CRD summary
This review assessed the association between delayed radiotherapy (RT) and the outcomes of RT in cancer patients. The authors concluded that a delay in initiating RT has an adverse effect on local control in breast, and head and neck cancer, and may constitute a risk in other cancer sites. The authors’ conclusions appear to be valid, but no causal association between delay in RT and outcome can be made due to the nature of the evidence base reviewed.

Authors' objectives
To assess the relationship between delay in radiotherapy (RT) and the outcomes of RT in patients with cancer.

Searching
MEDLINE and Cancerlit were searched from 1975 to June 2001 without any language restrictions; the search terms were provided. In addition, manual searches of studies presented at the American Society for Therapeutic Radiology and Oncology conferences and the annual meeting of the Royal College of Physicians and Surgeons of Canada were conducted. References were checked, and experts in the field were contacted for further unpublished studies.

Study selection
Study designs of evaluations included in the review
There were no specific inclusion criteria in relation to study design. Randomised controlled trials (RCTs) and case series studies were included in the review.

Specific interventions included in the review
Studies that assessed the timing of RT regimens, in which the delay in initiating RT was defined and described, were eligible for inclusion. RT could be used either in conjunction with chemotherapy or surgery, or alone.

Participants included in the review
Studies that included cancer patients undergoing treatment with RT were eligible for inclusion. The primary site of cancer in the included studies was the breast, head and neck, lung, brain, or prostate.

Outcomes assessed in the review
Studies that reported the local control rates, distant metastasis, or survival rates were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors stated that the titles and abstracts of studies identified in the search were scanned to exclude those that were irrelevant. However, no further details regarding the number of reviewers involved, whether the assessment was independent, or how discrepancies were resolved were reported.

Assessment of study quality
The authors developed a 9-point quality scale to distinguish between studies with a greater or lesser potential for bias. The scale assessed the following factors: demographic characteristics (age and gender), disease-related factors (tumour stage or size, histology or tumour grade and status of surgical margin), intervention-related factors (RT dose and fractionation, surgical procedure, and chemotherapy regimen), and completeness of follow-up. Studies with a score of 5 or more on the scale were classified as high-quality studies, whilst those with a score of less than 5 were classified as low-quality studies. Two reviewers independently assessed the validity of the included studies. Any discrepancies were resolved before the data extraction.
Data extraction
Two reviewers independently extracted the data. Any discrepancies were resolved before the data were entered into the study database. Data were extracted on: the demographic characteristics of the patients (age, gender); year of publication; characteristics of the disease (primary site, stage or size of tumour, histology, grade, nodal status, and estrogen receptor status in breast cancer); type of surgery and status of surgical margins; definition of delay and the number of patients at each level of delay; details of RT (dose, fractionation, overall time); details of systemic therapy and its timing in relation to RT; median follow-up; and outcomes (rates of local recurrence rate, metastasis and survival). Where estimates of the outcome adjusting for patient-related, disease-related and intervention-related factors were reported as odds ratios (ORs) and their standard errors, these were used to calculate the overall pooled effects. Where adjusted estimates were not presented, these were calculated from the data provided, or were derived from univariate analysis.

Delay was defined differently according to the clinical context. For studies of post-operative RT after lumpectomy for breast cancer, the cut-off point was usually 8 weeks, while for post-operative RT for head and neck cancer, the cut-off point was 6 weeks. The outcomes were analysed at the 5-year follow-up where available, but earlier times were used when these data were not available.

Methods of synthesis
How were the studies combined?
The studies were combined according to the cancer site, and pooled in a meta-analysis using the random-effects model of DerSimonian and Laird. An OR of more than 1.0 indicated a worse outcome in the delayed group in comparison with the non-delay group.

How were differences between studies investigated?
Statistical heterogeneity among studies was tested by calculating Bayers factors. When heterogeneity was present among the studies, an exploratory analysis was performed for factors that might influence the effect of delay on outcomes; random-effects regression models were used. Age (at least 40 years versus younger than 40), extent of disease (stage III/IV versus stage I/II), residual of tumour (R1 versus R0), length of follow-up and study quality (high versus low) were included in the meta-regression model. Only main effects were considered.

The robustness of the overall results was also assessed by excluding lower quality studies from a secondary analysis.

Results of the review
Forty-six studies (total n=15,782) were included: 4 RCTs (n=934) and 42 case series (n=14,848).

Relationship between delay in RT and local control in breast cancer.
Ten case series (n=7,401) investigated the association between delay in initiating post-operative RT and local control in breast cancer (after lumpectomy in 9 studies and lumpectomy or mastectomy in 1 study). Eight of these studies compared local control between patients treated more than 8 weeks after surgery with those treated within 8 weeks of surgery. The results showed that there was a statistically significant increase in the local recurrence rate (LRR) at 5 years with a delay in starting post-operative RT. The pooled OR was 1.62 (95% confidence interval, CI: 1.21, 2.16), corresponding to an increase in the 5-year LRR from 5.8% in patients treated within 8 weeks to 9.1% in patients treated between 9 and 16 weeks after surgery. There was no significant heterogeneity observed among the 8 studies (P=0.66). The two remaining studies used different definitions of delay. One of these studies showed a significantly higher risk of local recurrence for patients who received RT more than 80 days after lumpectomy (P<0.05). However, the second study indicated no difference in recurrence rates between patients treated with post-operative RT within 4 weeks of surgery and those treated more than 4 weeks after surgery.

Twelve studies assessed the optimum sequencing of adjuvant RT and systemic chemotherapy after surgery for breast cancer (lumpectomy in 10, mastectomy in 1 and type of surgery not reported in 1). The results of the pooled OR from 11 studies (1 RCT, 10 case series; total n=1,927) showed an increase in the 5-year LRR from 6.0% in the RT-first group to 16.0% in the chemotherapy-first group. The OR for delayed RT was 2.28 (95% CI: 1.45, 3.57). When the results of 5 low-quality studies was excluded from the analysis, the association between delayed RT and increased LRR...
remained significant. There was no significant heterogeneity observed among these studies (P=0.70). Five studies assessed the association between delay in RT and the rate of distance metastasis. Based on the results of three studies, there was no significant increase in the rate of distance metastasis and delay in RT observed (OR 1.22, 95% CI: 0.94, 1.59). No studies assessed the association between RT delay and survival.

Relationship between delay in RT and local control in head and neck cancer.

Primary RT: five case series (n=2,500) assessed the association between delay in RT and local control in unresected cancers of the head and neck. One study that compared patients treated more than 40 days after surgery with those treated within 40 days of surgery showed a RR of local failure of 2.6 (95% CI: 1.1, 6.4) and a RR of neck failure of 2.7 (95% CI: 1.4, 5.4) in the delayed group. In the other four studies, which quantified the effect of each day of delay in treatment, the results showed that delay tended to increase the risk of local recurrence at 5 years in three studies and significantly increase it in the remaining study. However, the pooled OR was not significant (OR 1.17, 95% CI: 0.96, 1.44).

Post-operative RT: seven studies (n=851) compared local control in patients treated with RT more than 6 weeks after surgery with those treated within 6 weeks. The rate of recurrence was higher in all seven studies for patients in whom treatment was delayed. The pooled OR was 2.89 (95% CI: 1.60, 5.21). However, significant heterogeneity was found between the studies. When three studies of lower quality were excluded from the analysis, the findings remained significant, but the OR was reduced to 2.29 (95% CI: 1.15, 4.59). No heterogeneity between the studies was found.

Relationship between delay and outcomes of RT in other cancer types.

Lung cancer: in the three studies that assessed timing of thoracic RT in patients with limited stage small-cell lung cancer, one reported better local control, lower risk of brain metastasis, and improved overall survival in the early RT group. The other two studies reported no significant differences between the early and delayed RT groups.

Brain tumours: three studies reported on the effects of treatment delay in glioma patients. One study reported a significant 2% increase in risk of death for each day of waiting for primary RT, but no significant differences were observed between the groups in the other two studies.

Prostate cancer: one study reported on the effects of delay and local control in prostate cancer patients. The results showed that a delay of greater than 19 weeks from biopsy to the start of RT was associated with a decreased probability of control.

Authors' conclusions
A delay in initiating RT has an adverse effect on local control in breast and head and neck cancer. There is no good evidence that delay is without risk in other situations.

CRD commentary
The review question was clear in terms of the intervention, participants and outcome measures. A number of sources were searched for relevant studies, no language restrictions were applied, and efforts were made to identify unpublished literature. It was unclear whether any efforts were made to minimise selection bias, as the number of reviewers involved in this process was not reported. However, efforts were made to minimise bias in both the assessment of study quality and data extraction processes.

The data were pooled using a random-effects model, but the authors pooled across different study designs, which may not be appropriate. Differences between the studies were appropriately assessed using meta-regression models and sensitivity analyses. The authors adequately discussed the results with recourse to study quality, and highlighted that the majority of the studies included in the review were retrospective, observational studies. Overall, the authors’ conclusions appear to be valid, but no causal association between delay in RT and outcome can be made.

Implications of the review for practice and research
Practice: The authors state that delays in initiating RT should be as short as reasonably achievable.

Research: The authors did not state any implications for further research.

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