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Original Article

# A Cost-Effectiveness Analysis of Contact X-ray Brachytherapy for the Treatment of Patients with Rectal Cancer Following a Partial Response to Chemoradiotherapy

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## Abstract

*Aims:* Following chemoradiotherapy in patients with rectal cancer, the addition of contact X-ray brachytherapy (CXB) in partial responders might increase the proportion of patients with a clinical complete response (cCR) and who are thus suitable for watch and wait management. However, the long-term cost-effectiveness of this approach has not been evaluated.
*Materials and methods:* Decision analytical modelling and a Markov simulation were used to compare long-term costs, quality-adjusted life years (QALYs) and cost-effectiveness from a third-party payer (National Health Service) perspective for treatment strategies after chemoradiotherapy; watch and wait with CXB when a cCR was not initially achieved after external beam radiotherapy (EBRT) ($WW_{CXB}$), watch and wait with EBRT alone ($WW_{EBRT}$) and radical surgery for all patients. The effect of uncertainty in model parameters and patient demographics was investigated.
*Results:* $WW_{CXB}$ had a higher QALY payoff than both radical surgery and $WW_{EBRT}$ and was less costly in most scenarios and demographic cohorts. In all plausible scenarios, $WW_{CXB}$ was the most cost-effective, at a threshold of £20 000/QALY. This finding was insensitive to uncertainty associated with model parameters.
*Conclusions:* $WW_{CXB}$ is likely to be cost-effective compared with both $WW_{EBRT}$ alone and radical surgery. These findings support the use of CXB boost as an adjunct to a watch and wait strategy.


*Key words:* Complete clinical response; contact brachytherapy; cost-effectiveness; organ preservation; rectal cancer; watch and wait

## Introduction

The clinical complete response (cCR) rate is low following conventional chemoradiation using external beam radiotherapy (EBRT) and concurrent fluoropyrimidine. A recent UK series reported that fewer than 12% of patients achieved a cCR [1]. The cCR rate can be improved by escalating the dose of radiation, but this may be associated with increased radiation toxicity. Contact X-ray brachytherapy (CXB) boost enables high doses of radiation to be delivered directly to the tumour with minimal damage to adjacent tissue [2–4]. There is evidence that CXB can be used in addition to EBRT to increase the proportion of patients who achieve a cCR [2,5,6]. CXB may therefore avoid the need for surgery. Perioperative

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mortality, particularly in elderly comorbid patients, is significant [7]. Over 50% of patients still have a stoma 18 months after surgery [8]. There is also significant systemic morbidity associated with surgery, for example 9% of patients suffer from major cardiac complications and 6% suffer from major respiratory complications [9]. This unquestionably has a significant effect on patient health-related quality of life (HRQoL).

The long-term cost-effectiveness of CXB, however, has not been evaluated. We therefore adapted a previously published decision-analytical model [10,11] to evaluate the long-term cost-effectiveness of CXB boost when used in addition to standard chemoradiotherapy to increase the cCR rate as part of a watch and wait strategy. We investigated and quantified the associated uncertainty. Finally, we carried out alternative analyses to investigate the effect of patient age and comorbidity.

## Materials and Methods

To evaluate the cost-effectiveness of CXB for patients who do not achieve a cCR following chemoradiotherapy with EBRT alone we compared the cost-effectiveness of three competing treatment strategies:

(i) Watch and wait for patients with a cCR following chemoradiotherapy with EBRT, with CXB boost for those patients who do not achieve a cCR. Patients who do not achieve a cCR following CXB, or have tumours too large for CXB, will undergo curative surgery. This strategy will henceforth be referred to as watch and wait with CXB boost ($WW_{CXB}$).
(ii) Watch and wait for patients with a cCR following chemoradiotherapy with EBRT. Patients who do not achieve a cCR will undergo curative surgery. This strategy will henceforth be referred to as watch and wait with EBRT alone ($WW_{EBRT}$).
(iii) Radical surgery for all patients following chemoradiotherapy with EBRT irrespective of whether or not a cCR is achieved. This strategy will be referred to as initial radical surgery.

The outcomes for these groups were modelled using a decision analytical model consisting of a combined decision tree and Markov chain simulation (Figure 1). Details of the model structure and interventions that patients undergo in each modelled state have previously been described (Supplementary File A) [10,11]. Table 1 shows the clinical parameters and Table 2 the economic data. Baseline and operative mortality have also been previously described (Supplementary File B) [10].

The analysis was carried out from a third-party payer perspective (UK National Health Service; NHS) according to the National Institute for Health and Care Excellence (NICE) guidelines on technology assessment [16]. Costs are reported in UK pound sterling (£). The effects of interventions were measured in quality-adjusted life years (QALYs). Incremental costs and effects were calculated for the lifetime of the hypothetical patient cohorts (a lifetime time-horizon). Costs and effects were discounted at 3.5% per annum. The analysis was carried out using decision-analytical software (TreeAge-Pro; Williamstown, MA, USA).

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

In the cohorts modelled, all patients were assumed to have rectal cancer threatening or involving the circumferential resection margin, with no distant metastasis (T3NXM0; or T2NXM0 in the case of some very low cancers) and therefore eligible for chemoradiotherapy, potentially followed by curative resection, according to current NICE guidelines [31]. All patients in the modelled cohorts were assumed to be fit enough to undergo curative surgery. In the radical surgery cohort, all patients underwent surgery after chemoradiotherapy with EBRT. In the $WW_{EBRT}$ cohort, patients with a cCR according to strictly defined criteria [11,32] were intensively followed up. Patients without a cCR after chemoradiotherapy underwent curative surgery. In the $WW_{CXB}$ cohort, patients who initially had a cCR after chemoradiotherapy with EBRT were treated in the same way as those in the $WW_{EBRT}$ cohort. Patients without a cCR and a residual tumour with a maximum circumference of greater than 3 cm on clinical examination, 6–8 weeks after chemoradiotherapy, underwent surgery. Patients with a residual tumour of maximal circumference of 3 cm or less were given a CXB boost. CXB was delivered as an outpatient treatment every 2 weeks using a Papillon plus machine (Ariane Medical Systems, UK). Patients received a total of 90 Gy delivered in three fractions over 4 weeks [33]. In our modelled cohort, patients who had a cCR after CXB boost were managed in the same way as those in the $WW_{EBRT}$ cohort. Patients without a cCR after CXB boost underwent surgery. It was assumed that 10% of patients who underwent CXB had some form of intervention such as argon plasma coagulation for rectal bleeding.

We assumed that follow-up for patients undergoing initial surgery, or salvage surgery in the watch and wait cohorts, was according to NICE guidelines [31]. Follow-up for both surgical and watch and wait cohorts has previously been described [10] and is detailed in Supplementary File A. We assumed that if tumour recurrence had occurred, patients underwent full oncological restaging and salvage surgery where appropriate. Patients in whom salvage surgery was not possible underwent palliative surgery (defunctioning stoma or stent) and chemotherapy. Patients with distant metastasis underwent palliative chemotherapy and a proportion of patients, reflecting actual clinical practice, underwent liver resection [34]. As fewer than 1% of patients with colorectal lung metastasis undergo resection we did not account for this in our model [12].

To investigate whether the results of our analysis were sensitive to patient age and comorbidities, an analysis was carried out with appropriate operative mortality, baseline mortality and operative costs for a 60-year-old male (fm60) and an 80-year-old male cohort with mild comorbidities (fm80) (Charlson Score $< 3$) and an

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