Radiotherapy and Oncology 120 (2016) 370–377

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Population benefit of radiotherapy

The population benefit of radiotherapy for gynaecological cancer: Local control and survival estimates

Timothy P. Hanna [a,b,*], Geoffrey P. Delaney [a], Michael B. Barton [a]

[a] Collaboration for Cancer Outcomes Research and Evaluation (CCORE), Ingham Institute for Applied Medical Research, University of New South Wales, Liverpool, Australia; and
[b] Division of Cancer Care and Epidemiology, Cancer Research Institute at Queen's University, Kingston, Canada

ARTICLE INFO

Article history:
Received 17 December 2015
Received in revised form 29 March 2016
Accepted 4 April 2016
Available online 25 April 2016

Keywords:
Population benefit
Radiotherapy
Endometrial cancer
Cervical cancer
Vulval cancer
Ovarian cancer

ABSTRACT

Background: The population benefit of radiotherapy for gynaecological cancer (GC) if evidence-based guidelines were routinely followed is not known. This study's aim was to address this.
Methods: Decision trees were utilised to estimate benefit. Radiotherapy alone (RT) benefit was the absolute proportional benefit of radiotherapy over no radiotherapy for radical indications, and over surgery alone for adjuvant indications. Chemoradiotherapy (CRT) benefit was the absolute incremental benefit of concurrent chemotherapy and RT over RT alone. Citation databases were systematically queried for the highest level of evidence defining 5-year Local Control (LC), and 2-year and 5-year Overall Survival (OS) benefit. Meta-analysis was performed if there were multiple sources of the same evidence level. Deterministic and probabilistic sensitivity analysis was performed.
Findings: Guidelines supported 22 radiotherapy indications, of which 8 were for CRT. 21% of all GC had an adjuvant or curative radiotherapy indication. The absolute estimated population-based 5-year LC and OS benefits of RT, if all patients were treated according to guidelines, were: endometrial cancer LC 5.7% (95% CI (3.5%,8.2%)), OS 2.3% (1.2%,3.4%), ovarian cancer (nil), vulval cancer LC 10.0% (1.6%,18.2%), OS 8.5% (0.5%,15.9%). Combined with prior estimates for cervical cancer, RT benefits for all GC were LC 9.0% (7.8%,10.3%), OS 4.6% (3.8%,5.4%). The incremental benefit of CRT for all GC was LC 0.7% (0.4%,0.9%), OS 0.5% (0.2%,0.8%). Benefits were distinct from the contribution of other modalities. The model was robust in sensitivity analysis. Most radiotherapy benefit was irreplaceable by other modalities.
Interpretation: Radiotherapy provides important and irreplaceable LC and OS benefits for GC when optimally utilised. The population model provided a robust means for estimating this benefit.
 Radiotherapy and Oncology 120 (2016) 370–377

Radiotherapy plays an important role in the management of gynaecological cancer (GC). It would be valuable to know what the benefit of radiotherapy is in the population of patients with gynaecological cancer if all patients were treated according to evidence-based guidelines. This would assist in modelling the impact of underutilisation of radiotherapy and calculating the benefits if resources were planned according to evidence-based need [1–3]. It would also provide inputs for economic analyses of radiotherapy for GC, and a tool for planning for optimal radiotherapy service provision [4].

In this study, the population benefit of radiotherapy when used according to GC guidelines was investigated. This builds on previous work on breast cancer and cervical cancer [5,6]. Using a standardised methodology, 2-year and 5-year overall survival and 5-year local control benefits of radiotherapy will be estimated. The incremental benefit of chemoradiation over radiation alone for GC will also be estimated.

* Corresponding author at: Division of Cancer Care and Epidemiology, Cancer Research Institute at Queen's University, 10 Stuart Street, 2nd Level, Kingston, Ontario K7L3N6, Canada.
E-mail address: thanna@kgh.kari.net (T.P. Hanna).

http://dx.doi.org/10.1016/j.radonc.2016.04.008
0167-8140/

Panel 1. Research in context.

Evidence before this study

The population benefit of external beam radiotherapy when used according to guidelines is largely unknown. Studies published in the past decade have considered only breast cancer and cervical cancer. We systematically queried PubMed and Medline databases with the terms 'gynecological', 'gynaecological', 'cancer', 'radiotherapy', 'population', 'benefit' 1946-November Week 3, 2015. Some studies reported on population outcomes for specific gynaecological cancer indications. None addressed outcomes with guideline-based use of radiotherapy for the entire population of gynaecological cancer patients.

Added value of this study

Our study is the first to describe population benefits of a population-based radiotherapy programme for gynaecological cancer patients. We used a decision tree model describing the proportional incidence of external beam radiotherapy indications in the Australian population with guideline-based use of radiotherapy. We considered 2-year and 5-year overall survival and 5-year local control. The incremental benefit of chemoradiation over radiotherapy alone was separately estimated. Absolute proportional benefits were determined based on a systematic review, providing an estimate of the proportion of the population deriving a benefit specifically from radiotherapy. We found that about one in ten women with gynaecological cancer will derive a 5-year local control benefit from optimally utilised radiotherapy, and one in twenty a 5-year overall survival benefit. The contribution of radiotherapy to gynaecological cancer outcomes was largely irreplaceable by other modalities (e.g. surgery, chemotherapy).

Implications of all the available evidence

Radiotherapy provides important and irreplaceable contributions to gynaecological cancer outcomes when optimally utilised. The modest incremental benefit of chemoradiation over radiotherapy alone emphasises that appropriately delivered radiotherapy is fundamental to combined modality treatment benefits. Efforts should be made to ensure adequate access to radiotherapy as part of national gynaecological cancer programmes.

Methods

Definitions of benefit

Benefits were estimated for all gynaecological cancers representing 2% or more of all GC incident in Australia (ovarian, endometrial, vulval and cervical cancer) [7]. Results for cervical cancer were previously reported and are included in this report in summary only [6].

The *external beam radiotherapy alone* (RT) benefit was defined as the absolute benefit of RT compared to no treatment for radical radiotherapy indications. Given historic data indicating extremely poor long-term survival for most untreated cancers, the radical RT benefit was considered as equal to the survival of patients treated with RT [8]. For the poor performance status group of inoperable endometrial cancer requiring radical radiotherapy, competing risks were considered. For adjuvant indications, the RT benefit was that of adjuvant radiotherapy over surgery alone.

The *chemoradiation* (CRT) benefit was the absolute benefit of chemotherapy given concurrently with radiation, over the benefit of RT alone.

5-year actuarial local control (LC) and 2-year and 5-year overall survival (OS) benefits of RT and CRT were estimated in order to determine the overall population radiotherapy benefit. Benefits of brachytherapy alone and palliative or quality of life benefits were not considered.

A separate analysis was performed to estimate the irreplaceable benefit of radiotherapy for GC. An indication for radiotherapy was defined as *irreplaceable* if there was no standard of practice alternative to the radiotherapy indication. In the case where surgery was an accepted alternative and that surgery was followed by adjuvant radiotherapy according to guidelines, the adjuvant radiotherapy benefit was taken as the irreplaceable benefit.

Systematic review of evidence for radiotherapy benefit

A systematic review was performed to identify the highest level of evidence defining radiotherapy benefits for each indication. The National Health and Medical Research Council (NHMRC) levels of evidence were utilised [9]. Consideration was given to risk of bias, and generalisability to population outcomes. Appendix 1 describes the generic form of the search strategy. A keyword-based search within Ovid was utilised. This allowed simultaneous query of multiple electronic citation databases: Medline, EMBase and all Ovid evidence-based medicine sources. Publicly available population-based outcomes data from SEER were also queried. To ensure completeness, hand searches of key article reference lists were performed. Key articles were queried in Pubmed to identify related articles, and Google™ Scholar keyword searches were performed. In cases where more than one appropriate source of the same level of evidence was identified, a meta-analysis was performed. Searches covered the literature December 1990 to August 2015 for vulval and endometrial cancer. Benefit estimates from previously developed cervical cancer models were utilised [6].

Calculation of radiotherapy population benefit

TreeAge™ Pro 2008 software was used in the development and assessment of the population models. Decision trees were developed, pictorially representing the overall population of GC considered in the analysis. This study built on models developed by Delaney et al. [2,10,11]. FIGO 1988 endometrial cancer staging was utilised in order to maintain compatibility with the many clinical trials and observational studies reported in this convention.

Each branch in the decision tree represented a certain clinical characteristic or treatment decision point involved in subdividing patients into specific subgroups with a specific indication for radiotherapy. The diagram flows from left to right with subgroups defined on the right. In some cases where further subdivisions were needed to define distinct subgroups, international evidence-based guidelines (Appendix 2) and epidemiological data were utilised to extend the models, as previously described [12,13].

Radiotherapy benefits were associated with each radiotherapy indication. The *population benefit of radiotherapy* was determined by first multiplying the proportion of patients in the whole population with an indication by the proportional indication benefit. These products were then summed for the population benefit estimate. The RT population benefit thus provided an estimate of the additional proportion of patients in the whole population achieving a benefit (for example overall survival), due to guideline-based RT, compared with no RT.

Statistical analysis

Meta-analysis

Using Review Manager software version 5.1, a generic inverse variance meta-analysis method was used in cases where there was more than one source of the same level of evidence defining benefit. Standard errors were calculated, where necessary, from survival curves. In these cases, a previously developed method