Comparative Effectiveness Review
Number 20

Effective Health Care Program

Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer

Executive Summary

Background

Head and neck cancers, specifically those arising in the oral cavity, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses/nasal cavity, salivary glands, and occult primaries, account for approximately 3 to 5 percent of cancers in the United States. According to the National Comprehensive Cancer Network, it was estimated that 47,560 new cases would occur in 2008, with an estimated 11,260 deaths.

The main challenge in radiation therapy for cancer is to attain the highest probability of tumor control or cure with the least amount of morbidity and toxicity to normal surrounding tissues (sometimes referred to as "organs at risk"). Radiation therapy designs have evolved over the past 20 years from being based on two-dimensional (2D) to three-dimensional (3D) images, incorporating increasingly complex computer algorithms. 2D radiotherapy consists of a single beam from one to four directions with the radiation fields designed on 2D fluoroscopic simulation images, whereas 3D conformal radiotherapy (CRT) employs computed tomography (CT) simulation. Intensity-modulated radiotherapy (IMRT) allows for the modulation of both the number of fields and the intensity of radiation within each field, allowing for greater control of the dose distribution to the target. Although proton beam therapy has been used to treat

Effective Health Care Program

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tumors for more than 50 years, it has been used mostly in the treatment of prostate cancer.

Radiation is associated with early and late toxicities, which can have a profound effect on a patient's quality of life, and chemoradiation may be associated with enhancement of these toxicities (particularly mucositis and xerostomia). Therapy-related toxicities are particularly relevant in the treatment of head and neck cancer because of the close proximity of many important dose-limiting normal tissues. Treatment effects can affect basic functions like chewing, swallowing, and breathing and the senses (e.g., taste, smell, and hearing), and can significantly alter appearance and voice.

Key Questions

This Comparative Effectiveness Review addresses four key questions to compare alternative radiotherapy modalities in the treatment of head and neck cancer. Four alternative radiotherapy modalities will be reviewed: IMRT, 3DCRT, 2DRT, and proton beam.

1. What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding adverse events and quality of life?
2. What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding tumor control and patient survival?
3. Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy for specific patient and tumor characteristics?
4. Is there variation in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy because of differences in user experience, target volume delineation, or dosimetric parameters?

Conclusions

When assessing a body of evidence, the AHRQ approach to grading its strength recommends that conclusions about comparative effects take into account the risk of bias, consistency of findings, directness of evidence, precision, dose-response association, plausible influence of confounding, strength of association, and publication bias. For the body of evidence reviewed here, the quality of evidence was moderate in a few instances and was insufficient for the majority of key questions and outcomes addressed.

Comparison: IMRT Versus 3DCRT

- The strength of the body of evidence is moderate for IMRT reducing late xerostomia and improving quality-of-life domains related to xerostomia compared with 3DCRT. In a randomized, controlled trial presented at a conference but not yet published, the risk difference of late xerostomia grade 2 or higher was 35 percentage points with a 95 percent confidence interval between 12.6 and 55.5 percentage points. There is insufficient detail about methods used in the yet-to-be published randomized trial, so it is difficult to assess its quality and contribution to the overall body of evidence. The six observational studies that reported late xerostomia all favored IMRT. Of the five studies that reported frequencies, the reported range of differences is 7 to 79 percentage points. Quality of life was reported in three observational studies and generally favored IMRT in domains primarily related to xerostomia, such as dry mouth, swallowing, and sticky saliva.
- The strength of evidence is insufficient to draw conclusions about the comparative effects of IMRT and 3DCRT for other adverse events. Acute xerostomia, acute mucositis, late mucositis, acute dysphagia, late skin toxicity, late osteoradionecrosis, and bone toxicity were reported in some and typically favored IMRT, but differences were not consistently statistically significant. Among studies of acute skin toxicity, neither the size of the difference nor the direction was consistent.
- No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 3DCRT. The single randomized, controlled trial had too small of a sample size and too short of a followup to ascertain differences in tumor control or survival. The strength of the body of evidence for tumor control and patient survival is insufficient. Estimating between-group differences in disease-specific and overall survival is complex and requires greater controls for confounding and bias.
- No conclusions can be reached on how patient and tumor characteristics affect outcomes, or on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions.

Comparison: 3DCRT Versus 2DRT

- The strength of evidence is insufficient to draw conclusions about the comparative adverse events or quality of life associated with 3DCRT and 2DRT. Among four studies reporting on late xerostomia, one reported a large statistically significant difference; all others were either nonsignificant or of unclear significance. One study compared quality-of-life outcomes between 3DCRT and 2DRT but did not report a statistical comparison. Acute xerostomia, acute mucositis, late mucositis, acute dysphagia, acute skin toxicity, late skin toxicity, and late osteoradionecrosis and bone toxicity were reported in a few studies and differences between 3DCRT and 2DRT were small. The studies are of poor quality, and the results are not consistently statistically significant.
- No conclusions on tumor control or survival can be drawn from the body of evidence comparing 3DCRT versus 2DRT. The strength of the body of evidence for tumor control and patient survival is insufficient. Estimating between-group differences in disease-specific and overall survival is complex and requires greater controls for confounding and bias.
- No conclusions can be reached on how patient and tumor characteristics affect outcomes, or on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions.

Comparison: IMRT Versus 2DRT

- The strength of the body of evidence is moderate for IMRT reducing late xerostomia and improving quality of life domains related to xerostomia compared with 2DRT. The direct evidence reviewed on IMRT versus 2DRT, although of limited quality, suggests a true effect in favor of IMRT. Indirect evidence from the comparison of IMRT versus 3DCRT shows that greater conformality of radiation reduces late xerostomia and improves quality-of-life domains related to xerostomia. Thus, inference from comparison of IMRT versus 3DCRT provides additional support for this conclusion.
- Nine studies reported on late xerostomia, and eight were statistically significant in favor of IMRT. Among the studies that reported frequency, the range of differences between IMRT and 2DRT was 43 to 62 percentage points. Quality of life was reported in one randomized, controlled trial and two observational studies and generally favored IMRT in domains primarily related to xerostomia.
- The strength of evidence is insufficient to draw conclusions about the comparative effects of IMRT and 2DRT for other adverse events. The quality of available studies is poor and no strongly consistent results were reported.
- No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 2DRT. The strength of the body of evidence for tumor control and patient survival is insufficient. Estimating between-group differences in disease-specific and overall survival is complex and requires greater controls for confounding and bias.
- No conclusions can be reached on how patient and tumor characteristics affect outcomes, or on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient, as no comparative studies addressed these key questions.

Proton Beam Therapy Versus Other Techniques

The strength of evidence is insufficient as there were no studies comparing proton beam therapy to any other radiotherapy modality. Therefore, no conclusions can be reached regarding the comparative effectiveness of proton beam therapy for any of the four key questions.

Remaining Issues

In principle, IMRT may offer advantages over 3DCRT and 2DRT because it is more conformal and has a steeper dose gradient. Dose planning studies have shown that IMRT can lower doses to normal tissues while maintaining or increasing the dose to the central tumor. In using IMRT to treat patients with head and neck cancer, theoretical dose delivery advantages must be translated into improved therapeutic outcomes. There is potential to introduce small errors at each step. It is precisely because there may be discrepancies between the planned dose and the amount delivered to a specific patient that treatment planning studies are not sufficient to demonstrate the comparative effectiveness of an approach. Differences in patient susceptibilities to specific adverse events, e.g., xerostomia, are also an intervening variable. Therefore,

comparative evidence on clinical outcomes is necessary to establish that the technical capabilities of IMRT do indeed benefit patients, not only by decreasing xerostomia, but also by achieving similar or improved tumor control and survival.

The capability of IMRT to deliver steep dose gradients around a tumor site may present a risk as well as potential benefit. If the planned dose does not align with the tumor contour and other anatomic attributes of the patient, the planned and actual dose may diverge substantially. As a result, the patient may be at risk of greater adverse effects from an inadvertently high dose to adjacent healthy tissues, or, conversely, be at risk of suboptimal tumor control because of an inadvertently low dose to the tumor. Thus, operator performance may prove to be critical in determining the outcomes of IMRT in clinical practice.

Xerostomia has a significant impact on quality of life. It appears to be common in patients with certain tumor sites, radiotherapy treatments, and chemotherapeutic regimens. Older age and certain therapies for chronic diseases may increase susceptibility for this adverse effect. Research to improve the management of xerostomia and to disseminate that knowledge to clinical practice could potentially improve morbidity and quality of life for cancer patients.

The challenges of conducting research in head and neck cancer need to be acknowledged. Head and neck cancers are not common, so the pace of patient accrual may be slow; this may be accompanied by changes in practices, both for the technology of radiotherapy itself and other aspects of management and treatment. On the other hand, the length of followup needed to study head and neck cancer treatments is relatively short compared to some common cancers, such as breast or colon cancer.

Future research should put high priority on multicenter trials to hasten patient accrual and trial completion. There are considerable obstacles to conducting randomized, controlled trials to ascertain tumor control and survival effects. These are: wide dissemination of IMRT, reluctance to randomize patients when effects on xerostomia are already known, the large patient numbers such trials would require, and other priorities for funding. Nonetheless, certainty about tumor control and survival outcomes can ideally be obtained through a robust randomized, controlled trial. Recognizing that observational studies will continue to be attractive to investigators, the usefulness and generalizability of such can be improved by conducting prospective studies that compare contemporaneous treatments. The patient groups being compared should be similar in terms of key variables, such as anatomic site, disease stage, and prior treatment. Multivariable regression analyses can be helpful in controlling for potential confounders and should adhere to good modeling practices.

Standardization in terminology and measurement would improve the quality of randomized controlled trials and observational studies. Standardization of tumor control and toxicity outcome terminology with common practices for data analysis and presentation would facilitate comparison among studies. Quality-of-life and patient-reported outcomes should be assessed with validated instruments for which clinically significant improvements have been quantified empirically.

Full Report

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