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Intensity-Modulated Radiotherapy, Not 3 Dimensional Conformal, Is the Preferred Technique for Treating Locally Advanced Disease With High-Dose Radiotherapy: The Argument Against

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Intensity-modulated radiotherapy (IMRT) allows the delivery of high-dose radiotherapy to target volumes, while sparing adjacent normal tissues. This has been mooted as a method of treating larger and otherwise untreatable lung cancers or of escalating radiotherapy doses. The possibility of achieving these aims has been confirmed in many planning studies, but there is little supporting clinical data. No randomized trial has compared conformal and IMRT, few studies have reported the late outcomes of IMRT, and there is no evidence for improved control of lung cancer with increased radiation dose. Currently IMRT should be regarded as a promising but unproven experimental therapy in locally advanced non–small cell lung cancer. Searches of PubMed were performed looking for the terms "lung cancer and radiotherapy" and "lung cancer and intensity-modulated radiotherapy." The former was carried out for the period 2007, when the author last reviewed this topic, until 2014 and the latter from the first reference to this topic to the present. The first search produced 8000 and the second 929 hits. A standard hierarchy of evidence exists for interventions in medicine, ranging from systematic reviews of randomized trials to case-control studies and mechanism-based reasoning. The best evidence so far available for IMRT in stage III lung cancer is level 3 or 4 (low level evidence), and no currently accruing phase II or phase III trials are listed on the National Cancer Institute clinical trials website, although 1 study at the MD Anderson is open but not currently recruiting patients. This evidence will be reviewed. It would not be regarded as remotely adequate for the licensing of a new pharmacologic agent, and it does not seem unreasonable that the same standards of evidence for efficacy and safety should apply to the 2 branches of nonsurgical oncology.
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Planning and In Silico Studies

The hypothesis that intensity-modulated radiotherapy (IMRT) would improve outcomes for patients with stage III disease comes initially from planning rather than clinical studies.[1-4]

Grills et al[5] in an early study of 18 patients, 10 with stage III disease, reported a 7%-8% increase in mean target dose but with greater heterogeneity, and 15% reduction in V_{20} and mean lung dose with IMRT compared with 3-dimensional (3D) conformal radiotherapy (CRT) in node-positive tumors. These normal tissue differences were not seen in node-negative tumors, and target dose was not analyzed according to node status.

Murshed et al[6] replanned 41 cancers treated with 3D CRT using IMRT and observed a 7%-10% reduction in lung V_{10} and V_{20} but an increase in V_5 in more than half the patients.

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Christian et al[7] constructed intensity-modulated plans for 10 patients and compared these with 3D conformal plans, using the planning target volume 90: lung V_{20} ratio as an end point. All 5, 7, and 9 field intensity-modulated plans were superior to the 3D conformal plans, whereas the 9 field plans were also superior to the 5 and 7 field plans.

More recently, volumetric-modulated arc therapy (VMAT) has been proposed as an even more effective way of achieving these ends. Scorsetti et al[8] found that planning objectives were achieved in all 24 patients treated with Rapid Arc, although the contralateral mean lung dose was 13.7 ± 3.9 Gy. Chan et al[9] reported that VMAT produced a 2% reduction in V_{20} and 0.5-Gy reduction in mean lung dose compared to 3D conformal therapy, a statistically significant but rather small difference in these metrics, which might not be expected to be associated with changes in clinical outcome. Bertelsen et al[10] reported similarly small differences in favor of VMAT over IMRT. This was further reinforced by a study of 13 patients by Guckenberger et al,[11] which found a 5.6% reduction in mean lung dose with IMRT compared with 3D CRT. Warren et al[12] investigated the feasibility of using IMRT to escalate the dose to central tumors, but could not exceed 70.2 Gy, comparable to the dose achieved in INDAR (individualized isotoxic accelerated radiotherapy).[13]

One of the concerns about intensity-modulated radiotherapy has been the effect of the increased lung volume receiving doses up to 10 Gy, a feature of the "lung bath" produced by the multiple fields or arcs used in IMRT and VMAT. A high mortality rate with IMRT in mesothelioma has been related to these dose levels.[14] A modeling study[15] of 18 patients treated with helical tomotherapy compared this plan with 3D CRT and fixed-field IMRT. The possibility was raised that although radiation pneumonitis might be less common in patients receiving IMRT without chemotherapy, the sensitizing effect of chemotherapy in the low-dose areas might make the risk of radiation pneumonitis higher when IMRT was combined with chemotherapy. A study by Stathakis et al[16] suggested a 30% increased risk of second malignancy owing to these increased low-dose volumes.

These planning studies suggest that modest increases in prescribed dose and reductions in lung toxicity might be possible with IMRT. They have not shown that larger cancers might be treated more effectively with IMRT than with 3D CRT. Whether early and late lung toxicity is more affected by the increased volume receiving a low radiation dose or the reduced mean dose will only be made clear by prospective comparative studies.

Clinical Studies

The clinical evidence for the use of IMRT derives from retrospective studies published from various centers in the US, Holland, China, and Korea. No formal prospective phase II or phase III studies with a predefined primary end point have been reported.

Yom et al[17] reported the incidence of radiation pneumonitis in 68 patients with advanced lung cancer treated with concurrent chemotherapy and IMRT between 2002 and 2005, compared with 222 "similar" patients receiving concurrent chemotherapy and 3D CRT, although the decision to use IMRT was based on the inadequacy of 3D conformal plans. The radiotherapy doses were similar, whereas the treatment volumes were slightly larger with IMRT. Grade 3 or greater pneumonitis was observed in 8% of those receiving IMRT and 32% of those receiving 3D CRT. Liao et al[18] reported a second, overlapping, series of 91 patients with advanced lung cancer treated at the MD Anderson with concurrent chemotherapy and IMRT between 1999 and 2006, compared with 318 "similar" patients receiving concurrent chemotherapy and 3D CRT. Median survival rate was 16.8 ± 16.3 months with IMRT and 10.2 ± 6.4 months with 3D CRT (hazard ratio = 0.64 [0.41-0.98], $P = 0.039$). Although the difference appeared mainly in local control, this result might have been influenced by the substantially greater use of positron emission tomography/computed tomography in staging the IMRT group. A third series[19] from this center covering the period 2005-2006 comprised 165 patients of whom 125 had stage III and 22 stage IV disease, and not all of whom had received chemotherapy in addition to radiotherapy. The series included some with undefined stage IV disease, making survival comparisons with other reports unhelpful, but 2-year overall survival rate was 46%. The pneumonitis rate was 14%. A fourth series[20] from the MD Anderson reported by Lopez Guerra compared changes in transfer factor between patients receiving photons, 3D conformal, and IMRT. No differences were seen.

Sura et al[21] reported 55 patients treated with IMRT at Memorial Sloan Kettering between 2001 and 2005. The 2-year survival rate was 58%, and 11% developed radiation pneumonitis. No comparison was made with other radiotherapy techniques.

In a series[22] of 188 patients from the Netherlands Cancer Institute, the 2-year survival rate was 52%, but 35% patients experienced grade 3 toxicity or higher, of which 22% was either esophageal (15%) or pulmonary (7%). In a second Dutch single-center retrospective review, Govaert et al[23] reported a 2-year survival rate of 56% without any grade 3 toxicity or treatment-related deaths. Their planning used "a standard radiation beam geometry not encompassing the healthy contralateral lung."

Two reports have raised concerns about the volume of lung receiving low doses of radiotherapy. Song et al[24] reported a 2-year survival rate of 56% in 37 patients treated with helical tomotherapy. However, there were 4 fatal radiation-induced lung injuries. When the volume of contralateral lung receiving 5 Gy was >60%, pneumonitis occurred in 35%, but in no patients where this was less than 60%. Shi et al[25] thought the key parameter was a $V_{10} < 50\%$, with 29% pneumonitis when this figure was exceeded and 6% when it was not.

A phase II study[26] of 30 participants who were treated with intensity-modulated radiotherapy and weekly cetuximab reported a 2-year survival rate of 35% and 3% grade III pneumonitis; survival and toxicity both less than would be expected from standard chemoradiotherapy techniques.

Scorsetti et al[27] reported 75 patients with stage III non–small cell lung cancer receiving 54-72 Gy with VMAT. The 5-year actuarial local control was 67%, but median survival was only