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Economic evaluation of single-fraction versus multiple-fraction palliative radiotherapy for painful bone metastases in breast, lung, and prostate cancer

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ABSTRACT

Introduction

Single and multiple-fraction external beam radiotherapy (SFX-EBRT and MFX-EBRT) are palliative treatment options for localised metastatic bone pain. MFX is the preferred choice in many developed countries. Evidence shows little difference in how effectively SFX and MFX reduce pain. However, SFX is associated with higher retreatment (and in one meta-analysis) pathological fracture rates. MFX is however more time-consuming and expensive. We estimated the cost-effectiveness of SFX versus MFX for metastatic bone pain in breast, prostate, and lung cancer in New Zealand.

Methods

We constructed a Markov microsimulation model to estimate health gain (in quality-adjusted life-years or QALYs), health system costs (in real 2011 NZ dollars), and cost-effectiveness. The model was populated using effect estimates from randomised controlled trials and other studies, and New Zealand cancer and cost data. Disability weights from the 2010 Global Burden of Disease study were used in estimating QALYs.

Results
Across all three cancers, QALY gains were similar for SFX compared to MFX, and per patient costs were less for SFX than MFX, with a difference of NZ\$1469 (95% uncertainty interval \$1112 to \$1886) for lung cancer, \$1316 (\$810 to \$1854) for prostate cancer, and \$1344 (\$855 to \$1846) for breast cancer. Accordingly, from a cost-effectiveness perspective, SFX was the preferable treatment option. Various sensitivity analyses did not overturn the clear preference for SFX.

Conclusion

For all three cancers, SFX was clearly more cost-effective than MFX. This adds to the case for desisting from offering MFX to patients with metastatic bone pain, from a cost-effectiveness angle.

Keywords –bone pain, cost-effectiveness analysis, metastatic cancer, single fraction, radiotherapy

INTRODUCTION

Breast, prostate and lung cancer are some of the most common cancers to metastasise to bone, (1) with bone metastases occurring in 70% of advanced breast and prostate cancer. (2) Bone metastases cause significant morbidity such as pain, pathological fracture, decreased mobility, hypercalcaemia and nerve compression, reducing a patient's quality of life and functional status. (3) Bone pain is the most common complication of metastatic bone disease, caused by periosteal irritation, structural damage and nerve entrapment. (4)

Radiotherapy is an effective and well-tolerated treatment for metastatic bone pain. Radiotherapy reduces pain, improves and preserves function and mobility, and prevents future complications such as pathological fractures and vertebral collapse. (5) Complete pain relief is achieved in a third of patients four weeks after receiving radiotherapy.(6) Patients with mild, moderate or severe pain are equally likely to respond to radiotherapy. (7)

The current mainstay for the palliative treatment of pain and prevention of the morbidity caused by localised bone metastases is external beam radiotherapy (EBRT), which is more effective and has less side effects than oral analgesics (8). The optimal radiation dose of EBRT has been the focus of extensive research activity and debate for the past two decades (e.g. (8, 9)). Over 3500 patients have been involved in randomised controlled trials typically comparing single-fraction (SFX) with multiple-fraction (MFX) EBRT, and these trials then subjected to four meta-analyses. (6, 10-13). Each meta-analysis presents similar findings, showing no difference in complete, partial or overall pain response from treatment between dose fractionation schedules. Accordingly, the International Atomic Energy Agency states there is no role for MFX-EBRT in the treatment of uncomplicated bone metastasis, (14) and the Clinical Practice Guidelines for metastatic prostate cancer produced by the Australian Cancer Network in 2010 recommend that a single dose of 8Gy (Gray-unit of ionising radiation dose) is as effective for pain response in metastatic bone pain as multiple higher fractionated doses. (15)

Despite this long-standing evidence, MFX continues to be the preferred choice for the treatment of bone metastases in many countries (including New Zealand, Australia, United Kingdom, Canada and United States of America). (9, 16). Not only is MFX more expensive and time-consuming to deliver compared to SFX, there is also a potentially negative impact on the overall quality of life for the terminally ill patient, due to increased time spent in hospital receiving treatment and associated travel costs.

One concern in defence of MFX is that the rate of subsequent pathological fractures may be less than with SFX. Sze et al (2004) in a Cochrane meta-analysis pooled five trials and found that patients in the SFX arms were about 1.8 times more likely to have had a pathological fracture at one year post treatment than patients in the MFX arms (3.0% of SFX patients compared to 1.6% of MFX patients). (6) A subsequent meta-analysis found no difference in pathological fracture rate between SFX and MFX.(12) However, we used the study by Sze et al (2004) to inform our model parameters as

the treatment regimens most closely matched those used in New Zealand. Therefore including this outcome in the economic comparison represents a worst case scenario.

This raises the question as to whether the possibility of lower pathological fracture rates with MFX is worth the extra cost and imposition on patients. The main objective of this study was to compare the cost-effectiveness of SFX versus MFX for metastatic bone pain across breast, prostate, and lung cancer, using New Zealand as the context. There have been previous cost-effectiveness analyses on palliative radiotherapy. (17-19). However, this study is the first to include pathological fracture rates, as well as being the first specific to New Zealand.

METHODS

We constructed a Markov microsimulation model to compare the health gains, health system costs, and cost-effectiveness of SFX versus MFX across breast, prostate, and lung cancer. The main comparison of interest was SFX versus MFX, although each was also compared to analgesia.

In general, a health system perspective was used i.e. we did not include gains and costs outside of the health system such as productivity. We did however include private travel and accommodation costs for patients as outlined in our costing protocol (20). We used a lifetime horizon, following our cohorts until death or age 110 years, whichever happened first. Health gains were quantified in quality-adjusted life-years (QALYs). We used a modified version of a traditional QALY called a QALY^{DW}, using disability weights from the Global Burden of Disease study (21) (rather than say EQ 5D utilities). The survey used to estimate these disability weights is comprehensive and recent, based on pair-wise comparisons using 30,000 respondents in multiple countries. Using disability weights also allowed us to incorporate 'background' non-cancer related morbidity (see Web Appendix for more detail). We use the term QALY^{DW} in the Methods section but default to QALYs elsewhere.

Health system costs were quantified in real New Zealand dollars for the year 2011. We applied a 3% discount rate to both health gains and health system costs to optimise comparisons with international work(22). Modelling was conducted in TreeAge Pro 2012 R2.0.

POPULATION

The study population was patients with Stage IV metastatic breast, prostate, and lung cancers in 2011, for whom we had survival data (23) and socio-demographic data (age, sex, ethnicity, deprivation tertile) (see Web Appendix for more detail).

INTERVENTIONS

The main comparison of interest was SFX versus MFX, although each was also compared to simple analgesia. Based on the most commonly used fractionated schedules internationally, we defined SFX as 8 Gy x1 and MFX as 4Gy x5 (i.e. 20Gy in 5 fractions). Single 8 Gy fraction has been confirmed as more effective than lower doses (i.e. single 4 Gy fraction) at providing pain relief (24). Both MFX and SFX involve a simulation visit prior to therapy, with SFX involving a one-off treatment and MFX consisting of five separate treatments on consecutive days. This is consistent with average clinical practice in New Zealand.

EFFECTS/ OUTCOMES

Within the Markov microsimulation model, SFX, MFX, and analgesia were compared in terms of the following effects or outcomes: treatment/retreatment, partial pain response, full pain response, pain relapse, and pathological fracture rate. Death from cancer and death from other causes were also states in the model. Spinal cord compression rates and side effects from radiotherapy (both acute and long term) were not incorporated in the model as they have been repeatedly shown to be very similar between the two fractionation schedules .(6) Further detail on the model structure is provided in the Web Appendix. A full list of input parameters used in the model is also provided in Table 1. Selected parameters are discussed briefly below.

Cancer Incidence, Cancer Mortality & 'Background' Mortality

Incidence rates for metastatic breast, lung, and prostate cancer was sourced from the New Zealand Cancer Registry by age, sex (for lung cancer), ethnicity (Māori and non-Māori), and deprivation (three-levels) (25). The three levels of deprivation correspond to three groups of deciles in the 2006 New Zealand Index of Deprivation; level 1 being deciles 1 to 3, level 2 as deciles 4 to 7 and level 3 as deciles 8 to 10 with decile 1 being the least deprived 10% and decile 10 being the most deprived 10%.(26) Cancer mortality rates by time since diagnosis (again for all above sub-populations) were estimated using excess mortality rate modelling (27, 28) on cancer registry data linked

to mortality data. (23) The background population mortality rates from lifetables by subpopulation were used for the rates of death from other causes.(29)

Pain Response

Out of the eleven randomised controlled trials (RCTs) in the Cochrane meta-analysis comparing the effectiveness of SFX versus MFX, (6) the Bone Pain Trial Working Party Study most closely matched our intervention definitions (30). It was also one of the largest studies in the meta-analysis, with 761 patients spanning five years in the UK and New Zealand. The onset of pain response and level of pain response is similar between SFX and MFX. The duration of pain response is slightly less with SFX but this was not statistically significant. We thus assumed the same monthly rates of partial pain response, full pain response and pain relapse in both SFX and MFX.

Retreatment

The Cochrane meta-analysis indicated that retreatment with further radiotherapy is more likely to be offered following SFX than MFX (odds ratio 3.49 (95% confidence interval 2.71-4.5)). This is more likely to be due to factors such as timing of treatments and concerns about total dose, rather than a poorer pain response (there is little evidence for the latter, as discussed above).(6) In our model we assumed retreatment with radiotherapy was only offered to those treated with SFX-EBRT initially and the retreatment consists of further SFX-EBRT, consistent with 'average' clinical practice in New Zealand. As no published data is available on the average clinical practice of palliative radiotherapy in New Zealand we relied on data obtained from discussions with four radiation oncologists working in different areas of New Zealand. Up to three SFX retreatments were allowed in the model (however, the vast majority of patient simulations resulted in death before a third retreatment was received). A monthly retreatment rate was estimated based on time-to-event data from the Bone Pain Trial Working Party Study.(30) In our monthly-cycle model, retreatment (first retreatment or subsequent retreatments) occurred two months from the onset of pain relapse.

Pathological Fracture

As discussed in the introduction, the Cochrane meta-analysis by Sze et al pooled five trials and found that 3.0% (37/1240) of patients in the SFX arms had a pathological fracture by one year post-treatment, compared with 1.6% in the MFX arms (20/1236), with an odds ratio of 1.82 (95% CI 1.06 to 3.11).(6) It should be noted here that a later meta-analysis by Chow et al pooled ten trials, but instead found that the risk of

pathological fractures was not significantly different between the SFX arms (71/2120 or 3.3%) and the MFX arms (65/2159 or 3.0%), with an odds ratio of 1.10 (95% CI 0.65 to 1.86).(12) We chose to use the results from Sze et al (higher risk of pathological fracture with SFX than MFX) in our base model as the treatment regimens in this meta-analysis matched the New Zealand context more closely, the studies were explicitly quality-assessed, and including pathological fracture differences represents a worst-case scenario.

COSTS

Health system costs were calculated as per the BODE³ costing protocol.(20) Briefly, the direct cost of SFX or MFX was obtained from New Zealand's Outpatient purchase unit cost.(31) To estimate the difference in average travel costs for SFX and MFX, we estimated the average number of kilometres travelled by each group of patients (by cancer type) to their nearest radiotherapy centre, then applied a cost of 24.5 cents (excluding good and services tax) per kilometre, representing the running costs of a private vehicle. (20) The distance was calculated as the distance travelled by road from the population-weighted centroid point of the patient's Census Area Unit to the nearest appropriate radiotherapy centre within their DHB catchment area. We included the cost of four additional nights of accommodation for those receiving MFX for the proportion of patients living more than 100km from a radiotherapy centre for each cancer (as they are entitled to an accommodation grant).

The pathological fracture cost was a sum of: specialist appointment with orthopaedics (registrar or consultant; \$269.18); pre-operative assessment, investigations, bone fixation surgery and inpatient stay (\$4674.83); continued rehabilitation in community (\$80.88 per appointment); cost of follow-up appointment with orthopaedic surgeon (registrar or consultant; \$217.57). This data was obtained from a range of routine New Zealand costing sources (New Zealand Outpatient Purchase Unit cost, New Zealand Casemix Framework for Publicly Funded Hospitals).(31, 32)

Routine analgesia costs were estimated at \$55 per month with considerable uncertainty, based on costing data reported in an Australian and a Dutch study (19, 33). This involved estimating a crude average of type and dose of analgesia across all cancers. The analgesia cost was assigned to all states, except full pain response (as in our model, full pain response is only achieved with radiotherapy, not analgesia on its

own). We excluded other health systems costs due to the intervention and comparator having no difference in mortality.

ANALYSIS

Base-Case Analysis

Our base-case analysis was conducted using Monte Carlo simulation. The model was run separately for each of the three cancers, and each run consisted of thousands of simulations. Each simulation randomly sampled from distributions of possible values for each input parameter, thus capturing genuine input parameter uncertainty in addition to stochastic variation (see Web Appendix for further detail). This uncertainty is reflected in the results as average/median, 2.5th and 97.5th percentile values for each of QALYs, costs, and cost-effectiveness.

In terms of cost-effectiveness, we calculated net monetary benefit (NMB) as well as the more typical incremental cost-effectiveness ratios (ICERs) for a fuller picture of the results. NMB is calculated as $\lambda \times [\text{QALYs}] - [\text{net cost}]$, where λ is the decision-maker willingness to pay for a QALY gained.(34) We used NZ\$45,000 for λ as per a conservative interpretation of World Health Organization guidance that an intervention is very cost-effective if a QALY costs the equivalent of a country's GDP per capita (NZ\$45,000 in New Zealand) or less.(35, 36) Having calculated the NMBs for each of analgesia, SFX and MFX, the 'optimal' choice for a decision maker is that intervention with the greatest NMB.

Sensitivity and Scenario Analyses

We conducted univariate sensitivity analyses to test which of the input parameters were critical to the model. We also conducted scenario analyses to assess the impact of changing structural assumptions such as discount rate, and assessing best and worst-case scenarios for pathological fracture rates.

RESULTS

Figure 1 shows the cost-effectiveness planes for the three cancers for SFX, MFX and analgesia. Each iteration is represented by a dot, and all the iterations form a cloud (the larger the cloud, the greater the amount of input parameter uncertainty). Whilst the QALYs gained for lung cancer were less than either breast or prostate cancer, within

cancers two patterns were clearly evident: MFX always had a higher net cost; QALYs for SFX and MFX were always larger than for analgesia only. Across all three cancers, Figure 1 visually suggests SFX is preferred, as it gains as many QALYs as MFX but at a much lower cost.

Turning to the incremental comparisons in Table 2, both SFX and MFX have incremental QALY gains compared with analgesia only. Average incremental costs (and 2.5th percentile costs) are always greater for MFX compared to analgesia across all three cancers. However, for SFX compared to analgesia, average costs for prostate and breast cancers are less, meaning that in cost-effectiveness terms SFX 'dominates' analgesia for both prostate and breast cancer (more QALY gains, and cheaper).

The main comparison of interest in this paper is SFX compared to MFX (last column of Table 2). The SFX average cost is always less than MFX average cost across all three cancers, and SFX average QALYs are always greater than for MFX (albeit small ranging from 0.0001 for lung to 0.00155 for prostate cancer). Thus, SFX dominates MFX on average for all three cancers (slightly more QALY gains, and cheaper). In a minority of simulations there was a positive incremental cost and very small positive QALY gain for SFX compared to MFX, but more importantly for decision-making, SFX was preferred to MFX (i.e. SFX dominated MFX) in the majority of simulations.

Looking at NMB at a willingness to pay of \$45,000 per QALY gained, SFX was clearly preferable to MFX with the 95% uncertainty interval of the incremental comparison of SFX with MFX always excluding zero). Full results are provided in the Web Appendix.

As mentioned earlier, there is unavoidable and considerable uncertainty in many of the input parameters. The Tornado plots in Figure 2 are a series of univariate sensitivity analyses, showing how using the 2.5th and 97.5th percentiles for various input parameters (but fixing all other input parameters at their expected value) affects the incremental NMB for SFX compared to MFX. The wider the bar, the greater that parameter's contribution to the overall uncertainty in the model. Uncertainty about the cost of analgesia, fracture rates, and the cost of SFX and MFX all contribute substantive uncertainty to the incremental NMB, but importantly in no instance does the incremental NMB lessen by more than a third; SFX is always preferred by a substantive margin.

Finally, Table 3 shows scenario analyses about assumptions in our model structure, and its impact on the incremental NMB for SFX compared to MFX. Changing the

discount rates and differential pathological fracture rates did not overturn the preference for SFX, across all cancers.

DISCUSSION

Our finding that SFX is more cost-effective than MFX is consistent with previous cost-effectiveness analyses (17, 18). A strength of our analysis is the inclusion of differential pathological fracture rates between SFX and MFX (to our knowledge, this assumption has not been included in other cost-effectiveness analyses). Furthermore, we subjected our model to many sensitivity and scenario analyses; in all instances SFX was preferred to MFX.

Our analysis does have several limitations. As with any modelling study, assumptions about both model structure and input parameters are necessary. The outcomes of the Bone Pain Trial Working Study used to inform response parameters did not include the use of analgesics, and were calculated before the international consensus on palliative radiotherapy endpoints for clinical trials were published.(37) Additionally, in our model we assumed retreatment with radiotherapy was only offered to those treated with SFX-EBRT initially. This is consistent with 'average' clinical practice in New Zealand, but it is recognised that radiation oncologists may be more willing to offer retreatment to patients following SFX rather than MFX, independent of pain scores i.e. based on factors such as timing of treatments and concerns about total dose, as well as expected effectiveness of treatment schedules.(38) It should also be noted that MFX has been identified as improving bone stabilisation more than SFX, due to increased re-calcification(39). Metastatic lesion characteristics have a key role to play in influencing pathological fracture risk perhaps over and above radiotherapy dose (40, 41).

Our parameterization of the analgesia arm was the least informed by empirical estimates (e.g. we were unable to source data on pathological fracture rates for people with bone metastases only receiving analgesia). However, 'analgesia only' is in most instances a hypothetical option as most people receive radiotherapy. We also did not apply a change in disability weight during the radiotherapy treatment itself as it is short lived with minimal side effects. However, as MFX is associated with four extra days of travel and treatment this would only further strengthen the case for SFX over MFX. Our costing of analgesia in MFX and SFX was also fairly simplistic; we simply assumed

about \$55 per month for all states except full pain relief (which was \$0). However, given the \$1300 to \$1500 lesser net health system cost for SFX compared to MFX, it would take implausibly large variations in analgesia use between SFX and MFX to overturn our conclusions.

In summary, our study further strengthens the case for using SFX in the palliation of metastatic bone pain, from a cost-effectiveness perspective. As highlighted elsewhere, it is unclear why MFX is still being so commonly used (14). However, decisions on which health services are funded and provided depend on multiple criteria, of which cost-effectiveness is just one. Factors such as patient expectations may be particularly important here. Patients are likely to consider treatment options based on travel time and cost, accommodation needs and length of treatment. For this reason patients may opt for SFX over MFX across the different cancers. Future research could be directed at further illuminating such considerations and the role they play in clinical decision-making.

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Figure 1: Cost-effectiveness plane for SFX, MFX, and analgesia across three cancers

Figure 2: Tornado plots showing the impact of uncertainty in input parameters (2.5th percentile solid black bars and 97.5th percentile white bars) on the net monetary benefit (NMB) for SFX compared to MFX at a willingness-to-pay of NZ\$45,000 per QALY

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Table 1: Input parameters used in model (see Web Appendix for further detail)

Input parameter	Description	Characterisation and/or parameterization
Incidence of stage IV prostate, breast and lung cancer	For all combinations of age (45+), sex (for lung cancer), ethnicity (Māori, non-Māori), and deprivation (three-levels) . Used as sampling weights for individuals in micro-simulation.	Not applicable.
Monthly rate of death from cancer (Dc)	Excess mortality rates (EMR) for each cancer (prostate cancer, breast cancer and lung cancer) from NZ cancer registry data, with calibration to distant stage (equivalent to stage IV).	First order. Table of time-dependent EMRs.
Monthly rate of death from other causes (Doc)	Population mortality rates from lifetables (heterogeneous by socio-demographic strata)	First order. Table of time-dependent background mortality rates.
Monthly rate of partial pain relief following completion of radiotherapy treatment (s1→s2)‡	Modelled as a function of time, $r = \alpha t^\beta$, where t is number of months since entering model (i.e. since starting treatment for bone pain). α and β were estimated by calibration to the data provided by the 1999 published study by the Bone Pain Trial Working Party .	First order. $\alpha = 0.3284$; $\beta = -0.7448$
Monthly rate of partial pain relief following analgesia (s1→s2) ‡		First order. $\alpha = 0.3284$; $\beta = -0.7448$
Monthly rate of full pain relief following completion of radiotherapy treatment (s1→s3) ‡		First order. $\alpha = 0.0010$; $\beta = -8.2618$

Input parameter	Description	Characterisation and/or parameterization
Monthly rate of full pain relief (following partial pain relief <i>i.e. from the second month onwards</i>) ($s_2 \rightarrow s_3$) ‡		First order. $\alpha = 1.0484$; $\beta = -0.4580$
Monthly rate of pain relapse from either partial or full pain relief, among radiotherapy treated ($s_2 \rightarrow s_4$) or ($s_3 \rightarrow s_4$) ‡		First order. $\alpha = 0.7712$; $\beta = -1.537$
Monthly rate of pain relapse from partial pain state in analgesia arm only ($s_2 \rightarrow s_4$) ‡	Base model, assume relapse rate 1.25 times that from radiotherapy (<i>i.e.</i> 1.25 times $R_{P \rightarrow R}$ and $R_{F \rightarrow R/RX}$). (In scenario analyses, assume 1.0 and 1.5 times greater rate of relapse.)	First order. $\alpha = 0.8950$; $\beta = -0.4512$ (Scenario analyses: $\alpha = 0.7160$ and $\alpha = 1.0740$)
Monthly rate of radiotherapy retreatment following pain recurrence among radiotherapy treated	Modelled as a function of time $r = \alpha t^\beta$ calibrated against the data provided by the 1999 published study by the Bone Pain Trial Working Party , but t is time since relapse.	First order. $\alpha = 0.7160$; $\beta = -0.4512$
Monthly rate of pathological fracture following MFX-EBRT †	Proportion of patients who suffer a pathological fracture at one year following MFX-EBRT is 1.7% and SFX-EBRT is 3.0%, which were converted to constant rates allowing for competing mortality.	Second order. $\text{LogNormal} \sim (-6.40; 0.68)$ (<i>i.e.</i> expected rate = $\exp(-6.40) = 0.0031$ per month.)
Monthly rate of pathological fracture following SFX-EBRT		Second order. $\text{LogNormal} \sim (-5.78; 0.39)$
Monthly rate of pathological fracture for analgesia only arm	Assumed to be twice as high as SFX, with uncertainty	Second order. $\text{LogNormal} \sim (-5.09; 0.38)$

Input parameter	Description	Characterisation and/or parameterization
<i>Morbidity/ Disability Weights (DW)s</i>	(All disability weights apart from background morbidity not stratified by age or sex)	
Pre-terminal (PT) disability weights (DW)	Lung: 0.539 (0.379-0.691) Breast: 0.513 (0.355 to 0.668) Prostate: 0.416 (0.271 to 0.576)	Second order. Lung: <i>Beta</i> ($\alpha=11.84$, $\beta=10.13$) Breast: <i>Beta</i> ($\alpha=11.26$; $\beta=10.69$) Prostate: <i>Beta</i> ($\alpha=9.36$; $\beta=13.14$)
Bone pain, no response to radiotherapy	0.374 (95% UI 0.252-0.506). Using the DW from the GBD for low back pain with chronic with leg pain.	Second order. <i>Beta</i> ($\alpha=11.84$; $\beta=19.82$)
Bone pain, partial response to radiotherapy	Assumed to be half of above 0.374 =0.187 (0.117-0.286)	Second order. <i>Beta</i> ($\alpha=8.77$; $\beta=38.13$)
Pathological fracture DW (<i>during the 3 month state that one has pain from fracture and treatment</i>)	0.284, calculated as a weighted average with DW of vertebral fracture 0.132 and incidence proportion 0.30; DW of non-vertebral 0.349, incidence 0.70.	Second order. <i>Beta</i> (6.2; 16)
Expected background comorbidity	Calculated as the average years of life lived with disability for a given sex, age and ethnic group in 2006 from the NZ Burden of Disease Study. Range: 0.015 for non-Māori female infant to 0.50 for 85+ year old Māori male.	No uncertainty.
<i>Intervention Costs (per patient) (\$NZ)</i>		

Input parameter	Description	Characterisation and/or parameterization
Radiotherapy cost (including travel costs and overnight accommodation)	SFX-EBRT: Breast \$NZ378.0, Prostate \$NZ374.70, Lung \$NZ380.47 MFX-EBRT: Breast \$NZ1890.0, Prostate \$NZ1873.50, Lung \$NZ1902.35. (See text; all specified with uncertainty on a Gamma distribution such that the SD was about 10% of the expected value.)	Second order. Breast SFX- <i>Gamma</i>(98.95;0.26) Prostate SFX- <i>Gamma</i>(102.55;0.27) Lung SFX- <i>Gamma</i>(100.25;0.26) Breast MFX- <i>Gamma</i>(98.95;0.05) Prostate MFX- <i>Gamma</i>(100.37; 0.05) Lung MFX- <i>Gamma</i>(102.24;0.05)
Pathological fracture cost	\$5242.46 (See text; SD 10% of expected value)	Second order. <i>Gamma</i>(99.95;0.019)
Analgesia cost (for all states except full pain response)	\$55 per month (See text; SD 20% of expected value) This involved estimating a crude average of type and dose of analgesia across all cancers.	Second order. <i>Gamma</i>(30.25;0.55)

Table 2: Costs, QALYs, ICERs and NMBs for analgesia, SFX, MFX, and selected incremental comparisons*

Incremental comparisons			
LUNG CANCER	<i>MFX vs Analgesia</i>	<i>SFX vs Analgesia</i>	<i>SFX vs MFX</i>
Cost (NZ\$)	\$1,654 (\$1,280 - \$2,056)	\$186 (\$-4 - \$358)	-\$1,469 (\$-1,886 – \$-1,112)
QALYs	0.0145 (0.0078 - 0.0229)	0.0146 (0.0077 - 0.0231)	0.0001 (-0.0002 - 0.0005)
ICER	\$115,155 (\$67,094 - \$211,297)	\$12,587 (Dominant - \$30,401)	Dominant (Dominant - Dominant)
NMB	\$-1,002 (\$-1,520-\$-481)	\$472 (\$110-\$905)	\$1,474 (\$1,111-\$1,895)
PROSTATE CANCER	<i>MFX vs Analgesia</i>	<i>SFX vs Analgesia</i>	<i>SFX vs MFX</i>
Cost (NZ\$)	\$998 (\$368 - \$1,605)	-\$318 (\$-870 - \$170)	-\$1,316 (\$-1,854 - \$-810)
QALYs	0.0698 (0.0411 - 0.1084)	0.0713 (0.0422 - 0.1100)	0.0016 (0.0000 - 0.0038)
ICER	\$20,422	Dominant	Dominant

	(\$7,860- \$41,828)	(Dominant - \$3,334)	(Dominant - Dominant)
NMB	\$2,141 (\$612-\$4,024)	\$3,527 (\$2,029-\$5,348)	\$1,386 (\$857-\$1,948)
BREAST CANCER	<i>MFX vs Analgesia</i>	<i>SFX vs Analgesia</i>	<i>SFX vs MFX</i>
Cost (NZ\$)	\$1,095 (\$512 - \$1,652)	-\$249 (\$-779 - \$179)	-\$1,344 (\$-1,846 – \$-855)
QALYs	0.0551 (0.0304 - 0.0880)	0.0562 (0.0309 - 0.0886)	0.0010 (-0.0002 - 0.0029)
ICER	\$14,577 (\$4,970- \$30,071)	Dominant (Dominant - \$2,205)	Dominant (Dominant - Dominant)
NMB	\$1,386 (\$83-\$2,969)	\$2,777 (\$1,538-\$4,353)	\$1,391 (\$892-\$1,913)

SFX=single-fractionated radiotherapy

MFX=multiple-fractionated radiotherapy

QALYs=quality-adjusted life-years

ICER=incremental cost-effectiveness ratio

NMB=net monetary benefit, at a willingness-to-pay of NZ\$45,000

* Central estimates are average values for all measures apart from ICERs (median values). 95% uncertainty intervals in brackets.

Dollars are NZ\$, for the year 2011. All costs and QALYs discounted at 3%.

Table 3: Scenario analyses showing impact of different scenarios on net monetary benefit (NMB) for SFX versus MFX

<i>Net monetary benefit (NMB) for SFX versus MFX</i>			
	LUNG CANCER	BREAST CANCER	PROSTATE CANCER
Expected value	\$1,457	\$1,380	\$1,383
Scenarios			
No difference in pathological fracture rates	\$1,511	\$1,531	\$25,362
Pathological fracture rate in SFX is 4 times higher than MFX	\$1,380	\$1,158	\$1,152
Re-treatment option in SFX removed	\$1,457	\$1,351	\$1,325
0% discount rate applied to costs and QALYs (instead of 3%)	\$1,454	\$20,777	\$26,959
6% discount rate applied to costs and QALYs (instead of 3%)	\$1,457	\$18,572	\$23,937

NMB is for willingness-to-pay of NZ\$ 45,000 per QALY. All results are expected value only; there is no input parameter uncertainty (due to long run time of models). Therefore the results differ slightly from those in Table 1 (which does include input parameter uncertainty). Dollars are in NZ\$, for the year 2011.

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Figure 2: Tornado plots showing the impact of uncertainty in input parameters (2.5th percentile solid black bars and 97.5th percentile white bars) on the net monetary benefit (NMB) for SFX compared to MFX at a willingness-to-pay of NZ\$45,000 per QALY

