A Cost-Effectiveness Analysis of Contact X-ray Brachytherapy for treatment of patients with a partial response to Chemoradiotherapy for Rectal Cancer

**Authors:** Mr Christopher Rao MRCS PhD, Specialist Registrar in General Surgery;1 Fraser Mc Lean Smith FRCSI MD, Consultant Colorectal Surgeon;2 Profesor Thanos Athanasiou FRCS PhD, Professor of Surgery;3 Mr Omar Faiz FRCS PhD, Senior Lecturer and Consultant Colorectal Surgeon;3,4 Mr Antony Paul Martin MSc, Health Economist;5 Dr Brendan Collins PhD, Health Economist;6 Professor Arthur Sun Myint FRCR, Consultant Clinical Oncologists and Honorary Professor in Gastroenterology.7

**Institutions:** (1)University Hospital Lewisham, London (2) The Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool. (3) Department of Surgery and Cancer, Imperial College London. (4) Epidemiology, Trials and Outcome Centre (SETOC), St Mark’s Hospital, Harrow. (5) National Institute for Health Research, Collaborations for Leadership in Applied Health Research and Care, North West Coast (NIHR CLAHRC NWC), University of Liverpool. (6) Department of Public Health and Policy, University of Liverpool. (7) The Clatterbridge Cancer Centre, Merseyside.

**Individual Author Contributions:** CR, FS, TA, OF, APM, BC and ASM were involved with the conception and design of the study. CR, FS, OF, APM, BC and ADM were involved with acquisition of data. CR, FS, TA, APM and BC were responsible for analysis and interpretation of data. All authors contributed to drafting the article, revising it critically for important intellectual content and had final approval of the version to be published.

**Conflicts of Interest and Source of Funding:** This study was not supported by any external funding. CR, FS, TA, OF, APM, BC and ASM have not received any honoraria, does not have a relationship with any commercial organisations. APM was supported by the National Institute of Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The other authors do not hold any relevant research grants. The authors have no other conflict of interest to declare.

**Corresponding Author:** Mr Christopher Rao MRCS PhD. Address: Department of Colorectal Surgery, University Hospital Lewisham, High Street, London SE13 6LH, United Kingdom.Telephone: +44 (0) 7796 954 284 E-mail:[christopher.rao@nhs.net](mailto:christopher.rao@nhs.net)

**Word Count:** 3,081 excluding title page, abstract, references, tables, and figure legends.

**Running Head:** Economics- Rectal ca contact brachytherapy

**Keywords:** Rectal, radiotherapy, neoadjuvant, watch and wait, complete clinical response, elderly, cost-effectiveness

**Category:** Colorectal/Anal neoplasia

# Abstract

**Background:** Radical surgery (RS) is associated with significant morbidity and mortality. A “watch and wait” approach (WW) may provide equivalent survival and oncological outcomes in patients with a clinical complete response (cCR) after neoadjuvant chemoradiotherapy (CRT). In some series, however, almost 90% of patients do not achieve a cCR after CRT. Contact X-ray Brachytherapy (CXB) enables very high doses of low energy radiation to be delivered directly to rectal cancers with minimal damage to adjacent tissue. It can be used in addition to external beam radiotherapy (EBRT) to increase the chance that a cCR is achieved. It has been hypothesised that this may reduce the morbidity and mortality associated with RS for patients who do not achieve a cCR. There is evidence to suggest that CXB boost may improve the incidence of bowel continuity. The long-term cost-effectiveness, however, of the addition of a CXB boost to a WW strategy has not been evaluated.

**Objective:** To compare the cost-effectiveness of WW with CXB boost, to WW with EBRT alone, and RS for patients with rectal cancer treated with CRT.

**Design:** Decision analytical modelling and a Markov simulation were used to model long-term costs, quality-adjusted life years (QALYs), and cost-effectiveness. Sensitivity analysis was used to investigate the effect of uncertainty in model parameters.

**Setting:** A third-party payer (NHS) perspective was adopted.

**Patients:** A 60-year-old male cohort with no comorbidities (fm60), 80-year-old male cohorts with no comorbidities (fm80) and significant comorbidities (cm80).

**Interventions:** WW with CXB boost, WW with EBRT alone, and RS following CRT

**Main Outcome Measures:** Incremental cost, effectiveness and cost-effectiveness ratio over the entire lifetime of the hypothetical patient cohorts

**Results:** CXB was more effective than WW with EBRT alone (fm60: 0.09QALYs, 95%CI -0.46-0.65QALYs. fm80: 0.10QALYs, 95%CI -0.16-0.35QALYs. cm80: 0.12QALYs, 95%CI -0.15-0.37QALYs) and less costly (fm60: £1,271.07, 95%CI -£1,399.51-£4,622.05. fm80: £972.29, 95%CI -£1,583.04-£4,412.30. cm80: £769.21, 95%CI -£1,803.61-£3,877.89) independent of patient cohort age and comorbidity. Similarly it was more effective than RS (fm60: 0.17QALYs, 95%CI -0.70-1.02QALYs. fm80: 0.23QALYs, 95%CI -0.21-0.55QALYs. cm80: 0.21QALYs, 95%CI -0.16-0.58QALYs) and less costly (fm60: £2,873.51, 95%CI -£1,425.60-£7,915.88. fm80: £2,317.09, 95%CI -£1,746.44-£7,525.92. cm80: £2,030.33, 95%CI -£2,119.66-£6,559.74). Consequently WW with CXB boost was more cost-effective with a high degree of certainty (60.1-74.2%) at a threshold of £20,000/QALY.

**Conclusions:** WW with CXB is likely to be cost-effective compared to both WW with EBRT alone and RS. These findings strongly support the use of CXB boost as an adjunct to a WW strategy.

# Introduction

The standard of care for locally advanced rectal cancer is currently neoadjuvant chemoradiotherapy (CRT) followed by radical surgery (RS).1, 2 Perioperative mortality, particularly in elderly co-morbid patients following RS is significant.3 There is also significant morbidity associated with RS. Significantly, 83% of patients had a stoma following surgical resection (either because the rectum was removed, or “temporary” defunctioning stomas). Over 50% of patients, however, still had a stoma 18 months following surgery. This unquestionably has a significant effect on patient health-related quality of life (HRQoL).4

Significantly, a complete pathological response (pCR), with absence of cancer cells in the resected specimen, has been reported in between 15-44% of patients.5, 6 Subsequently, several studies have demonstrated the safety of adopting a “watch and wait” (WW) strategy after CRT in patients for whom a clinical complete response (cCR) has been achieved where no evidence of residual tumour can be identified.7, 8 These approaches eliminate perioperative mortality, deliver equivalent oncological outcomes if cCR is maintained, and preserve bowel continuity in patients for whom a stoma is unsuitable or unacceptable.9 While disease does recur in some patients, limited data suggests that should this occur, subsequent RS can be performed with equivalent oncological outcomes to patients initially treated with RS.8, 10 There is now emerging evidence to suggest that long-term survival and oncological outcomes following WW and RS may be comparable.11 Modelled data from our group suggests that not only does WW provide equivalent survival, it is also cost-effective.12, 13

Unfortunately, cCR is low with conventional external beam radiotherapy (EBRT). A recent UK series reported that 12% of patients achieved a cCR.11 Consequently, there is an urgent need to improve and sustain cCR rates following CRT. One practical means to improve and sustain cCR is to escalate the dose of radiation delivered, however this is associated with the side-effects of radiation toxicity. Contact X-ray Brachytherapy (CXB) boost can be used to achieve this with limited collateral damage to surrounding normal tissues.14-16 Several case series suggest that CXB may improve both the rate and sustainability of a cCR. There is randomised evidence to support an improved cCR following CXB.14 However, the effect that this may have on long-term quality-of-life and cost-effectiveness is uncertain.

Therefore, in this study we aim to compare both the clinical and cost-effectiveness of WW with CXB boost, WW with EBRT alone, and RS. We will investigate and quantify the associated uncertainty. We also aim to perform alternative analyses to investigate if these results are sensitive to patient age and comorbidity.

# Materials and Methods

Outcomes in patients with a cCR following neoadjuvant CRT treated with WW with CXB boost, WW with EBRT alone, and RS were modelled using a decision analytical model adapted from the published literature consisting of a decision tree and Markov chain simulation.13 Figure 1 illustrates the structure of the model. Decision nodes are square, and chance nodes are circular. The model terminates either with death (when patients do not survive surgery) or a Markov simulation. The transition probabilities are determined by initial treatment and whether a pCR was achieved following CRT. Details of all interventions that patients undergo in each modelled state have previously been described.13 Table 1 describes clinical parameters used to populate the model. These parameters were used in previous work and represent best available estimates12, 13. The economic data used to populate the model is listed in Table 2. Table 3 shows perioperative mortality used to populate the model extracted from the Hospital Episodes Statistics (HES) database, and Table 4 shows baseline mortality data used to populate the model based on UK Office of National Statistics (ONS) Life Tables).

Analysis was performed from a third party-payer perspective (UK National Health Service, NHS) according to the National Institute for Health and Care Excellence guidelines on technology assesment.17 Costs are reported in UK pound sterling (£).18 The effects of interventions were measured in Quality-Adjusted Life Years (QALYs), a summary measure of survival and utility. Incremental costs and effects were calculated for the lifetime of the hypothetical patient cohorts. Costs and effects were discounted at 3.5% per annum according to guidelines on cost-effectiveness analysis.17 Probabilistic sensitivity analysis was performed to investigate and quantify associated uncertainty.19 Decision analytical software (TreeAge-Pro, TreeAge; Williamstown, MA) was used to perform the analysis. This study was exempt from Institutional Review Board ethical approval as it is a modelling study and did not require any interface with patients.

## Definition of Treatment Strategies, Modelled Patient Populations and Outcomes of Interest

In our modelled cohorts all patients underwent CRT. In the RS modelled cohort all patients underwent RS after CRT. In the WW cohort patients with a cCR according to strictly defined criteria12, 20 were managed with WW approach. Patients without a cCR in the WW cohort underwent RS. In the WW with CXB boost patients who initially had a cCR following CRT were treated with a WW approach. Patients without a cCR and a tumour greater than 2cm underwent RS, patients with a residual tumour of 2cm or less were given a CXB boost. CXB was delivered as an outpatient treatment every 2 weeks using a Papillon plus machine (Ariane, UK). Patients received a total of 80 gray unit (Gy) delivered in 3 fractions over 4 weeks. We have previously described in more detail the treatment regime for CXB boost.21 In our modelled cohort patients who had a cCR following CXB boost were managed with a WW approach. Patients without a cCR following CXB boost underwent RS.

We assumed that follow-up for patients undergoing surgery was according to national guidelines22. Briefly, these recommend a minimum of 2 CTs of the chest, abdomen, and pelvis in the first 3 years. In addition, a surveillance colonoscopy at 1 year is offered after initial treatment. If this is normal, a further colonoscopy is considered after 5 years. In the WW cohort follow-up was more intensive with 2 CTs per year for the first 3 years, 3 pelvic MRIs a year for the first 2 years and then 2 MRIs in the following year. Clinical examination was performed every 3 months for the first 2 years accompanied by alternating rigid and flexible sigmoidoscopy. In the third year this was performed every 6 months, and subsequently every year until 5 years following initial treatment. Finally, a surveillance colonoscopy at 1 year is offered after initial treatment. If this is normal, a further colonoscopy is considered after 5 years.

We assumed that should tumor recurrence occur in either cohort, patients underwent full oncological restaging and salvage surgery where appropriate. Patients in whom salvage surgery was not possible underwent palliative surgery and chemotherapy. Patients with distant metastasis underwent palliative chemotherapy and a proportion of patients, reflecting actual clinical practice, underwent liver resection.23 It was assumed that patients received the maximum dose of radiotherapy and so our model did not account for further costs associated with palliative radiotherapy. As less than 1% of patients with colorectal metastasis in the lung undergo resection we did not account for this in our model (Figures 1-3).24

To investigate whether the results of our analysis were sensitive to patient age and comorbidities, an analysis was performed for a 60-year-old male (fm60) and 80-year-old male cohort with mild comorbidities (fm80) (Charlson Score<3), and an 80-year-old male cohort with significant comorbidities (cm80) (Charlson Score≥3). The Charlson Comorbidity Index is an established tool to predict mortality for a patient who may have a range of comorbid conditions.25

## Model Parameters

Post-operative mortality in the first 90 days for each demographic cohort was obtained from the HES database, a national database which describes the care provided to patients in NHS hospitals (Table 1, Table 3). HES data is widely used for NHS quality assurance, by government agencies and in the academic literature26. Baseline mortality estimates were extracted from UK ONS Life Tables (Table 4)27.

Estimates of other clinical parameters used to populate the model were extracted from published literature.5, 7, 10, 12, 28-40 The rationale for using these estimates has previously been discussed.12 Estimates of the costs associated with treatment were based on NHS reference costs (2014-2015) 41 or previous NICE reports in the case of palliative chemotherapy42 (Table 2). The preferred approach of micro-costing (bottom-up) was taken to estimate the costs of CXB with medical and administrative support from Clatterbridge Cancer Centre. Patients were assumed to have an average of three sessions of CXB with a predicted 20% upper and lower bound. Information on the efficacy of CXB boost was derived from the published literature. The cCR following CRT was derived from the UK OnCoRe study, as we felt this probably best reflected current UK practice and the populations modelled in this study.11 It should be noted that the cCR rate is significantly less than that reported in some studies and thus must be considered a conservative estimate of the cCR.5, 6 The cCR rate following CXB boost was extracted from a randomised study comparing CXB boost with CRT alone.14 This is congruent with the findings of other studies.43 The proportion of patients with a cPR following CRT who were suitable for CXB boost was derived from a recently published study from own centre,21 as this reflects a similar population with similar initial treatment from the same geographical area as those in the OnCoRe study.11 Finally, the costs associated with CXB boosts were based on a primary costing study undertaken at our own institution, details of this study are given in the supplementary data file.

## ***Sensitivity Analysis***

Deterministic sensitivity analysis was performed to investigate the sensitivity of the study to assumptions made about the value of individual model parameters. Each model parameter was varied with plausible ranges (Table 1, Table 2). In order to estimate the combined effect of uncertainty associated with all model parameters, a probabilistic sensitivity analysis was performed using a Monte Carlo simulation. Briefly, all parameters including transition probabilities were randomly sampled from assigned distributions (Table 1, Table 2). It was assumed that parameters were independent, i.e. not correlated with each other. The model was then run to simulate a “virtual” cohort of 1000 “matched” patients using these sampled probabilities for each intervention. All model parameters were then re-sampled and the model was then run again to generate data for a further virtual cohort of 1000 patients. This process was repeated until data had been generated for 1000 matched virtual cohorts of 1000 patients. This allowed QALY payoffs and costs to be estimated for both treatment strategies. Crucially however, it also allowed estimates of the uncertainty associated with these outcomes to be calculated. As cost parameters may by closely correlated, it is possible that the assumption that all model parameters are not correlated may overestimate the uncertainty. Consequently alternative analysis was performed in which all cost parameters were assumed to be perfectly correlated.

# Results

In all modelled patient cohorts WW with CXB boost was both less costly and more effective than RS and WW with EBRT alone, and thus could be said to be dominant. Compared to WW with EBRT alone, WW with CXB boost in the fm60 cohort WW was less costly by £1,271.07; 95%CI -£1,399.51 to £4,622.05; and more effective by 0.09QALYs; 95%CI -0.46QALYs to 0.65QALYs. In the fm80 cohort it was less costly by £972.29; 95%CI -£1,583.04 to £4,412.30; and more effective by 0.10QALYs; 95%CI -0.16QALYs to 0.35QALYs. In the cm80 cohort it was less costly by £769.21; 95%CI -£1,803.61 to £3,877.89; and more effective by 0.12QALYs; 95%CI -0.15QALYs to 0.37QALYs. Compared to RS, WW with CXB boost in the fm60 cohort WW was less costly by £2,873.51; 95%CI -£1,425.60 to £7,915.88; and more effective by 0.17QALYs; 95%CI -0.70QALYs to 1.02QALYs. In the fm80 cohort it was less costly by £2,317.09; 95%CI -£1,746.44 to £7,525.92; and more effective by 0.23QALYs; 95%CI -0.21QALYs to 0.55QALYs. In the cm80 cohort it was less costly by £2,030.33; 95%CI -£2,119.66 to £6,559.74; and more effective by 0.21QALYs; 95%CI -0.16QALYs to 0.58QALYs (Table 5).

## Deterministic Sensitivity Analysis

The results of deterministic sensitivity analysis at a willingness-to-pay/ cost-effectiveness threshold (CET) of £50,000/QALY is shown in Figure 4. Each panel has the plausible ranges for a variable plotted on each axis. The boundary between the shaded areas represents the tipping point of the model at which there is equipoise. The area shaded green indicates values at which WW with CXB boost is cost-effective, the blue indicates where WW with EBRT alone is cost-effective, and the red indicates RS is cost-effective. Deterministic sensitivity analysis did not suggest that the results of the model were sensitive to individual model parameters, moreover as the bivariate sensitivity analysis in Figure 4 shows, the model remains insensitive to the effect of individual model parameters in all the demographic cohorts modelled.

## Probabilistic Sensitivity Analysis

The results of probabilistic sensitivity analysis are shown Figure 5 demonstrating the effect of the combined uncertainty associated with all model parameters. At a CET of £20,000/QALY, WW with CXB boost is most cost-effective in all modelled cohorts. The cost-effectiveness acceptability curve (CEAC) is a method for summarising information on uncertainty in cost-effectiveness. The CEAC identifies the probability that the intervention is cost-effective compared to the alternative based upon the data provided for a given CET.19 In the fm60 cohort WW with CXB was most cost-effective in 60.1% of model iterations, this increased to 70.9% in the fm80 cohort, and 74.2% in the cm80 cohort at a CET of £20,000/QALY (Figure 5).

# Discussion

The modelling results presented in this study suggest with a high degree of certainty that the addition of CXB boost as an adjunct to WW management in order to optimise the proportion of patients who achieve a cCR and are thus eligible for non-operative management is cost-effective. The degree of certainty associated with these findings is in part because the addition of a CXB boost for this indication is both cost-saving and effective, resulting in an increased QALY payoff, and consequently could be said to be dominant. These findings were true in all three modelled demographic cohorts (fm60, fm80, and cm80). Predictably however, as age and patient co-morbidities increase the uncertainty associated with these findings decreases. This is unsurprising as by increasing the cCR rate compared to WW with EBRT alone, CXB can result in RS can being avoided in some patients, and the effect of avoiding RS in elderly and co-morbid patients is likely to be more marked. The reason that the incremental QALY payoff is not more marked in elderly in the fm80 and cm80 cohort is that these patients have a significantly lower life-expectancy than the fm60 cohort, and consequently the QALY payoff for each death avoided is therefore less.

Previous work that we have undertaken suggests that WW offers at least comparable clinical outcomes to RS.12 This is supported by emerging clinical evidence.11 Moreover, uncertainty in the external validity of CXB cost estimate (with the use of a micro-costing approach) has been characterised within the analysis. We have also shown that WW is cost-effective compared to RS for patients with a cCR to CRT.13 In view of these findings, evidence from the literature about the efficacy of CXB boost14, and the findings of this study on the relative cost-effectiveness of WW with EBRT alone and WW with CXB boost, it is not surprising that WW with CXB boost dominates RS alone in all the modelled demographic cohorts. Whilst this may not be a surprising finding, arguably the cost-savings suggested by this comparison may be most relevant to decision makers as most UK centres which do not have a formal WW programme of any kind yet.

UK National guidelines (NICE) already suggest that Papillon in conjunction with external-beam radiotherapy is safe and efficacious in patients who are unable to undergo RS.44 NICE also suggests that whilst Papillon is safe in patients who are able to undergo RS but choose not to, its effectiveness remains uncertain and consequently these patients should be enrolled in clinical audit or research programmes.44 These guidelines are supported by our study, and as one of a plethora of studies that support the use of CXB boost specifically and WW in general it is possible that these guidelines may need to be further revised. The cost-savings that this study suggest could be achieved with CXB, without compromising clinical outcomes are particularly relevant in view of the challenges faced in the wider UK healthcare environment. Formal analysis of the cost of implementation of this strategy nationally was not undertaken in this study, and analysis of future research priorities was also not undertaken.

All studies based on decision analytical modelling represent a simplification of complex real-world scenarios, and consequently the results of these studies must be interpreted with caution. All models are vulnerable to uncertainty associated with model parameters, and consequently we have endeavoured to populate our model with the most relevant and robust estimates, and to fully quantify the uncertainty associated with these model parameters.

In summary, this study strongly suggests that WW with CXB boost is cost-effective compared to both WW with EBRT alone and RS. This has implications both for clinicians working in this field, and policy makers.

Acknowledgements

We would like to thank Helen Wong for providing additional clinical CXB data for the cost analysis

# References

1. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R, German Rectal Cancer Study G. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-40.

2. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997;336:980-7.

3. Mamidanna R, Almoudaris AM, Faiz O. Is 30-day mortality an appropriate measure of risk in elderly patients undergoing elective colorectal resection? Colorectal Dis 2012;14:1175-82.

4. NBOCA, National Bowel Cancer Audit Report 2015. In: Editor ed.^eds. Book National Bowel Cancer Audit Report 2015. City: Health Quality Improvement Partnership Ltd. (HQIP), 2015:75.

5. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Br J Surg 2012;99:918-28.

6. Garcia-Aguilar J, Shi Q, Thomas CR, Jr., Chan E, Cataldo P, Marcet J, Medich D, Pigazzi A, Oommen S, Posner MC. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. Ann Surg Oncol 2012;19:384-91.

7. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Jr., Silva e Sousa AH, Jr., Campos FG, Kiss DR, Gama-Rodrigues J. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711-7; discussion 7-8.

8. Smith JD, Ruby JA, Goodman KA, Saltz LB, Guillem JG, Weiser MR, Temple LK, Nash GM, Paty PB. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg 2012;256:965-72.

9. Kennelly RP, Heeney A, White A, Fennelly D, Sheahan K, Hyland JM, O'Connell PR, Winter DC. A prospective analysis of patient outcome following treatment of T3 rectal cancer with neo-adjuvant chemoradiotherapy and transanal excision. Int J Colorectal Dis 2012;27:759-64.

10. Habr-Gama A, Perez RO, Proscurshim I, Campos FG, Nadalin W, Kiss D, Gama-Rodrigues J. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. J Gastrointest Surg 2006;10:1319-28; discussion 28-9.

11. Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS, Rooney PS, Susnerwala S, Blower A, Saunders MP, Wilson MS, Scott N, O'Dwyer ST. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol 2016;17:174-83.

12. Smith FM, Rao C, Oliva Perez R, Bujko K, Athanasiou T, Habr-Gama A, Faiz O. Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical response after neoadjuvant therapy: results of a decision-analytic model. Dis Colon Rectum 2015;58:159-71.

13. Rao C, Sun Myint A, Athanasiou T, Faiz O, Martin AP, Collins B, Smith FM. Avoiding Radical Surgery in Elderly Patients With Rectal Cancer Is Cost-Effective. Dis Colon Rectum 2017;60:30-42.

14. Ortholan C, Romestaing P, Chapet O, Gerard JP. Correlation in rectal cancer between clinical tumor response after neoadjuvant radiotherapy and sphincter or organ preservation: 10-year results of the Lyon R 96-02 randomized trial. Int J Radiat Oncol Biol Phys 2012;83:e165-71.

15. Sun Myint A, Grieve RJ, McDonald AC, Levine EL, Ramani S, Perkins K, Wong H, Makin CA, Hershman MJ. Combined modality treatment of early rectal cancer: the UK experience. Clin Oncol (R Coll Radiol) 2007;19:674-81.

16. Gerard JP, Chapet O, Nemoz C, Hartweig J, Romestaing P, Coquard R, Barbet N, Maingon P, Mahe M, Baulieux J, Partensky C, Papillon M, Glehen O, Crozet B, Grandjean JP, Adeleine P. Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: the lyon R96-02 randomized trial. J Clin Oncol 2004;22:2404-9.

17. Guide to the methods of technology appraisal 2013. In: Editor ed.^eds. Book Guide to the methods of technology appraisal 2013. City: National Institute for Health and Care Excellence (NICE), 2013.

18. Forex U (2016) GBP to USD Exchange Rate. Available at: [www.ukforex.co.uk;](http://www.ukforex.co.uk;) Accessed 26th Febuary 2016 2016.

19. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation Oxford: Oxford University Press, 2006.

20. Habr-Gama A, Perez RO, Wynn G, Marks J, Kessler H, Gama-Rodrigues J. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. Dis Colon Rectum 2010;53:1692-8.

21. Myint AS, Smith FM. Dose escalation using Contact X-ray brachytherapy for radical treatment of rectal cancer. Outcomes from a single centre experience. Int J Radiat Oncol Biol Phys 2017:Submitted.

22. Colorectal cancer: diagnosis and management. In: Editor ed.^eds. Book Colorectal cancer: diagnosis and management. Updated 2014 ed. City: National Institute for Health and Care Excellence (NICE), 2011.

23. Meriggi F, Bertocchi P, Zaniboni A. Management of potentially resectable colorectal cancer liver metastases. World J Gastrointest Surg 2013;5:138-45.

24. Zisis C, Tsakiridis K, Kougioumtzi I, Zarogoulidis P, Darwiche K, Machairiotis N, Zaric B, Katsikogiannis N, Kesisis G, Stylianaki A, Li Z, Zarogoulidis K. The management of the advanced colorectal cancer: management of the pulmonary metastases. J Thorac Dis 2013;5 Suppl 4:S383-8.

25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.

26. (2013) Hospital Episode Statistics (HES). Available at: <http://www.hscic.gov.uk/hes;> Accessed May 12th 2013 2013.

27. (2013) National Life Tables: United Kingdom. Available at: <http://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies;> Accessed 12th May 2013 2013.

28. Smith FM, Waldron D, Winter DC. Rectum-conserving surgery in the era of chemoradiotherapy. Br J Surg 2010;97:1752-64.

29. Neuman HB, Elkin EB, Guillem JG, Paty PB, Weiser MR, Wong WD, Temple LK. Treatment for patients with rectal cancer and a clinical complete response to neoadjuvant therapy: a decision analysis. Dis Colon Rectum 2009;52:863-71.

30. Valentini V, van Stiphout RG, Lammering G, Gambacorta MA, Barba MC, Bebenek M, Bonnetain F, Bosset JF, Bujko K, Cionini L, Gerard JP, Rodel C, Sainato A, Sauer R, Minsky BD, Collette L, Lambin P. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol 2011;29:3163-72.

31. Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ, Calvo FA, Garcia-Aguilar J, Glynne-Jones R, Haustermans K, Mohiuddin M, Pucciarelli S, Small W, Jr., Suarez J, Theodoropoulos G, Biondo S, Beets-Tan RG, Beets GL. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835-44.

32. Guillem JG, Chessin DB, Cohen AM, Shia J, Mazumdar M, Enker W, Paty PB, Weiser MR, Klimstra D, Saltz L, Minsky BD, Wong WD. Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. Ann Surg 2005;241:829-36; discussion 36-8.

33. Garcia-Aguilar J, Hernandez de Anda E, Sirivongs P, Lee SH, Madoff RD, Rothenberger DA. A pathologic complete response to preoperative chemoradiation is associated with lower local recurrence and improved survival in rectal cancer patients treated by mesorectal excision. Dis Colon Rectum 2003;46:298-304.

34. Tepper JE, O'Connell M, Hollis D, Niedzwiecki D, Cooke E, Mayer RJ, Intergroup S. Analysis of surgical salvage after failure of primary therapy in rectal cancer: results from Intergroup Study 0114. J Clin Oncol 2003;21:3623-8.

35. van den Brink M, Stiggelbout AM, van den Hout WB, Kievit J, Klein Kranenbarg E, Marijnen CA, Nagtegaal ID, Rutten HJ, Wiggers T, van de Velde CJ. Clinical nature and prognosis of locally recurrent rectal cancer after total mesorectal excision with or without preoperative radiotherapy. J Clin Oncol 2004;22:3958-64.

36. Hahnloser D, Nelson H, Gunderson LL, Hassan I, Haddock MG, O'Connell MJ, Cha S, Sargent DJ, Horgan A. Curative potential of multimodality therapy for locally recurrent rectal cancer. Ann Surg 2003;237:502-8.

37. Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzen F, Saltz L. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008;26:2006-12.

38. Konski A, Watkins-Bruner D, Feigenberg S, Hanlon A, Kulkarni S, Beck JR, Horwitz EM, Pollack A. Using decision analysis to determine the cost-effectiveness of intensity-modulated radiation therapy in the treatment of intermediate risk prostate cancer. Int J Radiat Oncol Biol Phys 2006;66:408-15.

39. Van Den Brink M, Van Den Hout WB, Stiggelbout AM, Klein Kranenbarg E, Marijnen CA, Van De Velde CJ, Kievit J, Dutch Colorectal Cancer G. Cost-utility analysis of preoperative radiotherapy in patients with rectal cancer undergoing total mesorectal excision: a study of the Dutch Colorectal Cancer Group. J Clin Oncol 2004;22:244-53.

40. Miller AR, Cantor SB, Peoples GE, Pearlstone DB, Skibber JM. Quality of life and cost effectiveness analysis of therapy for locally recurrent rectal cancer. Dis Colon Rectum 2000;43:1695-701; discussion 701-3.

41. NHS Reference Costs 2013-2014. In: Editor ed.^eds. Book NHS Reference Costs 2013-2014. City: Department of health, 2014.

42. Hoyle M, Crathorne L, Peters J, Jones-Hughes T, Cooper C, Napier M, Tappenden P, Hyde C. The clinical effectiveness and cost-effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal No.150 and part review of technology appraisal No. 118): a systematic review and economic model. Health Technol Assess 2013;17:1-237.

43. Jakobsen A, Ploen J, Vuong T, Appelt A, Lindebjerg J, Rafaelsen SR. Dose-effect relationship in chemoradiotherapy for locally advanced rectal cancer: a randomized trial comparing two radiation doses. Int J Radiat Oncol Biol Phys 2012;84:949-54.

44. Low energy contact X ray brachytherapy (the Papillon technique) for early stage rectal cancer. In: Editor ed.^eds. Book Low energy contact X ray brachytherapy (the Papillon technique) for early stage rectal cancer. City: National Institute for Health and Care Excellence (NICE), 2015.

# Figure and Table Legend

***Table 1.*** Estimates of clinical parameters and utilities. cCR = complete clinical response; pCR = complete pathological response; pPR = partial pathological response. Transition probabilities were described by beta distributions based on the listed expected value and range.

***Table 2.*** Gamma distributions used to describe economic parameters.

***Table 3.*** Ninety-day mortality data after proctectomy from Hospital Episode Statistics database. Mortality was best described by beta distributions. The mean and SE are used to facilitate comparison with other literature.

***Table 4.*** Age-specific UK baseline mortality.

***Table 5.*** Summary of the results of analysis

***Figure 1.*** Schematic representation of our decision-analytic model, consisting of a decision tree and Markov chain simulation to investigate the long-term outcomes associated with the competing interventions. Decision nodes are represented by boxes in the main figure, and chance nodes are depicted by circles. The decision tree terminates either with the patients dying (in the case of patients who do not survive surgery), shown by a triangle, or a Markov chain simulation, shown by a circle with an “M” inside. The structure of the Markov simulation is depicted by the bubble diagram shown in the insert. The transition probabilities for the Markov chain simulation are determined by initial treatment and whether a pathologic complete response was achieved after chemoradiotherapy and are described in Table 1.

***Figure 2.*** Detailed description of the costs incurred by hypothetical patients in each Markov state following RS.

***Figure 3.*** Detailed description of the costs incurred by hypothetical patients in each Markov state following WW.

***Figure 4.*** Deterministic (Bivariate) sensitivity analysis at a CET of £20,000/QALY. The boundary between the shaded areas represents the tipping point of the model at which there is clinical equipoise. The area shaded green indicated values at which WW with CXB is most cost-effective, the red area corresponds to RS, and the blue area WW with EBRT alone. This figure shows the insensitivity of the analysis to the values of individual model parameters. The top panels show that this is the case as operative mortality varies (Figures A-E), and the bottom panel shows that this is the case as baseline mortality varies (Figures F-J), suggesting that this is the case for all demographic cohorts.

***Figure 5.*** Willingness-to-pay curves showing the proportion of model iterations and hence the certainty with which RS, WW, or WW with CXB boost is most cost-effective for different Willingness-to-pay (Cost-effectiveness thresholds). The results of probabilistic sensitivity analysis from the fm60 cohort is shown in the top panel, the fm80 cohort in the middle panel and the cm80 cohort in the bottom panel.

Table 1

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model parameter** | **Expected Value** | **Range** | **Distribution** | **α** | **β** |
| % of patients where cCR = pCR after CRT7, 12, 28, 29 | 70% | 0-100% | Beta | 4.44 | 3.40 |
| Surgical mortality after salvage surgery for primary tumor12, 26 | See Table 3 | 0-16.4% | Beta | - | - |
| Relapse if true pCR and surgery5, 12, 29-33 | 17% | 0-30% | Beta | 9.01 | 247.50 |
| % of recurrences that are distant if pCR and surgery12, 29-33 | 81% | 50-100% | Beta | 18.87 | 5.64 |
| Relapse if true pCR and observation alone12, 29 | 17% | 0-30% | Beta | 9.01 | 247.50 |
| % of recurrences that are distant if pCR and observation alone12, 29 | 81% | 50-100% | Beta | 18.87 | 5.64 |
| Relapse if pPR and surgery12, 29-33 | 36% | 0-80% | Beta | 4.77 | 7.57 |
| % of recurrences that are distant if pPR and surgery12, 29-33 | 83% | 26-100% | Beta | 8.98 | 3.91 |
| Relapse if pPR and observation alone12, 29 | 70% | 0-80% | Beta | 6.53 | 6.53 |
| % of recurrences that are distant if pPR and observation alone12, 29 | 43% | 0-71% | Beta | 6.01 | 9.81 |
| % of patients with cPR who are suitable for CXB21 | 80% | 50-100% | Beta | 183 | 46 |
| % of patients with cCR following CRT with EBRT alone11 | 12% | 0-50% | Beta | 31 | 228 |
| % of patients with cCR following CXB Boost14 | 26% | 0-50% | Beta | 11 | 34 |
| Salvage surgery for local recurrence if prior rectal surgery12, 29, 34, 35 | 37% | 10-70% | Beta | 8.89 | 13.90 |
| Salvage surgery for local recurrence if observation10, 12, 29 | 80% | 50-90% | Beta | 31.53 | 11.47 |
| Surgical mortality after salvage surgery for local recurrence12, 26 | See Table 3 | - | Beta | - | - |
| Survival after local recurrence with surgical salvage12, 29, 36, 37 | 50% | 20-60% | Beta | 26.27 | 130.81 |
| Survival after local recurrence without surgical salvage12, 29, 36, 37 | 30% | 0-50% | Beta | 7.55 | 13.18 |
| Survival with distant metastatic disease12, 29, 34, 37 | 20% | 0-30% | Beta | 12.18 | 17.33 |
| Baseline Mortality (See Table 4)27 | - | - | - | - | - |
| Utility of observation after radiation29, 38 | 0.91 | 0.85-1 | Beta | 107.42 | 9.34 |
| Utility of surgery after radiation29, 39 | 0.86 | 0.7-1 | Beta | 41.87 | 7.20 |
| Utility of Local recurrence with associated morbidity29, 40 | 0.78 | 0.5-0.85 | Beta | 19.20 | 6.06 |
| Utility of Distant recurrence with associated morbidity29, 39 | 0.7 | 0.5-0.85 | Beta | 19.92 | 7.24 |

Table 2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Model parameter** | **Mean**  **(£)** | **Lower Quartile (£)** | **Upper Quartile (£)** | **Distribution** | **α** | **λ** |
| Cost of Radical Surgery (Abdominoperineal resection) -Comorbidities41 | 11,885.96 | 7,726.96 | 14,959.0 | Gamma | 4.923 | 0.00042 |
| Cost of Radical Surgery (Abdominoperineal resection) -Without Comorbidities41 | 9,027.26 | 6,524.94 | 10,527.21 | Gamma | 9.27 | 0.0010 |
| Cost of Liver Resection - Comorbidities41 | 9,243.24 | 6,396.18 | 10,329.71 | Gamma | 10.06 | 0.0011 |
| Cost of Liver Resection – Without Comorbidities41 | 6,870.48 | 5,328.16 | 8,133.0 | Gamma | 10.94 | 0.0016 |
| Cost of Palliative Surgery - Comorbidities41 | 7,014.06 | 4,918.21 | 8,427.36 | Gamma | 7.28 | 0.0010 |
| Cost of Palliative Surgery – Without Comorbidities41 | 5,422,16 | 4,290.19 | 6,016.5 | Gamma | 17.98 | 0.0033 |
| Cost of Examination under Anesthesia41 | 1,220.16 | 898.92 | 1,402.57 | Gamma | 10.70 | 0.0088 |
| Cost of Rigid Sigmoidoscopy41 | 179.58 | 119.88 | 215.0 | Gamma | 6.49 | 0.036 |
| Cost of Flexible Sigmoidoscopy41 | 197.2 | 105.73 | 244.0 | Gamma | 3.71 | 0.019 |
| Cost of Colonoscopy41 | 333.84 | 207.46 | 494.0 | Gamma | 2.47 | 0.0074 |
| Cost of Magnetic Resonance Imaging of Pelvis41 | 138.46 | 103.69 | 160.93 | Gamma | 10.67 | 0.077 |
| Cost of Computerised Tomography of Chest, Abdomen and Pelvis41 | 128.54 | 94.31 | 161.5 | Gamma | 6.67 | 0.052 |
| Cost of Multi-disciplinary Discussion of Patient Management41 | 123.17 | 72.64 | 145.36 | Gamma | 5.23 | 0.042 |
| Cost of Outpatient Appointment41 | 105.04 | 75.23 | 122.71 | Gamma | 8.93 | 0.085 |
| Cost of Palliative Chemotherapy42 | 53,000 | - | - | Gamma | 7.78 | 0.00015 |
| Cost of Contact Brachytherapy | 1,445.88 | 1,156.70 | 1,735.06 | Triangular | - | - |

Table 3

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **90 Day Mortality(%) Charlson<3** | | | | | | **90 Day Mortality(%) Charlson>3** | | | | | |
| **Age** | **90 Day Mortality** | **Total Number of Patients** | **Representative Mean Mortality\*** | **Representative SE\*** | **Parameter for Beta Distribution** | | **90 Day Mortality** | **Total Number of patients** | **Representative Mean Mortality\*** | **Representative SE\*** | **Parameter for Beta Distribution** | |
| **** | **** | **** | **** |
| <61 | 49 | 4086 | 1.2 | 0.003 | 49 | 4037 | 47 | 1739 | 2.7 | 0.009 | 47 | 1692 |
| 61-70 | 130 | 5186 | 2.5 | 0.003 | 130 | 5056 | 133 | 2764 | 4.8 | 0.008 | 133 | 2631 |
| 71-80 | 271 | 4883 | 5.5 | 0.005 | 271 | 4612 | 242 | 2613 | 9.3 | 0.011 | 242 | 2371 |
| >80 | 179 | 1512 | 11.8 | 0.021 | 179 | 1333 | 129 | 785 | 16.4 | 0.047 | 129 | 656 |

Table 4

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Age** | **Baseline Mortality (%)** | **Age** | **Baseline Mortality (%)** | **Age** | **Baseline Mortality (%)** | **Age** | **Baseline Mortality (%)** |
| 60 | 0.9 | 70 | 2.2 | 80 | 6.3 | 90 | 15.6 |
| 61 | 0.9 | 71 | 2.4 | 81 | 7.0 | 91 | 16.7 |
| 62 | 1.0 | 72 | 2.7 | 82 | 7.7 | 92 | 18.8 |
| 63 | 1.1 | 73 | 3.0 | 83 | 8.5 | 93 | 20.9 |
| 64 | 1.3 | 74 | 3.3 | 84 | 9.6 | 94 | 22.8 |
| 65 | 1.4 | 75 | 3.7 | 85 | 10.7 | 95 | 24.9 |
| 66 | 1.5 | 76 | 4.1 | 86 | 11.8 | 96 | 26.6 |
| 67 | 1.7 | 77 | 4.5 | 87 | 12.9 | 97 | 28.7 |
| 68 | 1.9 | 78 | 5.0 | 88 | 14.1 | 98 | 30.3 |
| 69 | 2.1 | 79 | 5.6 | 89 | 14.6 | 99 | 31.4 |

Table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Cohort** | **Cost Saving (£)** | | **Incremental Effectiveness (QALY)** | | **Uncertainty; Percentage of model simulations intervention most cost-effective (%)** |
| **Mean** | **95% CI** | **Mean** | **95% CI** | **CET 20,000£/QALY** |
| **WW with CXB Boost vs WW with EBRT alone** | | | | | |
| fm60 | 1,271.07 | -1,399.51 to 4,622.05 | 0.09 | -0.46 to 0.65 | WW with CXB - 60.1%, WW with EBRT alone – 17.4%, RS – 22.5% |
| fm80 | 972.29 | -1,583.04 to 4,412.30 | 0.10 | -0.16 to 0.35 | WW with CXB - 70.9%, WW with EBRT alone – 14.6%, RS – 14.5% |
| cm80 | 769.21 | -1,803.61 to 3,877.89 | 0.12 | -0.15 to 0.37 | WW with CXB - 74.2%, WW with EBRT alone – 15.5%, RS – 10.3% |
| **WW with CXB Boost vs RS** | | | | | |
| fm60 | 2,873.51 | -1,425.60 to 7,915.88 | 0.17 | -0.70 to 1.02 | WW with CXB - 60.1%, WW with EBRT alone – 17.4%, RS – 22.5% |
| fm80 | 2,317.09 | -1,746.44 to 7,525.92 | 0.23 | -0.21 to 0.55 | WW with CXB - 70.9%, WW with EBRT alone – 14.6%, RS – 14.5% |
| cm80 | 2,030.33 | -2,119.66 to 6,559.74 | 0.21 | -0.16 to 0.58 | WW with CXB - 74.2%, WW with EBRT alone – 15.5%, RS – 10.3% |

Figure 1

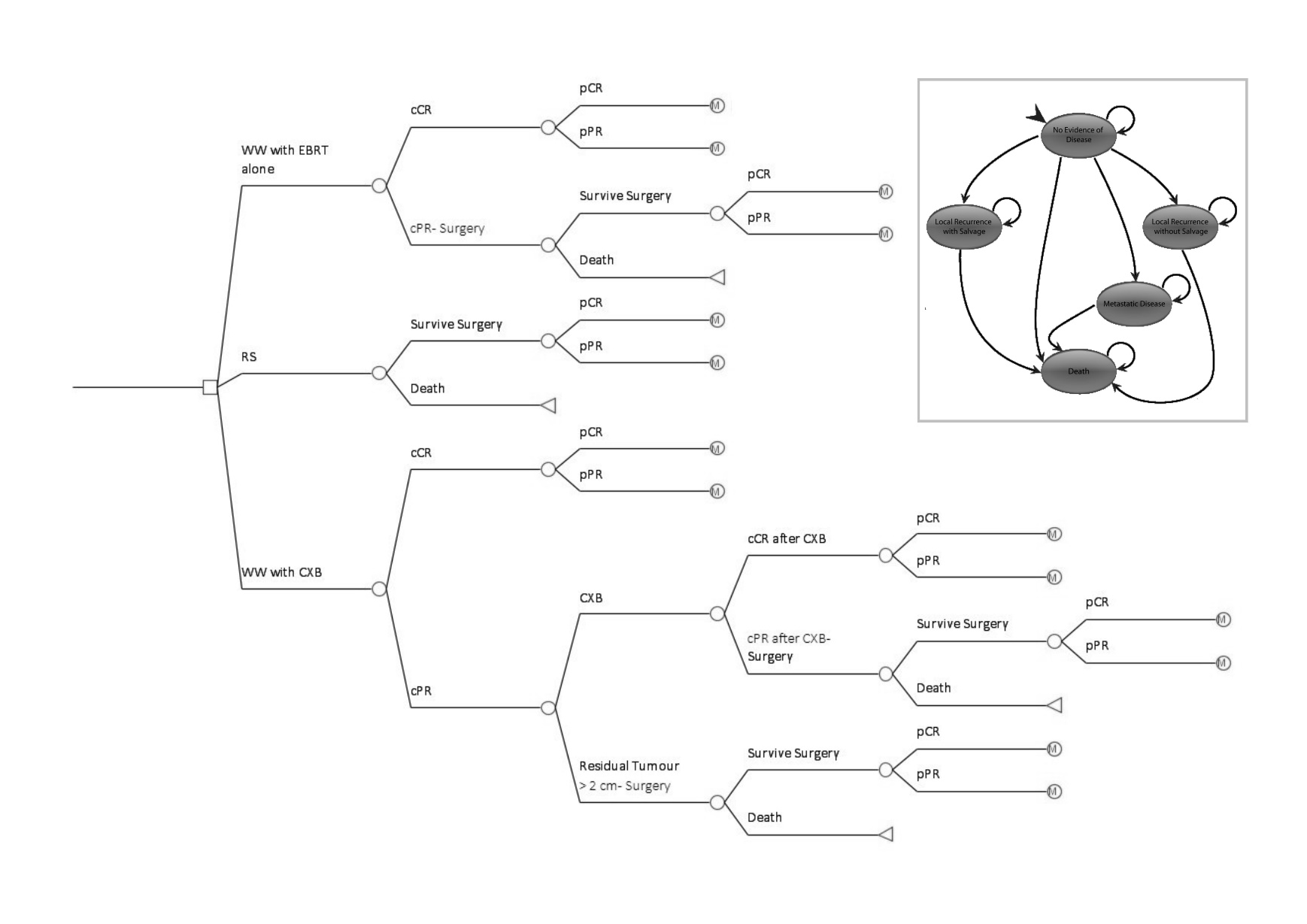


Figure 2



Figure 3



Figure 4

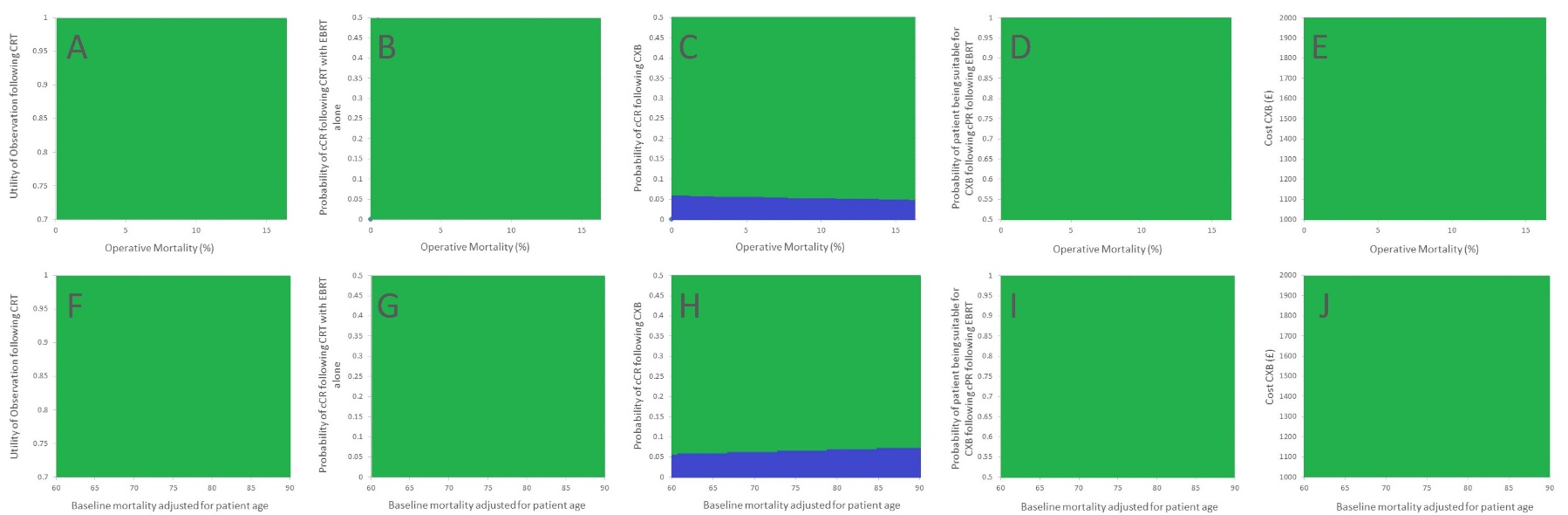


Figure 5

