Hyperfractionated radiotherapy of human tumors: overview of the randomized clinical trials

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Authors' objectives
To assess the effectiveness of hyperfractionated and conventional fractionated irradiation.

Searching
MEDLINE and CancerLit were searched from January 1980 to February 1995, using the terms: (random* or phase III) and (hyperfraction* or bid or tid or twice daily or two fractions or three fractions or multiple fractions) and (radiation or radiotherapy).

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) without a planned break of more than 14 days in the treatment arm, with overall treatment times in both arms not differing by more than 2 weeks, and with total radiation doses in the hyperfractionated arm equal to or greater than those in the conventionally-fractionated arm. Radiotherapy had to be the major treatment modality.

Specific interventions included in the review
Hyperfractionated and conventional radiotherapy for the treatment of localised tumour with curative intent for head and neck cancer, bladder cancer, non-small cell lung cancer or malignant gliomas.

For head and neck cancer: conventional radiotherapy total doses ranged from 60 to 70 Gy delivered at 2 Gy per fraction daily over a period of 6 to 7 weeks; hyperfractionated radiotherapy total doses ranged from 70.4 to 80.5 Gy delivered at 1.1 to 1.2 Gy per fraction twice daily over a period of 6 to 7 weeks.

For bladder cancer: conventional radiotherapy total doses ranged from 60 to 64 Gy delivered at 2 Gy per fraction over a period of 8 weeks; hyperfractionated radiotherapy total doses ranged from 60 to 84 Gy delivered at 1.0 to 1.2 Gy per fraction twice daily over a period of 7.5 to 9 weeks.

For non-small cell lung cancer: conventional radiotherapy total doses ranged from 60 to 65 Gy delivered at 1.8 to 2.5 Gy per fraction daily over a period of 6 to 7 weeks; hyperfractionated radiotherapy total doses ranged from 69.6 to 71.5 Gy delivered at 1.15 to 1.375 Gy per fraction twice daily over a period of 5.5 to 6.5 weeks.

For malignant gliomas: conventional radiotherapy total doses ranged from 50 to 60 Gy delivered at 1.93 to 2 Gy per fraction daily over a period of 5 to 6 weeks along with chemotherapy (misonidazole, lomustine, carmustine); hyperfractionated radiotherapy total doses ranged from 50 to 66 Gy delivered at 0.89 to 1.1 Gy per fraction twice or thrice daily over a period of 4 to 6 weeks.

Participants included in the review
No patient inclusion criteria are given. The stage of cancer in patients varied by trial.

Outcomes assessed in the review
The outcomes were survival, incomplete tumour response and local recurrence.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The quality of the studies was scored by the method of Chalmers et al (Controlled Clinical Trials 1981;2:31-49). This considers aspects of design and conduct as well as analysis and presentation and gives a score ranging from 0 (poor) to 1 (high quality). The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

**Data extraction**

The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

**Methods of synthesis**

How were the studies combined?

The observed and expected number of events were calculated for each study along with the variance according to the Peto method. Results from trials of the same tumour entity were pooled to provide a grand total. Odds ratios were calculated and two-sided t-tests of the hypothesis of no difference between treatment arms were undertaken. Survival rates (up to 5 years) were obtained from published survival curves. Standard errors of the survival and local recurrence rates were calculated according to Greenwood's formula (Kalbfleisch and Prentice. The statistical analysis of failure time data. New York: Wiley and Sons, 1980).

How were differences between studies investigated?

The studies were analysed by cancer type. No statistical tests for heterogeneity are reported.

**Results of the review**

Twelve RCTs (2,376 patients) were included. There were 4 trials (1,158 patients) of head and neck cancer, 2 trials (345 patients) of bladder cancer, 3 trials (442 patients) of non-small cell lung cancer, and 3 trials (431 patients) of malignant gliomas.

Head and neck cancer: the methodological quality scores varied across the trials with a median value of 0.43. Survival data were available from 3 of the 4 studies and gave a pooled odds ratio for death of 0.48 (95% CI: 0.40, 0.58; p<0.0001) for hyperfractionation. The odds ratio for incomplete response was 0.43 (95% CI: 0.32, 0.57; p<0.0001), and for local recurrence was 0.35 (95% CI: 0.28, 0.45; p<0.0001).

Bladder cancer: the median value of the methodological quality score was 0.45. The pooled odds ratio for death was 0.55 (95% CI: 0.37, 0.80; p=0.002) for hyperfractionation. The odds ratio for incomplete response was 0.44 (95% CI: 0.27, 0.72; p=0.001). Data for local recurrence were not available.

Non-small cell lung cancer: the median value of the methodological quality score was 0.57. The pooled odds ratio for death was 0.69 (95% CI: 0.51, 0.95; p=0.02) for hyperfractionation. The odds ratio for incomplete response was 0.46 (95% CI: 0.19, 1.12; p=0.09). Data for local recurrence were not available.

Malignant gliomas: The methodological quality of one the studies was poor, but no scores were presented. The pooled odds ratio for death was 0.67 (95% CI: 0.48, 0.93; p=0.02) for hyperfractionation. Data for incomplete response and local recurrence were not available.

There was insufficient data to perform a meta-analysis of late normal tissue effects. However, in no trial with a minimum time interval between fractions of 4.5-6 hours was there a significant increase in severe late effects.

**Authors' conclusions**

The effectiveness of radiotherapy is consistently higher for hyperfractionation than for conventional fractionated irradiation. The assumption that tumours have a small effective fractionation sensitivity seems to be fulfilled especially for head and neck cancers.
CRD commentary
The search is restricted to two computerised databases and the authors do not appear to have checked the reference lists of relevant articles or searched for unpublished studies. Although the inclusion criteria are given, it is not clear how the authors have judged whether the primary studies evaluated treatment of localised cancer with curative intent (for example, what measures were taken to ensure the disease had not metastasised). Insufficient information about patient characteristics is provided to judge whether the results are generalisable (for example, some of the studies may be restricted to patients with good performance status). More details of the primary studies included and clearer explanation of the statistical analysis would have been helpful. The total number of patients presented in the tables does not correspond to that quoted in the text.

The authors' conclusions follow from the results presented; however without further information on the included patients, it is unclear how generalisable the results are, and thus the strength of the authors' conclusions can be questioned.

Implications of the review for practice and research
The authors stated that there is a need for large well-conducted randomised controlled trials on hyperfractionation to supply evidence that the results of optimized conventionally fractionated radiotherapy, at high total doses, and with modern planning techniques, can be improved by hyperfractionation, and to further define the gain of hyperfractionation in dependence on histopathological tumour type, site and stage of disease. In a next step, cost-benefit evaluations are necessary.

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