Radiotherapy and Oncology 121 (2016) 225–231

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prophylactic cranial irradiation

Patient preferences regarding prophylactic cranial irradiation: A discrete choice experiment

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ARTICLE INFO

Article history:
Received 29 May 2016
Received in revised form 29 August 2016
Accepted 11 September 2016
Available online 4 October 2016

Keywords:
Lung cancer
Prophylactic cranial irradiation
Patient preferences

ABSTRACT

Introduction: In patients with non-small cell lung cancer (NSCLC) treated with chemoradiotherapy (CRT), prophylactic cranial irradiation (PCI) is not standard practice. This study determined patient preferences for PCI with respect to survival benefit, reduction in brain metastases (BM) and acceptable toxicity.
Methods: A Discrete Choice Experiment was completed pre- and post-treatment. Patients made 15 hypothetical choices between two alternative PCI treatments described by four attributes: amount of life gained, chance of BM, ability to care for oneself, and loss of memory. Participants also chose between PCI and no PCI.
Results: 54 and 46 surveys were completed pre- and post-treatment. The most important attributes pre-treatment were: a survival benefit >6 months, of 3–6 months, avoiding severe problems with memory and self-care, avoiding quite a bit of difficulty with memory and maximally reducing BM recurrence. Post-treatment, BM reduction became more important. 90% of patients would accept PCI for a survival benefit >6 months, with a maximal reduction in BM even if severe memory/self-care problems occurred. With a 10% reduction in BM and mild problems with memory and self-care 70% of patients pre- (90% post-treatment) would accept PCI for a survival benefit of 1–3 months, and 52% pre- (78% post-treatment) for no survival benefit.
Conclusion: Improvement in survival is the most important attribute of PCI with patients willing to accept significant toxicity for maximum survival and less toxicity for less survival benefit. BM reduction became more important after treatment. The majority of patients would accept PCI for no survival benefit and a reduction in BM.
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Brain metastases (BM) develop in 22–55% of patients with locally advanced non-small cell lung cancer (LA-NSCLC) treated with curative intent [1–4]. Technological advances in tumour staging, radiation therapy (RT) planning and delivery, and the concurrent administration of chemotherapy with RT, has translated into improved local control and survival rates [5,6]. However, improvements in survival provide a longer time period for micrometastatic disease to manifest and it is hypothesised that the incidence of BM will increase.

In selected patients with limited- and extensive-stage small cell lung cancer (SCLC), the use of PCI is considered standard of care as PCI results in a decreased incidence of BM and an improvement in disease-free survival (DFS) and overall survival (OS) [7–9]. In LA-NSCLC, PCI is not part of standard practice due to a lack of proven survival benefit and concerns regarding neurotoxicity. The Radiation Therapy Oncology Group (RTOG) 0214 study randomised patients with Stage III NSCLC treated with CRT to PCI or observation. PCI reduced the incidence of BM at 1 year (18% v 7.7%, $p = 0.004$) but was not associated with an improvement in DFS or OS. However, the study was underpowered for a survival endpoint [10]. The use of PCI was associated with some adverse effects, namely a decline in delayed recall on the Hopkins Verbal Learning Test (HVLT). However, there were no differences observed between the study arms on Mini Mental Status Examination, Activities of Daily Living scale or quality of life (QOL) assessments [11].

The present study aimed to determine the preferences of patients with LA-NSCLC undergoing CRT with respect to PCI. Specifically, this study aimed to (i) estimate the relative importance of different characteristics potentially associated with PCI (survival gains, reduced chance of BM, reduction in ability to care

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http://dx.doi.org/10.1016/j.radonc.2016.09.003
0167-8140/

for oneself and memory loss) for patients; (ii) estimate the impact of changes of these characteristics on the likelihood that patients would accept PCI, and (iii) explore whether undertaking CRT for lung cancer has an impact on patients' preferences for PCI.

Methods

A Discrete Choice Experiment (DCE) was used in a prospective cohort of patients with LA-NSCLC undergoing CRT at a single tertiary institution in Queensland, Australia, between June 2012 and December 2014. The DCE is a popular method for quantifying and evaluating patient preferences in healthcare [12,13]. In a DCE, a medical intervention is described by its attributes (e.g. improvement in survival, or adverse effects). A series of hypothetical choice sets is constructed in which the levels of these attributes change in a systematic way (according to an underlying experimental design). In each choice set, the participant is asked to perform a pairwise comparison of these hypothetical alternatives and choose their preferred alternative. Thus, participants exercise their preferences by making repeated trade-offs and choices across these hypothetical scenarios.

Attributes and attribute levels

The choice of the most relevant attributes and levels of PCI for LA-NSCLC was based on literature findings [10,11]. The attributes chosen were: amount of life gained, chance of developing BM, ability to care for oneself and loss of memory. Each attribute was described using four levels that were felt to represent potential outcomes from PCI. Each level was presented in a way that was felt to be meaningful to patients. For example, to assess the importance of developing BMs, patients were asked to choose between different "chances of cancer coming back in your brain" with the chances given as 20%; 4 in 20 patients, (to approximate the 18% incidence of BM in the observation arm of RTOG 0214), 10%; 2 in 20 patients (to approximate the 7.7% incidence of BM in the treatment arm of RTOG 0214) with an intermediate level (15%; 3 in 20 patients) and a best case scenario level (5%; 1 in 20 patients). For amount of life gained, levels ranged from no extra life (reflecting ROTG 0214 results) to a hypothetical best case scenario of >6 months of life gained, with intermediate levels of 1–3 and 3–6 months of extra life. Similarly, to assess the importance of impact on memory and self-care, levels ranged from no problem or difficulty to severe problems or difficulties. The attributes and the associated levels are presented in Table 1.

Table 1
Attributes and Levels for the DCE choice sets.

Attribute	Levels
Extra Life	No extra time 1–3 months 3–6 months More than 6 months
Chance of your cancer coming back in your brain is...	20%; 4 in 20 patients 15%; 3 in 20 patients 10%; 2 in 20 patients 5%; 1 in 20 patients
Taking care of yourself	No problems Slight problems Moderate problems Severe problems
Memory	No difficulty A little difficulty Quite a bit of difficulty Severe difficulty

DCE choice set design and survey

NGENE software (ChoiceMetrics, 2012) was used to combine the attributes and levels into 16 choice sets, using a D-optimal design approach [14]. This ensured a statistically efficient approach was used to capture the choice data. In each choice set the presented attribute levels were varied in order to capture the different trade-offs which individuals usually face with respect to their radiation treatment options. Participants were initially asked to choose between two alternative PCI treatments in each choice set. They were then asked to choose between their preferred PCI alternative and an opt-out alternative of no PCI. The opt-out alternative was described as providing no extra life, a 20% risk of BM, and no change in ability to take care of oneself or memory. An example choice situation is found in Supplementary Fig. 1.

To assess whether the experience of undergoing conventional therapy impacted on participant choices, the DCE was undertaken two time points: (1) just prior to commencement of CRT or during the first week of therapy; and (2) during the last week of therapy. In addition, the impact of patient sociodemographic factors and self-reported health status (obtained from the EQ-5D-5L instrument) on patient preferences was assessed [15]. The survey was pilot tested in an interview-based setting prior to data collection, to ensure the survey was understood by patients and had face validity.

Sample and administration

Ethical approval was obtained from the hospital Human Research Ethics Committee. Patients were eligible if they were diagnosed with Stage III NSCLC and were to receive definitive CRT. Patients were identified at the weekly Lung Cancer Multidisciplinary Meeting. Once consent had been obtained, the DCE was administered by trained nurses. The nurse presented each alternative to the participant in a face-to-face interview setting using a booklet, and recorded their choice. Participants were informed that the scenarios were hypothetical.

Data analysis

The choice data were analysed using mixed logit regression (MXL) models to indicate the relative importance of improvements in each attribute for treatment preference [16]. In a mixed logit model, the participant's choices are related to the corresponding treatment attribute levels and a set of socioeconomic individual characteristics. Such an approach allows an estimate of the relative importance of each treatment attribute, in addition to the implied trade-offs between selected attributes, i.e. how much of one attribute a participant is willing to forgo in order to gain a fixed amount of another. It also allows an estimate of likely uptake for an intervention.

The MXL model was specified as a linear function of the attribute levels. The constant term associated with treatment uptake was treated as random (following a normal distribution, using 1000 Halton draws for estimation) and dependent on other sociodemographic variables including the participant's age, education level, employment status, marital status, and self-reported health status. All attribute levels were effects coded, except for BM which was coded continuously. The opt out alternative of no PCI was specified with a fixed utility equal to that associated with no extra survival and a 20% chance of BM, as these were the levels used to describe the setting of "no PCI" in the DCE survey.

The size of the coefficients in the models indicates the importance of improvements in different PCI treatment attributes. To