

# Medical Services Advisory Committee (MSAC) Public Summary Document

## *Application No. 1525.1 – Low dose rate brachytherapy for intermediate- and high-risk prostate cancer*

**Applicant:** BXTAccelyon Australia Pty Ltd

**Date of MSAC consideration:** 30-31 March 2023

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#).

### 1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of low dose-rate brachytherapy (LDR-BT) for intermediate and high-risk prostate cancer was received from the BXTAccelyon Australia Pty Ltd by the Department of Health and Aged Care.

### 2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety and clinical effectiveness, MSAC did not support progression to the second (economic) stage of the assessment for low dose-rate brachytherapy (LDR-BT) boost (following primary external beam radiotherapy [EBRT]) for intermediate and high-risk prostate cancer. MSAC considered that the limited new evidence presented did not change its previous conclusions from August 2019 that, compared with dose-escalated DE-EBRT, EBRT plus LDR-BT boost has inferior safety and uncertain effectiveness. Compared with high dose-rate (HDR) brachytherapy boost following EBRT, MSAC considered that the additional very low certainty evidence assessed in this resubmission suggested that LDR-BT boost has uncertain safety (possibly noninferior safety over the longer term) and uncertain effectiveness. MSAC considered that there is insufficient evidence to support use of biochemical progression-free survival as an intermediate clinical endpoint in prostate cancer radiation therapy-based trials, in the absence of other direct evidence of clinical benefit.

#### Consumer summary

This is an application from BXTAccelyon Australia requesting Medicare Benefits Schedule (MBS) listing of low dose-rate brachytherapy (LDR-BT) for the treatment of intermediate- and high-risk prostate cancer. This is a resubmission that is in the first stage of a two-stage application process, so only effectiveness and safety were considered (i.e. not value for money or costs).

Radiation therapy is commonly used in cancer treatments, where radioactivity is used to kill cancer cells. In low dose-rate brachytherapy, small radioactive “seeds” are placed into the prostate gland and stay there permanently to deliver radiation close to the tumour. This is done to boost the radiation dose after a patient has already had radiation directed at the tumour from outside the body (called external beam radiotherapy, or EBRT). Other options for patients who have already had EBRT are more doses of EBRT (called dose-escalated EBRT or

## Consumer summary

DE-EBRT) or temporary radiation given through a small tube into the prostate (called high dose-rate brachytherapy, or HDR-BT).

Low dose-rate brachytherapy is already listed on the MBS for use in patients who have low-risk prostate cancer. This application is requesting MBS listing for low dose-rate brachytherapy to be used as a radiation boost after EBRT in patients with intermediate- to high-risk prostate cancer.

Overall, MSAC considered the new studies provided in the resubmission to be of very low quality, so there was no evidence to prove that low dose-rate brachytherapy benefits people with intermediate- and high-risk prostate cancer. Furthermore, MSAC considered that low dose-rate brachytherapy is less safe than other treatments when used in these patients.

### MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support progressing this application for low dose-rate brachytherapy for the treatment of intermediate- and high-risk prostate cancer. Overall, MSAC considered low dose-rate brachytherapy to be less safe than other treatments for these patients, and was not convinced of its effectiveness.

## 3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from BXTAccelyon Australia Pty Ltd was requesting Medicare Benefits Schedule (MBS) listing of low dose-rate brachytherapy (LDR-BT) for intermediate- and high-risk prostate cancer. LDR-BT is used as a boost following external beam radiotherapy (EBRT) to deliver a higher dose of radiation to the prostate, which is supported in current international prostate cancer consensus guidelines.

MSAC noted that it previously considered LDR-BT for intermediate- and high-risk prostate cancer groups at its [August 2019 meeting](#). MSAC did not support public funding of LDR-BT boost (following EBRT, i.e. EBRT+LDR-BT boost) because comparative safety and effectiveness were too uncertain relative to dose-escalated EBRT (DE-EBRT) and no evidence was provided relative to high dose-rate (HDR) brachytherapy boost following EBRT (EBRT+HDR-BT boost) or radical prostatectomy (RP). MSAC concluded that, relative to DE-EBRT, EBRT+LDR-BT boost has superior effectiveness for biochemical progression-free survival (bPFS), but uncertain effectiveness for overall survival (OS), metastasis-free survival (MFS) and prostate cancer-specific survival (PCSS). MSAC also concluded that EBRT+LDR-BT boost has inferior safety relative to DE-EBRT.

MSAC noted that in August 2019, it advised that a future resubmission should include:

- comparative safety data based on up-to-date practice, ideally for all three comparators
- effectiveness data for EBRT+HDR-BT boost and RP
- updated cost-effectiveness analyses to reflect any newly relevant comparative safety and effectiveness data.

MSAC noted that, for this resubmission, the applicant has chosen to undergo a two-stage assessment report pathway – an option available to applicants as per the [MSAC Process Framework](#). The applicant has provided evidence for safety and clinical effectiveness that has become available since the previous MSAC consideration in 2019. If this first stage is successful, the applicant will submit an economic evaluation and financial impact analysis in the second stage.

MSAC noted from the pre-MSAC response that EBRT+LDR-BT boost has been adopted in most countries and is considered standard therapy for the treatment of intermediate and high-risk prostate cancer.

MSAC noted that this resubmission proposed changes to the PICO-rated population, reclassifying patients with intermediate-risk prostate cancer as having a prostate-specific antigen (PSA) of >10.0 ng/mL and <20.0 ng/mL, and/or a Gleason score of 7, and/or T2b-c; and high-risk prostate cancer as having a PSA >20.0 ng/mL, and/or a Gleason score of 8–10, and/or T3a, or two or more intermediate risk factors. MSAC noted that the revised population is not consistent with the current NCCN Prostate Cancer Guidelines, which stratifies the intermediate-risk category into “favourable” (low-intermediate risk) and “unfavourable” (high-intermediate risk) subgroups. According to the current NCCN guidelines, only the “unfavourable” subgroup would be eligible for EBRT+LDR-BT boost.

MSAC noted that the applicant had modified the two proposed item descriptors – one for a radiation oncologist and one for a urologist – from the previous submission to include revised histological grading (the International Society of Urological Pathway [ISUP] Grade Group system), which MSAC considered appropriate.

MSAC noted from the pre-MSAC response that, although the applicant considered the current proposed item descriptor is reasonable considering the complexities, they are open to any alterations that MSAC considers appropriate. MSAC noted that ESC had considered the current item descriptors to be very specific regarding the appropriate population and consistent with the pivotal ASCENDE-RT trial and PICO population. ESC had considered that using international staging/risk groupings is important, but using NCCN-specific risk groups could result in an outdated item descriptor as the guidelines are continually updated; MSAC considered that the use of any grading system is potentially problematic. MSAC noted ESC’s advice that the “current” World Health Organization (WHO) “Blue Book” classification system could be considered as the grading system used in the item descriptors; the WHO 2022 system is current, and it is expected this will be updated every 3 to 6 years. MSAC considered it important that the item descriptor reflects contemporary clinical practice.

MSAC noted there are several MBS-reimbursed comparator options available for this patient population: DE-EBRT or EBRT+HDR-BT boost. MSAC agreed with the applicant-developed assessment report (ADAR) that RP exclusion from the comparator list is appropriate.

MSAC noted that one of the primary outcomes of the revised PICO was quality of life, and that only limited evidence for this had been provided. MSAC also considered that some of the secondary outcomes outlined in the revised PICO would usually be considered as primary outcomes (e.g. OS, MFS and PCSS).

MSAC noted that the resubmission identified 16 mostly retrospective studies (including four from the ASCENDE-RT trial), but that the commentary deemed only one randomised controlled trial (RCT) – the ASCENDE-RT, included in the previous submission – and four observational studies to be relevant to the assessment, as the other studies did not include an eligible comparator. MSAC considered these exclusions appropriate. MSAC also noted that no new evidence was reported in the resubmission for comparative safety and effectiveness of EBRT+LDR-BT boost versus DE-EBRT, relying on updated data from the ASCENDE-RT trial identified in the commentary. MSAC noted the pre-ESC response that stated that the ASCENDE-RT trial will continue to be the largest trial ever performed in this patient population. MSAC noted that all four retrospective studies informing safety and clinical effectiveness of EBRT+LDR-BT boost vs EBRT+HDR-BT boost had a moderate to serious risk of bias, and had issues around patient selection, missing data, outcome measurements and a lack of risk stratification, making it difficult to generalise the findings to the population of interest. MSAC noted that there is an ongoing randomised controlled trial (RCT)

comparing quality of life and PSA recurrence-free survival of EBRT+LDR-BT boost versus EBRT+HDR-BT boost (NCT01936883).

MSAC noted that the clinical claim of superiority versus DE-EBRT and noninferiority versus EBRT+HDR-BT boost is the same as that from the previous application.

Regarding comparative safety of EBRT+LDR-BT boost versus DE-EBRT, MSAC recalled that results from the ASCENDE-RT trial showed that 5-year cumulative incidence of Grade 3 genitourinary (GU) toxicity events was significantly higher for EBRT+LDR-BT boost (18.4% versus 5.2%;  $P < 0.001$ ). Compared with EBRT+HDR-BT boost, MSAC noted that EBRT+LDR-BT boost had a greater number of GU toxicity events, but there was no difference in severe ( $\geq$ ) Grade 3 toxicity. Differences in toxicity between the intervention and comparator were most prominent in the short term, but resolved with long-term follow-up; MSAC considered that, compared with EBRT+HDR-BT boost, EBRT+LDR-BT boost has possibly inferior safety over the short term and noninferior safety over the longer term. However, MSAC noted that there was a serious risk of bias with the retrospective studies, and that these studies were likely underpowered for the safety outcomes. Therefore, MSAC considered the conclusions to be highly uncertain. Overall, based on the evidence provided, MSAC considered that EBRT+LDR-BT boost has inferior safety compared with DE-EBRT and uncertain safety compared with EBRT+HDR-BT.

Regarding comparative effectiveness, MSAC noted that updated results for the survival outcomes from the ASCENDE-RT trial over a median follow-up of 10 years (Oh et al. 2022) showed that EBRT+LDR-BT boost had superior time to treatment progression compared with DE-EBRT, but there was no difference in OS or time to distant metastasis. Overall, MSAC considered that longer term results from the ASCENDE-RT trial continues to suggest that compared with DE-EBRT, EBRT+LDR-BT boost has superior effectiveness for bPFS and noninferior effectiveness for other outcomes – but uncertainty remains because the trial was underpowered to assess differences in survival endpoints. MSAC agreed with ESC that the arguments made by the applicant concerning the importance of bPFS do not override the conclusions from the ASCENDE trial – that, with long-term follow-up, improved PSA control did not translate to improvement in any other disease-related end point.

For effectiveness compared with EBRT+HDR-BT, MSAC noted that very limited and poor-quality evidence suggested that EBRT+LDR-BT boost is superior in terms of bPFS but no different for other survival outcomes. MSAC also noted that, while there was no difference in Expanded Prostate Cancer Index Composite (EPIC) score, the outcomes for urinary incontinence score/urinary irritative symptoms, International Prostate Symptom Score (IPSS) and bowel function were worse for EBRT+LDR-BT boost. Therefore, MSAC considered EBRT+LDR-BT boost to have uncertain effectiveness compared with EBRT+HDR-BT boost. MSAC also considered that, without evidence of improved quality of life, an economic analysis would not find this treatment to be worthwhile given the worse early toxicity associated with EBRT+LDR-BT boost.

Regarding the use of bPFS as the primary outcome measure, MSAC considered that, while the systematic review provided by the applicant (Van den Broeck et al. 2019<sup>1</sup>) showed a strong relationship between biochemical relapse (BCR), PCSS and distant metastases, the relationship between BCR and OS was less clear. MSAC also noted a meta-analysis by Xie et al. (2020)<sup>2</sup> that concluded that event-free survival (a prostate specific antigen based composite endpoint) was an inappropriate surrogate for OS for prostate cancer treated with radiation. MSAC acknowledged

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<sup>1</sup> Van den Broeck T et al. (2019). [Prognostic value of biochemical recurrence following treatment with curative intent for prostate cancer: a systematic review](#). *European Urology* 75(6):967-987.

<sup>2</sup> Xie et al. (2020). [Event-free survival, a prostate-specific antigen-based composite end point, is not a surrogate for overall survival in men with localized prostate cancer treated with radiation](#). *J Clin Oncol* 38(26):3032-3041.

that EBRT+LDR-BT boost may show a benefit in effectiveness, but considered that it was important to demonstrate benefit beyond just a biochemical outcome – other cancer treatments often have other clinical evidence of benefit.

Overall, MSAC considered that the resubmission did not adequately address its concerns from August 2019. There was no new evidence reported in the resubmission for comparative safety and effectiveness of EBRT+LDR-BT boost versus DE-EBRT. The four retrospective studies informing safety and clinical effectiveness of EBRT+LDR-BT boost versus EBRT+HDR-BT boost had a moderate to serious risk of bias and had issues that make it difficult to generalise the findings to the population of interest. MSAC also considered the evidence to support using bPFS as an intermediate clinical end point in prostate cancer radiation therapy-based trials to be insufficient, and that the increased bPFS seen with the intervention did not justify the increased toxicity. Therefore, MSAC considered that the new evidence does not change its previous advice, which was based on comparative safety and clinical effectiveness (and not health economics or financial impact), so advised that the application should not progress to the next stage of the assessment report pathway.

MSAC advised that a resubmission should provide adequately powered RCT evidence demonstrating increased PCSS or MFS, although MSAC acknowledged that the use of brachytherapy treatment is declining. Alternatively, a resubmission should provide evidence to support using bPFS as an intermediate clinical end point in prostate cancer radiation therapy-based trials, ideally using individual patient data.

## 4. Background

MSAC has previously considered low dose-rate brachytherapy (LDR-BT) boost for intermediate and high-risk prostate cancer in 2019. MSAC did not support public funding of LDR-BT boost (following primary external beam radiotherapy [EBRT]) due to limited comparative safety and effectiveness evidence.

MSAC advised<sup>3</sup> that any future resubmission should include:

- comparative safety data based on up-to-date practice, ideally for all three comparators: radical prostatectomy, dose-escalated external beam radiation therapy (DE-EBRT) and high dose-rate brachytherapy (HDR-BT) boost following primary EBRT;
- effectiveness data for the other two comparators (radical prostatectomy and EBRT+HDR-BT boost); and
- cost-effectiveness analyses should be updated to reflect any newly relevant comparative safety and effectiveness data.

The key matters of concern from previous considerations, as presented in the Applicant Developed Assessment Report (ADAR), are summarised in Table 1.

The applicant has taken the option of a two-stage pathway, providing evidence for safety and clinical effectiveness that has become available since the previous MSAC consideration in 2019. If successful, an economic evaluation and financial impact analyses would follow in the second stage.

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<sup>3</sup> Medical Services Advisory Committee (2019). Public Summary Document, application no. 1525 – Low dose-rate (LDR) brachytherapy for intermediate and high-risk prostate cancer. Commonwealth of Australia, Canberra, ACT. Available at: [http://www.msac.gov.au/internet/msac/publishing.nsf/Content/03EA3F4282C75C49CA25821E001C2D23/\\$File/1525%20-%20Final%20PSD.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/03EA3F4282C75C49CA25821E001C2D23/$File/1525%20-%20Final%20PSD.pdf)

Item 37220 for LDR-BT has been available on the MBS for the treatment of low-risk prostate cancer since 2001. The indication was expanded in 2006 to include low-risk prostate cancer with Gleason score 7. Low risk is defined as localised prostatic malignancy at clinical stages T1 (clinically inapparent tumour not palpable or visible by imaging) or T2 (tumour confined within prostate), with a Gleason score of  $\leq 7$  and a prostate-specific antigen (PSA) of  $\leq 10$  ng/mL at the time of diagnosis. In this indication, LDR-BT is used alone, not in combination with EBRT.

**Table 1 Summary of key matters of concern**

<b>Component</b>	<b>Matter of concern (as presented in the ADAR)</b>	<b>How the current assessment report addresses it</b>	<b>Commentary feedback</b>
Comparator	No comparative safety and efficacy data were presented comparing EBRT + LDR-BT boost with RP.	DE-EBRT boost and HDR-BT boost remain the nominated comparators. The ADAR explained the exclusion of RP (included in Ratified PICO) as a relevant comparator.	MSAC may wish to consider if RP exclusion from the comparator list is appropriate.
Comparative safety data	No safety data were provided comparing EBRT + LDR-BT boost with RP or EBRT + HDR-BT boost	The ADAR provided comparative safety data for EBRT + LDR-BT versus EBRT + HDR-BT.	Addressed. Some of the included evidence was not relevant.
Clinical effectiveness- primary outcome	The ASCENDE-RT trial suggested superior effectiveness of EBRT + LDR-BT boost versus DE-EBRT for biochemical progression-free survival. However, there was no difference in overall survival, metastasis-free survival or prostate cancer-specific survival, and the study was not powered or long enough to assess survival outcomes.	The ADAR provided a justification for b-PFS as the primary outcome measure. Reasoning included highlighting the rarity at which overall survival is used as a primary outcome in trials in the population of interest. It was also highlighted that a systematic review found BCR to be an independent risk factor for the development of distant metastases, prostate cancer-specific survival and overall survival.	Partially addressed. The review (by Van den Broeck et al. 2019 <sup>4</sup> ) concluded that there was a strong relationship between BCR and cancer-specific survival and occurrence of distant metastases. The relationship between biochemical recurrence and overall survival was less clear. The review noted disparities depending on the definition of biochemical relapse (ASTRO versus Phoenix criteria).
Clinical effectiveness	No data were provided comparing effectiveness of EBRT + LDR-BT boost with either RP or EBRT + HDR-BT boost. MSAC therefore concluded that EBRT + LDR-BT boost has uncertain effectiveness relative to EBRT + HDR-BT boost and RP.	The ADAR provided comparative clinical effectiveness data for EBRT + LDR-BT versus EBRT + HDR-BT.	Partially addressed. Provided studies have limited applicability due to including all intermediate-risk and high-risk patients.

<sup>4</sup> Van den Broeck, T., et al., Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review. *Eur Urol*, 2019. 75(6): p. 967-987.

Component	Matter of concern (as presented in the ADAR)	How the current assessment report addresses it	Commentary feedback
MBS Item descriptor	MSAC confirmed that the item descriptor should specify that LDR-BT is intended for use as a boost following EBRT and in association with androgen blockade.	The ADAR proposed modifications to the MBS item descriptors.	Partially addressed. Modification of the MBS item descriptor is not the same as suggested in the 1525 PSD. The risk group definitions presented in the ADAR item descriptor are not aligned either with the Ratified PICO or with the latest NCCN risk stratification <sup>5</sup> .
Included population	ESC noted that the designation of intermediate and high risk is arbitrary from a clinical point of view and queried which definition of intermediate risk should be used (NCCN or PICO).	The ADAR proposed including all intermediate-risk and high-risk patients along with two arguments: 1) Population definition should be standardised and follow clinical practice guidelines (NCCN) 2) Population in the original PICO was modified to minimise overtreatment in low intermediate-risk population that could be treated with LDR-BT monotherapy.	Not addressed. This change is not supported by the most recent NCCN guidelines <sup>5</sup> (published September 2022) in which intermediate risk group is divided into favourable and unfavourable intermediate-risk populations. As per these guidelines only the unfavourable intermediate-risk group would receive EBRT + LDR-BT boost with the favourable intermediate group being treated with either EBRT or Brachytherapy as monotherapies.
Applicability of trial	Johnson study <sup>6</sup> is at a high risk of bias and low applicability because the majority of patients were at low-intermediate risk.	The ADAR proposed a change in the population definition, including all intermediate-risk and high-risk patients, and noted that if accepted, Johnson study <sup>6</sup> would no longer have applicability issues.	Not addressed. This change is not supported by the most recent NCCN risk stratification and treatment guidelines (NCCN 2022) <sup>5</sup> which provide different treatment guidelines for favourable and unfavourable intermediate risk patients.

Source: Table 2 of the ADAR, with third and fourth column developed for the commentary

ADAR = Applicant Developed Assessment Report; BCR= biochemical recurrence; b-PFS = biochemical progression-free survival; EBRT = external beam radiation therapy; ESC = Evaluation Sub-Committee; HDR-BT = high dose-rate brachytherapy; LDR-BT = low dose-rate brachytherapy; MSAC = Medical Services Advisory Committee; NCCN = National Comprehensive Cancer Network; PSD = Public Summary Document; RP = radical prostatectomy<sup>3</sup>. Prerequisites to implementation of any funding advice

LDR-BT requires a radioactive seed which is a therapeutic good that is included on the Australian Register of Therapeutic Goods (ARTG). Several products are listed on the ARTG (

<sup>5</sup> National Comprehensive Cancer Network (2022). Clinical Practice Guidelines in Oncology Prostate Cancer Version 1.2023 – September 16, 2022. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf)

<sup>6</sup> Johnson, S.B., et al., *Brachytherapy Boost Utilization and Survival in Unfavorable-risk Prostate Cancer*. Eur Urol, 2017. **72**(5): p. 738-744.

Table 2). The intervention does not require a new device.



**Table 2 List of inclusions of brachytherapy seeds on ARTG**

Device	ARTG
Advantage I-125 Seed	154457
BrachySource® I-125 Implant	225229, 225230, 225231, 225237, 225238
TheraStrand Rx with AgX100 Brachytherapy Kit	205063
I-Seed AgX100 Cartridge Brachytherapy Kit	205023
Advantage I-125 Pre-load	175081

Source: Table 3 of the ADAR

## 5. Proposal for public funding

The ADAR proposed two MBS item descriptors, presented in Table 3 (radiation oncology component) and Source: Table 9 of the ADAR  
<sup>a</sup> Reflects the 1 November 2022 Greatest Permissible Gap (GPG) of \$93.20. All out-of-hospital Medicare services which have an MBS fee of \$621.50 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

Table 4 (urology component). They are based on the proposed item descriptors from the Ratified PICO, on MSAC’s advice (outlined in Table 1) and on the 2020 description updates to brachytherapy item numbers. However, the proposed item descriptors did not incorporate the wording suggested by the Department (and noted by ESC) in the Public Summary Document 1525<sup>3</sup>. Both modifications (the Department’s and the ADAR’s are shown in item descriptors (Table 3, Table 4).

The ADAR also proposed to change the definitions of intermediate and high risk according to their modification of the PICO. These are not aligned either with the original PICO, or with the latest NCCN risk stratification (NCCN 2022<sup>5</sup>). Additionally, a mix of outdated and current tumour grade nomenclature was used within the MBS item descriptor (i.e., Gleason score and Grade Group).

**Table 3 Proposed item descriptor for LDR brachytherapy for intermediate to high-risk prostate cancer (radiation oncology); ADAR modifications based on MSAC’s previous advice in italics and wording suggested by the Department in 1525 PSD in strikethrough**

Category 3 – THERAPEUTIC PROCEDURES
MBS item *XXXX
PROSTATE, radioactive seed implantation (radiation oncology component), using transrectal ultrasound guidance, for localised (non-metastatic) prostatic malignancy classified as intermediate risk (defined as having a prostate specific antigen (PSA) of 10-20 ng/ml and/or a Gleason score of 7 (Grade Group 2 or 3) and/or a tumour classified as T2b-c or high risk (defined as having a PSA of greater than 20 ng/ml and/or a Gleason score of 8-10 (Grade Group 4 or 5) and/or a tumour classified as T3a. <del>For the population above this procedure will be rebated if it is performed at an approved site as a boost treatment in addition to external beam radiotherapy and in association with androgen blockade, in association with a radiation oncologist.</del> <i>It is intended for use as a boost following EBRT and in association with androgen blockade, in addition to external beam radiotherapy, at an approved site in association with a radiation oncologist</i>
Fee: \$989.10 Benefit: 75% = \$741.85 85% = \$895.90 <sup>a</sup>

Source: Table 9 of the ADAR

<sup>a</sup> Reflects the 1 November 2022 Greatest Permissible Gap (GPG) of \$93.20. All out-of-hospital Medicare services which have an MBS fee of \$621.50 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

**Table 4 Proposed item descriptor for LDR brachytherapy for intermediate to high-risk prostate cancer (urology); ADAR modifications based on MSAC’s previous advice in italics and wording suggested by the Department in 1525 PSD in strikethrough**

Category 3 – THERAPEUTIC PROCEDURES
MBS item *XXXX PROSTATE, radioactive seed implantation (urology component), using transrectal ultrasound guidance, for localised (non-metastatic) prostatic malignancy classified as intermediate risk (defined as having a prostate specific antigen (PSA) of 10-20 ng/ml and/or a Gleason score of 7 (Grade Group 2 or 3) and/or a tumour classified as T2b-c or high risk (defined as having a PSA of greater than 20 ng/ml and/or a Gleason score of 8-10 (Grade Group 4 or 5) and/or a tumour classified as T3a. <del>For the population above this procedure will be rebated if it is performed at an approved site as a boost treatment in addition to external beam radiotherapy and in association with androgen blockade, in association with a urologist. It is intended for use as a boost following EBRT and in association with androgen blockade, in addition to external beam radiotherapy, at an approved site in association with an urologist</del>
Fee: \$1,103.90 Benefit: 75% = \$827.95

Source: Table 10 of the ADAR

## 6. Population

The original Ratified PICO proposed the following two populations for LDR-BT boost following primary EBRT:

- patients with high-intermediate risk prostate cancer: PSA >10.0 ng/mL <20.0 ng/mL and Gleason = 7 and T2b-c
- patients with high-risk prostate cancer: PSA >20.0 ng/mL and/or Gleason 8-10 and/or T3a.

The ADAR proposed to change the population to the following definitions:

- patients with intermediate risk prostate cancer: PSA >10.0 ng/mL <20.0 ng/mL and/or Gleason = 7 and/or T2b-c
- patients with high-risk prostate cancer: PSA >20.0 ng/mL and/or Gleason 8-10 and/or T3a *OR 2 or more intermediate risk features.*

The resubmission’s revised population is not coherent with the current NCCN Prostate Cancer Guidelines. Previous versions of the guidelines, which included a single definition of intermediate risk, are now outdated. The current version of the NCCN guidelines<sup>5</sup> further stratifies the intermediate-risk category into ‘Favourable’ (low-intermediate risk) and ‘Unfavourable’ (high-intermediate risk) subgroups. Only the Unfavourable (high-intermediate) risk subgroup is eligible for EBRT + brachytherapy boost according to the current guidelines. The updated NCCN risk categorisation and treatment guidelines appear to validate the PASC’s original decision to stratify the intermediate-risk group into lower and higher risk, and to limit the use of LDR-BT boost to high-intermediate risk group. The ADAR’s proposal to include all intermediate-risk and high-risk patients may be inappropriate. See Table 5 for comparison of risk stratification definitions across different approaches.

**Table 5 Risk stratification of prostate cancer – comparison of different approaches**

Risk category	Ratified PICO 1525	NCCN 2017	NCCN Version 1.2023 (NCCN 2022)	
Intermediate risk	Low-intermediate: NA (not of interest)	<ul style="list-style-type: none"> <li>PSA &gt; 10.0 &lt; 20.0 ng/mL and/or</li> <li>Gleason = 7 and/or</li> <li>T2b-c</li> </ul>	All of the following: <ul style="list-style-type: none"> <li>No high-risk group features</li> <li>No very-high-risk group features</li> <li>≥1 or IRFs:                             <ul style="list-style-type: none"> <li>cT2b-cT2c</li> <li>Grade Group 2 or 3</li> <li>PSA 10-20 ng/mL</li> </ul> </li> </ul>	Favourable: all of the following: <ul style="list-style-type: none"> <li>1 IRF</li> <li>Grade Group 1 or 2</li> <li>&lt;50% biopsy cores (+)</li> </ul>
	High-intermediate: <ul style="list-style-type: none"> <li>PSA &gt; 10.0 &lt; 20.0 ng/mL and</li> <li>Gleason = 7 and</li> <li>T2b-c</li> </ul>	Unfavourable: one or more of the following <ul style="list-style-type: none"> <li>2 or 3 IRFs</li> <li>Grade Group 3</li> <li>≥50% biopsy cores (+)</li> </ul>		
High risk (non-metastatic)	<ul style="list-style-type: none"> <li>PSA &gt;20.0 ng/mL and/or</li> <li>Gleason 8-10 and/or</li> <li>T3a</li> </ul>	<ul style="list-style-type: none"> <li>PSA &gt;20.0 ng/mL and/or</li> <li>Gleason 8-10 and/or</li> <li>T3a or</li> <li>≥2 intermediate-risk features</li> </ul>	No very-high-risk features and exactly one high-risk feature: <ul style="list-style-type: none"> <li>cT3a or</li> <li>Grade Group 4 or 5 or</li> <li>PSA &gt;20 ng/mL</li> </ul>	

Source: Developed for commentary

IRF = intermediate risk factor; NA = not applicable; PSA = prostate-specific antigen

## 7. Comparator

The original MSAC application 1525 nominated two comparators:

- DE-EBRT (Table 6) and
- EBRT + HDR-BT boost (Table 7).

During the PASC process, a third comparator was added:

- radical prostatectomy (Table 8)

All three comparators are currently funded through MBS.

**Table 6 Relevant MBS items for DE-EBRT**

Category 3 – THERAPEUTIC PROCEDURES
<p>MBS item 15555</p> <p>SIMULATION FOR INTENSITY-MODULATED RADIATION THERAPY (IMRT), with or without intravenous contrast medium, if:</p> <ol style="list-style-type: none"> <li>1. treatment set-up and technique specifications are in preparations for three-dimensional conformal radiotherapy dose planning; and</li> <li>2. patient set-up and immobilisation techniques are suitable for reliable CT-image volume data acquisition and three-dimensional conformal radiotherapy; and</li> <li>3. a high-quality CT-image volume dataset is acquired for the relevant region of interest to be planned and treated; and</li> <li>4. the image set is suitable for the generation of quality digitally-reconstructed radiographic images.</li> </ol> <p><b>Fee:</b> \$751.20 Benefit: 75% = \$563.40 85% = \$658.00</p>
<p>MBS item 15550</p> <p>SIMULATION FOR THREE DIMENSIONAL CONFORMAL RADIOTHERAPY without intravenous contrast medium, where:</p> <ol style="list-style-type: none"> <li>(a) treatment set up and technique specifications are in preparations for three dimensional conformal radiotherapy dose planning; and</li> <li>(b) patient set up and immobilisation techniques are suitable for reliable CT image volume data acquisition and three dimensional conformal radiotherapy treatment; and</li> <li>(c) a high-quality CT-image volume dataset must be acquired for the relevant region of interest to be planned and treated; and</li> <li>(d) the image set must be suitable for the generation of quality digitally reconstructed radiographic images</li> </ol> <p><b>Fee:</b> \$696.25 Benefit: 75% = \$522.20 85% = \$603.05</p>
<p>MBS item 15559</p> <p>DOSIMETRY FOR THREE DIMENSIONAL CONFORMAL RADIOTHERAPY OF LEVEL 2 COMPLEXITY where:</p> <ol style="list-style-type: none"> <li>(a) dosimetry for a two phase three dimensional conformal treatment plan using CT image volume dataset(s) with at least one gross tumour volume, two planning target volumes and one organ at risk defined in the prescription; or</li> <li>(b) dosimetry for a one phase three dimensional conformal treatment plan using CT image volume datasets with at least one gross tumour volume, one planning target volume and two organ at risk dose goals or constraints defined in the prescription; or</li> <li>(c) image fusion with a secondary image (CT, MRI or PET) volume dataset used to define target and organ at risk volumes in conjunction with and as specified in dosimetry for three dimensional conformal radiotherapy of level 1 complexity.</li> </ol> <p>All gross tumour targets, clinical targets, planning targets and organs at risk as defined in the prescription must be rendered as volumes. The organ at risk must be nominated as planning dose goals or constraints and the prescription must specify the organs at risk as dose goals or constraints. Dose volume histograms must be generated, approved and recorded with the plan. A CT image volume dataset must be used for the relevant region to be planned and treated. The CT images must be suitable for the generation of quality digitally reconstructed radiographic images</p> <p><b>Fee:</b> \$916.10 Benefit: 75% = \$687.10 85% = \$822.90</p>
<p>MBS item 15248</p> <p>RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - 1 field - treatment delivered to primary site (prostate)</p> <p><b>Fee:</b> \$63.05 Benefit: 75% = \$47.30 85% = \$53.60</p>

<p>MBS item 15263</p> <p>RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - 2 or more fields up to a maximum of 5 additional fields (rotational therapy being 3 fields) - treatment delivered to primary site (prostate)</p> <p>The <b>fee</b> for item 15248 plus for each field in excess of 1, an amount of \$40.15</p>
<p>MBS item 37217</p> <p>Prostate, implantation of radio-opaque fiducial markers into the prostate gland or prostate surgical bed, under ultrasound guidance, being an item associated with a service to which item 55603 applies</p> <p>Multiple Operation Rule (Anaes.)</p> <p><b>Fee:</b> \$146.20 Benefit: 75% = \$109.65 85% = \$124.30</p>
<p>MBS item 45566</p> <p>TISSUE EXPANSION not being a service to which item 45539 or 45542 applies - insertion of tissue expansion unit and all attendances for subsequent expansion injections</p> <p>Multiple Operation Rule (Anaes.)</p> <p><b>Fee:</b> \$1,132.50 Benefit: 75% = \$849.40</p>

Source: [www.mbsonline.gov.au](http://www.mbsonline.gov.au), based on Contracted Assessment 1525

**Table 7 Relevant MBS items for HDR-BT**

<p>Category 3 – THERAPEUTIC PROCEDURES</p>
<p>MBS item 37227</p> <p>PROSTATE, transperineal insertion of catheters into, for high dose rate brachytherapy using ultrasound guidance including any associated cystoscopy. The procedure must be performed at an approved site in association with a radiation oncologist, and be associated with a service to which item 15331 or 15332 applies.</p> <p>Multiple Operation Rule (Anaes.) (Anaes.)</p> <p><b>Fee:</b> \$598.15 Benefit: 75% = \$448.65 85% = \$508.45</p>
<p>MBS item 15331</p> <p>IMPLANTATION OF A SEALED RADIOACTIVE SOURCE (having a half-life of less than 115 days including iodine, gold, iridium or tantalum) to a site (including the tongue, mouth, salivary gland, axilla, subcutaneous sites), where the volume treated involves multiple planes but does not require surgical exposure and using manual afterloading techniques (Anaes.)</p> <p><b>Fee:</b> \$788.40 Benefit: 75% = \$591.30 85% = \$695.20</p>
<p>MBS item 15332</p> <p>MPLANTATION OF A SEALED RADIOACTIVE SOURCE (having a half-life of less than 115 days including iodine, gold, iridium or tantalum) to a site (including the tongue, mouth, salivary gland, axilla, subcutaneous sites), where the volume treated involves multiple planes but does not require surgical exposure and using automatic afterloading techniques (Anaes.)</p> <p><b>Fee:</b> \$788.40 Benefit: 75% = \$591.30 85% = \$695.20</p>

Source: [www.mbsonline.gov.au](http://www.mbsonline.gov.au), based on Contracted Assessment 1525

**Table 8 MBS item 37210, radical prostatectomy**

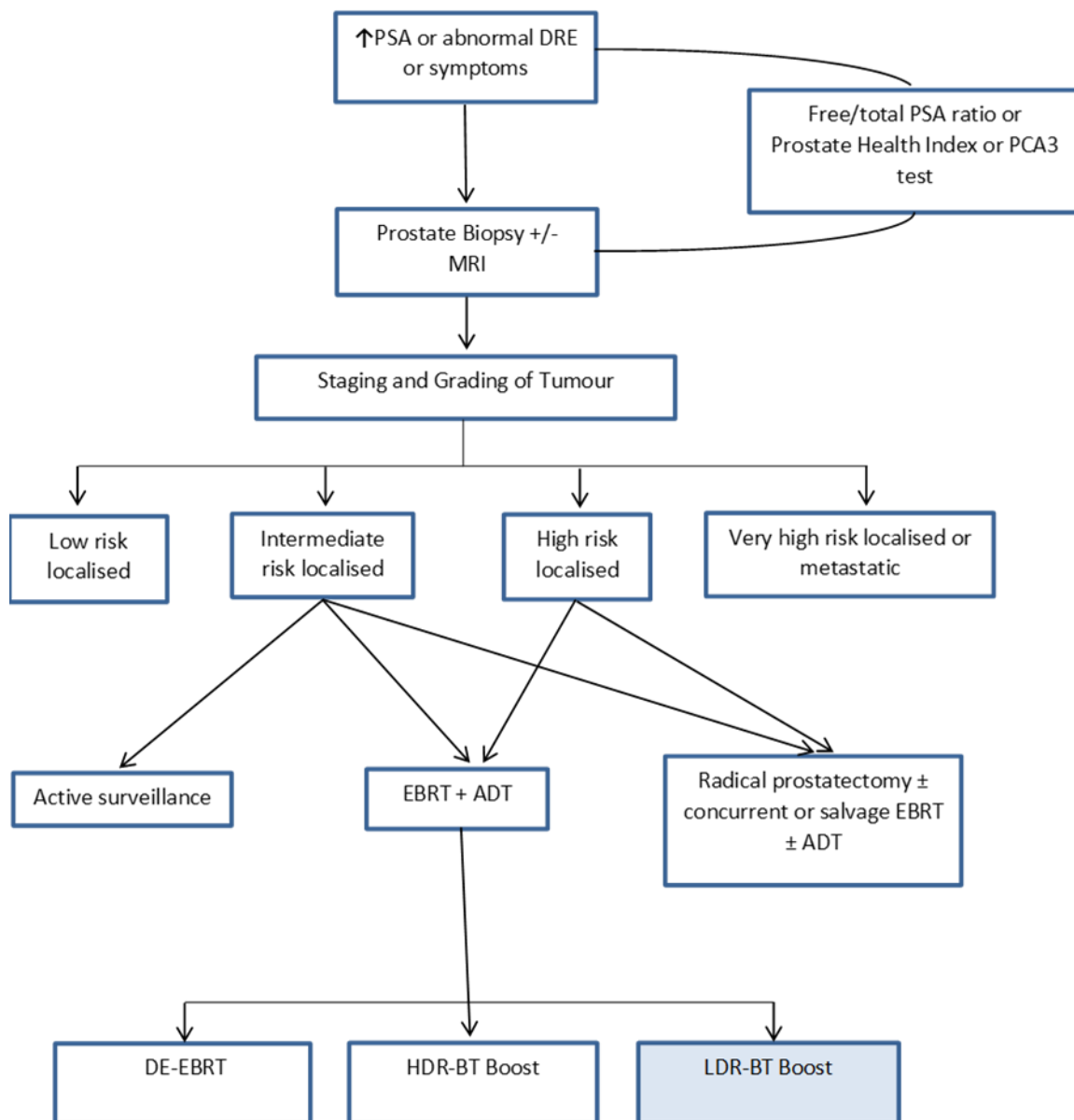
Category 3 – THERAPEUTIC PROCEDURES
MBS item 37210 Prostatectomy, radical, involving total excision of the prostate, sparing of nerves around the prostate (where clinically indicated) with or without bladder neck reconstruction, other than a service associated with a service to which item 30390, 30627, 35551, 36502 or 37375 applies Multiple Operation Rule (Anaes.) (Assist.)
Fee: 1,684.55 Benefit: 75% = \$1,263.45

Source: [www.mbsonline.gov.au](http://www.mbsonline.gov.au), based on Contracted Assessment 1525

The ADAR may have appropriately justified that radical prostatectomy was not a relevant comparator to EBRT + LDR-BT boost because the decision to undergo either surgical or radiation treatment occurs in a previous step within the clinical management algorithm (Figure 1). The ADAR argued that patient, tumour, treatment, and logistical factors will determine the option for either surgical or radiation therapy treatment for individual patients, and this is usually a personalised decision made in conjunction with the patient's treating physician<sup>7</sup>. Many patients are not suitable for surgery or will choose a non-surgical option based upon their individual circumstances.

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<sup>7</sup> Expert opinion from Dr David Malouf MBBS FRACS (UROL). Past President of the USANZ and past chair of Australian and New Zealand Association of Urological Surgeons. Currently Chair of the Awareness and Education Committee of Prostate Cancer Foundation of Australia



**Figure 1 Current and proposed (shaded) clinical algorithm**

Source: Figure 1 of the ADAR

## 8. Summary of public consultation input

Please refer to p4 of [1525 PSD](#) for the summary of public consultation feedback which was supportive of the previous application.

Consultation feedback for 1525.1 was received from two medical organisations but no consumers or consumer organisations:

- The Royal Australian and New Zealand College of Radiologists (RANZCR)
- The Urological Society of Australia and New Zealand (USANZ)

Both organisations were broadly supportive of having alternative treatment options available to patients in this population.

However, USANZ did not consider the evidence demonstrated that LDR brachytherapy was superior to current standard therapy and, as such, claims of superiority compared to standard care may be misleading.

RANZCR considered that the use of LDR brachytherapy should be confined to unit of sufficient skills and expertise in order to ensure the safe implementation of the service.

Both organisations suggested that LDR brachytherapy could be considered as an option for patients undergoing dose escalation for intermediate and high-risk prostate cancer.

## 9. Characteristics of the evidence base

The ADAR included two RCTs and eleven observational studies in the evidence base. However, after reviewing the included studies against the Ratified PICO criteria, only one RCT (ASCENDE-RT, with results reported across four papers, already included in the previous submission), and four observational studies were considered relevant to the assessment. Most studies were not relevant as they lacked an eligible comparator (this includes Tanaka et al. 2019<sup>8</sup> and Yamazaki et al. 2019<sup>9</sup>), The four observational studies provided comparative evidence for the safety and clinical effectiveness of EBRT + LDR-BT boost and EBRT + HDR-BT boost. Key features of the relevant evidence base are summarised in Table 9.

**Table 9 Key features of the included evidence**

References	N	Design/duration	Risk of bias	Patient population	Outcome(s)
<b>EBRT + LDR-BT boost vs DE-EBRT</b>					
ASCENDE-RT (Morris et al. 2017 <sup>10</sup> , Rodda et al. 2017a <sup>11</sup> , Rodda et al. 2017b <sup>12</sup> , Morris et al. 2018 <sup>13</sup> )	398	OL RCT	<i>Some concern</i>	Intermediate- and high-risk prostate cancer (proportions NR)	Survival (bPFS, OS) Safety HRQoL

<sup>8</sup> Tanaka, N., et al., Genitourinary toxicity after permanent iodine-125 seed implantation: The nationwide Japanese prostate cancer outcome study of permanent iodine-125 seed implantation (J-POPS). *Brachytherapy*, 2019. 18(4): p. 484-492.

<sup>9</sup> Yamazaki, H., et al., High-dose-rate brachytherapy monotherapy versus low-dose-rate brachytherapy with or without external beam radiotherapy for clinically localized prostate cancer. *Radiotherapy and Oncology*, 2019. 132: p. 162-170.

<sup>10</sup> Morris, W. J., Tyldesley, S., Rodda, S., Halperin, R., Pai, H., McKenzie, M., . . . Murray, N. (2017). Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer. *Int J Radiat Oncol Biol Phys*, 98(2), 275-285.

<sup>11</sup> Rodda, S., Tyldesley, S., Morris, W. J., Keyes, M., Halperin, R., Pai, H., . . . Murray, N. (2017a). ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer. *Int J Radiat Oncol Biol Phys*, 98(2), 286-295.

<sup>12</sup> Rodda, S., Morris, W. J., Hamm, J., & Duncan, G. (2017b). ASCENDE-RT: An Analysis of Health-Related Quality of Life for a Randomized Trial Comparing Low-Dose-Rate Brachytherapy Boost With Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer. *Int J Radiat Oncol Biol Phys*, 98(3), 581-589.

<sup>13</sup> Morris, W.J., Pickles, T. & Keyes, M. (2018). Using a surgical prostate-specific antigen threshold of >0.2 ng/mL to define biochemical failure for intermediate- and high-risk prostate cancer patients treated with definitive radiation therapy in the ASCENDE-RT randomized control trial. *Brachytherapy*, 17(6), 837-844.



References	N	Design/duration	Risk of bias	Patient population	Outcome(s)
<b>EBRT + LDR-BT boost vs EBRT + HDR-BT boost</b>					
Dhere et al. (2021) <sup>14</sup>	106	Secondary analysis of registry data Follow-up 18-20 months	<i>Serious risk</i>	Favourable intermediate risk (26%) Unfavourable intermediate risk (42%) High-risk (30%)	Functional outcomes Safety HRQoL
King et al. (2019) <sup>15</sup>	122,896	Retrospective analysis of the National Cancer Database	<i>Moderate risk</i>	Intermediate- and high-risk prostate cancer (proportions NR)	Survival (OS)
Parry et al. (2020) <sup>16</sup>	54,642	Retrospective case series	<i>Moderate risk for survival and safety</i> <i>Serious risk for functional outcomes</i>	Intermediate-, high-risk and locally advanced prostate cancer (proportions NR)	Mortality (PCS) Functional outcomes Safety
Slevin et al. (2020) <sup>17</sup>	287	Cohort study	<i>Serious risk</i>	Intermediate- and high-risk prostate cancer (proportions NR)	Survival (bPFS) Safety

bPFS = biochemical progression-free survival; HRQoL = health-related quality of life; NR = not reported; OL = open label; OS = overall survival; PCS = prostate-cancer specific; RCT = randomised controlled trial

## 10. Comparative safety

### *EBRT + LDR-BT boost versus DE-EBRT*

The safety outcomes of the ASCENDE-RT trial comparing DE-EBRT and EBRT + LDR-BT boost were reported in the previous submission; no new findings were reported in the resubmission.

Previously MSAC concluded that, relative to DE-EBRT, EBRT + LDR-BT boost has inferior safety in men with high-intermediate and high-risk prostate cancer. This conclusion remains unchanged as no new evidence was presented.

### *EBRT + LDR-BT boost versus EBRT + HDR-BT boost*

Relevant evidence for the gastrointestinal and genitourinary toxicity of EBRT + LDR-BT boost compared with EBRT + HDR-BT boost is summarised in Table 10.

Generally, EBRT + LDR-BT boost was associated with higher cumulative late toxicity incidence than EBRT + HDR-BT boost, however, the differences did not always reach statistical significance and depended on the choice of outcome measurement (i.e., severity). One study reported significantly worse gastrointestinal and genitourinary toxicity Grade  $\geq 2$  after EBRT + LDR-BT boost

<sup>14</sup> Dhere, V. R., Fischer-Valuck, B. W., Goyal, S., Liu, Y., Morgan, T. M., Ghavidel, E., . . . Patel, S. A. (2021). Patient-reported outcomes after Low-dose-rate versus High-dose-rate brachytherapy boost in combination with external beam radiation for intermediate and high risk prostate cancer. *Brachytherapy*, 20(6), 1130-1138.

<sup>15</sup> King, M. T., Yang, D. D., Muralidhar, V., Mahal, B., Butler, S., Devlin, P. M., . . . Orio, P. F., 3rd. (2019). A comparative analysis of overall survival between high-dose-rate and low-dose-rate brachytherapy boosts for unfavorable-risk prostate cancer. *Brachytherapy*, 18(2), 186-191.

<sup>16</sup> Parry, M. G., Nossiter, J., Sujenthiran, A., Cowling, T. E., Patel, R. N., Morris, M., . . . Aggarwal, A. (2021). Impact of High-Dose-Rate and Low-Dose-Rate Brachytherapy Boost on Toxicity, Functional and Cancer Outcomes in Patients Receiving External Beam Radiation Therapy for Prostate Cancer: A National Population-Based Study. *Int J Radiat Oncol Biol Phys*, 109(5), 1219-1229.

<sup>17</sup> Slevin, F., Rodda, S. L., Bownes, P., Murray, L., Bottomley, D., Wilkinson, C., . . . Henry, A. M. (2020). 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*, 20, 1-8.

compared with EBRT + HDR-BT boost. It should be noted that the studies were likely underpowered for the safety outcomes. Additionally, all three studies had applicability concerns, including a broader population than the Ratified PICO 1525, and were at risk of bias.

Overall, EBRT + LDR-BT boost may have inferior safety compared with EBRT + HDR-BT boost.

**Table 10 Results of safety across the studies**

Study ID	Risk of bias	Intervention EBRT + LDR-BT boost	Comparator EBRT + HDR-BT boost	Relative difference
<b>Gastrointestinal toxicity</b>				
Parry et al. (2020)	Moderate	5-year cumulative incidence (grade ≥2): 32.3% (95% CI 26.9-37.2)	5-year cumulative incidence (grade ≥2): 16.7% (95% CI 15.2-18.2)	<b>sHR*=2.08 (95% CI 1.43-2.94)</b>
		5-year cumulative incidence (severe, grade ≥3): 5.1% (95% CI 2.9-8.2)	5-year cumulative incidence (severe, grade ≥3): 1.8% (95% CI 1.4-2.8)	p-value NR
Dhere et al. (2021)	Serious	Late toxicity (grade ≥2) at years 1-3 post-treatment: 2.6%	Late toxicity (grade ≥2) at years 1-3 post-treatment: 2.0%	p=1.00
Slevin et al. (2020)	Serious	5-year cumulative incidence (severe, grade ≥3): 5%	5-year cumulative incidence (severe, grade ≥3): 1%	p=0.13
<b>Genitourinary toxicity</b>				
Parry et al. (2020)	Moderate	5-year cumulative incidence (grade ≥2): 15.8% (95% CI 11.9-20.2)	5-year cumulative incidence (grade ≥2): 16.6 (95% CI 15.1-18.2)	NS
		5-year cumulative incidence (severe, grade ≥3): 11.1% (95% CI 7.8-15.1)	5-year cumulative incidence (severe, grade ≥3): 9.0% (95% CI 7.9-10.2)	p-value NR
Dhere et al. (2021)	Serious	Late toxicity (grade ≥2) at years 1-3 post-treatment: 67.5%	Late toxicity (grade ≥2) at years 1-3 post-treatment: 42.9%	<b>p&lt;0.001</b>
		Late toxicity (severe, grade ≥3) at years 1-3 post-treatment: 12.5%	Late toxicity (severe, grade ≥3) at years 1-3 post-treatment: 0%	p-value NR
Slevin et al. (2020)	Serious	5-year cumulative incidence (severe, grade ≥3): 8%	5-year cumulative incidence (severe, grade ≥3): 4%	p=0.17

\* HR was inverted for purposes of this table using 1/HR

CI = confidence interval; EBRT = external beam radiation therapy; HDR-BT = high dose-rate brachytherapy; LDR-BT = low dose-rate brachytherapy; NR = not reported; NS = not significant; sHR = subdistribution hazard ratio

## 11. Comparative effectiveness

### *EBRT + LDR-BT boost versus DE-EBRT*

The clinical effectiveness outcomes of the ASCENDE-RT trial comparing DE-EBRT and EBRT + LDR-BT boost were reported in the previous submission (see pp7-9 of [1525 PSD](#)); No new relevant findings were provided in the resubmission. Of note the updated analysis of the ASCENDE-RT trial survival outcomes was recently published (Oh J, et al. (2022)) after the ADAR was submitted. The authors concluded that although men randomised to the LDR-PB boost arm continue to experience a large advantage in TTP compared to patients randomized to the DE-EBRT arm, the trial was not powered to detect differences in overall survival (OS), metastasis free

survival (MFS) and prostate cancer specific survival (PCSS) and none were detected at 10-year median follow-up.<sup>18</sup>

Thus, relative to DE-EBRT, EBRT + LDR-BT boost has superior effectiveness for biochemical progression-free survival (b-PFS). The effectiveness for OS, MFS and PCSS remains uncertain as the ASCENDE-RT was underpowered for these outcomes and because no new evidence for the comparison with DE-EBRT was provided in the resubmission.

*EBRT + LDR-BT boost versus EBRT + HDR-BT boost*

Relevant evidence for the clinical effectiveness of EBRT + LDR-BT boost compared with EBRT + HDR-BT boost is summarised in

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<sup>18</sup> Oh J, et al.,(2022). An Updated Analysis of the Survival Endpoints of ASCENDE-RT. Int J Radiat Oncol Biol Phys. 2022 Dec 15:S0360-3016(22)03518-0. doi: 10.1016/j.ijrobp.2022.11.005. Epub ahead of print. PMID: 36528488

Table 11.

One small cohort study reported better 5-year biochemical progression-free survival (bPFS) after LDR-BT boost compared with HDR-BT boost. Two studies reporting on prostate cancer-specific mortality (Parr et al. 2020) and overall survival (King et al. 2019) did not find any differences between the two treatments. Both studies had large patient populations, so they are likely to be powered for detecting differences in these outcomes. Limitations of these studies should be considered when interpreting the data (e.g. selection bias, unknown details of co-treatments and dosing regimens).

Two studies reported functional outcomes (such as bowel function, urinary function, and erectile function) results. Bowel function and urinary function scores were worse in patients undergoing LDR-BT boost compared with the HDR-BT boost group in one study, but no difference was observed in the second study. One study reported health-related quality of life, the scores were worse for patients undergoing LDR-BT boost than in the patients undergoing HDR-BT boost (up to 3 years post treatment).

It should be noted that all four studies had applicability concerns, including a broader population than the Ratified PICO 1525, and were at risk of bias.

Overall, EBRT + LDR-BT boost may have superior effectiveness for b-PFS (surrogate outcome), and noninferior effectiveness for OS and PCSS compared with EBRT + HDR-BT boost.

**Table 11 Results of clinical effectiveness across the studies**

Study ID Outcome	Risk of bias	Intervention EBRT + LDR-BT boost	Comparator EBRT + HDR-BT boost	Relative difference
<b>bPFS</b>				
Slevin et al. (2020)	Serious	3-year bPFS: 94.1% 5-year bPFS: 90.5%	3-year bPFS: 93.7% 5-year bPFS: 77.6%	5-year bPFS: <b>p=0.01</b> <b>HR=0.43 (95% CI 0.25-0.89)</b>
<b>Prostate cancer-specific mortality</b>				
Parry et al. (2020)	Moderate	5-year cumulative mortality: 2.7% (95% CI 1.0-5.9)	5-year cumulative mortality: 2.7% (95% CI 2.0-3.5)	NS
<b>OS</b>				
King et al. (2019)	Moderate	NR	NR	aHR*=0.97 (95% CI 0.90-1.04) aHR* (IPTW)=0.99 (95% CI 0.91-1.08)
<b>Functional outcomes</b>				
Parry et al. (2020) EPIC-26	Serious	Bowel: M=77.3	M=85.8	<b>SS, CS</b>
		Urinary incontinence: M=87.0	M=86.0	NS
		Urinary irritation/obstruction: M=72.2	M=78.9	NS
Dhere et al. (2021) EPIC-CP	Serious	Bowel:		p=0.60; NCS
		Urinary incontinence:		p=0.10; NCS
		Urinary irritation:		<b>2-18 months post-treatment: p=0.002; CS</b> 18-30 months post-treatment: NCS
		Erectile dysfunction:		p=0.88
<b>HRQoL</b>				
Dhere et al. (2021) IPSS	Serious			LDR-BT boost worse than HDR-BT boost; <b>p=0.003</b>

\*HR was inverted for purposes of this table using 1/HR

aHR = adjusted hazard ratio; bPFS = biochemical progression-free survival; CI = confidence interval; CS = clinically significant; EBRT = external beam radiation therapy; EPIC-26 = Expanded Prostate Cancer Index Composite 26-item version; EPIC-CP = Expanded Prostate Cancer Index Composite for Clinical Practice; HDR-BT = high dose-rate brachytherapy; HR = hazard ratio; HRQoL = health-related quality of life; IPSS = International Prostate Symptom Score; IPTW = inverse probability of treatment weighting; LDR-BT = low dose-rate brachytherapy; NCS = not clinically significant; NR = not reported; NS = not significant; SS = statistically significant

### Clinical claim

#### *EBRT + LDR-BT boost versus DE-EBRT*

The ADAR proposed that EBRT + LDR-BT boost has superior effectiveness and inferior safety compared with DE-EBRT.

The ADAR did not present any new relevant effectiveness data for the comparison of EBRT + LDR-BT boost with DE-EBRT. MSAC's previously concluded that EBRT+LDR-BT boost has superior effectiveness for biochemical progression-free survival. However, there was no difference in overall survival, metastasis-free survival or prostate cancer-specific survival, and the study was

not powered or long enough to assess survival outcomes. Thus, MSAC concluded that EBRT+LDR-BT boost has uncertain effectiveness for overall survival, metastasis-free survival or prostate cancer-specific survival, relative to DE-EBRT.

#### *EBRT + LDR-BT boost versus EBRT + HDR-BT boost*

The ADAR proposed that EBRT + LDR-BT boost has similar effectiveness and uncertain safety compared to EBRT + HDR-BT boost.

The interpretation of the clinical claim is that EBRT + LDR-BT boost has noninferior effectiveness and inferior safety compared with EBRT + HDR-BT boost. Note, this is inconsistent with the ADAR proposing that EBRT + LDR-BT boost has similar effectiveness and uncertain safety compared to EBRT + HDR-BT boost. One small cohort study showed some improvement in b-PFS in EBRT + LDR-BT over EBRT + HDR-BT at 5 years but this evidence was considered inadequate to claim superiority for b-PFS.

## **12. Other relevant information**

The ADAR made an argument for equitable access to brachytherapy services highlighting the significant infrastructure required to deliver HDR brachytherapy (currently available on MBS for intermediate and high-risk prostate cancer) which would not be needed for LDR brachytherapy since it can be delivered in any setting licenced to use low dose rate sealed radioactive materials.

## **13. Key issues from ESC to MSAC**

### **Main issues for MSAC consideration**

#### **Clinical issues:**

- Clinical claim for EBRT+LDR-BT boost vs. DE-EBRT – longer-term follow-up data from the ASCENDE-RT pivotal trial continues to suggest that compared with DE-EBRT, EBRT+LDR-BT boost has inferior safety, superior effectiveness for bPFS and noninferior effectiveness for other survival endpoints (OS, MFS and PCSS) – but that uncertainty remains because the trial was underpowered to detect differences in survival endpoints.
- Clinical claim for EBRT+LDR-BT boost vs. EBRT+HDR-BT boost – the new evidence in the resubmission is limited but this low-quality evidence suggests that EBRT+LDR-BT boost has likely noninferior safety and effectiveness.
- Primary outcome justified to be bPFS– the applicant’s argument regarding the importance of b-PFS was considered; however, that this doesn’t change the conclusion of the study results showing that improved PSA control does not translate to any other disease endpoint improvement.
- Proposed MBS items – the current item descriptors are very specific about the appropriate population (the item descriptor does not specify treating all intermediate-risk patients), and are consistent with the pivotal ASCENDE-RT trial and originally agreed PICO population. Furthermore, using NCCN-specific risk groups could result in an outdated item descriptor as guidelines are continually updated and can be difficult to retrospectively apply.
- Radical prostatectomy is excluded as a relevant comparator.

## ESC discussion

ESC noted that this application from BXTAccelyon Australia is requesting Medicare Benefits Schedule (MBS) listing of low dose-rate brachytherapy (LDR-BT), for intermediate- and high-risk prostate cancer. LDR-BT is used as a boost following external beam radiotherapy (EBRT) to deliver a higher dose of radiation to the prostate, which is supported in current international prostate cancer consensus guidelines. LDR-BT delivered as monotherapy is currently listed on the MBS for low-risk prostate cancer (MBS item 37220).

ESC noted that MSAC previously considered LDR-BT for intermediate- and high-risk prostate cancer groups at its [August 2019 meeting](#). MSAC did not support public funding of LDR-BT boost (following EBRT, i.e. EBRT+LDR-BT boost) because comparative safety and effectiveness were too uncertain relative to dose-escalated EBRT (DE-EBRT) and no evidence was provided relative to high dose-rate (HDR) brachytherapy boost following EBRT or radical prostatectomy (RP). MSAC noted evidence from the pivotal ASCENDE trial suggested EBRT+LDR-BT boost has superior effectiveness for biochemical progression-free survival (bPFS) compared with DE-EBRT. However, there was no difference in overall survival (OS), metastasis-free survival (MFS) or prostate cancer-specific survival (PCSS), but this conclusion was uncertain as the trial was not powered or long enough to assess survival outcomes. MSAC also concluded that EBRT+ LDR-BT boost had inferior safety relative to DE-EBRT.

In August 2019, MSAC advised that a future resubmission should include:

- comparative safety data based on up-to-date practice, ideally for all comparators
- effectiveness data for EBRT+HDR-BT and RP
- updated cost-effectiveness analyses to reflect any newly relevant comparative safety and effectiveness data.

ESC noted that the applicant has chosen for this resubmission to undergo a two-stage assessment report pathway – an option available to applicants as per the [MSAC Process Framework](#). The applicant has provided evidence for safety and clinical effectiveness that has become available since the previous MSAC consideration in 2019. If this first stage is successful, the applicant will submit an economic evaluation and financial impact analysis in the second stage.

ESC noted that the two proposed item descriptors – one for a radiation oncologist and one for a urologist – were modified from the previous submission to include revised histological grading (the International Society of Urological Pathway [ISUP] Grade Group system).

ESC recalled from the previous submission, ESC had considered that it may be more appropriate to define the eligible population using National Comprehensive Cancer Network (NCCN) risk definitions to be consistent with international classification systems. For this resubmission, ESC noted the commentary considered that the revised population is not consistent with the current NCCN Prostate Cancer Guidelines, which stratifies the intermediate-risk category into “favourable” (low-intermediate risk) and “unfavourable” (high-intermediate risk) subgroups. According to the current NCCN guidelines, only the “unfavourable” subgroup would be eligible for EBRT+LDR-BT boost. The commentary stated that it may be inappropriate to include all intermediate-risk patients as it would lead to favourable patients being overtreated. However, ESC considered that the current item descriptors are very specific about the appropriate population (the item descriptor does not specify treating all intermediate-risk patients), and are consistent with the pivotal ASCENDE-RT trial and PICO population. Furthermore, ESC considered it does agree using international staging/risk groupings are important, but using NCCN-specific risk groups in this item application could result in an outdated item descriptor as the guidelines are continually updated –the use of any grading system is potentially problematic for the same reasons (e.g. including the Gleason score and Grade group as proposed in the MBS items), and

can be difficult to retrospectively apply. Furthermore, ESC noted the issue that there are 'different Gleason grades' as different organisations use definitions that are in conflict with each other. To that end, ESC suggested that the "current" World Health Organisation (WHO) ['Blue Book'] classification system of the urinary and male genital tumours<sup>19</sup> could be considered as the grading system used in the item descriptors. The WHO 2022 system is current, and it is expected this will be updated every 3 to 6 years. ESC also noted that this could be an issue more broadly across existing MBS items for prostate cancer which may use outdated grading systems which may need to be reviewed (e.g. MBS item 37220 uses the Gleason score).

ESC noted that PASC had previously nominated RP as an additional comparator in the Ratified PICO confirmation. However, the applicant argued that RP is not a relevant comparator as the choice of treatment is either surgery or radiation therapy, and within radiation therapy, the options are EBRT alone, brachytherapy alone (i.e. monotherapy), or EBRT + brachytherapy (LDR-BT or HDR-BT boost). ESC agreed that RP should be excluded as a comparator.

ESC noted that no public consultation feedback was received for this resubmission. ESC noted that there is a lack of high-quality data on patient experiences and outcomes beyond survival for prostate cancer, despite it being a non-rare disease. ESC considered real world data on patient experience in this cohort would be useful to collect in future trials.

ESC noted that the resubmission identified 16 studies, but that the commentary deemed only one randomised controlled trial (RCT) – the ASCENDE-RT, included in the previous submission – and four observational studies to be relevant to the assessment, as the other studies did not include an eligible comparator. ESC noted that the pre-ESC response did not dispute these exclusions.

No new evidence was reported in the resubmission for comparative safety and effectiveness of EBRT+LDR-BT boost vs. DE-EBRT. ESC noted the commentary included updated results for survival outcomes from the ASCENDE-RT trial over a median follow-up of 10 years (compared with 6.5 years from the previous submission). These longer-term results showed that EBRT+LDR-BT had superior time to treatment progression, but there was no difference in OS or time to distant metastasis.

ESC noted that the four retrospective studies informing safety and clinical effectiveness of EBRT+LDR-BT boost vs EBRT+HDR-BT boost had a moderate to serious risk of bias, and have issues around patient selection, missing data, outcome measurements and a lack of risk stratification, making it difficult to generalise the findings to the population of interest. ESC noted that the pre-ESC response agreed, as the most recent studies available are already small in terms of patient numbers and that further risk stratification is unlikely to be able to demonstrate statistically significant differences in outcomes. ESC also noted that the pre-ESC response highlighted that the ASCENDE-RT trial will continue to be the largest trial ever performed in this patient population. The ASCENDE-RT trial remains the best available evidence in this population.

In terms of safety compared with EBRT+HDR-BT boost, ESC noted that EBRT+LDR-BT boost had a greater number of genitourinary toxicity events, but there was no difference in severe ( $\geq$ ) Grade 3 toxicity. Additionally, differences in toxicity between the intervention and comparator were most prominent in the short term, but resolved with long-term follow-up (see Table 10). However, ESC noted that strong conclusions could not be drawn as there was a serious risk of bias with retrospective studies, and that these studies were likely underpowered for the safety outcomes.

In terms of clinical effectiveness compared with EBRT+HDR-BT boost, ESC noted that very low quality evidence suggested that EBRT+LDR-BT boost had superior effectiveness in terms of bPFS

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<sup>19</sup> Netto et al. The 2022 World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs-Part B: Prostate and Urinary Tract Tumors. *Eur Urol.* 2022 Nov;82(5):469-482. doi: 10.1016/j.eururo.2022.07.002.



but no differences for other survival outcomes. In terms of functional outcomes and health-related quality of life, ESC noted that there were some differences between the intervention and comparator groups, but some of these resolved over longer term follow-up. For example, there was no difference in Expanded Prostate Cancer Index Composite (EPIC) score, but urinary incontinence score/urinary irritative symptoms were worse after LDR-BT boost than after HDR-BT boost for up to 18 months after treatment ( $p=0.002$ , the difference reached both statistical and clinical significance), but there were no meaningful differences over 18-30 months (see Table 11).

ESC noted that the applicant's claims in the resubmission is that EBRT+LDR-BT boost has superior effectiveness and inferior safety compared to DE-EBRT, and similar effectiveness and uncertain safety compared to EBRT+HDR-BT boost. ESC considered that the longer term results from the ASCENDE-RT trial continues to suggest that compared with DE-EBRT, EBRT+LDR-BT boost has inferior safety, superior effectiveness for bPFS and noninferior effectiveness for other survival endpoints – but uncertainty remains because the trial was underpowered to assess differences in survival endpoints. Compared with EBRT+HDR-BT boost, ESC considered that, based on the limited evidence, EBRT+LDR-BT boost has likely noninferior effectiveness and noninferior safety.

ESC noted that the applicant has placed importance on bPFS as an outcome measure. In the resubmission the applicant concluded that, because few trials were powered for survival in the intermediate-high risk groups or reported OS, survival outcomes in this population are impractical and rarely demonstrated. The applicant also provided a systematic review (Van den Broeck et al. 2019<sup>20</sup>) showing biochemical (prostate-specific antigen, or PSA) recurrence had a strong relationship with cancer-specific survival and occurrence of distant metastases. However, the commentary noted that the relationship between biochemical recurrence and OS was less clear; OS difference was noted in subgroups, but these were a mix of patients treated with surgery and radiation therapy. ESC noted that in the pre-ESC response, the applicant stated that it is difficult to demonstrate OS benefit in early-stage prostate cancer trials given that prostate cancer is an indolent disease. ESC acknowledged this issue but considered that the arguments provided by the applicant do not override the conclusions from the ASCENDE trial: with long term follow-up, improved PSA control did not translate to any other disease endpoint improvement.

ESC considered that because the resubmission did not include any new clinical data for EBRT+LDR-BT boost vs. DE-EBRT and that longer-term results from the ASCENDE-RT trial (included in the commentary) do not appear to change the interpretation of the clinical claim, that an updated economic analysis for this comparator was not required in the second stage of the assessment pathway (i.e. the previous economic results would apply). ESC advised that if this application proceeds to the second stage of the assessment pathway, MSAC may wish to consider whether an updated economic evaluation should only be provided for EBRT+LDR-BT boost vs. EBRT+HDR-BT boost.

ESC noted that more broadly the use of brachytherapy for prostate cancer is declining and that contemporary standard practice in radiation therapy uses external beam radiotherapy with advanced techniques such as intensity modulated radiation therapy that allows higher doses to be delivered over shorter durations (previous 8 weeks decreasing to 4 weeks) for treating localised (non-metastatic) prostate cancer. Also, newer advanced techniques such as stereotactic radiotherapy for prostate cancer can deliver treatment over 5 days. Therefore, there are increasing non-brachytherapy radiotherapy options for prostate cancer patients that are non-invasive and comparatively convenient. ESC also noted there were no new data on the risk of

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<sup>20</sup> Van den Broeck T et al. (2019). [Prognostic value of biochemical recurrence following treatment with curative intent for prostate cancer: a systematic review](#). *European Urology* 75(6):967-987.

development of secondary cancers in this cohort over the longer term, but that as both the intervention and comparator used radiotherapy that this risk would apply to both groups.

## **14. Applicant comments on MSAC's Public Summary Document**

The applicant is disappointed by the outcome of this application that Australian men are still being restricted access to a medical treatment that has been the standard of care in most major developed countries following the publication of the ASCENDE-RT study. This is acknowledged by expert groups to be the largest and most robust clinical trial in this patient population and yet MSAC do not consider this evidence as significant and continue to downgrade the conclusions of this research and the follow-up evidence this population continues to produce. The applicant disagrees with the MSAC's advice and considers it contradicts all the internationally well renowned, professional and public bodies (including NICE, NCCN, ABS). It is the applicant's opinion that while the evidence available for LDR brachytherapy is more extensive and superior to other therapies that are included on the MBS, the applicant has been asked to supply an unrealistic and unattainable level of evidence for LDR Brachytherapy which is not available for therapies that currently receive public funding.

## **15. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#).