Report 2 / Rapport 2
Due Date / Date Limite: October 14 Octobre 2005

Request for Applications (RFA): Toward Canadian Benchmarks for Health Services Wait Times – Evidence, Application and Research Priorities

Appel de demandes: Établir des points de repères canadiens concernant les temps d'attente dans les services de santé - Preuves, application et priorités de recherche

FRN # / N^{o} NRF :
NOMINATED PRINCIPAL INVESTIGATOR / CHERCHEUR PRINCIPAL DÉSIGNÉ:
TEL / TÉL.: (613) 533-6895
FAX / TÉLÉC: (613) 533-6794
MAILING ADDRESS / ADRESSE POSTALE: **Dr. W.J. Mackillop,** **Division of Cancer Care and Epidemiology,** **Queen's University Cancer Research Institute,** **10 Stuart Street, Level 2,** **Kingston, Ontario K7L 3N6**
TITLE OF YOUR RESEARCH GRANT / TITRE DE VOTRE SUBVENTION DE RECHERCHE: **Toward Canadian Benchmarks for Waiting Times for Radiotherapy for Cancer: Synthesizing the Evidence and Establishing Research Priorities**

CO-PRINCIPAL INVESTIGATORS AND CO-INVESTIGATORS:
List all co-principal investigators and co-investigators and their university (or other) affiliation. Additional space/pages may be used if required. Describe briefly significant changes, if any that have occurred (e.g. include changes to the research team, list new co-investigators, collaborations, collaborations that are no longer in place, etc.).

CO-CHERCHEURS PRINCIPAUX ET CO-CHERCHEURS :
Énumérez tous les co-chercheurs principaux ainsi que les co-chercheurs et leur affiliation universitaire (ou autre). Vous pouvez ajouter des pages au besoin. Décrivez brièvement les changements importants qui sont survenus, s'il y a lieu (p. ex. changements à l'équipe de recherche, liste des nouveaux co-chercheurs, nouvelles et anciennes collaborations, etc.).

Co-Applicants:

Shortt, Samuel Edward - Queen's University
Feldman-Stewart, Deb - Queen's University
King, Will - Queen's University
Brouwers, Melissa - McMaster University
Brundage, Michael - Queen's University
Coldman, Andrew - British Columbia Cancer Agency

Collaborators:

Berman, Neil -Public Health Agency of Canada
Browman, George -Tom Baker Cancer Centre,
Caulfield, Timothy - Health Law Institute
Hall, Stephen - Queen's University
Milosevic, Michael - Princess Margaret Hospital
Pearcey, Robert - University of Alberta
Pickles, Thomas - British Columbia Cancer Agency
Schacter, Brent - Canadian Association of Provincial Cancer Agencies
Sutcliffe, Simon - British Columbia Cancer Agency

No changes to the research team at this time

CONSENT :
Following the 30 day period after the receipt of your report and with your consent, CIHR may post this report and/or its executive summary on the CIHR website and/or use the information therein to prepare communication materials, such as news releases. As such, do you consent to the use and disclosure of this report? **Yes XX☐ No ☐.**

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A) SUMMARY OF RESEARCH RESULTS:
Provide, in one page or less, a bulleted list of the report's main messages, for objectives #1 and #2 of the RFA, followed by a two to three page executive summary of your report.

Note: The bulleted list and executive summary should summarize the detailed answers provided for questions B) and C) below.

A) RÉSUMÉ DES RÉSULTATS DE RECHERCHE :
Veuillez fournir, en une page ou moins, une liste (style télégraphique) des messages principaux de votre rapport, pour le premier et deuxième objectif de cet Appel de demande, suivi d'un résumé de deux à trois pages de votre rapport.

Note : La liste et le résumé devraient résumer les réponses détaillées aux questions B) et C) ci-dessous.

Re: Objective # 1

We have completed a systematic review of the literature which has identified over 70 clinical reports of the relationship between waiting times and the outcomes of radiotherapy (RT). The impact of delay in RT has been studied in many different clinical contexts, but the majority of the reports in the literature have focused on breast cancer, and head and neck cancer. Most of the reported studies are retrospective case series. The majority report on the relationship between waiting times for RT and the risk of local recurrence; a minority also describe the relationship between delay and the probability of long term survival. Our main conclusions based on this review are as follows:

1) There is strong evidence that delay in starting RT is associated with an increased risk of local recurrence in breast cancer and head and neck cancer, the two clinical situations in which most information was available. The risk of recurrence appears to increase continuously with increasing delay; we found no evidence to suggest that there is a threshold below which delay has no adverse effect.

2) There is also some evidence of an association between delay and the risk of local recurrence in several other types of cancer, but there have been too few reports, and too few individual cases studied, to permit firm conclusions. There is, however, no evidence that delay in RT is free of risk in any clinical situation. There are theoretical reasons to believe that delay may increase the risk of local recurrence to a greater degree in patients with types of cancers that are known to grow more rapidly, but there is no clinical evidence either to confirm or refute this hypothesis.

3) There is also some evidence that delay in RT may decrease the probability of long term survival in certain situations in which RT is used with curative intent, including head and neck cancer and cervical cancer.

4) There is almost no information about the effect of delay in RT on symptoms or quality or life.

5) The field of radiobiology provides a well established theoretical framework that predicts a decrease in the probability of local control of cancer with increasing delay in start of RT. There is also a large body of evidence from experimental studies in animals that delays in RT are associated with a decrease in local cancer control rates. Mathematical models of the effects of delay in RT, based on radiobiological principles and the known growth characteristics of human cancers, predict increases in local recurrence rates with increasing delay. The magnitude of the observed increase in recurrence rates observed in the clinical studies is compatible with that predicted by the radiobiological models.

Re: Objective #2

We have completed a search for guidelines and benchmarks for waiting times for RT in the medical literature and on the internet. We have confirmed that various governmental and professional organizations in several different countries and several Canadian provinces have already created and disseminated benchmarks or guidelines for waiting times for RT. Our main conclusions based on this review are as follows:

1) Definitions used by different organizations to define wait times vary widely, but there is evidence of consensus that any unnecessary delay in starting radiotherapy should be avoided. Most organizations have established comprehensive guidelines for waiting times that cover all indications for RT for cancer. The maximum acceptable waiting times for RT that have been established by different groups are remarkably similar.
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2) Published guidelines for waiting times for RT are usually created by experts without the involvement of patients or other stakeholders. The processes used to create existing waiting time guidelines for RT are usually not well documented. However, almost all current guidelines appear to be based on expert opinion and are not explicitly linked to the available evidence.

3) The guidelines for waiting times for RT that have been created and disseminated by of the Canadian Association of Radiation Oncologists (CARO) and were recently adopted by the Canadian Wait Times Alliance (WTA), are very similar in scope and content to those adopted by other organizations around the world.

Although not explicitly linked to the available clinical evidence, the CARO/WTA waiting time standards are consistent with the clinical and experimental evidence that any delay carries at least a small increase in the risk of recurrence. They are based on the principle that waiting times should be "as short as reasonably achievable", a concept borrowed from the field of environmental risk assessment.

4) The CARO/WTA standards for waiting times for RT provide a reasonable benchmark for the practice of radiation oncology in Canada today. However, in future, they should be refined to make them more specific and comprehensive, based on the results of further research.

Re: Additional Comments

It is important to recognize that the centralization of RT services in Canada has the potential to compromise access to care in a way that is entirely invisible through the monitoring of wait times. There is evidence that the problems of inadequate spatial accessibility, and lack of awareness of the indications for RT among primary care givers, may compromise access to RT even more than waiting lists. These problems are invisible unless utilization rates are monitored as well as waiting times. Methods for establishing appropriate rates of RT utilization have been developed and methods for monitoring utilization rates using administrative data are available. We recommend a comprehensive program for monitoring access to care that will monitor utilization rates as well as waiting times.

B) RESEARCH RESULTS - OBJECTIVE 1:

Describe in detail the extent to which the first objective of the RFA has been achieved. Specifically, the following point must be addressed:

1) Synthesis of research evidence regarding relationships between patient characteristics (e.g. age, clinical severity or stage of illness, co-morbidities, etc.), health services wait times and mortality, health status or quality of life.

B) RÉSULTATS DE RECHERCHE – OBJECTIF 1: Décrivez, de façon détaillée, jusqu'à quel point le premier objectif de l'appel de demandes a été atteint. Abordez plus particulièrement le point suivant:

1) Synthèse des données de recherche sur les liens entre les caractéristiques des patients (p. ex., âge, gravité clinique ou stade de la maladie, co-morbidités, etc.), les temps d'attente pour avoir accès aux services de santé et la mortalité, l'état de santé ou la qualité de vie.

BACKGROUND

Radiotherapy (RT) is an effective form of treatment that is required in about 50% of patients with cancer. It is used for diverse purposes. RT is the sole curative option available for many cancers that are inoperable either because of their location or because the patient is unfit for surgery. RT may also be the treatment of first choice in patients in whom an operation is feasible but would result in greater disfigurement or loss of function. RT is used widely in combination with surgery. Adjuvant postoperative RT is used to permit surgeons to carry out smaller-than-conventional operations without compromising the chance of cure, eg., lumpectomy for breast cancer, or to reduce the risk of local recurrence following conventional surgery, eg., in rectal cancer. In patients with incurable cancer, palliative RT is widely used to relieve pain due to bone metastases, to reduce neurological symptoms due to brain metastases, to relieve the thoracic symptoms of lung cancer; and to prevent paraplegia due to spinal cord compression. In almost all the situations in which it is widely used today, the effectiveness of RT has been demonstrated in randomized controlled trials (RCT's)

Demand for radiotherapy (RT) has increased during the last 20 years because of the increasing incidence of cancer and the results of clinical trials that have identified new indications for RT (1-3). Where supply has not kept pace with demand, waiting lists for RT have developed (4-7). Waiting lists for RT may have direct effects on the well-being of individual patients, and also indirect effects mediated by changes in clinical practice (8,9). It is widely accepted that waiting for RT causes psychological distress, and also that the persisting symptoms of an untreated cancer may adversely affect quality of life, but the greatest concern is that delay may have an adverse effect on the long term outcomes of RT.

Theoretical Framework: There are good reasons to suspect that delay may reduce the probability of local control of cancer by RT. Cancer is characterized by growth and invasion, and RT is a local treatment that can only cure a cancer if it is confined to a volume of tissue that can safely be irradiated. There are abundant clinical and experimental data to indicate that the chance of eradicating a tumor with radiation decreases with increasing tumor size (10-14). The expected effect of treatment delay on local control by RT has been calculated on the basis of existing knowledge about the doubling times of human tumors and the relationship between tumor volume and local control (15). Delay would be expected to have the most effect on the local control of fast-growing tumors, or tumors that have been stimulated to proliferate by

previous cyto-reductive treatment (15). The consequences of an increase in local failure rate would depend on the site and stage of the cancer. In some situations, local failure may be successfully treated by subsequent surgery, whereas in others it inevitably leads to death.

There are also reasons to suspect that delay in initiating RT may increase the risk of distant metastasis. It is known that the size of the primary tumor is associated with the risk of distant metastasis in many different types of cancer (16-19). It is also known that the development of a local recurrence is associated with an increased risk of distant metastasis (20-23). Although these associations do not necessarily indicate a causal relationship between tumor size and metastasis (24), some studies do show that the initial size of the primary tumor and local failure following RT are independent predictors of distant metastasis (20,25,26). There is, for example, increasing evidence that preventing loco-regional failure with RT decreases the risk of distant metastasis in breast cancer (27,28).

The Need for Empirical Research: For the theoretical reasons outlined above, the risks of delay in RT seem self-evident to many radiation oncologists, but this type of deductive reasoning is not persuasive to everyone. Managers of publicly funded healthcare systems today are faced with demands for additional resources from many different sectors of the medical community, each of which is equally concerned about its own waiting lists, and duty-bound to make the best case it can for its own clients. Managers may be skeptical about claims for priority that are based only on expert opinion. It is, therefore, important to document the observed risks of delay in RT as objectively and thoroughly as possible.

Ethical and Practical Constraints on Study Design: From a methodological perspective, the best way to establish the relationship between treatment delay and the outcomes of RT in any specific context would be to conduct a randomized controlled trial of delayed versus prompt treatment. From an ethical perspective, however, such trials would be almost impossible to justify, and none have ever been done. A few randomized trials, aimed at optimizing the sequencing of RT and chemotherapy, have randomly assigned patients either to early RT followed by chemotherapy or early chemotherapy followed by delayed RT. However, in this type of study, the initial chemotherapy in the delayed RT arm may reduce the impact of delay in RT on local control. Furthermore, the delay in giving chemotherapy in the early RT arm may increase the risk of distant metastasis. Such trials may, therefore, underestimate the magnitude of any adverse effect of delay on the outcomes of RT. Thus, in studying associations between delays in RT and cancer outcomes, we have to rely primarily on observational as opposed to experimental data in This creates the difficult challenge of controlling for potential confounding factors that may be independently associated both with the exposure of interest (waiting time) and the outcome of interest (eg risk of local recurrence). Although we recognize that the information provided by observational studies is subject to potential bias, there is little prospect of better information becoming available in the future. We, therefore, decided to proceed with a systematic review and meta-analysis of the relevant literature while attempting to identify and as far as possible control for potential sources of bias in the data.

The Original Systematic Review: In 2002 we carried out the first systematic review aimed at determining whether delay in starting RT affected the outcomes of treatment (29). This review, which included 46 studies involving more than 15,782 patients, was published in 2003. The main findings of that review were that there was good evidence that longer wait times for RT were associated with higher rates of local recurrence in the two clinical situations in which the relationship between wait times and the outcomes of RT have been studied extensively (breast cancer and head and neck cancer). Consistent with radiobiological theory and experimental studies in animals, we found no evidence of any threshold below which delay was entirely safe in those situations. The published article, which was peer-reviewed, is attached as Appendix 1.

The Updated Systematic Review: Since completion of our original systematic review, new evidence relating to this topic has become available. For the purposes of the present report we therefore expanded the original review to include literature published between January 2002 and May 2005. In addition, we have taken the opportunity to develop and apply a more rigorous approach to the data analysis that will enable us to better quantify the magnitude of the association between delay in RT and the outcomes of treatment. This component of the work has not yet been completed and we therefore confine ourselves here to reporting the results of a conventional analysis of the data provided by the updated systematic review, based on the same methods used in our previous report (29).

METHODS

Search strategy: In updating our systematic review, we followed the search strategy used in our initial published report. (29). We searched the MEDLINE and CANCERLIT databases using the following text words or Medical Subject Heading (MeSH) terms: delay, waiting times, waiting lists, neoplasm, clinical outcome, radiation treatment, radiotherapy, sequence, interval, local control, relapse, recurrence rate, metastasis, quality of life, and survival. All studies in all languages that examined the relationship between delay in RT and the outcomes of treatment were eligible for inclusion. The titles and abstracts of studies identified in the computerized search were scanned to exclude those that are clearly irrelevant. The database searches were supplemented by manual searches of studies presented at the annual meetings in the of the American Society for Therapeutic Radiology and Oncology (ASTRO) of the Canadian Association of Radiation Oncologists (CARO) and the American Society of Clinical Oncology (ASCO).Additional reports from the reference lists of key articles and also article searches using the names of key authors were included. If the same study had been published more than once, only the most recently published data were used. Published abstracts were included in the analysis only when a full article was not available. Where the published material provided incomplete information, an attempt was made to obtain more detailed information by directly contacting investigators. Attempts were also made to find unpublished data by contacting experts in the field, but this process did not yield any additional information.

Data Collection; The following data were abstracted from each report: year of publication; characteristics of the patients (age, sex); characteristics of the disease (primary site, stage or size of tumor, histology, grade, nodal status, and estrogen receptor status in breast cancer); type of surgery and status of surgical margins; definition of delay and number of patients at each level of delay; details of RT (dose, fractionation, overall time); details of any systemic therapy and its timing in relation to RT; median follow-up; and outcomes (rates of local recurrence rate [LRR], metastasis, and survival). Two of the investigators abstracted this information independently and any discrepancies were reconciled before entry into the database.

Inclusion Criteria; The following inclusion criteria were established: all patients were treated with RT; the delay in initiating RT was defined and described; and relevant outcomes were reported quantitatively.

Stratification: Both the original systematic review (29) and the present update analyzed the studies in groups defined by the reported primary cancer site. Definitive RT was analyzed separately from postoperative RT. Studies of the sequencing of RT and chemotherapy were analyzed separately from pure RT studies.

Measures of exposure to delay: In our original systematic review, we found that most reports in the literature did not treat waiting time as a continuous variable but instead grouped patients into broad

waiting time categories. In most studies, cases were assigned to two or three groups on the basis of duration of delay. The cutoff points used to define the groups differed depending on the clinical context. In order to use as many studies as possible in the meta-analysis, the data were dichotomized using the cutoff points most frequently reported in each specific clinical context. The "consensus cutoff point" for postoperative RT after lumpectomy for breast cancer, for example, was 8 weeks, and for postoperative RT for head and neck cancer it was 6 weeks. This enabled us to compare outcomes between more or less "delayed" groups but it did not permit us to quantify the detrimental effects of delay *per unit time.* Moreover, it also made it impossible to include in the meta-analyses any reports that did not use the consensus cutoff point in creating groups of patients. For the purposes of the present report we have retained this approach because it has already been accepted in the peer reviewed literature. We have also developed an improved analytic approach which will, in future, allow us to convert the categorical data into a continuous measure of delay and to include all available studies in the meta-analyses, regardless of the cut-offs used to define delay.

Statistical analysis: In both the original systematic review (29) and the present update, data from individual studies were combined to calculate overall pooled effects using the random effects model as described by Der Simonian and Laird (30). Heterogeneity among studies was tested by the Q-statistic and when present the magnitude of the heterogeneity was estimated using the I^2 statistic (31) When there was heterogeneity among the results of different studies, an exploratory analysis was performed for factors that might influence the effect of delay on outcomes using random-effects regression models and the following factors: age (≥ 40 *v* < 40), extent of disease (stage III/IV *v* stage I/II), residual of tumor (R_1 *v* R_0), length of follow-up, and quality of study (high *v* low). All factors were coded as 1 or 0, and only main effects (no interactions) were considered. For the present update, the quality of study factor was not used for further analysis. We were concerned that negative findings might be more frequently published in abstract form only, or described in less detail than positive findings. Therefore, lower quality studies were not excluded from the main analyses, but the robustness of the overall findings was tested by excluding the lower quality studies in our secondary analyses.

RESULTS

Study Characteristics

Original Systematic Review

The original systematic review (29) included a total of 46 studies involving 15,782 patients (32-81). Sixteen studies compared early RT followed by chemotherapy with delayed RT preceded by chemotherapy (one study looked at both issues). Forty-two out of the forty-six studies obtained were conducted in North America (Canada and the United States) or Europe. Forty-three were published after 1990. Eleven studies had a sample size of more than 500 patients. Thirty-one studies directly examined the association between delay in RT and the outcomes of treatment. With the exception of four randomized controlled trials of the sequencing of RT and chemotherapy, all were retrospective case series. A total of nine studies were published in abstract form only. In four of the abstracts more detailed information was obtained directly from the investigators (34,40,46,53). The relationship between delay and the outcomes of RT was described in many different clinical contexts, but the majority of studies focused on either breast cancer (21 studies) or head and neck cancer (12 studies). Thirty-nine studies described the association between delay and loco-regional control, 21 described distant metastases, and 19 described survival.

Updated Systematic Review

The updated review identified 19 additional studies that met the search criteria and included 16,466

additional patients (82-100). All were conducted in North America (Canada or the United States) or Europe, except one trial that was performed in Israel (88). Eight studies had a sample size of more than 500 patients (83-86,90,91,95,98). With the exception of two prospective case series (89,100), all were retrospective chart audits (82-88,90-99). Thirteen of the studies were set in single institutions (85,87-94,96-99); however, four studies were multi-centre (82-84,86), and two studies provided no data on the number of locations (95,100). A total of three studies were published in abstract form only (85,86,95) and two studies were published as letters (94,100). Eleven studies described the association between delay and loco-regional control (82,83,86-88,90-93,98,99), 10 described distant metastases (82,83,87,88,90-93,98,99), and eight described survival (82-84,88,91-93,97).The relationship between delay and the outcomes of RT were described in many different clinical contexts, but most studies focused on breast cancer (six trials involving 11,795 patients) (82-87) or head and neck cancer (six trials involving 1,968 patients) (88-93). Other disease sites reported on were lung (94), prostate (95), colorectal (96), gynecological (97), and sarcoma (98,99). One study that described the relationship between delay in RT and quality of life outcomes included several disease sites (100).

Breast Cancer

Original Systematic Review

Ten retrospective studies involving 7,401 patients investigated the association between delay in initiating postoperative RT and local control in breast cancer (after lumpectomy in nine studies and lumpectomy or mastectomy in one study) (32-41). Eight of these studies compared local control between patients who were treated more than 8 weeks after surgery and those treated within 8 weeks of surgery. Pooling the data on LRR for each of these studies found that delay in starting postoperative RT was associated with an increase in LRR at 5 years. The pooled random-effects OR from the combined analysis was 1.62 (95% CI, 1.21 to 2.16), corresponding to an increase in the 5-year LRR from 5.8% in those patients treated within 8 weeks to 9.1% in those patients treated between 9 and 16 weeks after surgery. There was no significant heterogeneity among the eight studies ($P = .66$). The relationship between delay and the risk of local recurrence remained significant when the one low-quality study (38) was excluded (OR = 1.60, 95% CI, 1.20 to 2.14). The remaining two studies used different definitions of delay and could not be included in the combined analysis. One study showed a significantly higher risk of local recurrence for patients who waited for more than 80 days after lumpectomy ($P < .05$) (34). The other study reported no significant difference in any recurrence between patients treated with postoperative RT within 4 weeks after surgery and those treated more than 4 weeks after surgery ($P = .44$) (40).

Twelve studies explored the optimum sequencing of adjuvant RT and systemic chemotherapy after surgery for breast cancer (lumpectomy in 10, mastectomy in one, and type of surgery not specified in one) (41-51,76). One report provided insufficient information for inclusion in the combined analysis. It showed no significant association between delay in RT and local control ($P = .92$) or distant failure ($P = .41$) (46). The remaining 11 studies involved 1,927 patients. One study was a randomized controlled trial and the others were observational cases series. The pooled random-effects OR from the combined analysis of these 11 studies was 2.28 (95% CI, 1.45 to 3.57), corresponding to an increase in the 5-year LRR from 6.0% in the RT-first group to 16.0% in the chemotherapy-first group. When the five low-quality studies (38,47,48,51,76) were excluded from the analysis, the association between delayed RT and increased local failure remained significant (OR = 2.38, 95% CI, 1.29 to 4.40). There was no significant heterogeneity between the results of these studies (p = .70).

Five studies on RT delay reported the association between delay in RT and the rate of distant metastasis (36-40). There was no good evidence of an increase in the risk of metastasis with increasing delay in RT. Three compared the rate of distant metastasis between women receiving postoperative RT more than 8

weeks after surgery and those women treated within 8 weeks after surgery (37-39). On the basis of analyses of these three studies, the pooled random-effects OR was 1.22 (95% CI, 0.94 to 1.59). The other two studies did not report their results in a way that permitted their inclusion in the combined analyses, but both reported that there was no significant association between delay and the rate of distant metastasis (36,40). There were no reports of the association between delay and survival in the original review.

Updated Systematic Review

Benk et al (82) provide a high quality report in which the authors carefully control for the known prognostic factors. Individual waiting times were included in a regression analysis as a continuous variable. They report RR of recurrence per month of delay, which is most informative, but does not map directly onto the way that others have reported their results. However, they report a significant increase in the risk of recurrence with increasing delay that is similar in magnitude to that estimated in our original meta-analysis. The authors analyzed outcomes in RT only and chemotherapy subgroups "separately and together" and obtained similar results in each analysis.

Hebert-Croteau et al (83) report on a high quality population-based study which controlled for all significant prognostic factors. The authors report a statistically significant increase in local recurrence in patients who waited greater than 12 weeks for RT compared to those who waited a shorter time. The reported relative risk of recurrence (RR=1.75) in the delayed group was consistent with the results of the initial meta analysis.

Vukovic et al (85) describe the same series of 568 cases reported previously and add no cases that were not included in the original review. Singh et al (86) did not *measure* wait times. They report on outcomes in groups defined by the order in which they received radiotherapy and chemotherapy.

Yock et al (87) report on a unique series of patients who all received chemo first followed by RT. RT waiting time groups were quite well balanced for prognostic factors known to be associated with local control, but there were many more mastectomies in the longest delay group, and mastectomy cases had worse distant control rates. This may be taken as indirect evidence that there were worse cases in the late group but, even in the face of this, there was no evidence at all of any adverse effect of delay. This suggests that the impact of delay may be mitigated by chemotherapy.

Three of the additional studies reported on the rates of distant metastasis (82,83,87). There was again no evidence of increased risk with increasing delay in RT.

Two of the new reports describe the relationship between delay and survival. One high quality paper found no significant association (82). The other which was a large population-based study from the UK based entirely on administrative data, reported that delay began to be associated with a decrease in survival after nine weeks, and became significant after 20 weeks (RR=1.49; 95%CI, 1.16 – 1.92; $p<0.05$) (84). The authors were unable to control for type of chemotherapy used, and acknowledge the risk that adriamycin-based regimens, which mandate delay in RT, were probably used more frequently in patients with a worse prognosis. Thus the observed association between delay and survival may have been due to confounding. We are also concerned that delay in RT might have been associated with delay in chemotherapy, because the same doctors are usually responsible for giving both types of treatment in the UK. Long RT wait times may have resulted from long waits to see an oncologist which would have resulted in delays in starting chemotherapy as well as RT. A stratified analysis of the RT only cases would have been more informative but the authors do not report having done this. The observed association between delay and survival here is not supported by similar findings from better controlled clinical series. Furthermore, a causal association between delay in RT and decreased survival of the magnitude reported is highly implausible given the very limited impact of RT on survival in this context.

Head and Neck Cancer

Original Systematic Review

Primary RT: Five retrospective studies, involving 2,500 patients, described associations between delay in RT and local control in unresected cancers of the head and neck region. Four studies included squamous cell carcinomas at any head and neck site (52,53,55,56) and the other study dealt exclusively with nasopharyngeal cancer (54). One study compared patients treated more than 40 days after surgery with those treated within 40 days after surgery, and reported a relative risk of local failure of 2.6 (95% CI, 1.1 to 6.4) and a relative risk of neck failure of 2.7 (95% CI, 1.4 to 5.4) in the delayed group (53). The other four studies quantified the effect of each day of delay on local recurrence by Cox regression. We estimated the effect of delay for 1 month (HR_{month}) on the basis of the effect of each day delay (HR_{day}): [HR_{month} = (HR_{day}) (33)]. Pooling LRR data from four studies with one month of RT delay did not detect significant differences in the risk of local recurrence at 5 years (OR=1.17; 95% CI, 0.96 to 1.44; p=0.06). However, significance was detected in one study (52), and the three remaining studies showed a trend towards significance (52,55,56). There was no significant statistical heterogeneity between studies (Chi-square = 4.64, p = .20).

Only one study explored the association between delay and the rate of distant metastasis in unresected head and neck cancer, and no significant association was found (54)

Survival was reported in only one study of delay in RT for unresected head and neck cancer (53). Five-year survival rates of 73%, 62%, and 54% were reported for patients treated with primary RT for laryngeal cancer at ≤30 days, 31 to 40 days, and more than 40 days after diagnosis, respectively. The difference in survival among groups was statistically significant in a multivariate analysis ($p < .05$).

Postoperative RT: Seven studies involving 851 patients compared local control in patients treated with RT more than 6 weeks after surgery for head and neck carcinoma with those patients treated within 6 weeks of surgery were pooled (58-63,80). The pooled OR was 2.89 (95% CI, 1.60 to 5.21). However, considerable heterogeneity was found among the seven studies (p = .01). To explore the potential sources of the heterogeneity, a regression analysis taking into account the potential effect of other factors was performed. Only disease stage, study quality, median of follow-up time, and year of publication were included in the model because this information was available in all of these studies. The magnitude of association was significantly modified by study quality (p = .03). When the three studies with low-quality data were excluded from the analysis (60,61,80), the findings remained significant, but the pooled random-effects OR was reduced to 2.29 (95% CI, 1.15 to 4.59). The probability of local recurrence was higher in the delayed cases in all seven studies, and significantly higher in two of them (58,60).

None of the studies of delay in postoperative RT report on rates of distant metastasis.

Information on survival was available from two studies of postoperative RT for head and neck carcinomas. In one study (59), delay in RT was associated with a significant decrease in survival; actuarial 5-year survival rates were 61%, 46%, and 30% for patients treated at 1 to 6 weeks, at 7 to 8 weeks, and at more than 8 weeks after surgery, respectively (p = .046 by the Cox model). In the other such study, 5-year survival rates of 35% and 28% were reported for patients treated with RT for pharyngeal cancer at ≤30 days and > 30 days after surgery, respectively, but the difference in survival was not statistically significant (63).

Updated Systematic Review

Marshiak et al (88) report on clinical outcomes in relation to wait times for RT in a small series of 44 patients with unresected T3 and T4 cancers of the larynx. Based on a univariate analysis, they report a higher probability of loco-regional control in patients who waited <42 days for RT compared to those who waited longer, but this difference was not statistically significant (89% vs 76%, p=0.25). They also report

a significantly higher probability of 5 year survival among patients who started RT in <42 days (93% vs 65%). Delay was not however significantly associated with either outcome in a multivariate analysis. Suwinski et al (90) report on the outcomes of post operative RT following surgery for head and neck cancer in 868 patients over 18 years at a single center in Poland. The median wait time from surgery to RT was 63 days. Patients were grouped into waiting times <30, 30-60, 61-90, >90 days. There was a significant association between waiting time and the probability of local control at 5 years in a univariate analysis in which waiting time was treated as a categorical variable. Local control rates at five years were higher in the groups that waited for a shorter periods (WT< 30, LRR=76%, WT 30-60, LRR=72%, WT 60-90, LRR=61%: p=0.04). The association between WT and LRR remained significant in a multivariate analysis that controlled for the major prognostic factors (RR 1.28, p=0.02).

Lung cancer

Original systematic review:

The timing of thoracic RT in patients with limited stage small-cell lung cancer (SCLC) was studied in three controlled trials that randomized patients to receive initial RT followed by chemotherapy, or initial chemotherapy followed by RT (72-74). One study reported better local control (p = .036), lower risk of brain metastasis, and improved overall survival (p = .008) in the early RT arm (74). However, these differences were not confirmed in two other two trials (72,73).

One study describes the effect of delay in postoperative RT in patients with non–small-cell lung carcinoma (67-81). In an analysis that controlled for the status of resection margins, nodal involvement, and performance status, the 165 patients who were irradiated at ≥36 days after surgery had a significantly better survival compared with the 175 patients irradiated at < 36 days after surgery. Another small study involving 58 patients with inoperable disease reported a 12% 5-year survival rate in patients treated early, compared with 0% in those treated later (p = .31).

Updated Systematic Review

No relevant new publications.

Brain tumors

Original systematic review:

One study reported a 2% significant increase of risk of death for each day of waiting for primary RT in patients with grade 3/4 glioma (69), but there was no significant association between delay and survival in two other studies that focused on low-grade gliomas (64,65).

Updated Systematic Review

No relevant new publications.

Prostate Cancer

Original systematic review:

One study that described the association between delay and local control of prostate cancer in patients treated with external beam radiation therapy alone was obtained (71). A delay of greater than 19 weeks from biopsy to the start of RT was found to be associated with a decreased probability of local control, but the detailed analytic results were not presented in the abstract, and a full-text article was not available.

Updated Systematic Review

One additional report, examined the effect of delay in primary RT for prostate (95) in a study involving

1,498 patients. This was published in abstract from only. The median time from biopsy to start of RT was 3.3 months. Patients were grouped by wait times from biopsy to start of RT as follows: under 3 months (589), 3-6 months (629), 6-9 months (94), and >9 months (67). There was no significant difference in overall survival, disease free survival, probability of metastasis, or freedom from biochemical failure among the 4 WT groups, after controlling for risk group (based on psa, gleason score, and T category), dose, age and use of hormone deprivation therapy.

Rectal Cancer

Original systematic review

One report described waiting times from date of referral to start of preoperative RT for rectal cancer in a study involving 65 patients (96). No data on long-term outcomes were presented, but there was no significant association between delay and pathological stage

Cervical Cancer

Original Systematic Review

No relevant reports identified

Updated Systematic Review

One recent report describes the effect of delay in definitive RT on outcomes in 195 patients with cervical cancer (97) . Waiting times to start of RT were reported from date of diagnosis, from date of consultation, and from date of examination under anaesthetic. The relationship between waiting times and outcomes was described after a median follow-up of 30 months, range 2-121 months. 80 patients had died and 89 patient had developed evidence of progression (local failure only in 31, distant failure only in 43, and both local and distant in 15 cases). Overall 5-year survival was 53%. Univariate analysis showed no significant association between the duration of waiting times and the probability of local failure, distant failure, cause specific survival or overall survival. The authors found strong evidence that selection bias that might have confounded these univariate results. Younger patients and patients with larger tumours had significantly longer wait times. When the investigators controlled for these and other known prognostic factors in a multivariates analysis, they found a significant association between waiting times and cancer cause-specific survival and also with overall survival The relative risks of death and cancer-related death in patients who waited greater than 5 weeks compared to those who were treated earlier were 2.0 and 2.2 respectively, and both of which were statistically significant. There was also a trend towards increase in the probability of local failure which did not reach statistical significance; the authors point out that their study was powered only to detect a RR of 1.7 or greater. The authors describe the presence of a significant association between WT's and survival in the absence of a significant association with local control as an "incongruity", and recommend further studies to validate these findings. (very thoughtful paper, very careful analysis. Pity they did not provide more raw results and suppressed their non-significant findings).

Soft tissue Sarcoma

Original Systematic Review

No relevant reports identified

Updated Systematic Review

Two reports examined the effect of delay on the outcome of soft tissue sarcoma (98,99) involving a total 857 patients. Schwartz et al (99) describe rates of local failure, distant failure and overall survival in 58 patients who received post operative RT following surgery for soft tissue sarcoma of the trunk and extremity over a period of 18 years. They report a significantly higher probability of freedom from local relapse at 5 years in patients who received their RT less than 4 months after surgery compared to those who waited longer (LC: 88% vs 62%, p=0.048), but no significant difference in the probability of survival without distant metastasis. However, the short and long delay groups were not balanced with respect to prognostic factors. The group that experienced the longer delays had a higher proportion of patients with high grade tumors; for that reason a higher proportion had chemotherapy initially with a consequent increase in waiting time for RT. The reported association between delay and local control may therefore have been confounded by treatment selection bias and the authors did not carry out a multivariate analysis to explore this possibility.

Ballo et al (98) report on the outcomes observed in 799 consecutive cases who received post op RT following grossly complete resection of soft tissue sarcoma over a period of 41 years. They report that the probability of local control was lower in patients who received their RT within 30 days of surgery, compared to those who waited longer (82% vs 75%) but this difference was not statistically significant (p=0.07). Moreover, the authors show that the 2 groups were not balanced with respect to known prognostic factors and concluded that this might well explain the observed difference in local control. Waiting time was not significantly associated with local control in a multivariate analysis that controlled for known prognostic factors. (No RR is reported). There was essentially no difference in the probability of overall survival (50% vs 48%), or metastasis free survival (68% vs 68%) at 15 years.

Quality of Life

Original Systematic Review

No relevant reports identified

Updated Systematic Review

A letter to the editor on the effect of delay in various disease sites provided the data obtained on quality of life (100). In this prospective case-series 55 patients with head and neck cancer, prostate cancer, breast cancer, or other cancer were evaluated while waiting to receive definitive RT or adjuvant RT. The majority of patients reported worrying about the potential effects delays may have on their treatment outcomes although health-related quality of life scores do not decrease significantly while waiting for treatment.

DISCUSSION

Summary of Main Findings

Our original systematic review revealed a significant association between waiting times for RT and the risk of local recurrence in breast cancer and head and neck cancer, the only two clinical situations in which a substantial body of information was available. There was little information available about the risks of delay in other clinical situations but we found no evidence that delay was without risk in any situation. None of the reports on other diseases had sufficient power to be able to detect an increase in the risk of local recurrence of the same magnitude as that observed in breast and head and neck cancer. There was

little evidence that delay was associated with an increase in the risk of metastasis or death from cancer in any situation except for head and neck cancer where two reports suggested an association between delay and a decrease in the probability of survival.

The additional publications identified in the updated review provide added evidence of an association between delay and an increase in the rate of local recurrence in breast and head and neck cancer. There is still no evidence that similar risks are *not* present in other clinical situations, and indeed there were a number of new reports that suggested associations between delay and local recurrence similar in magnitude to those observed in breast and head and neck cancer. The updated review also provided additional evidence that delay may increase the risk of death from cancer in the head and neck malignancies and new evidence of a similar association with survival in cancer of the cervix.

Interpretation

These results must be interpreted with great caution because they are based primarily on observational studies and are vulnerable to confounding**.** Apart from a few randomized trials that studied the sequencing of RT and chemotherapy, the only reports of the relationship between delay and the outcomes of RT come from retrospective, observational studies. Although there is a significant association between waiting time and the local recurrence rates in breast and head and neck cancer, this does not in itself imply a causal relationship between delay and recurrence. In interpreting observational data in a clinical setting, one can obtain some guidance from the conventional rules used in interpreting observational data in other contexts. In general, the likelihood of a causal relationship increases with the strength of the association, the consistency of the observations, the evidence of a dose-response effect, and the plausibility of a causal mechanism (101). The associations between delay and local recurrence were moderately strong and consistent across several different studies conducted at several different centers. A dose-response relationship between the duration of the delay and the magnitude of the decrease in local control was observed in the few studies that provided the necessary data (52,69). Furthermore, there is a plausible mechanism for a causal association between delay and local failure (10-14). These findings support the hypothesis that delay in RT *causes* an increase in the probability of local recurrence.

Nonetheless, there is potential for bias in the selection of patients in the promptly treated and delayed arms in all these case series. Although the better quality studies controlled for the extent of the tumor and other known prognostic factors, there is still some potential for confounding by prognostic factors not adequately controlled for in the analysis. Confounding might either obscure or exaggerate the effect of delay. For example, if patients with more advanced disease were selected for earlier treatment this would cause us to underestimate the magnitude of the association between delay and outcomes. In contrast, if delays in wound healing were associated with RT delays, and if this problem occurred more frequently in patients with more advanced disease, this might lead to an increase in treatment failure rate and cause us to overestimate the impact of delay. However, the scope for confounding is limited in many well controlled, high quality studies that support our main findings. It is highly improbable that the association between delay and local recurrence is explained by confounding.

There is also a risk that the results available in the literature may have been skewed due to publication bias. We did access the grey literature to try to identify reports that had not been published as full papers, but it remains possible that some negative studies may never have been reported at all. Given the strong and consistent associations observed in head and neck and breast cancer, however, the unidentified studies

would have to be numerous, or large, or both to have substantially influenced our conclusions.

We conclude that there is good evidence that delay in initiating RT has an adverse effect on local control in breast and head and neck cancer, and no good evidence that delay is without risk in other situations. The magnitude of the observed association between delay and local control is consistent with previous predictions based on radiobiological evidence (15). There is no theoretical or empirical basis to suggest that there is a threshold level of delay below which there is no risk; the longer RT is delayed, the poorer the outcome is likely to be (15). We therefore recommend that delays in initiating RT should be as short as reasonably achievable (15).

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Table 1. Characteristics of Additional Studies of relating Delay in RT to Outcomes

	Total		Study on Radiotherapy Delay		Sequencing	
	No. of studies (%) (n=19)	Sample size (n=16466)	No. of studies (n=16)	Sample size (n=15827)	No. of studies (n=7)	Sample size (n=3536)
Country						
United States	6 (31.6)	4446	6	4446	3	1941
(86,87,93,95,98,99)	7 (36.8)	9614	5	9543	2	51
Europe (84,89-92,94,96)	5 (26.3)	2362	4	1794	2	1544
Canada (82,83,85,97,100)	1 (5.3)	44	1	44	0	0
Israel (88)						
Primary Site						
Breast (82-87)	6 (31.6)	11795	4	3427	5	11227
Head and neck (88-93)	6 (31.6)	1968	5	1930	2	51
Lung (94)	1 (5.3)	33	0	0	0	0
Prostate (95)	1 (5.3)	1498	1	1498	0	0
Colorectal (96)	1 (5.3)	65	1	65	0	0
Gynecological (97)	1 (5.3)	195	1	195	0	0
Sarcoma (98,99)	2 (10.5)	857	2	857	1	58
Various† (100)	1 (5.3)	55	1	55	0	0
Year of Publication						
2002	5 (26.3)	1947	4	1914	2	1651
2003	5 (26.3)	2515	4	2477	2	51
2004	8 (42.1)	11809	7	11241	3	1834
2005	1 (5.3)	195	1	195	0	0
Study Size						
<100	7 (36.8)	306	5	235	3	109
100-299	3 (15.8)	693	3	693	1	290
300-499	1 (5.3)	482	1	482	1	482
500-999	4 (21.1)	3032	3	2464	0	0
≥1000	4 (21.1)	11953	4	11953	2	2655
Study Design						
Retrospective chart audit	17 (89.5)	16398	14	15759	6	3523
Prospective case series	2 (10.5)	68	2	68	1	13
Setting						
Single institution	13 (68.4)	3976	10	3337	4	399
Two or more institutions	4 (21.1)	10937	4	10937	3	3137
Unknown	2 (10.5)	1553	2	1553	0	0
Status of Publication						
Full text	14 (73.7)	12719	13	12681	6	1943
Abstract only	3 (15.8)	3659	2	3091	1	1593
Letter	2 (10.5)	88	1	55	0	0
Study End Point LC/LRC						
Yes	11 (57.9)	6239	3	556	1	1593
No	8 (42.1)	10227	13	15271	6	1943
Metastasis						
Yes	10 (52.6)	4646	2	348	0	0
No	9 (47.4)	11820	14	15479	7	3536
Survival						
Yes	8 (42.1)	10626	3	9070	0	0
No	11 (57.9)	5840	13	6757	7	3536

Abbreviations: LC/LRC, local control/local regional control

†head and neck (n=14), prostate (n=11), breast (n=12), and other (n=8).

C) RESEARCH RESULTS – OBJECTIVE 2:
Describe in detail the extent to which the second objective of the RFA has been achieved. Specifically, the following points must be addressed:

1) Summary of wait time wait time benchmarks that are currently used nationally or internationally.

2) Synthesis of research evidence (if any) that has been used to support these benchmarks.

C) RÉSULTATS DE RECHERCHE – OBJECTIF 2: Décrivez, de façon détaillée, jusqu'à quel point le deuxième objectif de l'appel de demandes a été atteint. Abordez plus particulièrement les points suivants :

1) Résumé des points de repère relatifs aux temps d'attente actuellement utilisés sur la scène nationale ou internationale.

2) Synthèse des résultats de recherche (s'il en est) sur lesquels on en a appuyé la sélection des points de repères.

We have completed a search for guidelines and benchmarks for waiting times for RT in the medical literature and on the internet. A summary of the existing guidelines is shown in Figure 2. We have confirmed that various governmental and professional organizations in several different countries and several Canadian provinces have already created and disseminated benchmarks or guidelines for waiting times for RT. Our main conclusions based on this review are as follows:

1) Definitions used by different organizations to define wait times vary widely, but there is evidence of consensus that any unnecessary delay in starting radiotherapy should be avoided. Most organizations have established comprehensive guidelines for waiting times that cover all indications for RT for cancer. The maximum acceptable waiting times for RT that have been established by different groups are remarkably similar.

2) Published guidelines for waiting times for RT are usually created by experts without the involvement of patients or other stakeholders. The processes used to create existing waiting time guidelines for RT are usually not well documented. However, almost all current guidelines appear to be based on expert opinion and are not explicitly linked to the available evidence.

3) The guidelines for waiting times for RT that have been created and disseminated by of the Canadian Association of Radiation Oncologists (CARO) and were recently adopted by the Canadian Wait Times Alliance (WTA), are very similar in scope and content to those adopted by other organizations around the world.

Although not explicitly linked to the available clinical evidence, the CARO/WTA waiting time standards are consistent with the clinical and experimental evidence that any delay carries at least a small increase in the risk of recurrence. They are based on the principle that waiting times should be "as short as reasonably achievable", a concept borrowed from the field of environmental risk assessment.

The strengths of these guidelines are that:

- they are clear, simple and easy to understand;
- they are "auditable" ;
- they have been shown to be achievable in routine practice;
- they are entirely consistent with benchmarks recommended by many other governmental and professional organizations around the world (although such benchmarks vary in the way they define waiting times and are not always strictly comparable);
- they have been in place for more than a decade and are already widely accepted by Canadian radiation oncologists.

- The weakness of these guidelines are that:

  - They are not sufficiently specific: they recognize that some patients should be treated more urgently than routine cases, but the specific circumstances in which shorter wait times are appropriate are not defined;
  - They are not comprehensive: they stipulate maximum acceptable waiting times only from the date the patient is referred to a radiation oncologist, and do not stipulate wait times in relation to earlier milestones.
  - they are not explicitly based on the relevant scientific evidence;
  - they were created by the medical specialists (radiation oncologists) alone without input from other stakeholders;

Considering both their strengths and weaknesses, the CARO/WTA standards for waiting times for RT provide a reasonable benchmark for the practice of radiation oncology in Canada today. However, in future, they should be refined to make them more specific and comprehensive, based on the results of further research.

Figure I illustrates the content and structure of waiting time guidelines evaluated to date. **Note that the guidelines adopted Canadian *Wait Times Alliance* in early 2005 are generally consistent with those articulated by other major health care organizations,** although differences in definitions preclude direct comparisons. Details of current guidelines are available on the following websites:

References to Current RT Wait Time Guidelines: See Figure 1 for a Schematic Illustration of their Content

1. Policy and Guidance: Cancer Waiting Times available at:
   http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Cancer/CancerArticle/fs/en?CONTENT_ID=4001800&chk=dpRNWQ
   NHS Cancer Plan avaiable at:
   http://www.dh.gov.uk/assetRoot/04/01/45/13/04014513.pdf Page 48 May,2001
2. Joint Council for Clinical Oncology (JCCO) target times for the commencement of radiotherapy http://www.rcr.ac.uk/docs/oncology/pdf/breast.pdf (Appendix 3, Page 45)
3. Improving Non-Surgical Cancer Treatment Services in New Zealand: National booking time priorities for radiation treatment of patients with cancer (July 2001)
   http://www.moh.govt.nz/moh.nsf/ea6005dc347e7bd44c2566a40079ae6f/3b4fd60baa73eaaecc256d4900725bc9?OpenDocument#Appendix%202A%3A
4. Institute for Clinical Systems Improvement. Breast Cancer Treatment. Sept. 2004. pp 14, 18 and 22-23 (http://www.icsi.org/knowledge/detail.asp?catID=29&itemID=154)
5. Quote from Dr. Robert Pearcey, President, CARO in press release "New Canadian Study on Breast Cancer Treatment May Reduce Treatment Waiting Lists", May 24, 2000.
   Available on-line at: http://www.caro-acro.ca/caro/new/caro/press/ma24.htm
6. No more time to wait: Toward benchmarks and best practices in wait time management: AN INTERIM REPORT BY THE WAIT TIME ALLIANCE FOR TIMELY ACCESS TO HEALTH CARE. Available: http://www.eyesite.ca/pdf/no_more_time_to_wait.pdf
7. Canadian Medical Association, 2004. Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. pp 12-13.
   Available on-line at: http://www.cmaj.ca/cgi/data/158/3/DC1/21
8. Cancer Care Ontario Practice Guideline Initiative. Breast irradiation in women with early stage invasive breast cancer following breast-conserving surgery. Toronto ON. Updated January 2002. pp.7-8.
   Available on-line at: http://www.cancercare.on.ca/pdf/full1_2.pdf.
9. Definition of urgency categories used in waitlists (Nova Scotia)
   http://secure.cihi.ca/cihiweb/en/pub_login_prtwg_DM_31a-DM_e.html

D) ADDITIONAL COMMENTS (e.g. challenges you have faced and how you have/are addressed/ing them, deviation(s) from your original research proposal…)

D) COMMENTAIRES ADDITIONNELS (p. ex. des obstacles que vous avez rencontrés et la façon dont vous les avez / que vous les surmontés, tout écart par rapport à votre proposition de recherche initiale…)

It is important to recognize that the centralization of RT services in Canada has the potential to compromise access to care in way that is entirely invisible through the monitoring of wait times. There is evidence that the problems of inadequate spatial accessibility, and lack of awareness of the indications for RT among primary care givers, may compromise access to RT even more than waiting lists. These problems are invisible unless utilization rates are monitored as well as waiting times. Methods for establishing appropriate rates of RT utilization have been developed and methods for monitoring utilization rates using administrative data are available. We recommend a comprehensive program for monitoring access to care that will monitor utilization rates as well as waiting times.

For a comprehensive discussion of indicators of access to RT, and a full list of key references, readers are referred to the attached discussion paper entitled, "Monitoring Access to Radiotherapy", which will be presented at the Annual Meeting of the Canadian Association of Provincial Cancer Agencies in Vancouver on October 22, 2005 (Appendix 2).

SIGNATURE OF PRINCIPAL INVESTIGATOR: **DATE:**
SIGNATURE DU CHERCHEUR PRINCIPAL DÉSIGNÉ : **DATE :**