Latest information for the thoracic surgeon from the Annual Meeting of the American Society of Clinical Oncology

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The 45th Annual Meeting of the American Society of Clinical Oncology was held May 29 through June 2, 2009, in Orlando, Florida. This review briefly summarizes new findings about early non-small cell lung cancer (NSCLC) presented at this meeting.

SURGICAL QUALITY

Accurate lymph node (LN) staging is prognostic in early surgical NSCLC. Sampling of at least 10 LNs is recommended at the time of surgery; however, practice patterns among surgeons vary. A retrospective analysis of patient records undergoing resection confirmed improved survival with the National Comprehensive Cancer Network guideline-based Good Quality Resection (negative margins, minimum segmentectomy, LN sampling from stations 10–14, and >2 mediastinal stations).¹ The 3-year survivals for those with and without a Good Quality Resection were 72% and 63%, respectively ($P = .5$). The paramount reason for lack of Good Quality Resection was the lack of LN sampling, with 2 mediastinal LN samples in 18% of the cases and 3 or more in only 10%. Almost a third of the patients did not have sampling of a mediastinal LN.^{1,2}

DIAGNOSTIC PATHOLOGY

Although histologic type has not consistently been associated with clinical outcome in advanced NSCLC, it has recently emerged as a potential predictive factor of response or survival with respect to specific chemotherapeutic agents. Histologic diagnoses rely on cellular architecture and immunohistochemical analysis. To ascertain the diagnostic reproducibility of a diagnosis of squamous cell carcinoma, 96 samples from a surgical cohort were prospectively examined by lung cancer “expert” and “community” pathologists.³ Slides were scored according to 44 World Health Organization diagnostic categories. Overall, the level of agreement between pathologists with the hematoxylin–eosin staining for diagnosis of squamous versus nonsquamous carcinoma was only moderate (κ coefficient 0.55, 95% confidence interval [CI] 0.55–0.58). Agreement was proportional to the

level of confidence of the pathologist in the diagnosis and increased with better differentiated carcinoma (51% with moderately differentiated carcinoma and 35% with poorly differentiated).

PREDICTORS OF OUTCOME

In a prospective and observational study, patients scheduled to undergo pulmonary resection performed a preoperative incremental exercise test with expired gas analysis to assess cardiorespiratory fitness (peak oxygen consumption). Cox proportional hazards models estimated the risk of all-cause mortality according to cardiorespiratory fitness category defined by peak oxygen consumption (<0.96 L min⁻¹, 0.96 – 1.29 L min⁻¹, and >1.29 L min⁻¹), with adjustment for age, sex, and performance status. Of the 398 patients, 335 underwent surgical resection and 63 were deemed not eligible for resection. Median follow-up was 30.8 months, and 294 deaths were reported during this period. For the entire sample, mortality rates declined across increasing peak oxygen consumption categories (adjusted $P_{\text{trend}} = .012$).⁴

Following up on the previously reported results about *ERCC1* and p27 in the International Adjuvant Lung Trial (IALT-Bio), investigators presented new data about *MSH2*, a DNA repair gene. The study demonstrated the predictive values of *ERCC1* and *MSH2* statuses in resected tumors.⁵ Similar to *ERCC1* data, cisplatin-based adjuvant chemotherapy improved survival in the *MSH2*-negative group (hazard ratio [HR] for death 0.76, 95% CI 0.59–0.97, $P = .03$) but not the *MSH2*-positive group (HR for death 1.12, 95% CI 0.81–1.55, $P = .48$). In patients with tumors negative for both markers, a survival improvement with cisplatin chemotherapy was maintained (HR for death 0.65, 95% CI 0.47–0.91, $P = .01$), whereas survival appeared to be the worst for patients whose tumors expressed both *ERCC1* and *MSH2* and who received cisplatin chemotherapy (HR for death 1.32, 95% CI 0.88–1.99, $P = .19$).⁵ These biomarker analyses have demonstrated the effect of patient selection on improving modest outcomes.

PERIOPERATIVE CHEMOTHERAPY

Few studies have shown benefits of neoadjuvant chemotherapy in select subsets of patients. Pooling results of the published neoadjuvant studies, however, meta-analyses have provided evidence of a statistically significant survival benefit with chemotherapy of a magnitude similar to that provided by adjuvant chemotherapy. The NeoAdjuvant Taxol Carboplatin Hope (NATCH) trial was designed to

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FIGURE 1. NeoAdjuvant Taxol Carboplatin Hope (NATCH) study schema. *chemo*, Chemotherapy; *Adj chemo*, adjuvant chemotherapy; *pre-op*, preoperative; AUC, area under the concentration curve.

compare surgery alone with either neoadjuvant chemotherapy followed by surgery or surgery followed by adjuvant chemotherapy.⁶ Six-hundred twenty-four patients with stage I (>2 cm), II, and T3N1 were randomly allocated to the three arms (Figure 1). The 5-year disease-free survival did not show any significant difference among the three arms. The 5-year and median disease-free survivals were 39% and 28 months for surgery alone, 40.5% and 32 months for preoperative chemotherapy ($P = .17$ vs surgery alone), and 39.3% and 24 months for postoperative chemotherapy ($P = .73$ vs surgery). No differences in overall survival were observed. Response to induction chemotherapy was 53%, including a 9% rate of complete response. Neoadjuvant therapy was better tolerated than was adjuvant chemotherapy, with 90% of patients receiving all planned cycles of treatment versus only 62% of patients in the adjuvant arm. Although the study did not show differences in survival among the three treatments, NATCH did emphasize the greater tolerability of chemotherapy before surgery and the absence of increased postoperative mortality.

Long-term follow up of the JBR.10 study confirmed the survival benefit of adjuvant cisplatin with vinorelbine.⁷ In this study, which enrolled patients with stage IB and II disease, after 9.3-year median follow-up this benefit continued to be confined to those with N1 disease (HR for death 0.68, 95% CI 0.5–0.9) and T2N0 tumors of at least 4 cm (HR for death 0.66, 95% CI 0.3–1.1). At long-term follow up, there was a significant reduction in disease-related deaths with adjuvant chemotherapy ($P = .02$).

PROPHYLAXIS AFTER DEFINITIVE TREATMENT

Brain metastases constitute 30% of failures after definitive treatment for stage III NSCLC. Unable to accrue suffi-

cient patients to meet its goal, the RTOG 0214 study closed prematurely after randomly allocating only 356 out of 1058 planned patients to receive prophylactic cranial irradiation (PCI) or observation after locoregional treatment with surgery or radiation for stage III disease.⁸ Even though PCI significantly reduced the 1-year incidence of brain metastases (18% vs 7.7%, $P = .004$), there were no differences in 1-year overall survival (76% PCI, 77% observation, $P = .86$). Plausible explanations include insufficient numbers to find a true difference in survival with PCI and a lack of impact of brain metastases on overall survival because NSCLC is a systemic disease.

SUMMARY

Survival of patients with NSCLC has improved incrementally during the last decade. Continued follow-up of adjuvant clinical trials underscores the durable benefits of adjuvant chemotherapy. The magnitudes of these improvements, however, have been modest. Retrospective analyses suggest that these benefits can be improved further by patient selection with molecular profiling of the tumors. Ongoing clinical trials will validate these findings prospectively. Efforts need to be made to generalize findings of research advances. For example, there is a pressing need for standardization of adequate LN dissection in surgical patients. To affect outcomes further, advances in technology need to be accompanied by validation, reproducibility, and, most importantly, universal availability.

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