Survival of Patients Treated with High-dose Radiotherapy and Concurrent Chemotherapy for Unresectable Non-small-cell Lung Cancer

Steven E Schild, MD[1] and Helen J Ross, MD[2]

1. Professor of Oncology, and Chair, Department of Radiation Oncology; 2. Associate Professor of Medicine, and Thoracic Medical Oncologist, Department of Hematology/Oncology, Mayo Clinic

Abstract

Radiotherapy (RT) has been used to treat cancers for 110 years. Today, megavoltage RT is delivered with very precise linear accelerators. Computed tomography and/or positron-emission tomography are used to define both tumor and normal tissue volumes. Powerful computers analyze these volumes in 3D space and design complex treatment plans. Over time, the ratio of dose administered to tumor compared with dose administered to the normal structures has increased, resulting in a better therapeutic index and improved survival. In the 1970s and 1980s, the five-year survival rate of unresectable non-small-cell lung carcinoma was 5% with standard RT alone. Adding chemotherapy before or after radiation improved the five-year survival to about 15%. More recently, concurrent chemotherapy and RT has achieved five-year survival rates of up to 29%. Pilot trials employing chemotherapy and higher-dose RT have resulted in still better local control and survival. A phase III trial of chemotherapy plus either standard-dose RT (60Gy/30) or high-dose RT (74Gy/37) is ongoing. New technology is providing ways to improve the therapeutic ratio and administer greater RT doses more safely.

Keywords

Lung cancer, radiation therapy, radiotherapy (RT), chemotherapy, high-dose radiotherapy, 3D treatment planning

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Correspondence: Steven E Schild, MD, Professor and Chairman, Department of Radiation Oncology, Mayo Clinic, 13400 E. Shea Blvd, Scottsdale, AZ 85259. E: sschild@mayo.edu

Lung cancer is the leading cause of cancer deaths, having caused an estimated 1.18 million deaths worldwide in 2002.[1] In the US alone, lung cancer resulted in an estimated 159,300 deaths in 2009.[2] Most deaths are from non-small-cell lung cancer (NSCLC), which accounts for more than 80% of lung cancers diagnosed in the US. Sadly, most patients present with advanced, inoperable disease. While stage IV patients remain incurable, there is now potentially curative therapy that can be offered to most patients with stage III NSCLC.[3]

Radiotherapy Becomes Standard Treatment for Unresectable Non-small-cell Lung Cancer

Over 40 years ago, Wolf et al. established the role of RT in the treatment of lung cancer. Their randomized phase III trial compared radiotherapy (RT) versus placebo for clinically inoperable lung cancer (including both small-cell and NSCLC). RT was delivered with 200–250kV X-rays and included the delivery of 40–50Gy in 1.5–2.0Gy daily fractions. The median survival of patients given RT was 142 days compared with 112 days for those who received the placebo (p=0.05).[4] A phase III Radiation Therapy Oncology Group (RTOG) trial evaluated the effect of dose on outcome by randomly assigning patients to receive 40Gy in 20 daily fractions, 50Gy in 25 daily fractions, or 60Gy in 30 daily fractions. The local failure rates determined with serial chest X-rays were 48% with 40Gy, 38% with 50Gy, and 27% with 60Gy. Although the differences in survival were not significant, this study defined the standard RT dose as 60Gy in 30 daily fractions.[5] This dose fractionation pattern remained the standard of care for decades. Conventional RT alone resulted in a median survival of 10 months and a five-year survival of 5%. Until the 1990s, the standard treatment for locally advanced inoperable lung cancer was RT alone.[5]

Combined Radiotherapy (RT) plus Chemotherapy Supplants RT Alone as Standard Therapy

In order to improve the outcome of treatment, chemotherapy was added to RT. Phase III trials demonstrated a survival advantage following the addition of chemotherapy to RT for NSCLC.[6,7] The Cancer and Leukemia Group B reported that induction chemotherapy (cisplatin plus vinblastine) followed by conventional RT (60Gy/30 fractions) resulted in significantly better survival than conventional RT alone.[6] The median and five-year survivals were 13.7 months and 17% for the combined therapy versus 9.6 months and 6% for RT alone (p=0.012).[6] Additional phase III trials confirmed that cisplatin-based chemotherapy plus RT produced better survival rates than RT alone.[7–10] Subsequent phase III trials established that concurrent chemotherapy plus RT resulted in significantly better survival than sequential therapy.[11,12] Modern trials of concurrent chemotherapy plus RT have reported five-year survival rates of up to 29%.[13]

Local Failures Remain a Significant Problem

Local control rates based on radiographic studies appear substantially better than those based on pathological findings. Le Chevalier et al.

performed a trial that compared RT (65Gy) alone versus RT plus chemotherapy. All patients underwent serial bronchoscopic biopsies and were found to have local control rates at one year of only 15% with RT alone and 17% with combined modality therapy.[9] It appears that local control is generally unsatisfactory following RT or RT plus chemotherapy. This should come as no surprise as studies performed over 30 years ago suggested that larger epithelial tumors required doses much greater than 60Gy to achieve local control.[14] In the classic article regarding RT dose–response, Fletcher and Shukovsky wrote that it would require 80–90Gy, conventionally fractionated, to locally control 56% of adenocarcinomas of the breast >5cm in diameter.[14] There is no reason to believe NSCLCs would respond differently, as they are often at least this large and most commonly adenocarcinomas in the US. Mehta et al. analyzed dose–response data and came to a similar conclusion, stating that "standard approaches to dose escalation using 2Gy per fraction, five fractions per week, require doses in excess of 85Gy to achieve 50% long-term control rate."[15] Higher doses in shorter treatment times and newer systemic agents are required to further improve disease control. One strategy to improve disease control is the use of higher RT doses with concurrent chemotherapy. This report examines the results of this treatment strategy.

Investigators Start Using Higher Doses of Radiotherapy

Studies using 3D treatment planning have allowed the safe escalation to higher radiation doses.[16–23] 3D planning systems permit the creation of RT beams directed from any angle to treat a tumor. RT planning computers integrate spatial data obtained from both computed tomography and positron emission tomography. Beam's-eye view technology is employed to choose fields that include the primary tumor and adenopathy but a minimal volume of normal tissue. Dose–volume histograms are used to compare various plans and determine which is best. Complex RT plans with carefully chosen fields can deliver greater than standard doses while respecting normal tissue tolerances.[23] The use of 3D technology was an important advance, as large multigroup trials performed prior to this era had major tumor targeting errors in as many as 31% of patients.[24]

One major shift in treatment strategy was the irradiation of radiographically apparent gross disease without prophylactic or elective nodal irradiation (ENI). ENI is the purposeful irradiation of radiographically uninvolved lymph nodes that may contain cancer cells. ENI was originally employed because imaging was so poor prior to computed tomography, when plain radiographs were used to define tumor volumes for RT planning.

There were several reasons for the shift in philosophy away from ENI. The dose of radiation commonly employed (60Gy/30 fractions) was not enough to sterilize bulky epithelial tumors.[14] It was believed that simply increasing the dose delivered to the large volumes of the chest included when prophylactically treating lymph nodes was likely to result in unacceptable toxicity.[19] Additionally, irradiating clinically uninvolved nodal areas prophylactically did not appear rational when the gross tumor was infrequently controlled.[9] The vast majority of dose-escalation trials do not include ENI to minimize the volume of normal tissues irradiated and decrease the risk of toxicity.

Many patients treated in the earlier dose-escalation trials received no chemotherapy or, in some cases, sequential therapy. Doses of RT administered have ranged up to 103Gy for smaller tumors. Investigators in Ann Arbor, Rotterdam, and New York reported favorable results with 18- to 21-month median survivals.[18,21,22] Isolated nodal failures in untreated areas were infrequent (0–6.5%).[18,21,22]

Rosenzweig[25,26] summarized the findings of the Memorial Sloan-Kettering (MSK), University of Michigan, and RTOG studies, dividing tumors by size.[16,17,22,24] Small tumors were peripheral coin lesions for which RT required a volume of total lung receiving >20Gy of <25%. Intermediate tumors were those >4cm with hilar or limited mediastinal adenopathy. Large tumors were those with massive thoracic and mediastinal disease. The maximum dose administered in various trials ranged from 84 to 102.9Gy for small tumors, from 75.6to 84Gy for medium tumors, and from 65.1 to 84Gy for large tumors. The maximum tolerated dose (MTD) was 83.8Gy (RTOG 9311) to 84Gy (MSK) for smaller tumors, 77.4Gy for intermediate-sized tumors (RTOG 9311), and 65.1Gy for the larger tumors (University of Michigan).[16,17,22,24]

Wang et al. summarized years of experience of treating stage III NSCLC at the University of Michigan. They reported that performance status ($p=0.02$), weight loss ($p=0.017$), chemotherapy (yes versus no; $p<0.001$), sequence of chemoradiation (sequential versus concurrent; $p<0.001$), and biological effective dose ($p<0.001$) were significant independent predictors of patient survival for stage III NSCLC. Biological effective dose is calculated with a mathematical formula and estimates the relative kill power of radiation using various parameters of administration, such as daily dose, number of fractions, total time of RT, and tumor sensitivity to RT.[27] Sura (MSK) and Rades (University Hospital Schleswig-Holstein) also found that higher RT doses were significantly associated with better patient survival.[26,28]

Socinski et al. reported a phase I trial that included induction chemotherapy (carboplatin, irinotecan, and paclitaxel) followed by concurrent RT plus chemotherapy (carboplatin and paclitaxel).[29] The RT employed in this study contrasted with the other 3D dose-escalation trials because it included ENI during the initial weeks of RT. Despite the inclusion of ENI in the initial RT fields and concurrent chemotherapy, they were able to boost tolerance in gross disease to 90Gy and conclude that this was safe based on acute toxicity.[29] Significant chronic toxicity did occur in three of the six patients who received 90Gy, however, which included one grade 2 esophageal stricture, one grade 3 pneumonitis, and one grade 5 hemoptysis.[29]

Later, this group of investigators led by Stinchcombe reported the long-term outcome[30] of a modified phase I/II trial investigating the incorporation of 3D RT with induction and concurrent carboplatin and paclitaxel in patients with unresectable stage IIIA/B NSCLC. Patients received two cycles of induction carboplatin (area under the curve [AUC] 6) and paclitaxel (225mg/m^2) on days one and 22. On day 43, concurrent RT and weekly carboplatin (AUC 2) and paclitaxel (45mg/m^2) was initiated. The RT dose was escalated from 60 to 74Gy in four cohorts (60, 66, 70, and 74Gy) and the 74Gy cohort was expanded into a phase II trial. With a median follow-up for survivors of approximately nine years, the

median survival was 25 months and the five-year survival rate was 27%. The long-term survival rate was felt to be quite favorable compared with other treatment approaches for stage III NSCLC.[30]

The RTOG completed a phase I/II trial that included 3D RT and concurrent weekly paclitaxel and carboplatin (RTOG-0117).[17] No ENI was employed. This trial was initially designed to escalate the total dose, with daily fractions greater than the standard 2Gy doses. The radiation dose was to be sequentially intensified by increasing the daily fraction size starting at 75.25Gy in 35 daily fractions of 2.15Gy. Toxicity with this fractionation pattern and concurrent chemotherapy exceeded their limit used to define the MTD. The next cohort received 74Gy in 37 fractions, which was found to be the MTD. This agreed precisely with the findings of an NCCTG phase I trial (N0028),[31] which is understandable as both trials employed similar concurrent weekly chemotherapy and RT parameters targeting gross disease alone. The phase II portion of RTOG 0117 revealed a favorable median survival (21.6 months) in the patients who received 74Gy with concurrent paclitaxel and carboplatin.[32]

NCCTG N0028 was a phase I trial performed to define the MTD of 3D RT given with weekly carboplatin and paclitaxel. The difference between this trial and RTOG-0117 was that N0028 used RT doses of 2.0Gy/day and started at 70Gy. The dose was escalated to 78Gy, but at that level toxicity exceeded the definition of the MTD and the dose was reduced to 74Gy. At this level, toxicity was considered acceptable, and this was found to be the MTD.[31] Later, these investigators reported that the median survival of all 25 patients included in this N0028 was 42 months and 40 months in the 20 patients with stage IIIa/b disease.[33] While this cohort was small, the survival was relatively impressive and confirms the potential utility of radiation dose escalation.

Yuan et al.[34] performed a phase III trial to determine the relative value of ENI with standard doses of RT compared with higher-dose RT without ENI. This trial included 200 patients with inoperable stage III NSCLC treated with concurrent chemotherapy plus radiotherapy. Patients were randomized to receive either involved field irradiation (IFI) or ENI. The planning target volume for IFI was the primary tumor and all clinically- or radiographically-involved lymph nodes with a short-axis diameter of >1cm. The target volume of ENI included the primary tumor and the ipsilateral hilum, the mediastinum (from the inferior head of the clavicle down to 5–8cm below the carina), and the supraclavicular fossa in patients with superior mediastinum metastasis. A dose of 44Gy was delivered to this ENI planning target volume. 3D conformal RT was delivered in daily fractions of 1.8–2Gy up to a total of 60–64Gy for ENI patients and 68–74Gy for IFI patients. Four to six cycles of cisplatin-based chemotherapy were also delivered. Concurrent therapy was started after the second cycle of chemotherapy. Patients in the IFI arm achieved a better five-year local control rate than those in the ENI arm (51 versus 36%; p=0.03).[34] The radiation pneumonitis rate in patients with IFI was lower than in those with ENI (17 versus 29%, p=0.04). Similar trends appeared in radiation esophagitis, myelosuppression, and radiation pericarditis rates between the two arms, although these differences were not significant. The two- and five-year survival rates were 25.6 and 18.3% for the ENI arm versus 39.4 and 25.1% for the IFI arm, respectively. The two-year survival rates were significantly different (p=0.048). IFI with higher than standard doses of RT was associated with a better patient outcome (less pneumonitis, better local control, and greater survival) than ENI with more standard RT doses.[34]

A Phase III Trial Opens to Compare Chemotherapy plus Standard- or High-dose Radiotherapy

The RTOG and NCCTG have performed separate trials that have included concurrent carboplatin, paclitaxel and escalating doses of RT without ENI. They have determined the maximum tolerated dose to be 74Gy. These studies have led to the opening of a multi-cooperative group phase III trial (RTOG 0617/NCCTG N0628/Cancer and Leukemia Group B 30609) comparing concurrent chemotherapy (carboplatin and paclitaxel) with conventionally fractionated RT at 2Gy/day at either standard-dose RT (60Gy/30) or high-dose RT (74Gy/37) without ENI.[17,31]

Biological therapy shows promise when combined with chemotherapy in advanced NSCLC. Pilot studies have demonstrated the safety of biological/chemotherapy combinations together with RT. The current intergroup trial incorporates a second concurrent randomization to chemotherapy plus RT versus chemotherapy with concurrent cetuximab plus RT. This trial will define, for the first time, the role of triple combined-modality therapy with chemotherapy, biological therapy, and dose-escalated RT in the treatment of patients with stage III NSCLC.

Future Directions and Conclusions

Future improvements in imaging and RT-delivery systems will lead to better outcomes for patients with unresectable NSCLC. These will include greater precision in defining tumor, adenopathy, and normal surrounding tissues spatially. In particular, thymidine positron-emission tomography scanning may better differentiate between nodes involved with tumor and inflammation and help guide more precise RT. Molecular analysis of tumors will allow physicians to choose more effective chemo- and biological therapies to combine with radiation. Newer delivery systems will allow the administration of a greater RT dose to the tumor and less to the surrounding normal structures. Technologies that are likely to be helpful in accomplishing these goals include the ever improving RT planning computers, intensity-modulated RT, image-guided RT, stereotactic body RT, and charged heavy-particle (hadron) RT. ■

Steven E Schild, MD, is a Professor and Chairman of the Department of Radiation Oncology at the Mayo Clinic in Scottsdale, where he cares for patients with many cancers, but with a primary focus on lung and prostate cancer. He is the Radiation Co-Chair of the North Central Cancer Treatment Group Lung Cancer Committee. This role focuses on generating and performing clinical trials to improve the care of lung cancer patients. Professor Schild is the co-author of over 160 published cancer articles, of which 36 have focused on lung cancer. He attended Creighton University for both undergraduate education and medical school. He then trained in radiation oncology at the Mayo Clinic in Rochester.

Helen Ross, MD, is an Associate Professor of Medicine and Thoracic Medical Oncologist at the Mayo Clinic College of Medicine in Arizona, where she specializes in lung cancer research and treatment. Dr Ross is the Chair of the Lung Cancer Disease Oriented Group at Mayo Clinic Cancer Center and participates in clinical research at Mayo Clinic and through the North Central Cancer Treatment Group and Eastern Cooperative Oncology Group.

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