Re: Assessing the impact of a brachytherapy boost with external beam radiotherapy for prostate cancer.

We welcome the comments from XXX et al. with respect to our recent publication on the impact of brachytherapy boost on outcomes in patients receiving EBRT for prostate cancer.

Low patient numbers were highlighted in the LDR-BB comparison group. However, there was sufficient power to enable reliable comparison and we are confident that our conclusions are robust. It is also important to note the agreement between two independent measures: the outcomes reported by patients and the toxicity measures derived from routinely collected administrative data. Importantly, this study included all patients who received a recognised radiotherapy regimen within NHS England between 2010 and 2016, which ensures its generalisability compared to single institution cases series.

We acknowledge that there may be a low and variable threshold for referral for diagnostic tests in patients who have undergone EBRT. However, our toxicity indicators were developed to include both diagnostic and procedure codes which maximises their specificity, and reduces the risk of misclassification bias and under-reporting which can occur with physician-only reporting. This ensures that simply undergoing a colonoscopy would not be flagged as 'toxicity' unless there was a specific diagnosis for a radiation-related condition (e.g. radiation proctitis or rectal bleeding).

The lack of baseline patient-reported outcomes is a potential limitation. However, our patient survey did include a question about recalled function at the time of diagnosis and we found that more men in the LDR-BB group reported 'no problem' with their bowel function at diagnosis (84%) than men in the HDR-BB (81%) or EBRT monotherapy groups (72%). Therefore, any difference in bowel function observed after treatment is likely to be an under-estimation. Furthermore, patients who did not respond to the survey were similar between treatment groups (LDR-BB: 25%; HDR-BB: 18%; EBRT monotherapy: 23%).

We agree that our findings are different to those of two RCTs in this area (1-4), but these trials were conducted before 2012 when lower EBRT radiation doses (55 and 66 Gy) and non-IMRT EBRT techniques were routinely used. Equally, the observational study of Slevin et al. (5) should be interpreted with caution given it only included 287 men and the comparison between brachytherapy boost types was made over two different time periods. Their study is therefore hypothesis generating and cannot be used as evidence for superior efficacy of LDR-BB compared to HDR-BB. The study's low power may be an explanation why the observed higher grade 3 GI toxicity after LDR-BB compared to HDR-BB was not statistically significant (5% versus 1%) (5).

Finally, there is still an ongoing debate with respect to the impact of rectal hydrogel spacers on radiation-induced toxicity but we expect that if spacers reduce toxicity, this would be observed in all treatment groups.

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2. Hoskin PJ, Motohashi K, Bownes P, Bryant L, Ostler P. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. *Radiother Oncol*. 2007;84(2):114-20.
3. Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol*. 2012;103(2):217-22.
4. Hoskin PJ, Rojas AM, Ostler PJ, Hughes R, Lowe GJ, Bryant L. Quality of life after radical radiotherapy for prostate cancer: longitudinal study from a randomised trial of external beam radiotherapy alone or in combination with high dose rate brachytherapy. *Clin Oncol (R Coll Radiol)*. 2013;25(5):321-7.
5. Slevin F, Rodda SL, Bownes P, Murray L, Bottomley D, Wilkinson C, et al. A comparison of outcomes for patients with intermediate and high risk prostate cancer treated with low dose rate and high dose rate brachytherapy in combination with external beam radiotherapy. *Clin Transl Radiat Oncol*. 2020;20:1-8.