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Critical Review

Radiation Therapy Intensification for Solid Tumors: A Systematic Review of Randomized Trials

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Purpose

To systematically review the outcomes of randomized trials testing radiation therapy (RT) intensification, including both dose escalation and/or the use of altered fractionation, as a strategy to improve disease control for a number of malignancies.

Methods and Materials

We performed a literature search to identify randomized trials testing RT intensification for cancers of the central nervous system, head and neck, breast, lung, esophagus, rectum, and prostate. Findings were described qualitatively. Where adequate data were available, pooled estimates for the effect of RT intensification on local control (LC) or overall survival (OS) were obtained using the inverse variance method.

Results

In primary central nervous system tumors, esophageal cancer, and rectal cancer, randomized trials have not demonstrated that RT intensification improves clinical outcomes. In breast cancer and prostate cancer, dose escalation has been shown to improve LC or biochemical disease control but not OS. Radiation therapy intensification may improve LC and OS in head and neck and lung cancers, but these benefits have generally been limited to studies that did not incorporate concurrent chemotherapy.

Conclusions

In randomized trials, the benefits of RT intensification have largely been restricted to trials in which concurrent chemotherapy was not used. Novel strategies to optimize the incorporation of RT in the multimodality treatment of solid tumors should be explored.

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Introduction

Over the past few decades, advances in treatment planning and delivery have allowed radiation oncologists to explore the benefits of radiation therapy (RT) intensification for a variety of solid tumors. By "intensification" we are referring to dose escalation and/or altered fractionation, both of which can enhance tumor cell kill in preclinical models (1) and might be expected to increase patient cure rates. This concept has now been tested for a wide variety of solid tumors in hundreds of clinical trials, many of which were randomized studies.

In this review, we examine the results of randomized trials testing RT intensification across a number of disease sites. We explore whether the outcomes of these studies seem to be modulated by the manner in which RT intensification is achieved or by the utilization of concurrent chemoradiotherapy (CRT). Where appropriate, we reference published meta-analyses or perform new meta-analyses to clarify these associations.

Methods

Selection of studies

On the basis of initial literature reviews, we identified the following relevant disease sites for this analysis: primary central nervous system (CNS) tumors, head and neck cancer, breast cancer, lung cancer, esophageal cancer, rectal cancer, and prostate cancer. Sites treated with palliative RT, such as brain or bone metastases, were not included. Pediatric tumors were also excluded from this review.

For each disease site, we performed a PubMed search for the terms "radiotherapy" and "randomized," as well as the disease site of interest. We applied filters to limit hits to studies published in 1993 or later and categorized as clinical trials. We reviewed each abstract and identified randomized controlled trials aiming to demonstrate a benefit for RT intensification through dose escalation (including use of a boost), altered fractionation, and/or RT acceleration. Noninferiority studies, such as those testing hypofractionated RT for breast cancer, were excluded. When more than 1 publication was identified from the same clinical trial, the most recent data were used in the final analysis. We also reviewed relevant review articles and meta-analyses.

Statistical analyses

Data extraction was conducted independently by 2 investigators (KY, NO) according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (2). For each study included in this analysis, we recorded the first author's last name, trial name and year of publication, number of patients, radiation treatment modality, radiation dose and schedule, overall treatment time, and use of chemotherapy. For trials with more than 1 experimental arm, the comparison of each experimental arm with the control arm was treated as a separate study. Hazard ratios (HRs) describing the impact of RT dose intensification on overall survival (OS) and local control (LC) were extracted directly from the original studies or were estimated indirectly by reading off survival curves, as described by Parmar et al (3). For prostate cancer, we analyzed biochemical control in lieu of LC.

For disease sites for which suitable data were available, we performed meta-analyses to synthesize the trials' data. Meta-analyses were performed using study-level data with the inverse variance method (4). For each meta-analysis, we calculated Cochran's Q, which is a classic measure of heterogeneity of effect sizes across trials (4). The assumption of homogeneity was considered invalid for P values of $<.10$ (a conservative cutoff). This prompted the use of a random-effects model instead of a fixed-effects model to derive summary statistics (4). A 2-tailed P value of $<.05$ was considered statistically significant. Publication bias was evaluated visually with funnel plots and statistically using the Egger test (5). All calculations were performed using customized scripts in MATLAB (The Mathworks, Natick, MA).

Findings

Primary CNS cancers

Two large, randomized trials have tested RT dose escalation after biopsy or resection for low-grade glioma (6, 7). Both used conventional fractionation and tested increases of 14.4 Gy in 8 fractions, and neither incorporated chemotherapy. Neither study demonstrated a benefit with dose escalation with respect to OS or progression-free survival. Fixed-effect meta-analyses of these 2 studies yield HRs of 1.03 (95% confidence interval [CI] 0.92-1.16, $P=.600$) for OS and 1.07 (95% CI 0.77-1.47, $P=.688$) for progression-free survival, numerically favoring standard dose RT and indicating that it is very unlikely that dose escalation provides meaningful benefits in this setting. Modern trials for low-grade glioma generally use an intermediate RT dose of 54.0 Gy.

For high-grade gliomas, historical studies established a dose of approximately 60 Gy delivered with conventional fractionation as the standard RT regimen (8, 9). Subsequent studies testing RT intensification have yielded negative results. Radiation Therapy Oncology Group (RTOG) 93-05 randomized 203 glioblastoma multiforme (GBM) patients to standard RT with or without a subsequent radiosurgical boost (10). A single-institution randomized study compared 59.4 Gy in 33 fractions with 70.4 Gy in 44 fractions delivered twice daily (11). Radiation Therapy Oncology Group 90-06 compared 60 Gy in 30 daily fractions against 72 Gy in 60 fractions administered twice daily. Both arms received carmustine (BCNU) chemotherapy as well. Data from 453