**Guidelines on Treatment of Stage IIIB Non-small Cell Lung Cancer**

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Stage IIIB disease includes patients with T4 tumors, any N, M0, and any T, N3, M0. It is estimated that 10–15% of all patients are stage IIIB at the time of diagnosis. The treatment options depend on the extent of disease and include surgery alone in carefully selected patients or a combination of chemotherapy and radiotherapy. Surgical resection after induction therapy may be appropriate in selected patients. Radiotherapy alone has been used in the past but should be limited to patients with poor performance score. Chemotherapy alone is not a good treatment option except for patients with malignant pleural effusion (discussed in the section on stage IV disease).

**METHODS**

This section of the evidence-based guidelines is based on an extensive review of the medical literature, including 8 guidelines, 5 meta-analyses, and 20 manuscripts and abstracts, with an emphasis on phase III randomized control trials. Selected key references are included in the bibliography.

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limited role of surgery

The 5-year survival of patients with clinically staged IIIB non-small cell lung cancer (NSCLC) is 3 to 7%. Data on pathologically staged IIIB disease was not available in the new Mountain International Classification. Stage IIIB disease includes T4N0–3M0 and T1–4N3M0. This section will not address treatment of patients with T4 disease due to malignant pleural or pericardial effusions or IIIB Pancoast tumors. Malignant effusions will be addressed in the section on stage IV disease, and Pancoast tumors will be discussed in the chapter on special treatment issues.

Surgery may be indicated for stage IIIB disease only in carefully selected situations. Patients who are T4N0–1 due solely to a satellite tumor nodule(s) within the primary tumor lobe have a 5-year survival of approximately 20% with surgery alone. Individuals with T4N0–1 disease due to main carinal involvement have been treated with carinal resection with or without pulmonary resection. Carinal resection carries an appreciable mortality of 10 to 15%, with an increased risk of local recurrence. The 5-year survival in these carefully selected series is approximately 20%.

Neoadjuvant chemotherapy, or chemoradiotherapy followed by surgical resection, has been used in patients with N2 (IIIA) disease. However, few phase II series have included carefully selected patients.
with T4 primary lesions or N3 nodes. A study by the Southwestern Oncology Group employed concurrent chemoradiotherapy in 51 patients with IIIB disease that excluded superior vena cava syndrome and malignant effusions. That study observed a resectability rate of 80%, with a median survival time of 17 months and a 3-year survival rate of 24%. These results were similar to those observed in patients with IIIA disease reported in that same trial. To date, however, there are no phase III trial data that demonstrate that neoadjuvant treatment followed by surgery in patients with IIIB disease results in prolonged survival compared with treatment with combination chemoradiotherapy.

Recommendations

1. Patients with clinical T4N0 NSCLC due to either satellite tumor node(s) in the same lobe or carinal involvement should be evaluated by a thoracic surgeon for possible resection. Level of evidence: fair; benefit: substantial; grade of recommendation: B.

2. For patients with stage IIIB NSCLC due to T4 (excluding Pancoast tumors) or N3 disease, treatment with neoadjuvant chemotherapy or chemoradiotherapy followed by surgery has been explored in limited phase II trials. At this time, there are no phase III trial data available to document that surgery adds to survival; therefore, this approach should not be considered as standard therapy. Level of evidence: poor; benefit: small/weak; grade of recommendation: I.

Radiotherapy Alone vs Combination Chemotherapy and Radiotherapy

The vast majority of patients with IIIB disease do not benefit from surgery and are best managed with chemotherapy plus radiotherapy or with radiotherapy alone, depending on sites of tumor involvement and performance score status. A trial by the Cancer and Acute Leukemia Group B randomly assigned patients with good performance score (PS 0, 1), minimal weight loss (≤5%), and stage IIIA or IIIB disease to treatment with thoracic radiotherapy alone (60 Gy/30 Fx) or to treatment with identical radiotherapy plus cisplatin and vinblastine chemotherapy. After more than 7 years of follow-up, the median survival time was 13.7 months for combined modality therapy and 9.6 months for radiotherapy alone. The 5-year survival rates were 17% and 6%, respectively (p = 0.01). Multiple randomized trials of radiotherapy alone vs combined chemotherapy and radiotherapy have included patients with inoperable IIIA and IIIB disease. Results of just the IIIB patients are not independently available. At least 3 meta-analyses have been performed on the randomized trials. The non-small cell lung cancer collaborative group meta-analysis evaluated 11 trials with cisplatin-based chemotherapy regimens. The results showed a significant overall benefit of chemoradiotherapy. There was a 13% reduction in the risk of death (hazard ratio of 0.87) and an absolute benefit of 4% at 2 years and 2% at 5 years (p = 0.005). Trials using noncisplatin chemotherapy were marginally, but not statistically, significant in favor of chemoradiotherapy. Results of two separate meta-analyses were similarly in favor of combination chemotherapy and radiotherapy.

Clinical practice guidelines issued by the American Society of Clinical Oncology in 1997 recommend the addition of a platinum-based regimen to thoracic radiotherapy in patients with unresectable IIIA/IIIB disease with a good performance score and minimal weight loss. The National Comprehensive Cancer Network practice guidelines and the Cancer Care Ontario Practice Guidelines (No. 7-3) agree with the American Society of Clinical Oncology recommendations. Accordingly, patients with unresectable stage IIIB NSCLC who have a good performance score and minimal weight loss (≤5%) should be treated with cisplatin-based chemotherapy in combination with thoracic radiotherapy. With combined modality therapy, the expected 5-year survival is 10 to 15%.

Recommendations

3. For patients with stage IIIB disease without malignant effusions, PS 0 or 1, and minimal weight loss (≤5%), combined chemoradiotherapy should be the standard of care. Level of evidence: good; benefit: substantial; grade of recommendation: A.

4. In patients with stage IIIB NSCLC and PS 2 or those with substantial weight loss (≥10%), combined modality treatment could be used after careful consideration. Level of evidence: poor; benefit: moderate; grade of recommendation: C.

Altered Fractions of Radiotherapy

It appears from studies in several epithelial tumor systems that the clinical effectiveness of radiation is the total dose per unit time. The clinical advantage of multiple daily fractions is a reduction in late tissue damage. In a virulent tumor such as lung cancer, it is unclear whether substantial clinical benefit can be derived from radiation optimization.
There has been interest in altered fractionation radiotherapy to increase control of the primary tumor and decrease the toxicity to normal tissue. Hyperfractionation is defined as the use of two or more fractions daily of smaller-than-conventional fraction size. The Radiation Therapy Oncology Group (RTOG) conducted a three-arm randomized control trial of standard once daily radiotherapy, combination chemotherapy, and standard once daily radiotherapy or hyperfractionated radiotherapy given twice daily without chemotherapy. Ninety-five percent of patients had stage IIIA or IIIB disease. The overall survival was statistically superior for the combined chemotherapy and once daily thoracic radiotherapy arm. Survival for patients receiving twice daily radiotherapy was not statistically superior. The median survival for the standard radiotherapy was 11.4 months, 13.2 months for the combined modality arm, and 12 months for the hyperfractionated irradiation treatment. The 5-year survival rates for these groups were 5%, 8%, and 6%, respectively.

Meta-analysis of this trial and two other smaller trials was performed, and it reported improved survival for hyperfractionated radiotherapy over standard radiotherapy (odds ratio 0.69; 95% confidence interval 0.51–0.95; p = 0.02). However, a second meta-analysis of these three studies, conducted at Cancer Care Ontario Practice Guidelines Initiation Resource Group and based on 2-year survival and a fixed effort model, did not demonstrate a significant benefit of hyperfractionated radiotherapy over standard radiotherapy (odds ratio 0.67; 95% confidence interval 0.42–1.07; p = 0.09).

Recently, a phase III trial by the North Central Cancer Treatment Group evaluated concurrent combined treatment with etoposide/cisplatin chemotherapy (both arms) and once daily or twice daily split course thoracic radiotherapy. There was no significant difference in survival or toxicity for the two arms. The median survival time was 14 vs 15 months, and the 2-year survival rates were 37% and 40%, respectively (p = 0.6). Accordingly, there is absence of convincing data that hyperfractionated (twice daily) thoracic radiotherapy is superior to standard once daily radiotherapy.

Accelerated radiotherapy is defined as the use of two or more fractions of standard fraction size daily to the same conventional total dose as standard radiotherapy, but increasing the number of fractions per week and shortening the overall treatment time. Hyperfractionated accelerated radiotherapy combines the features of accelerated and hyperfractionated regimen. It uses two or three fractions of smaller fraction size daily, delivered over a shorter period of time than conventional therapy. The goal is to reduce long-term normal tissue toxicity by smaller fraction size and to reduce repopulation in rapidly proliferating tumors. One randomized phase III trial in England compared continuous hyperfractionated accelerated radiotherapy (CHART) to standard radiotherapy (60 Gy/30 Fx). CHART consisted of three treatments per day (1.5 Gy/Fx), at least 6 h apart, for 12 days without a break (54 Gy). Sixty-one percent of patients were IIIA or IIIB. The 1- and 2-year survival rates for the CHART arm were 63% and 29%, respectively, vs 55% and 20% for standard radiotherapy. Overall, there was a 22% reduction in the relative risk of death (p = 0.008). Acute esophagitis was more severe for patients receiving CHART, but the incidence at 3 months was similar to patients receiving standard radiotherapy, and there was no difference in late morbidity. Recently, a phase III trial of HART (same as CHART except for no treatments on weekends) vs standard radiotherapy after induction chemotherapy had to be closed due to poor accrual in the Eastern Cooperative Oncology Group.

Accordingly, at this time we have one phase III trial of CHART that showed superior survival over standard radiotherapy, but it had only 61% of patients with stage IIIA and IIIB disease, and no data are available concerning the combination of CHART and chemotherapy. Additionally, the schedule of radiotherapy 3 times per day seems to have been rejected by radiotherapists in North America. Therefore, at this time, neither CHART nor HART can be recommended as standard therapy. Optional dose, volume, and fractionation schedules are evolving. An RTOG randomized phase III trial in the 1980s demonstrated that 60 Gy produced a nonstatistically significant survival improvement compared with 50 Gy or two different schedules of 40 Gy. Accordingly, the dose of 60 Gy in 6 weeks has been widely used for 20 years. However, this dose and fractionation schedule results in local control rates of 15 to 30%. Therefore, higher doses may yield better results. Guidelines of the American Society of Clinical Oncology advise that definitive dose thoracic radiotherapy should be at least 60 Gy in 1.8 to 2.0 Gy fractions.

**Recommendation**

5. For stage IIIB NSCLC patients, there are no convincing data that hyperfractionated (two or more fractions daily) radiotherapy is superior to standard once daily treatment. Continuous hyperfractionated accelerated radiotherapy (CHART) was demonstrated in one small trial to be superior to standard once daily therapy,
but the logistics of three treatments daily have not proven to be acceptable in a North American trial. No data are available in combining CHART with chemotherapy. Level of Evidence: poor; benefit: small/weak; grade of recommendation: I.

Concurrent vs Sequential Chemoradiotherapy

Concurrent treatment with chemoradiotherapy has become the standard in treatment of limited stage small cell lung cancer. There is less information available on treatment of NSCLC. The West Japan Lung Cancer Group conducted a randomized phase III trial of concurrent vs sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin, with over 150 patients participating in each arm. Seventy-two percent had stage IIIB disease. Radiation was begun on day 2 at a dose of 28 Gy (2 Gy/Fx × 14), followed by a rest of 10 days and then repeated for a total dose of 56 Gy. In the sequential arm, the same chemotherapy was given, but radiotherapy was initiated after completing chemotherapy and consisted of 56 Gy (2 Gy/Fx × 28) without a break. The median survival time was superior for patients in the concurrent therapy arm (16.5 vs 13.3 months), and the 5-year survival difference was 15.8% vs 8.9% (p = 0.039). The RTOG conducted a phase III trial of concurrent vs sequential chemoradiotherapy. The chemotherapy was vinblastine and cisplatin. Radiotherapy was begun on day 1 of chemotherapy or on day 50 after chemotherapy, and the total dose was 63 Gy. The median survival time was 17 months with concurrent therapy and 14.6 months with sequential treatment. This difference was significant at the time of a follow-up report in the fall of 2000.

A French cooperative group performed a phase III randomized trial of sequential vs concurrent chemoradiotherapy in unresectable IIIA/IIIB patients. The chemotherapy was cisplatin and vinorelbine for 3 cycles, followed by thoracic radiotherapy (66 Gy/33 Fx), or concurrent cisplatin/etoposide, with thoracic radiotherapy followed by cisplatin and vinorelbine. Seventy-five percent of patients had IIIB disease, and over 100 patients were enrolled in each arm. Incidence of grade 3/4 esophagitis was 26% in patients in the concurrent therapy arm vs 0% in the sequential arm. The median survival time was 13.8 months with sequential therapy and 15 months with concurrent therapy. The 2-year survival rates were 23% and 35%, respectively. While there was a trend in favor of concurrent therapy, it was not statistically significant at the time of this preliminary report. Therefore, based on these three large phase III randomized trials, concurrent chemoradiotherapy appears to result in better survival than sequential therapy. It is associated with some increased toxicity, mainly acute esophagitis, and should be reserved for patients with PS 0 or 1 and minimal weight loss.

Recommendation

6. For stage IIIB NSCLC patients with PS 0 or 1 and minimal weight loss, concurrent therapy would be recommended. Concurrent chemoradiotherapy is associated with an increase rate of acute esophagitis compared to sequential therapy. Concurrent therapy appears to be associated with improved survival over that of sequential therapy. Level of evidence: fair; benefit: substantial; grade of recommendation: B.

Summary of Recommendations

1. Patients with clinical T4N0 NSCLC due to either satellite tumor node(s) in the same lobe or carinal involvement should be evaluated by a thoracic surgeon for possible resection. Level of evidence: fair; benefit: substantial; grade of recommendation: B.

2. For patients with stage IIIB NSCLC due to T4 (excluding Pancoast tumors) or N3 disease, neoadjuvant chemotherapy or chemoradiotherapy followed by surgery has been explored in limited phase II trials. At the time this article was written, there were no phase III trial data available to document that surgery would improve survival rates, so this approach should not be considered as standard therapy. Level of evidence: poor; benefit: small/weak; grade of recommendation: I.

3. For patients with stage IIIB disease without malignant effusions, PS 0 or 1, and minimal weight loss (≤ 5%), combined chemoradiotherapy should be the standard of care. Level of evidence: good; benefit: substantial; grade of recommendation: A.

4. For patients with stage IIIB NSCLC and PS 2 or those with substantial weight loss (≥ 10%), combined modality treatment could be used after careful consideration. Level of evidence: poor; benefit: moderate; grade of recommendation: C.

5. For stage IIIB NSCLC patients, there are no convincing data that hyperfractionated (two or
more fractions daily) radiotherapy is superior to standard once daily treatment. Continuous hyperfractionated accelerated radiotherapy (CHART) was demonstrated in one small trial to be superior to standard once daily therapy, but the logistics of three treatments daily have not proven to be acceptable in a North American trial. No data are available in combining CHART with chemotherapy. Level of evidence: poor; benefit: small/weak; grade of recommendation: I.

6. For stage IIIB NSCLC patients with PS 0 or 1 and minimal weight loss, concurrent therapy would be recommended. Concurrent chemoradiotherapy is associated with an increased rate of acute esophagitis compared to sequential therapy. Concurrent therapy appears to be associated with improved survival vs sequential therapy. Level of evidence: fair; benefit: substantial; grade of recommendation: B.

REFERENCES