Current Surgical Therapy for Stage IIIA (N2) Non-Small Cell Lung Cancer

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Local therapy alone (surgery or radiation) leads to poor overall survival in patients with stage III non-small cell lung cancer because most of these patients die of distant metastases. During the past 20 years, studies have focused on developing effective chemotherapy regimens that can be combined with local therapies (surgery and/or radiation). The role of surgery has been evaluated, and the selection criteria for resection have been defined.

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MULTIMODALITY THERAPY: RATIONALE AND APPROACHES

Local therapy alone (either surgery or radiation) leads to poor overall survival rates for regionally advanced non-small cell lung cancer (NSCLC). Patients with stage IIIA (N2) NSCLC who undergo surgical resection alone have 5-year survivals of 20%-30% if single-level mediastinal lymph node disease is present and only 5%-10% with multilevel N2 disease.[1] These discouraging results relate to the fact that most patients develop distant metastases even after complete resection. Accordingly, the goal of treatment for stage IIIA/N2 disease has shifted to address both local control and the eradication of micrometastatic disease with systemic therapy. During the last 20 years, multimodality therapy has focused on developing optimal chemotherapy regimens and on ways to combine chemotherapy with surgery and radiation. This article reviews the literature leading up to the current state of multimodality therapy for resectable NSCLC, focusing on the role of surgery for stage IIIA (N2) disease.

SURGERY + ADJUVANT THERAPY

Adjuvant Chemotherapy

Multiple studies during the last 2 decades have established the beneficial impact of adjuvant chemotherapy in the treatment of resected NSCLC. In 1995, the NSCLC Collaborative Group reported a meta-analysis of 14 clinical trials addressing the role of adjuvant chemotherapy for resected NSCLC. No statistically significant survival benefit was seen with adjuvant chemotherapy, but a trend toward better survival prompted further studies.[2] In 2005, Berghmans et al[3] performed a follow-up meta-analysis of 25 recent randomized trials testing either induction or adjuvant chemotherapy in resectable NSCLC. The chemotherapy used in these trials included platinum-based regimens that were more effective and better tolerated than the regimens evaluated in the 1995 meta-analysis. A hazard ratio of 0.84 (95% confidence interval [CI], 0.78-0.89) favoring the use of adjuvant chemotherapy was seen. Subsequently, the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis was based on individual patient data collected from the 5 largest trials (4584 patients) of cisplatin-based adjuvant chemotherapy in completely resected patients with NSCLC performed after the 1995 NSCLC Collaborative Group meta-analysis.[4] This analysis also showed a significant survival benefit with adjuvant chemotherapy, with an overall hazard ratio (HR) of 0.89, translating into a 5-year absolute survival benefit of 5.4%. The benefit of chemotherapy was shown to vary with tumor stage. Adjuvant chemotherapy was detrimental for stage IA disease, of unclear benefit for stage IB tumors, but clearly beneficial for patients with resected stage II/III disease (HR for death for stage IA, 1.40; 95% CI, 0.95-2.06; for stage IB, 0.93; 95% CI, 0.78-1.10; for stage II, 0.83; 95% CI, 0.73-0.95; for stage III, 0.83; 95% CI, 0.72-0.94). The LACE meta-analysis also showed that the benefit of adjuvant chemotherapy was not without cost, citing a 66% incidence of grade 3 or 4 adverse events. A significant interaction was seen between chemotherapy effect and World Health Organization performance status

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(PS) (test for trend, $P = 0.009$ for overall survival and $P = 0.01$ for disease-free survival), with a significantly increased chemotherapy effect with better PS and possible detriment for PS of 2. Because of these studies, standard care for patients who have undergone resection of stage II or III NSCLC includes adjuvant platinum-based chemotherapy, with the expectation of achieving a survival benefit at 5 years for every 15 patients treated (number needed to treat based on LACE HR calculations).[5]

Adjuvant Radiation Therapy

The role of adjuvant radiation therapy has not been shown as clearly elucidated as that of chemotherapy. In 1998, the Postoperative Radiotherapy (PORT) Meta-analysis Trialists Group collected individual patient data (n = 2128) from all available randomized trials of PORT versus surgery alone conducted from 1965-1995.[6] They reported a 21% relative increase in the risk of death, equivalent to an absolute detriment of 7% at 2 years, with PORT reducing overall survival from 55% to 48% after resection. Subgroup analysis suggested that the adverse effect on overall survival was most notable for patients with stage I/II (N0-N1) tumors, whereas there was no clear evidence of either adverse effect or benefit for stage III disease. The results of the PORT meta-analysis are probably not applicable to current therapy because of recent major improvements in radiation treatment planning and delivery. Contemporary studies report more favorable outcomes. A large (n = 7465) retrospective Surveillance, Epidemiology and End Results Program (SEER) database analysis of patients with resected NSCLC who received PORT between 1988 and 2002 revealed no adverse impact on survival overall (HR, 1.048; 95% CI, 0.987-1.113; $P = 0.1269$).[7] Subset analyses showed a significant decrease in survival for patients with N0 (HR, 1.1176; 95% CI, 1.005-1.376; $P = 0.0435$) and N1 disease (HR, 1.097; 95% CI, 1.015-1.186; $P = 0.0196$) but significantly improved survival for patients with N2 disease (HR, 0.8555; 95% CI, 0.762-0.959; $P = 0.0077$). In addition, an unplanned subset analysis of patients who received PORT in the Adjuvant Navelbine International Trialist Association (ANITA) randomized study of adjuvant chemotherapy suggested a positive effect of PORT in pN2 disease and a negative effect on pN1 disease.[8] In aggregate, these data suggest that PORT is appropriate for patients with stage IIIA (N2) disease. At a minimum, PORT reduces the risk of locoregional recurrence and might improve overall survival for these patients. The ongoing Lung Adjuvant Radiation Trial, an international multi-institutional phase III trial in which patients with resected N2 disease are randomized to PORT and no PORT, might provide more definitive data.

INDUCTION THERAPY + SURGERY

In the LACE meta-analysis, 33% of patients in the chemotherapy arm did not start or finish the planned chemotherapy regimen, reflecting the difficulty of administering such taxing therapies to a postoperative population. Conceptually, the preoperative administration of chemotherapy and/or radiation therapy offers several benefits: (1) an improved likelihood of patients completing the planned total dose of chemotherapy, (2) the ability to assess tumor response as a prognostic marker, (3) the ability to treat micrometastatic disease preoperatively, and (4) the possibility of improving resectability through tumor regression. Current multimodality therapeutic strategies include preoperative chemotherapy alone followed by surgical resection, preoperative chemotherapy, and radiation followed by surgical resection, or chemotherapy with concurrent or sequential radiation therapy without surgical resection.

In 1993, Martini et al[9] reported the results of 136 patients at Memorial Sloan-Kettering Cancer Center (MSKCC) with "bulky" N2 disease (visible on chest radiograph) who underwent surgical resection after receiving induction chemotherapy (mitomycin, vindesine, or vinblastine and high-dose cisplatin). Median survival for all patients was 19 months, and 3-year survival was 41%, compared with a historical surgery-only control of 8% ($P = 0.001$). There were significant differences in survival between patients who had a major response to chemotherapy (78% of all patients) as compared with those with less than a major response (3-year survival, 34% versus 7%, respectively), as well as between patients who underwent complete resection versus incomplete or no resection (3-year survival, 41% versus 5%, respectively). Survival was best in patients with a complete pathologic response, with 71% 3-year survival and 61% 5-year survival. In 2002, Martin et al[10] published the long-term results of combined modality therapy (either preoperative chemotherapy alone or chemotherapy and radiation therapy) in patients with resectable NSCLC at MSKCC (n = 446). This retrospective review demonstrated again that survival was worse for patients who had persistent mediastinal nodal disease after induction therapy and improved if R0 resection could be accomplished. Median survival for N0/N1 disease was 27.8 months, compared with 15.6 months for patients with residual N2 disease ($P < 0.001$), and 3-year survival for N0/N1 patients was 43.3%, compared with 25.5% for N2 patients. There was also a significant differ-