Defining Local-Regional Control and Its Importance in Locally Advanced Non-small Cell Lung Carcinoma

A Radiation Therapy Oncology Group Analysis

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Introduction: Local-regional control (LRC) rates for non-small cell lung cancer after chemoradiotherapy were studied (using two different definitions of LRC) for the association between LRC and survival.

Methods: Seven legacy Radiation Therapy Oncology Group trials of chemoradiotherapy for locally advanced non-small cell lung cancer were analyzed. Two different definitions of LRC were studied: (1) freedom from local progression (FFLP-LRC), the traditional Radiation Therapy Oncology Group methodology, in which a failure is intrathoracic tumor progression by World Health Organization criteria; and (2) response-mandatory (strict-LRC), in which any patient not achieving at least partial response was considered to have failure at day 0. Testing for associations between LRC and survival was performed using a Cox multivariate model that included other potential predictive factors.

Results: A total of 1390 patients were analyzed. The LRC rate at 3 years was 38% based on the FFLP-LRC definition and 14% based on the strict-LRC definition. Performance status, concurrent chemotherapy, and radiotherapy dose intensity (biologically equivalent dose) were associated with better LRC (using either definition). With the strict-LRC definition (but not FFLP-LRC), age was also important. There was a powerful association between LRC and overall survival ($p < 0.0001$) on univariate and multivariate analyses. Age, performance status, chemotherapy sequencing, and biologically equivalent dose were also significantly associated with survival. Histology and gender were also significant if the strict-LRC model was used.

Conclusions: LRC is associated with survival. The definition of LRC affects the results of these analyses. A consensus definition of LRC, incorporating functional imaging and/or central review, is needed, with the possibility of using LRC as a surrogate end point in future trials.

Key Words: Non-small cell lung cancer, Local control, Chemoradiotherapy.

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It is axiomatic that cure of cancer cannot be achieved without control of the primary tumor site (local control). There have been many studies investigating the relationship between local control and survival in a variety of malignancies, including non-small cell lung cancer (NSCLC).[1] Most of these studies showed that cancer patients who have local control live longer than those who do not have local control.

A challenge in studying local control in stage III unresectable NSCLC is that it is difficult to assess local tumor status in this disease. With rare exceptions, these cancers are not evaluable on clinical office examination. Interpretation of chest radiography and computed tomography (CT) is hindered by extensive radiation-induced inflammation and fibrosis, which can mimic persistently active or recurrent/progressive tumor.

Data show that tumor control and survival has improved with the use of chemoradiotherapy when compared with radiotherapy alone.[2] Nevertheless, the reported rate of local-regional control (LRC) in scientific studies has varied widely, despite relatively similar radiotherapy techniques and chemotherapy regimens. This likely depends on the means with which LRC is assessed and analyzed. For example, an early Radiation Therapy Oncology Group (RTOG) study of radiotherapy alone for NSCLC suggested that with an x-ray therapy dose of 60 Gy continuous course, 2-year LRC was above 60%.[3] In contrast, a randomized

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trial by LeChevalier—in which postradiotherapy bronchoscopy/biopsy was routinely performed—suggested that true LRC was only achieved in about 20% of patients.[4] No other major, large randomized trial in unresectable stage III lung cancer required an attempt at postradiotherapy pathologic assessment of local control.

Because radiotherapy is a local-regional anticancer treatment, it is important to assess LRC in studies that involve radiotherapy even if pathologic assessment is not feasible.

We performed several analyses of the RTOG database to examine the probability of LRC after chemoradiotherapy. Our study specifically evaluates two different definitions of LRC: (1) the "traditional" RTOG measure of LRC, also referred to as freedom from local progression (FFLP-LRC) and (2) a more rigorous definition of LRC which requires objective local-regional tumor response in addition to FFLP, similar to the definition of LRC often used in studies of head and neck cancer (strict-LRC). We hypothesized that there would be significant differences in the analyses depending on how LRC is defined.

MATERIALS AND METHODS

This is a retrospective analysis of prospective data collected on patients treated with chemoradiotherapy in prospective RTOG protocols from 1988 through 2002. All patients eligible for analysis were included.

The studies analyzed were as follows:

- RTOG 88-08 (Phase III trial: chemo-RT arm only)[5]: This consisted of induction cisplatin/vinblastine chemotherapy followed by definitive radiotherapy (60 Gy).
- RTOG 90-15[6]: Phase I/II trial of concurrent cisplatin/vinblastine with definitive bid radiotherapy (69.6 Gy)
- RTOG 91-06[7]: Phase I/II trial of concurrent cisplatin/etoposide with definitive bid radiotherapy (69.6 Gy)
- RTOG 92-04[8]: Phase IIR trial; one arm was the same treatment as in RTOG 91-06, while the second arm was induction cisplatin/vinblastine followed by concurrent cisplatin/radiotherapy (63 Gy).
- RTOG 93-09[9]: Phase III study of immediate concurrent chemoradiotherapy (cisplatin/etoposide/RT [61 Gy]) with or without surgical resection (potentially operable IIIA only)—for this analysis only the patients randomized to no surgery were included.
- RTOG 94-10[10]: Phase III trial comparing chemo-RT as given in RTOG 88-08 versus immediate concurrent chemo-RT (cisplatin/vinblastine/RT [63 Gy]) versus the RTOG 91-06 regimen.
- RTOG 98-01[11]: Phase III trial of induction chemotherapy (carboplatin/paclitaxel) followed by concurrent chemoradiotherapy (carboplatin/paclitaxel/bid RT [69.6 Gy]) with or without amifostine.

Radiotherapy techniques and doses were similar for all of these studies. Specifically, all of these studies included elective nodal irradiation to the entire mediastinum and in some cases the supraclavicular and/or contralateral hilar nodes to 45 Gy. These comprehensive radiotherapy treatment fields were then followed by a boost to gross disease to at least 60 Gy (maximum 69.6 Gy in 1.2 Gy bid fractionation). "High technology" forms of modern radiotherapy such as intensity modulated radiation therapy, image-guided radiation therapy, adaptive radiotherapy, respiratory-gated radiotherapy, or air/tissue inhomogeneity corrected radiotherapy dosimetry were not used. CT-based simulation/planning and three-dimensional conformal planning and delivery of radiotherapy were allowed but not routinely used and certainly not required in any of these studies. Unfortunately, however, RTOG did not collect detailed information about the type of simulation and treatment planning that was used in the patients in these studies (as opposed to three-dimensional conformal-specific RTOG studies 93-11 and 01-17, which are not included in this analysis). The studies included in this analysis required that the prescription dose (60–69.6 Gy, depending on the exact study) be specified to isocenter, rather than renormalization of dose to a peripheral isodose.

Instructions for the assessment for tumor control were consistent among these studies. Specifically, all patients were required to undergo a postradiotherapy CT scan of the chest (including liver or adrenals) approximately 6 months after completing radiotherapy, then every 6 months for 2 years, and then annually. Additional CT scans were allowable at other intervals as clinically indicated, for example, if there was clinical suspicion for recurrence or progression. It was recommended that these CT scans be performed both with and without contrast and that CT slices be 5 mm or smaller. Bone scan and/or head CT/magnetic resonance imaging scanning in follow-up was only performed if metastatic disease was suggested by clinical evaluation. Positron emission tomography (PET) scans were not used for staging or posttreatment assessment in this study (patients in this analysis were treated between 1988 and 2002).

Local-regional failure was determined by the individual site and the radiation oncology physician investigators, who were charged with determining whether an "event" (progression of lung cancer) has occurred, and if so if it was in-field, at the edge of the field, or out of field. Any one of the following events constituted a local-regional failure:

1. Enlargement by >25% in the bidimensional product of two dimensions of a measurable index (pretreatment) lesion.
2. For a nonmeasurable lesion, estimated enlargement by >25% of tumor bulk, after taking into account postradiation pneumonitis/fibrosis.
3. The development of severe tumor-related local-regional complications such as postobstructive pneumonia and/or hemoptysis was also considered as criteria for local-regional failure if these clinical events could not be attributed to radiation toxicity and/or intercurrent disease.
4. The appearance of a new malignant lesion within the radiation field or at the edge of the radiation field.
5. Positive biopsy and/or surgical specimen after radiotherapy showing viable non-small cell lung carcinoma after radiotherapy.

