Radiotherapy and Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

The population benefit of evidence-based radiotherapy: 5-Year local control and overall survival benefits

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ARTICLE INFO

Article history:
Received 25 May 2017
Received in revised form 30 October 2017
Accepted 8 November 2017
Available online xxxx

Keywords:
Population benefit
Radiotherapy
Chemoradiation
Local control
Overall survival
Radiotherapy programs

ABSTRACT

Background: To describe the population benefit of radiotherapy in a high-income setting if evidence-based guidelines were routinely followed.
Methods: Australian decision tree models were utilized. Radiotherapy alone (RT) benefit was defined as the absolute proportional benefit of radiotherapy compared with no treatment for radical indications, and of radiotherapy over surgery alone for adjuvant indications. Chemoradiotherapy (CRT) benefit was the absolute incremental benefit of concurrent chemoradiotherapy over RT. Five-year local control (LC) and overall survival (OS) benefits were measured. Citation databases were systematically queried for benefit data. Meta-analysis and sensitivity analysis were performed.
Findings: 48% of all cancer patients have indications for radiotherapy, 34% curative and 14% palliative. RT provides 5-year LC benefit in 10.4% of all cancer patients (95% Confidence Interval 9.3, 11.8) and 5-year OS benefit in 2.4% (2.1, 2.7). CRT provides 5-year LC benefit in an additional 0.6% of all cancer patients (0.5, 0.6), and 5-year OS benefit for an additional 0.3% (0.2, 0.4). RT benefit was greatest for head and neck (LC 32%, OS 16%), and cervix (LC 33%, OS 18%). CRT LC benefit was greatest for rectum (6%) and OS for cervix (3%) and brain (3%). Sensitivity analysis confirmed a robust model.
Interpretation: Radiotherapy provides significant 5-year LC and OS benefits as part of evidence-based cancer care. CRT provides modest additional benefits.

Radiotherapy is indicated by evidence-based guidelines in up to half of all cancers [1]. The population-level benefits of evidence-based use of radiotherapy in high-income countries have been estimated for specific cancers by using a model-based approach, although the benefit of radiotherapy to the overall cancer population has not yet been described in this way [2–6]. Such information would be useful for informing health policy, quality improvement, and for performing economic analyses of radiotherapy.

In this report, the proportion of the whole cancer population deriving 5-year local control and overall survival benefit from radiotherapy is described. The population benefits of radiotherapy alone, and the additional benefit of concurrent chemotherapy with radiotherapy were estimated. The benefit to the subset with curative indications is described. The impact of sources of uncertainty on model estimates was quantified.

Methods

Defining indications for radiotherapy

A previously described population-based decision tree model was used to measure the proportion of patients with each evidence-based indication for radiotherapy (RUR) in the cancer population of Australia [1,7]. TreeAge Pro 2008 (Release 1.6, TreeAge Software, Inc.) was utilized to build, depict and analyze the model. Evidence-based indications in favor of first-course radiotherapy were based upon superior local control, toxicity profile, quality of life and/or overall survival. Indications were identified based on evidence-based treatment guidelines from national and international organizations [1,8]. The highest level of epidemiological evidence was utilized, according to a pre-specified hierarchy, in order to define the population-based proportion of patients with patient-related and disease-related characteristics defining the incidence of each radiotherapy indication [8]. Western population data were used to estimate the incidence of each indication in Australia. Australian epidemiological data were used where available. In clinical situations where

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https://doi.org/10.1016/j.radonc.2017.11.004
0167-8140/

radiotherapy was considered an equal option with surgery or chemotherapy, the other options were included in the model and sensitivity analysis was undertaken to determine a possible range in population proportion that radiotherapy was indicated for. In specific cases, the radiotherapy benefit model was expanded to account for end nodes in the decision tree where there were subgroups with different benefits of radiotherapy such as groupings of age, performance status or presence of different RT indications. In these cases, the methods used to develop the original model were utilized [8].

Definitions of benefit

Population benefit was defined as the absolute proportion of patients in the overall cancer population that benefited from external beam radiotherapy.

Benefit to the treated population was defined as the benefit of curative radiotherapy (i.e. radical or adjuvant) among patients with curative radiotherapy indications.

Endpoints were 5-year overall survival (OS) and 5-year local control (LC). These provided measures of radiotherapy benefit taking into account competing risks (OS), and a measure of the local effects of radiotherapy in the absence of competing risks (LC). For prostate cancer, LC was conservatively estimated as equivalent to biochemical control. Palliative benefits and brachytherapy alone benefits were not considered.

Radiotherapy alone (RT) benefit was estimated separately from the additional incremental benefit of concurrent chemotherapy and radiation (CRT). Radical RT benefits were defined as the absolute proportional benefit of RT over no treatment, and for adjuvant or neoadjuvant RT, the absolute proportional benefit of radiotherapy plus surgery over surgery alone. CRT benefit was the absolute proportional benefit of concurrent chemotherapy and RT over RT alone.

Systematic review of evidence of radiotherapy benefit

Systematic review was undertaken to define the highest level of clinical evidence defining the benefit (LC or OS) for each radiotherapy indication. The Australian National Health and Medical Research Council hierarchy of evidence [9] was used to rank evidence. Searches were undertaken in Ovid, querying Medline, Embase, and all evidence-based medicine sources (including Cochrane CENTRAL). This provided a comprehensive basis from which to identify studies reflecting outcomes of treatment in a high-income setting, including abstract-only sources. To supplement these queries, publicly available population-based outcome data from SEER were queried. To ensure completeness, hand searches of key article reference lists were performed, and Pubmed and Google Scholar were queried using keywords and related article searches. Prior publications and reports provide example search strategies [2–5,10,11]. In cases where more than one source of the same evidence level was identified, meta-analyses were performed. Generic inverse variance meta-analysis was performed using Review Manager software (Version 5.1–5.3, The Nordic Cochrane Centre, The Cochrane Collaboration). All searches for radiotherapy benefit were completed between January 2012 and June 2016. Guidelines were reviewed to ensure radiotherapy indications were up to date, up to at least June 2015. Results published in peer-reviewed manuscripts supersede earlier reports.

Radiotherapy population benefit

Radiotherapy population benefit was determined by multiplying the absolute proportional benefit of each radiotherapy indication by the absolute proportion in the whole cancer population with the indication, and then summing all such products. For example, in the simplified model of glottis cancer population 5-year OS benefit depicted in Fig. 1, there are two indication benefits (stage I–II radiotherapy, and stage II–IVB radiotherapy). The population benefit was calculated as: (% of stage I–II RT patients with treatment benefit) × (proportion of all glottis cancer with stage I–II RT indication) + (% of stage III–IVB RT patients with treatment benefit) × (proportion of all glottis cancer with stage III–IVB RT indication) = 0.62 × 0.66 + 0.20 × 0.20 = 0.45. This means that for this model, 45% of all glottis cancer patients would survive to 5 years due to radiotherapy utilized according to guidelines, as compared to no use of radiotherapy.

Sensitivity analysis

Deterministic (univariate) and probabilistic (multivariate) sensitivity analyses were undertaken. TreeAge Pro 2008 software was utilized. Uncertainties considered were: [1] Uncertainty in epidemiological evidence defining incidence of radiotherapy indications [2] Uncertainty or controversy regarding radiotherapy indications [3] Uncertainty in the frequency of radiotherapy use where equal alternatives to radiotherapy existed [4] Uncertainty in the magnitude of radiotherapy benefit.

Deterministic sensitivity analysis is depicted in tables, showing multiple one-way sensitivity analyses ordered according to the magnitude of influence on the benefit estimates.

Probabilistic sensitivity analysis was performed using Monte Carlo (MC) simulation. Standard errors were defined for all benefit estimates, utilizing previously described formulae for extracting summary statistics from published manuscripts [12,13]. Borkwof's hybrid variance estimator was utilized to define standard errors of Kaplan–Meier estimates of survival [14]. Flat probability distributions were utilized for epidemiological estimates where there was a range of values considered equally plausible. 10,000 iterations of each MC simulation were performed, with the 95% confidence interval defined based on the 2.5th and 97.5th percentile benefits.

Results

48% of all cancer patients had an indication for radiotherapy. 34% of all cancer patients had first course radical, adjuvant or neoadjuvant indications for radiotherapy and 14% had first course palliative indications. Radical, adjuvant and neoadjuvant indications represented 71% of all indications for first-course radiotherapy. 39% of all 170 curative radiotherapy indications were supported by level I or II evidence. The proportion supported by level I or II evidence was less for radiotherapy alone (25%) compared to chemoradiation (73%). The low proportion supported by level I/II evidence for radiotherapy alone related to the many radical indications for radiotherapy that have become entrenched standards of care such as in head and neck and cervix.

Radiotherapy population benefit for all cancers

In univariate analysis, the population benefit for all cancers combined was for 5-year LC: 10.9% RT, 0.6% CRT. For 5-year OS:

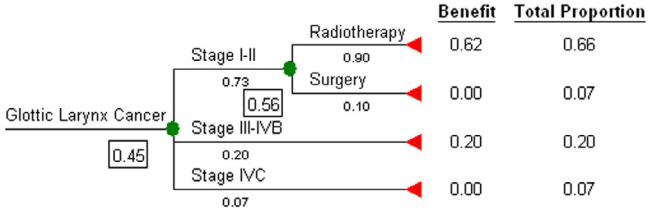

Fig. 1. Simplified radiotherapy population benefit model for glottic larynx cancer 5-year radiotherapy alone overall survival.

Please cite this article in press as: Hanna TP et al. The population benefit of evidence-based radiotherapy: 5-Year local control and overall survival benefits. Radiother Oncol (2017), https://doi.org/10.1016/j.radonc.2017.11.004