wall) NSCLC must be performed and if the tumor does not extend beyond the parietal pleura, an extra-pleural resection may be performed. In centrally located clinical T3 NSCLC, histologic assessment of mediastinal lymph nodes is recommended prior to resection, as preoperative identification of N2 lymph node metastases precludes surgical resection as an initial therapy in this setting.

Postoperative radiotherapy after complete resection of stage I or II NSCLC has been proposed with the goal of decreasing local recurrence rates and improving long-term survival. However, in various randomized controlled trials including a Cochrane collaboration review it has been shown to associated with a decrease in survival for patients with stage I (N0) and stage II (N1) NSCLC.

While surgery is the preferred treatment for early stage lung cancer, for those patients who are not candidates for surgery because of co-morbid conditions (“medically inoperable”) or those who refuse surgery, radiotherapy with curative intent may be undertaken for obtaining local control as well as for improving long term survival.

Treatment of Stage III NSCLC

Stage III comprises a fairly heterogeneous group of tumors and within most of these subgroups, there remains controversy regarding the optimal approach. Many stage III tumors lie at the borderline of what can be considered resectable, and since there is abundant evidence that an incomplete resection is of no value in NSCLC, it can be difficult to decide which of these patients should be offered surgery. For the same reason, surgery for stage III tumors has often been combined with adjuvant therapies, but even now, it remains controversial as to precisely which of these therapies should be employed (chemotherapy, radiotherapy, or combined chemo-radiotherapy), in which cases and in what sequence in relation to surgery (pre- or post-operatively).

Given the high risk of asymptomatic metastases, all patients with pulmonary tumors that appear by initial

studies to potentially be stage III should undergo a complete metastatic work-up. This ideally includes computed tomography (CT) of the chest including the adrenals and liver, magnetic resonance imaging (MRI) of the brain and positron emission tomography (PET).

Stage IIIA Tumors

This is a group of heterogeneous tumors, which consists mainly of masses invading the chest wall but also includes tumors invading the mediastinal pleura or pericardium or the mainstem bronchus within 2 cm of the carina, is the group in which the role of surgery is most clear.

Tumors that are T3N1 by virtue of mainstem bronchus involvement by the primary tumor within 2 cm of the carina but not involving the carina will, in expert surgical hands, most frequently undergo sleeve upper lobectomy. This procedure allows preservation of pulmonary function and diminished postoperative mortality when compared with the alternative (pneumonectomy), but it offers the same oncologic resection and opportunity for cure.

Although the use of neoadjuvant chemotherapy with or without radiotherapy may have potential advantages in the treatment of locally advanced lung cancer, there is a possible increase in morbidity and mortality of the subsequent lung resections.

After a meta-analysis in 1995 showing a statistically insignificant survival benefit of adjuvant therapy in completely resected stage III NSCLC, multiple randomized controlled studies has shown beneficial effects of adjuvant cisplatin based chemotherapy in this stage.

Many patients with stage IIIA lung cancer have less favorable presentations of their disease because they have bulky nodal involvement (N2 disease) and/or unresectable primary tumors. It is generally agreed that mediastinal lymph nodes > 1 cm diameter in short axis are suspicious. Surgical resection after induction chemotherapy has some survival benefit in such selected population of patients with N2 disease. However, it is unclear whether down-staging that is achieved with neoadjuvant chemotherapy in these patients would lead to similar survival rates as seen without surgical treatment (combination chemo-radiotherapy). Moreover, in the past, patients with locally advanced disease were treated with conventional radiotherapy alone with relatively poor long-term survivals, but in the past decade combination

chemo-radiotherapy appears to offer improved results. Thus, platinum-based chemotherapy given concurrently with radiotherapy is recommended. This, however, is associated with higher toxicity and morbidity than if the two are given sequentially i.e. chemotherapy followed by radiotherapy.

Stage IIIB Tumors

The optimal treatment for stage IIIB NSCLC depends on several variables, including the extent of disease, age, co-morbid risk factors, patient performance status (PS), and weight loss. Surgery can be offered to highly selected patients, either as a single modality or after induction (neoadjuvant) chemotherapy with or without RT. Concurrent chemo-radiotherapy is recommended for most cases. Patients who have T4N0-1 solely on the basis of a satellite tumor nodule(s) within the primary lobe have been reported to have 5-year survival rate of approximately 20%.

ADJUVANT CHEMOTHERAPY IN NSCLC – THE EVIDENCE

In early trials of adjuvant chemotherapy definitive survival benefits were not seen, and its role remained controversial for many years. Recently, several large randomized studies have demonstrated survival improvements with adjuvant chemotherapy in early-stage NSCLC, and these results have prompted the adoption of combined surgery and chemotherapy as a new standard of care.

The potential for a survival benefit with adjuvant chemotherapy in early-stage NSCLC was first suggested by the results of a large meta-analysis reported by the NSCLC Collaborative Group in 1995. Data from 52 randomized clinical trials enrolling over 9000 patients were evaluated. By the early 1980s, cisplatin-based regimens were more commonly used, and an analysis of data from 8 trials enrolling over 1300 patients found a trend toward a favorable survival benefit with cisplatin-based adjuvant chemotherapy. Cisplatin based chemotherapy was associated with a hazard ratio of 0.87 or a 13% reduction in the risk of death, and absolute survival benefits of 3% at 2 years and 5% at 5 years. Although these survival improvements did not reach statistical significance due to lack of power, the results were considered clinically meaningful and prompted additional studies of platinum-based combination therapy.

Following the findings of the BMJ meta-analysis, several randomized trials were undertaken to compare chemotherapy

with best supportive care following surgery. These trials laid the foundation for the future of adjuvant therapy in early-stage NSCLC.

The Big Lung Trial

The Big Lung Trial (BLT) was a large, multicenter trial designed to evaluate survival outcomes with short-term cisplatin-based adjuvant chemotherapy in patients with NSCLC. Among the patients studied, 381 patients with completely resected stage I through stage III NSCLC were randomized to either chemotherapy (n=192) or observation alone (n=189). Patients were to receive 3 cycles of chemotherapy every 3 weeks with one of four possible regimens: cisplatin and vindesine; mitomycin, ifosfamide, and cisplatin; mitomycin, vinblastine and cisplatin, or vinorelbine and cisplatin. With a median follow-up time of less than 3 years, a significant survival benefit with the addition of adjuvant chemotherapy was not seen [HR = 1.02; 95% CI 0.77–1.35; p=0.90].

Adjuvant Lung Project Italy (ALPI) Trial

The Adjuvant Lung Project Italy (ALPI) trial was a randomized study evaluating the survival benefit of adjuvant cisplatin-based chemotherapy in patients with completely resected stage I through stage III A NSCLC. A total of 1209 patients were randomized to either no chemotherapy (n=603) or mitomycin, vindesine and cisplatin (MVP) for 3 cycles administered every 3 weeks (n = 606). With a median follow-up time of 64.5 months, the study did not find any significant difference in OS [HR = 0.89; 95% CI 0.81–1.13; p=0.59].

Both the BLT and ALPI studies failed to confirm a survival benefit with cisplatin-based adjuvant chemotherapy suggested by the meta-analysis.

International Adjuvant Lung Cancer Trial (IALT)

In this trial 1867 patients with pathologically documented stage I through stage III NSCLC were randomized following surgical resection to either observation or cisplatin-based chemotherapy. Adjuvant therapy consisted of 3 to 4 cycles of cisplatin combined with vindesine, vinblastine, vinorelbine, or etoposide; 49% of patients received a cisplatin and etoposide combination. With a median follow-up time of 4.6 years, OS outcomes significantly favored the adjuvant chemotherapy arm [HR = 0.86; 95% CI 0.76–0.98; p<0.03].

The overall 5-year survival rates for adjuvant chemotherapy and observation arms were 44.5% and 40.4%, respectively. Disease-free survival was also improved with chemotherapy [HR = 0.83; 95% CI 0.74–0.94; p<0.0003]. The 5-year disease-free survival rates were 39.4% and 34.3% for adjuvant chemotherapy and observation arms respectively.

JBR. 10 Trial

The JBR.10 study, conducted by the National Institute of Canada Clinical Trials Group and the National Cancer Institute of the United States randomized 482 patients with completely resected stage IB or II NSCLC to either observation or adjuvant chemotherapy with 4 cycles of vinorelbine and cisplatin. The percentage of patients randomized to chemotherapy who received three and all four cycles was 55% and 45% respectively. With a median follow-up time of 5.1 years, OS was significantly improved in patients receiving adjuvant chemotherapy [HR = 0.69; 95% CI 0.52–0.91; p=0.04]. The 5-year OS rates were 69% in the chemotherapy arm compared with 54% in the observation arm. In subset analyses, patients with stage II disease had a significant survival benefit with adjuvant chemotherapy [HR = 0.59; 95% CI 0.42–0.85; p=0.004].

Adjuvant Navelbine International Trialist Association (ANITA) Trial

In this study 840 patients with completely resected pathologically staged IB-IIIa NSCLC were randomized to observation or 4 cycles of adjuvant vinorelbine and cisplatin. With a median follow-up time of over 70 months, OS significantly favored the adjuvant chemotherapy arm [HR = 0.80; 95% CI 0.66–0.96; p=0.017]. Median survival was 65.7 months with chemotherapy vs. 43.7 months for observation. For patients receiving chemotherapy in comparison to observation, OS rates were 68% vs. 63% at 2 years, 51% vs. 43% at 5 years, and 45% vs. 37% at 7 years. The 5-year OS rates by disease stage for chemotherapy versus observation were 62% vs. 63% for stage I, 52% vs. 39% for stage II and 42% vs. 26% for stage III patients respectively.

Lung Adjuvant Cisplatin Evaluation (LACE)

In the LACE meta-analysis, individual patient data from the above mentioned five large trials of cisplatin-based chemotherapy were pooled and analyzed. This yielded a database of 4584 patients with a median follow-up time of

5.2 years. As expected, an absolute benefit of 5.4% was observed with adjuvant chemotherapy in terms of 5-year survival. [HR = 0.89; 95% CI 0.82-0.96; p = 0.005]. However, as mentioned earlier, on subgroup analysis, no benefit was observed in stage IA. In stage IB, there was a trend towards improved survival but this did not achieve statistical significance. No variation in the effect of chemotherapy was observed with gender, age, type of surgery and histology with respect to either OS or disease free survival.

ADJUVANT CHEMOTHERAPY IN THE ELDERLY

More than 50% of lung cancer diagnoses are made in patients older than 65 years of age, and 30% to 40% in patients older than age 70. Unfortunately, despite the elderly population's being the most afflicted by lung cancer, they are the least well studied. Reports of the feasibility of surgery in elderly patients with early stage tumors show that operative procedures can be performed safely with OS results that are similar to those seen in younger patients.

A retrospective analysis of the JBR.10 trial was conducted to evaluate the influence of age on survival, adjuvant chemotherapy delivery and toxicity. Chemotherapy significantly prolonged OS for elderly (age > 65 years; n = 155) patients [HR = 0.61; 95% CI 0.38-0.98; p = 0.04] and the observed benefit was thus similar to that seen for all patients. There were no significant differences in toxicities, hospitalization, or treatment-related death by age group even though elderly patients received significantly fewer doses of both chemotherapeutic drugs and a lesser percentage completed treatment. Since combined-modality therapy consisting of surgery and adjuvant chemotherapy is potentially curative and the elderly population derives equal benefit without suffering increased toxicity, it is important that adjuvant chemotherapy is not withheld from these patients solely on the basis of age.

NEOADJUVANT CHEMOTHERAPY IN EARLY-STAGE NSCLC

Neoadjuvant chemotherapy treatment, also known as induction chemotherapy or pre-operative chemotherapy, has been evaluated for many years in NSCLC with promising results. The rationale behind neoadjuvant chemotherapy is similar to that for adjuvant chemotherapy namely the high incidence of disease recurrence after surgery. Since most

recurrences are due to micrometastasis and systemic in nature, delivering chemotherapy before surgery (neoadjuvant) may eradicate micrometastasis. In comparison to adjuvant chemotherapy, neoadjuvant chemotherapy is often better tolerated and results in a higher rate of treatment compliance. Neoadjuvant chemotherapy may also lead to more definitive surgical resections and may eliminate potential micrometastatic disease at the earliest possible time. An additional advantage is that neoadjuvant chemotherapy can be helpful in selecting responsive patients, as patients with disease progression on chemotherapy, do not benefit from surgery. Potential drawbacks of neoadjuvant chemotherapy are delayed surgical resection and less accurate staging, as only clinical staging can be done.

NEOADJUVANT CHEMOTHERAPY IN NSCLC – THE EVIDENCE

In a study by Depierre et al, 355 patients with resectable stage IB-III NSCLC were randomized to either 2 cycles of neoadjuvant chemotherapy with mitomycin, ifosfamide and cisplatin (MIP) followed by surgery or surgery alone. Patients responding to chemotherapy could receive an additional 2 cycles of MIP post-surgery. Radiation therapy was indicated for all patients with pathological T3 or N2 disease. Disease-free survival time was significantly longer in the chemotherapy arm. Moreover, for stages I and II, patients in the chemotherapy arm had statistically significant survival advantage compared to observation arm [Relative risk of death = 0.68; 95% CI 0.49-0.96; p = 0.027].

In another phase III trial by Pisters et al, 354 patients in clinical stages IB-IIIA (70% IB/IIA, 30% IIB/IIIA) were randomized to 3 cycles of induction platinum based chemotherapy (paclitaxel-carboplatin) followed by surgery or surgery alone. With a median follow up of 28 months, the chemotherapy arm had higher median progression free survival (29 vs. 20 months) and OS (42 vs. 37 months) although none of the differences were statistically significant.

A systematic review and meta-analysis on neoadjuvant platinum-based chemotherapy was performed for assessing its effect on OS in comparison to surgery alone. This involved 988 patients in seven trials and represented 75% of the available randomized evidence at the time of its publication. A significant increase in OS associated with the use of neoadjuvant chemotherapy was observed [HR = 0.82; 95%

CI 0.69-0.97; p = 0.022]. This was equivalent to an overall 18% relative and 6% absolute reduction in the risk of death with pre-operative chemotherapy. However, survival varies by stage of disease and using the baseline survival from the various stages gives a range in benefit of 3% to 7% for individual stages of disease.

Results of the largest phase III multi-centric randomized trial, in which 519 patients with operable NSCLC were randomized to receive three cycles of platinum-based neoadjuvant chemotherapy followed by surgery or surgery alone, were published recently by Gilligan et al. Most patients were of stage I and II (61% and 31% respectively) with only 7% in stage III. All three cycles of chemotherapy could be administered to 75% of patients and a complete resection was performed in more than 80%. Although chemotherapy did not lead to an increase in post-operative complications or impairment in quality of life, statistical significance in terms of overall survival benefit was not achieved [HR = 1.02; 95% CI 0.80–1.31; p=0.86]. Even when the authors added their results to and updated the above mentioned systematic review, they observed only a trend towards survival benefit with neoadjuvant chemotherapy [HR = 0.88; 95% CI 0.76–1.01; p=0.07] although this translates into an absolute improvement in survival of 5% at 5 years.

ADJUVANT VERSUS NEOADJUVANT CHEMOTHERAPY

There are no published trials that have compared neoadjuvant versus adjuvant chemotherapy. The Neoadjuvant versus Adjuvant Chemotherapy (NATCH) Trial that has been designed to detect differences in survival between preoperative chemotherapy, postoperative chemotherapy and surgery alone, is likely to shed some light on the unanswered question of chemotherapy timing in patients with resectable NSCLC. *However, from the evidence currently available, one can conclude that in case of early-stage NSCLC where surgery is the most important treatment modality either alone (stage IA) or as part of multi-modality approach (stages IB-IIIA), surgical resection should be performed as early as possible and systemic chemotherapy should preferably be administered postoperatively (adjuvant).* Pancoast (superior sulcus) tumors are a possible exception where superior results have been seen with induction chemotherapy (with/without radiotherapy) followed by surgery.

SUMMARY

Careful evaluation and staging of the disease form the corner stone of therapy in patients with resectable NSCLC. The preferred and recommended therapeutic approach is surgery alone for stage IA while it is surgery with adjuvant chemotherapy for stages II-IIIa and possibly IB. Neoadjuvant chemotherapy followed by surgery may be considered for a select subgroup of patients with stage IIIa.

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Ajmal Khan¹ M.D., Navneet Singh² M.D., D.M.

¹Senior Resident-cum-D.M. Fellow, ²Assistant Professor
Department of Pulmonary Medicine,
Postgraduate Institute of Medical Education and Research
(PGIMER), Chandigarh

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