What radiation dose is safe in patients with non-small-cell lung cancer?

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A recent study has found that high-dose radiation can be safely delivered for non-small-cell lung cancer provided careful consideration is given to the dose–volume relationship.

A recent paper by Kong et al. (see opposite) presents one of the most comprehensive and systematic investigations regarding dose escalation and pulmonary toxicity in non-small-cell lung cancer (NSCLC). The authors should be congratulated on the conduct and successive completion of this clever study. This adds to the substantial contribution of the University of Michigan group to our understanding of normal tissue dose–volume limits for a variety of organs. The authors treated 109 patients using doses ranging from 63 to 103 Gy. Over three-quarters of the patients received ≥69 Gy. The volume of lung anticipated to be irradiated was prospectively used to guide the selection of radiation dose. Patients were assigned to a radiation dose based on the V_{eff} (lung-effective volume – the percent of lung that, if exposed to the maximum dose in the current radiotherapy plan, would result in the same rate of complication). The primary endpoint was pulmonary toxicity, namely pneumonitis and clinical fibrosis. Follow-up was long, with a minimum of 5 years and a median of 9 years.

Dosimetric parameters including V_{eff}, V_{20} (the percentage of lung receiving 20 Gy or more), mean lung dose, and normal-tissue complication probability were found to be correlated with the risk of pulmonary toxicity. The total dose delivered to the tumour, however, was not related to this toxicity. Thus, their careful selection of dose based (at least in part) on the lung volume to be treated, was successful in defining 'safe' radiation doses. The authors therefore suggest that routine dose escalation can be employed in NSCLC, assuming the appropriate dosimetric constraints are respected.

There are several important points to note. First, in order to achieve the dose–volume constraints desired for the normal lung, elective nodal irradiation was not performed, and patients with supraclavicular disease were excluded. In addition, patients who, following neoadjuvant chemotherapy, were not able to meet the dosimetric constraints, i.e. the group that was probably not down-staged with chemotherapy, were excluded. Unfortunately, no indication is given as to what proportion of the overall population this represented. Over half of the patients studied had stage III disease; however, it is possible that patients with bulky/extensive mediastinal disease were not included because of the dose constraints.

Second, concurrent chemotherapy was not employed. On the one hand, this allows a more pure analysis of the radiotherapy effects on the lung. On the other hand, studies now show that, for unresectable lung cancer, standard-dose radiotherapy with concurrent chemotherapy is superior to sequential therapy.[1] Future work in the area of dose escalation for locally advanced lung cancer will need to investigate whether the addition of chemotherapy alters the threshold for pulmonary toxicity, necessitating modifications of the dose–volume

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parameters. Interestingly, the phase I portion of RTOG [Radiation Therapy Oncology Group] 0117 has found the maximum tolerated dose to be 74 Gy with concurrent chemotherapy.

Finally, 7% of initially enrolled patients were subsequently disqualified secondary to exceeding normal tissue constraints for organs other than the lung. As doses are escalated, other normal tissues, such as oesophagus, will need to be investigated systematically.[2]

This landmark study adds to a growing body of literature that promotes the safety of doses above 60–66 Gy in NSCLC. Some cooperative group protocols now call for the use of the 70 Gy dose, assuming that one or two dosimetric constraints are acceptable. It may be that future studies should be designed to allow the treating radiation oncologist to maximise the dose delivered, once normal lung dose–volume characteristics are achieved.

References

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Synopsis

F-M Kong, JA Hayman, KA Griffith et al. (2006) **Final toxicity results of a radiation-dose escalation study in patients with non-small-cell lung cancer (NSCLC): predictors for radiation pneumonitis and fibrosis.** *Int J Radiat Oncol Biol Phys 65:1075–1086*

Background. Retrospective analyses have suggested that there could be a radiotherapeutic dose–response effect for local control of non-small-cell lung cancer (NSCLC), with doses greater than 60 Gy improving overall survival and local disease control, although no randomised trials have been performed using these dose levels. There are concerns about injury to normal tissue, especially lung tissue, and radiation pneumonitis is an important dose-limiting toxicity.

Objectives. To determine the maximum safe dose of radiation that could be administered in patients with NSCLC as a function of normal-lung volume irradiated, and to identify potential predictors for clinically relevant radiation pneumonitis and fibrosis.

Design and intervention. This radiation-dose escalation trial enrolled patients with newly diagnosed or recurrent inoperable stage I–III NSCLC who had good performance status and had not previously received thoracic radiation. Radiation alone was given between 1992 and 1997, whereas neoadjuvant therapy (cisplatin and vinorelbine) was permitted from 1997 to 2000 in selected patients. The gross tumour volume for 3D conformal radiation was designed to include the primary tumour, any enlarged mediastinal or hilar lymph nodes, and any lesions detected by bronchoscopy or mediastinoscopy. Clinical target volume was formed by expanding the gross tumour volume by 0.5 cm, and additional volume was allowed for setup error and respiratory motion. Patients whose primary tumour or involved nodes were no longer visible on CT scan following chemotherapy still received radiotherapy to the former sites of disease. Radiation dose was escalated in five lung-effective volume (V_{eff}) bins independently, starting at 63–84 Gy. Daily treatment was administered in 2.1-Gy fractions.

Outcome measures. The primary outcome measure was radiation-induced lung toxicity, defined as pneumonitis and fibrosis. Secondary endpoints were non-lung toxicities.

Results. Estimated median follow-up duration was 110 months (9.2 years) in 109 patients. A dose of 103 Gy was reached before the trial was halted. Approximately one-third of patients had grade 2 to 3 acute toxicity. Pneumonitis, pulmonary fibrosis and oesophagitis occurred most frequently, but nausea (with or without emesis), fatigue, skin reactions, rib fractures, bronchial stenosis and pericardial effusion were also reported. Eighty-three patients received a radiation dose of 69.3 Gy or more, of whom 17 (14.6%) had grade 2–3 pneumonitis and 15 (13.8%) had grade 2–3 clinical fibrosis. No grade 4–5 lung toxicity occurred. Grade 2–3 pneumonitis, fibrosis or both occurred in 22 patients (20%). Toxicity was not associated with the dose prescribed for delivery to the tumour, but was significantly associated with the mean lung dose, percent of lung receiving doses of at least 13 and 20 Gy (V_{13} and V_{20} respectively), and lung normal-tissue complication probability ($P<0.001$).

Conclusion. Higher doses of radiation than previously used can be safely delivered to a majority of patients with NSCLC using individualised 3D conformal techniques and by omitting nodal irradiation.

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