Implantation of fiducial markers into the prostate gland or prostate surgical bed for external beam radiotherapy

June 2013

MSAC application no 1147

Assessment Report

Contracted Assessment Report for Application 1147 - Implantation of fiducial markers into the prostate gland or prostate surgical bed for external beam radiotherapy

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This report is a contracted technical report for use by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared for the MSAC by Elizabeth Seil, Sally Wortley and Briony Jack from the NHMRC Clinical Trials Centre with the assistance of the MSAC Health Expert Standing Panel. The report was commissioned by the Department of Health and Ageing on behalf of MSAC. It was edited by Louise Scahill of WordFix.

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Abbreviations

3D-CRT	3-dimensional conformal radiotherapy
AE	adverse event
ADT	androgen deprivation therapy
AACR	Australasian Association of Cancer Registries
AIHW	Australian Institute of Health and Welfare
ANROTAT	Assessment of New Radiation Oncology Treatments and Technologies
ANZAUS	Australian and New Zealand Association of Urological Surgeons
ANZCTR	Australian and New Zealand Clinical Trials Registry
ARTG	Australian Register of Therapeutic Goods
ASTRO	American Society for Therapeutic Radiology and Oncology
ASI	age-standardised incidence
ASM	age-standardised mortality
bNED	biochemical no evidence of disease
CCA	Cancer Council Australia
CT	computerised tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTV	clinical target volume
DAP	Decision Analytic Protocol
DoHA	Department of Health and Ageing
EBRT	external beam radiation therapy
EMSN	Extended Medicare Safety Net
EORTC	European Organisation for Research and Treatment of Cancer
EPI	electronic portal image
FM	fiducial marker
FROGG	Faculty of Radiation Oncology Genito-Urinary Group
FU	follow-up
GI	gastrointestinal
GU	genitourinary
Gy	Gray
HD	high-dose
HDRBT	high-dose rate brachytherapy
HESP	Health Expert Standing Panel
HR-QoL	health-related quality of life
HTA	health technology assessment
IG	image-guided or image guidance
IGRT	image-guided radiotherapy
IMRT	intensity-modulated radiotherapy
IPSS	International Prostate Symptom Score
kV	kilovoltage
LDRBT	low-dose rate brachytherapy
MBS	Medicare Benefits Schedule
MRI	magnetic resonance imaging
MV	megavoltage
MSAC	Medical Services Advisory Committee

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute (NCI)
NHMRC	National Health and Medical Research Council
NR	not reported
PASC	Protocol Advisory Sub-committee
PBS	Pharmaceutical Benefits Scheme
PICO	patient population, intervention, comparator and outcome
PSA	prostate-specific antigen
PTV	planning target volume
QoL	quality of life
RANZCR	Royal Australian and New Zealand College of Radiologists
RCT	randomised controlled trial
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group
TGA	Therapeutic Goods Administration
TROG	Trans-Tasman Radiation Oncology Group
TRUS	trans-rectal ultrasound
VAS	visual analogue scale

Executive summary

The Medical Services Advisory Committee (MSAC) has reviewed the implantation of fiducial markers (FMs) into the prostate gland or prostate surgical bed for external beam radiotherapy (EBRT) for prostate cancer. The MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to assessments, based on reviews of the scientific literature and other information sources, including clinical expertise. It is a multidisciplinary expert body, comprising members drawn from such disciplines as: diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

The Health Expert Standing Panel (HESP) has been established as a panel of the MSAC and is a pool of experts collated from various medical fields who are nominated by their associated professional body or by applicants. HESP members are engaged to provide practical, professional advice to evaluators which directly relates to each application and the service being proposed for the MBS. HESP members are not members of either the MSAC or its sub-committees like the Evaluation Sub-committee (ESC) or the Protocol Advisory Sub-committee (PASC). Their role is limited to providing input and guidance to the assessment groups to ensure that the pathway is clinically relevant and takes into account consumer interests. HESP members' advice is to inform the deliberations MSAC presents to the Minister. A list of the HESP members for the current assessment is listed in Appendix A.

This report summarises the assessment of the current evidence for the implantation of FMs into the prostate gland or prostate surgical bed for EBRT for prostate cancer.

Purpose of Application

- Date submitted and by whom
- Description of the proposed medical service
- Is it a new intervention or an extension of use for a current intervention?
- Medical condition(s) being addressed by the proposed intervention

An application requesting the MBS listing of implantation of fiducial markers (FMs) into the prostate gland or prostate surgical bed for radiotherapy (RT) was received from the Royal Australian and New Zealand College of Radiologists (RANZCR) and the Australian and New Zealand Association of Urological Surgeons (ANZAUS) by the Department of Health and Ageing (DoHA) in April 2010.

The proposed medical service involves the implantation of radio-opaque, sterile FMs into the prostate to serve as fiducial reference points during RT in patients with prostate cancer. Prior to RT treatment planning and delivery, FMs (usually 3-4) are implanted into the prostate using a trans-rectal or trans-perineal needle insertion approach under ultrasound guidance. Some form of anaesthesia (usually local) may also be used during the procedure. It may be provided in an ambulatory care setting or in a day surgery facility. Healthcare professionals involved in providing the service may include radiologists, urologists or radiation oncologists skilled in the use of trans-rectal ultrasound, anaesthetists or theatre staff as required. The proposed service is

not a therapeutic medical service on its own but rather is used as part of the delivery of dose-escalated image-guided radiotherapy (IGRT).

The proposed medical service is intended primarily for patients who undergo EBRT for the local control of prostate cancer. The current standard for EBRT in Australia is 3-dimensional conformal radiotherapy (3D-CRT) with intensity-modulated radiotherapy (IMRT) as an emerging technique. EBRT may be delivered alone or in combination with high-dose rate brachytherapy (HDRBT) as a boost. The Final Decision Analytic Protocol (DAP) for the current assessment also includes a smaller, secondary target population: prostate cancer patients who undergo adjuvant or salvage EBRT after radical prostatectomy. The overall target population for the proposed medical service is therefore: patients with prostate cancer, scheduled for EBRT (definitive or post-prostatectomy, using 3D-CRT or IMRT, with or without dose escalation or boost).

The proposed medical service is currently covered under an interim funded MBS item 37217, introduced on 1 July 2011 to enable collection of data on usage to inform the current assessment. The service had previously been claimed under another MBS item (37218) which referred to 'PROSTATE, needle biopsy of, or injection into (Anaes.)' without specifying what was injected or for what purpose. This was prohibited by the DoHA from 1 January 2010.

Proposal for public funding

- Applicant's MBS item descriptor and table of the MBS Schedule location
- Any restrictions to patients with specific clinical indications? No
- Any restrictions to patients due to prior interventions? No
- Identify any specialty groups who would perform the service delivering the intervention; and, if relevant, whether the proposed intervention should be restricted to any particular specialists or credentialed practitioners.

Table ES.1 presents the proposed MBS item descriptor for the proposed service.

Table ES.1 Proposed MBS item descriptor

Category 3 – THERAPEUTIC PROCEDURES
MBS [item number XXXXX] Prostate, implantation of radio-opaque fiducial markers into the prostate gland or prostate surgical bed to assist in the delivery of external-beam radiotherapy. The procedure must be performed by a urologist or a radiation oncologist at an approved site, and be associated with a service to which item 55603 applies. Multiple Services Rule (Anaes.) **Fee**: $138.30 **Benefit**: 75% = $103.75 85% = $117.60

Abbreviations: MBS = Medicare Benefits Schedule

For MBS notes on Multiple Services Rule, see Appendix E.

Proposed fee is based on the current schedule fee for MBS item 37217, as on 1 May 2013.

Source: Proposed item descriptor in Table 4, p. 11 in the Final DAP; MBS Online [accessed 1 May 2013]

The proposed item descriptor is essentially the same as that approved by the PASC in the Final DAP, except the proposed addition of the following qualifying statement:

> "The procedure must be performed by a urologist or a radiation oncologist at an approved site, and be associated with a service to which item 55603 applies."

The reasoning for the proposed addition is that the proposed procedure will be performed by a urologist or a radiation oncologist skilled in the use of trans-rectal ultrasound (as stated in p.14 of the Application), and that other similar implantation procedures also have similar item description (eg implantation of radioactive seeds for brachytherapy for MBS item 37220). **The MSAC may wish to consider whether the proposed inclusion is appropriate.**

The proposed schedule fee is the current schedule fee for the interim MBS item 37217, introduced on 1 July 2011 to cover the proposed medical service pending outcome of the current assessment (see Section A.3.2 below). Current MBS explanatory notes on multiple services rule are presented in Appendix E.

Current arrangements for public reimbursement

The proposed medical service is currently covered under interim-funded MBS item 37217 (Table ES.2) which was introduced on 1 July 2011 to enable collection of data on usage to inform the current assessment. Prior to that, the service was claimed under another MBS item (37218) which referred to 'PROSTATE, needle biopsy of, or injection into (Anaes.)' without specifying what was injected or for what purpose. This claiming practice was prohibited by the DoHA from 1 January 2010. With the introduction of the interim item, MBS item 37218 has now been amended to specifically exclude the implantation of radio-opaque markers (Table A.5).

Table ES.2 Current interim MBS item 37217 (from 1 July 2011)

Category 3 – THERAPEUTIC PROCEDURES
MBS 37217*   Prostate, implantation of gold fiducial markers into the prostate gland or prostate surgical bed   Multiple Services Rule   **Fee**: $138.30 **Benefit**: 75% = $103.75 85% = $117.60   (See para T8.54 of explanatory notes to this Category)
T8.54 Gold Fiducial Markers into the Prostate - (item 37217)   Item 37217 is for the insertion of gold fiducial markers into the prostate or prostate surgical bed as markers for radiotherapy. The service cannot be claimed under item 37218 or any other surgical item.   This item is introduced into the Schedule on an interim basis pending the outcome of an evaluation being undertaken by the Medical Services Advisory Committee (MSAC).   Further information on the review of this service is available from the MSAC Secretariat.

* Item Start Date: 1 July 2011; Description Start Date: 1 July 2011; Schedule Fee Start Date: 1 November 2012

For MBS notes on Multiple Services Rule, see Appendix E.

Source: MBS Online [accessed 1 May 2013]

Prerequisites to implementation of any funding advice

- If relevant, whether the intervention is required to be TGA approved?
- Whether the intervention has other prerequisites, e.g., a quality assurance program for a pathology test or a licensing program for an imaging technology.

The proposed service involves the use of a medical device that is not exempt from the regulatory requirements of the *Therapeutic Goods Act 1989* (Section 2.5, the Application).

The medical device, 'Nucletron Pty Limited – Marker, lesion localization, implantable; Australian Register of Therapeutic Goods (ARTG) Entry 143069' mentioned in the Application (Section 2.5) can no longer be located at the time of this assessment and the reason is not clear.

A number of implantable medical devices under the same product name of 'marker, lesion localization, implantable' relevant to the current assessment are identified in the ARTG (Appendix D). The list may not be exhaustive.

The Application also stated that while commercial packs of sterilised pre-loaded needles are available, many public hospitals with a radiation oncology department produce their own material (Section 6.3, the Application).

Background

- Any previous MSAC or related review(s)?
- If interim funded – dates of first review, interim listing, and due to cease/required to be reviewed.
- Any decision to assess more than one related intervention? [Note that an assessment of more than one related intervention might result in more than one PSD (and associated "synthesis template"), especially if this results in a need to compare across more than one set of clinical data.]

Table ES.3 presents a summary of the applications relevant to the current assessment.

Table ES.3 Other applications/reviews relevant to the current assessment

No	Application title	Progress
1319	The use of Image Guided Radiation Therapy (IGRT) in the treatment of cancer	2nd PASC in December 2012, Final DAP released
1211	Volumetric Modulated Arc Therapy for Lung, Prostate, breast and other extra-cranial cancers such as spine, kidney, liver and pancreatic	2nd PASC in December 2012, Final DAP released
1182	The use of Intensity Modulated Radiation Therapy (IMRT)	2nd PASC in December 2012, Final DAP released
1158	Robotic image-guided stereotactic precise beam radiosurgery and radiotherapy for lung cancer and prostate cancer	Completed, MSAC appraisal in December 2012, MSAC minutes released
1089.1	Review of Interim Funded Service: Brachytherapy for the Treatment of Prostate Cancer	Completed, considered by the MSAC in December 2010, MBS item 15338 implemented

Abbreviations: BT= brachytherapy; MSAC = Medical Services Advisory Committee; PASC = Protocol Advisory Sub-committee

Source: MSAC website [accessed 1 May 2013]

Applications (1319, 1182 and 1211) most relevant to the current assessment are under consideration in the MSAC assessment process and were recently considered by the PASC in December 2012.

Consumer impact statement

- Consumers agree to the value of the proposed intervention:
- Summary of consumer perceived advantage to public access to the intervention.

The use of implanted prostate FMs and planar kilovoltage (kV) or megavoltage (MV) imaging is the most frequently used IGRT technique in Australia (Hayden 2010). As the proposed service is not a new service yet to be introduced in Australia and is already reimbursed under interim MBS item 37217, the proposed listing is not anticipated to have any major impact/change in public access to the service.

Clinical need

- Will the proposed intervention be used:
    - in place of a current (alternative) intervention?
    - in addition to current interventions (rather than in place of a current intervention)?
    - where no current intervention is publicly funded?
    - where no current active intervention is available (for example "active surveillance", "watchful waiting", "best supportive care")?
    - in the context of a rare disease or circumstance (for example an "orphan" or minority population)?
- Summarise where the proposed intervention fits into the clinical management algorithm according to the applicant's post-PASC proposal for public funding (this should include the patient's clinical pathway up to the point where the proposed intervention is appropriate and the clinical management algorithm after this point – this type of information is considered in the Decision Analytical Protocol finalised by PASC).

Traditionally, external skin markers and bony landmarks are used as surrogates for prostate positioning. The disadvantage of this method is that these x-ray images do not confirm the position of soft tissues (the clinical target volume (CTV)) within the bony confines of the area of interest. As such, RT fields are planned (planning target volume (PTV)) to be larger than the soft tissue target to account for uncertainties in the position of the CTV. The consequences of this are that the surrounding volume of normal tissue is at risk of receiving radiation doses higher than desirable resulting in normal tissue toxicity and side effects, and there is a limit to the overall radiation dose that can be delivered to the CTV (usually the cancerous growth), resulting in reduced tumour control probability.

Pre-implanted radio-opaque FMs facilitate image-guided radiotherapy (IGRT) by allowing the position of these markers to be checked during the delivery of RT against reference images derived at the treatment planning process. This, in turn, creates the possibility of improving the treatment by decreasing the planning target volume (PTV) margin, the dose delivered to the adjacent critical structures (eg bladder and rectum) and thus may have the potential benefit of decreased RT-related toxicity. More accurate delivery of treatment may also allow escalated doses of RT to be delivered to the prostate.

The proposed medical service is intended to be used as image guidance in daily RT treatment verification/correction, in patients scheduled for definitive EBRT for prostate cancer or in patients scheduled for adjuvant/salvage EBRT post-radical prostatectomy. It is expected that the proposed medical service directly substitutes the use of bony landmark-based image guidance in radiotherapy treatment verification/correction. Prior to the listing of the interim funded MBS item 37217, clinicians had been performing the procedure but claiming them under item MBS 37218.

Comparator

Comparator to the proposed intervention

- If the proposed intervention is to be used in place of a current intervention, what it is this current intervention as specified by the applicant post-PASC?
- Is this comparator appropriate? If not, what is MSAC's preferred comparator and why?
- Hospital (public/private) or MBS for the MSAC-accepted comparator?
- If the MSAC-accepted comparator is MBS listed, the MBS item number(s), descriptor(s) and date(s) of listing.

The comparator is intermittent imaging of the prostate using bony landmarks. This is accepted as appropriate in the Final DAP.

Scientific basis of comparison

The assessment of comparative clinical effectiveness of FM-based versus bony landmark-based EBRT is based on non-randomised comparative clinical studies:

- Four single institution case series were treated with FM-based EBRT compared with historical series treated with bony landmark-based EBRT in the same institution (Gill 2011; Lips 2007; Singh 2013; Zelefsky 2012).
- A very small non-randomised comparative study (Chung 2009) was also included as reference only owing to the lack of quality evidence.

The assessment of the procedural safety of the implantation of FMs is based on four case series.

None of the non-randomised comparative studies included patients receiving adjuvant/salvage post-prostatectomy. None of the safety studies included patients receiving adjuvant/salvage post-prostatectomy.

Comparative clinical effectiveness

- What is the primary source(s) of evidence; where relevant, separated into the source(s) of evidence for safety and effectiveness?

- Identify the number(s) of each type of study (for example, randomised trials, indirect comparison across randomised trials, non-randomised studies - prospective or retrospective, classical observational design or quasi-scientific).
- If available, identify the number of number of meta-analyses or systematic overviews.

- What are the main results?
- Is clinical management with the proposed intervention more effective, non inferior or less effective than clinical management without it? [Note that investigative interventions do not have a direct impact on intended clinical outcomes. However, any information on consequent effects (i.e., those mediated through subsequent changes in clinical management conditioned by the results of the investigation) should be summarised here, whether harmful or beneficial to the patient.]

Key results

Table ES.4 presents a summary of the comparative clinical effectiveness of FM-based versus bony landmark-based EBRT.

Table ES.4 Summary of clinical evidence to inform comparative clinical effectiveness and safety

Clinical outcomes	Basis of evidence	Summary of evidence and interpretation
Survival	None	No comparative evidence identified
Local tumour control	One case series with historical controls (Zelefsky 2012)	• PSA relapse-free survival at 3 years was significantly better for high-risk patients in the high-dose IMRT (86.4 Gy) cohort with FM as image guidance (97%) versus the cohort without FM (77.7%) (Table B.12) Note however that only 35 high-risk patients contributed to the survival data in the FM group. In addition, it is not clear about the applicability of study results to clinical practice in Australia as the ultra-high dose of 86.4 Gy used in the study is rare in Australia (see eviQ clinical guidelines in Appendix C).
Health-related QoL	One case series with historical controls (Lips 2007)	• There was no significant difference in change in mean QoL scores between the FM group (IMRT) and non-FM group (3D-CRT) except for 6 QoL items at one month after completion of RT favouring FM for 5 of the 6 items (Table B.13) • Between-group difference was not statistically significant for any of the QoL items at 6 months after completion of RT Validity of results of between-group comparison is highly uncertain as the comparison groups differed in more than one aspect apart from the use of FMs in one group (eg dose-escalated IMRT was used in the FM group versus 3D-CRT without dose-escalation in the non-FM group; clinical practice may differ as there was a big gap in study period between the 2 groups-2003/04 versus 1997/2001)
Treatment-related morbidity – GI or rectal AEs	4 case series with historical controls	• Risk of acute grade 1 GI AEs appears to be greater with FM-based EBRT than with bony landmark-based EBRT, while risk of acute grade 2 GI AEs appears to be lower with FM-based EBRT (Table B.15) • Self-assessed moderate to severe rectal AEs (diarrhoea, rectal pain, urgency) were significantly lower in the FM group compared with the non-FM group at 8-26 months after 3D-CRT (Singh 2013; Table B.17) • 3-year ≥grade 2 rectal AEs was low and similar for both FM and non-FM groups, despite the use of ultra-high dose IMRT (86.4 Gy) (Zelefsky 2012)
Treatment-related morbidity – GU AEs	4 case series with historical controls	• Risk of acute grade 1 GU AEs was greater while grade 2 AEs was lower with the FM group than with the non-FM group in 2 studies (Zelefsky 2012; Chung 2009) (Table B.18) • Gill (2011) reported the reverse direction of results at 6 months after RT; in addition, risk of grade 3 GU AEs was lower with the FM group (Table B.18) • Self-assessed moderate to severe urinary AEs were similar in the FM and non-FM groups at 8-26 months after 3D-CRT (Singh 2013) • 3-year ≥grade 2 GU AEs were significantly lower in the FM group than in the non-FM group, despite the use of ultra-high dose IMRT (86.4 Gy) (Zelefsky 2012) (Table B.20)
Safety of the implantation of FMs	4 cohort studies/case series	Most complications were minor and were of a transitory nature, with few lasting longer than 2 weeks. The most serious complication occurred in a study of 234 men, where one patient developed a grade 4 infection (sepsis)

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; AE = adverse event; EBRT = external beam radiotherapy; FM = fiducial marker; GI = gastrointestinal; GU = genitourinary; Gy = Gray; IMRT, intensity-modulated radiotherapy; PSA = prostate-specific antigen; QoL = quality of life; RT = radiotherapy

Overall, there is a lack of quality evidence to inform on the comparative clinical effectiveness of FM-based EBRT versus bony landmark-based EBRT in patients receiving definitive EBRT for prostate cancer. There is no evidence available to inform on comparative clinical effectiveness in patients receiving adjuvant/salvage EBRT post-prostatectomy.

Safety of the implantation of FMs

- What is the primary source(s) of evidence; where relevant, separated into the source(s) of evidence for safety and effectiveness?
    - Identify the number(s) of each type of study (for example, randomised trials, indirect comparison across randomised trials, non-randomised studies - prospective or retrospective, classical observational design or quasi-scientific).
    - If available, identify the number of number of meta-analyses or systematic overviews.
- What are the main results?
- Is clinical management with the proposed intervention safer, of similar safety, or less safe than clinical management without it? [Note that investigative interventions can have a direct impact on safety. However, consequent effects (i.e., those mediated through subsequent changes in clinical management conditioned by the results of the investigation) should be summarised in Section 10, below.]

Key results

The assessment of the procedural safety of the implantation of FMs is based on four large case series (Gill 2012; İğdem 2009; Langenhuijsen 2007; Escudero 2010) which specifically assessed AEs/complications following implementation of FM for EBRT.

The majority of the AEs reported in the four case series were transitory in nature, with most resolving within two weeks of implantation. Minor AEs included haematuria lasting longer than three days, voiding complaints and obstructive symptoms. AEs reported across all four studies included rectal bleeding, pain and fever. For patients with pain, a proportion received analgesics; similarly, patients with fever were given antibiotics. In one study three patients required hospitalisation as a result of fever, with one of those patients developing septicaemia (grade 4 infection) following insertion of an FM (Gill 2012). Two studies reported marker migration or misplacement that did not result in any clinical sequelae (Escudero 2010; Langenhuijsen 2007).

Overall, the majority of patients who undergo implantation of FM have no, or minor AEs. However, a small percentage of patients may experience moderate complications, potentially resulting in further medical intervention. None of the safety studies included patients receiving adjuvant/salvage post-prostatectomy.

Economic evaluation

- Define the type of economic evaluation e.g., cost-effectiveness, cost minimisation, cost utility. If could not present an economic evaluation, explain why not and summarise what approach was taken instead.
- If could present an economic evaluation, summarise its structure, time horizon, its main inputs (e.g., resources) and outputs (e.g., clinical outcomes).

- Main results of economic evaluation, e.g., incremental cost-effectiveness ratio (ICER), cost of proposed intervention compared to comparator, other?
- If MBS funding is sought for the proposed intervention:
  - its proposed fee in the application, and the range of any alternative fees
  - the expected co-payment/out of pocket costs
  - if relevant, the Medicare Safety Net, Extended Medicare Safety Net, any capping proposal.

Owing to the lack of quality evidence to inform on comparative clinical effectiveness and safety of FM-based versus bony landmark-based EBRT, a simple cost comparison analysis is presented in this assessment report. Table ES.5 presents the results of the cost comparison analysis, based on the assumption of similar clinical effectiveness and safety of FM-based and bony landmark-based EBRT. Only the likely additional resource use directly relevant to the conduct of the proposed medical service is included. Key assumptions used are presented in Table D.1.

Table ES.5 Results of simple cost comparison analysis (base case)

Cost components	Cost with FM-based EBRT	Cost with bony landmark-based EBRT	Incremental cost
MBS	–	–	–
Implantation of FMs (proposed medical service or interim MBS 37217)	$138.30	$0.00	$138.30
Trans-rectal US guidance (MBS 55603)	$109.10	$0.00	$109.10
Specialist attendance (MBS 104)	$85.55	$0.00	$85.55
Anaesthesia	$0.00	$0.00	$0.00
Post-procedural plain antero-posterior and lateral pelvic radiograph (MBS 57715)	$0.00	$0.00	$0.00
Pre-treatment verification (MBS 15705; Table D.3)	$2,834.20	$766.00	$2,068.20
RT treatment cost (MBS 15248, 15263)	$7,823.65	$7,823.65	$0.00
Total (MBS)	**$10,990.80**	**$8,589.65**	**$2,401.15**
PBS	–	–	–
Prophylactic antibiotics (PBS 1208N, ciprofloxacin 500 mg tablet ×1)	$1.98	$0.00	$1.98
Total (PBS)	**$1.98**	**$0.00**	**$1.98**
TOTAL (MBS + PBS)	–	–	–
Total cost	**$10,992.78**	**$8,589.65**	**$2,403.13**

Abbreviations: EBRT = external beam radiotherapy; FM = fiducial marker; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RT = radiotherapy; US = ultrasound

* Cost with FM-based EBRT minus cost with bony landmark-based EBRT

Source: MBS Online [accessed 1 May 2013]

The estimated total cost (MBS) of FM-based EBRT is $10,990.80 versus $8,589.65 for bony landmark-based EBRT. The incremental cost (MBS) with FM-based EBRT is therefore estimated to be $2,401.15 per course of RT.

The biggest contributor to the cost difference is the increase in frequency of pre-treatment verification with FM-based EBRT, which contributed to 86% of the incremental cost (MBS).

The implantation procedure itself, together with the associated medical services, amounted to a cost of $332.95 per procedure (14% of the incremental cost to MBS). When the cost to PBS is included, the total incremental cost (MBS and PBS) is estimated to be $2,403.13 per course of RT.

Table ES.6 presents the results of sensitivity analyses.

Table ES.6 Estimated total incremental cost (MBS + PBS) – key sensitivity analyses

	FM-based EBRT	Bony landmark-based EBRT	Increment
Total cost (MBS + PBS) (Base case)	**$10,992.78**	**$8,589.65**	**$2,403.13**
No change in frequency of treatment verification*	$8,924.58	$8,589.65	$334.93
20% of patients requiring general anaesthesia (BC=0%)	$11,012.58	$8,589.65	$2,422.93
Dose escalation to 78 Gy with FM-based EBRT	$11,568.88	$8,589.65	$2,979.23
Dose escalation to 78 Gy with FM-based EBRT and no change in frequency of treatment verification*	$9,347.48	$8,589.65	$757.83
Dose escalation to 78 Gy with FM-based EBRT and 20% of patients requiring general anaesthesia	$11,588.68	$8,589.65	$2,999.03
Dose escalation to 78 Gy with FM-based EBRT and post-implantation pelvic x-ray included	$11,629.78	$8,589.65	$3,040.13
Dose escalation to 78 Gy with FM-based EBRT and RT treatment, 6 fields (IMRT)	$13,048.93	$9,993.80	$3,055.13

Abbreviations: BC = base case; EBRT = external beam radiotherapy; FM = fiducial marker; Gy = Gray

* No change in frequency of treatment verification refers to frequency of treatment verification with FM-based EBRT being the same as the verification frequency with bony landmark-based EBRT (ie daily offline first three fractions in the first week of radiotherapy, then weekly afterwards)

The estimated total incremental cost (MBS + PBS) with FM-based EBRT is most sensitive to whether there is an increase in the frequency of treatment verification associated with FM-based EBRT.

Overall conclusion with respect to comparative cost-effectiveness

The cost (MBS) of each implantation procedure (proposed item, MBS items 55603 and 104) alone to the MBS is a modest $332.95 (on the assumption that it is performed under local anaesthesia).

The incremental cost (MBS) of FM-based versus bony landmark-based EBRT to the MBS, however, is much greater: $2,401.15 per course of EBRT (assuming a total prescription dose of 74 Gy and daily pre-treatment verification/review by a radiation oncologist). The daily pre-treatment verification/review by a radiation oncologist (MBS 15705) contributed to 86% of the incremental cost to the MBS.

Financial impacts

- Likely volume of use of the proposed intervention per year.
- Frequency of use per patient per year over a lifetime.
- Patient numbers per year (prevalence or incidence or mix over time).
- Total cost of the proposed intervention to the MBS.

- Total cost of the charges service to the public.
- Net financial cost/year to the MBS (with and without safety net impacts).

Table ES.7 presents the estimated cost of the proposed medical service.

Table ES.7 Estimated cost of the proposed medical service

	Year 1 (2013-14)	Year 2 (2014-15)	Year 3 (2015-16)	Year 4 (2016-17)
Estimated utilisation: proposed medical service (number of services)	2,083	2,168	2,232	2,283
Estimated cost of the proposed medical service	$288,031	$299,859	$308,687	$315,738
Trans-rectal US guidance (MBS 55603)	$227,218	$236,548	$243,512	$249,074
Specialist attendance (MBS 104)	$178,171	$185,487	$190,949	$195,310
Pre-treatment verification (MBS 15705)	$5,902,659	$6,145,045	$6,325,964	$6,470,456
Treatment cost (MBS 15248, 15263)	$16,293,957	$16,963,051	$17,462,469	$17,861,330
Estimated total cost (MBS)	**$22,890,036**	**$23,829,990**	**$24,531,581**	**$25,091,907**
Estimated cost of prophylactic antibiotics	$4,115	$4,284	$4,410	$4,511
Estimated total cost (PBS)	**$4,115**	**$4,284**	**$4,410**	**$4,511**
Estimated total cost (MBS + PBS)	**$22,894,150**	**$23,834,273**	**$24,535,991**	**$25,096,418**

The number of services of the proposed medical service processed through Medicare Australia is estimated to be: 2,083 in Year 1, rising to 2,283 in Year 4 (Table E.2).

Based on the proposed fee of $138.30 for the proposed medical service, the cost (MBS) of the proposed procedure is estimated to be $288,031 in Year 1, rising to $315,738 in Year 4 (Table E.4).

The estimated cost (MBS + PBS) with the proposed listing is: $22,894,150 in Year 1, rising to $25,096,418 in Year 4 (Table E.7).

The estimated total cost (MBS + PBS) with FM-based EBRT is most sensitive to the accuracy of the projected estimates of utilisation and the change in frequency of treatment verification with FM-based EBRT versus bony landmark-based EBRT (Table E.8).

Key uncertainties

- Main issues around the evidence and conclusions for clinical effectiveness?

Key uncertainties on comparative clinical effectiveness and safety

- There are no head-to-head randomised clinical trials that evaluated the comparative clinical effectiveness and safety of FM-based versus bony landmark-based EBRT. The best evidence available on comparative clinical effectiveness is based on a few single institution case series that used FM-based EBRT versus historical case series that used bony landmark-based EBRT in the same institution. Apart from one study (Zelefsky 2012), the interventions used in the comparison groups were more that the use of FM-based versus bony landmark-based image guidance (eg different RT techniques were used in Lips (2009)).

- There are no comparative studies (randomised or non-randomised) that evaluated the comparative clinical effectiveness in patients receiving adjuvant/salvage EBRT post-prostatectomy.

Overall conclusion with respect to comparative clinical effectiveness and safety

Overall, there is a lack of quality evidence to inform on the comparative clinical effectiveness and safety of FM-based EBRT versus bony landmark-based EBRT in patients receiving definitive EBRT for prostate cancer or in patients receiving adjuvant/salvage EBRT post-prostatectomy.

- Other important clinical issues and areas of clinical uncertainty?

No

- Main issues around the evidence and conclusions for safety?

Key uncertainties on procedural safety

- Safety in terms of procedural complications in patients receiving adjuvant/salvage EBRT post-prostatectomy is not known. Local clinical guidelines (eviQ) recommend the use of online daily imaging matching to surgical clips or bony anatomy (Appendix C).

Overall conclusion with respect to procedural safety

Evidence for the safety of the implantation of FMs is based on four large case series. Overall, FM implantation appears to be safe and well tolerated, with the majority of patients experiencing either no or minor AEs. A small percentage of patients may experience moderate complications; however, the extent of the burden of these complications for both the patient and the health system remains uncertain.

- Main economic issues and areas of uncertainty?

Key uncertainties on results of the cost comparison analysis

- Validity of the assumption of similar clinical effectiveness and safety of FM-based versus bony landmark-based EBRT owing to the lack of quality evidence to affirm the assumption

- Any other important areas of uncertainty (e.g. budget impact, translation of clinical evidence into the economic evaluation, linkage between an investigative intervention and a subsequent therapeutic intervention and outcomes?

Key uncertainties on financial estimates

- Clinical practice (uptake of IGRT, IMRT, etc) may change with the results/outcome of other relevant MSAC reviews/assessment in progress.

Other relevant factors

The MSAC may wish to consider the issue of regulatory and quality assurance aspects associated with the implementation of FM-based EBRT.

A Details of the proposed medical service and its intended use on the MBS

A.1 Background

A.1.1 Prostate cancer in Australia

Prostate cancer is a malignant growth in the prostate gland, a male reproductive organ which is located just below the bladder and surrounds the urethra. It is primarily a disease of older males and is rare in males under the age of 40 years (AIHW 2012a).

Incidence

According to the latest cancer incidence data available, prostate cancer was the most commonly diagnosed cancer in men in 2009: 19,438 new cases; age-standardised incidence (ASI) rate 171.9/100,000 men, contributing to 30.2% of all male cancers (AIHW 2012b). Based on incidence data from 2000-2009, the Australian Institute of Health and Welfare (AIHW) estimated that prostate cancer would remain the most commonly diagnosed cancer in men in 2012: estimated 18,560 cases (ASI rate 147.9/100,000 men) (AIHW & AACR 2012).

Mortality

Prostate cancer was also ranked the second most common cause of death from cancer in males, after bronchus and lung cancer, in 2011: 3,294 deaths; crude rate 13.3% of all male cancer deaths; age-standardised mortality (ASM) rate 30.1/100,000 men (ABS 2013). Survival after diagnosis for prostate cancer is the third highest among all cancers: five-year relative survival was 92% for men diagnosed with prostate cancer in 2006-10, compared with 66% for all cancers combined (AIHW & AACR 2012).

Prevalence

With high incidence and high survival rates, prostate cancer was the third most prevalent cancer in Australia in 2007: 129,978 men (1.2% of male population) were diagnosed with prostate cancer in the previous 26 years (AIHW 2012a). Prostate cancer had the highest five-year prevalence: 72,582 men as at the end of 2007 (AIHW & AACR 2012). These are the latest prevalence data available.

Disease burden

In addition, prostate cancer was the third most common reason for hospitalisation with a principal diagnosis of cancer in 2010-11, accounting for 8.7% of all hospitalisations with cancer as principal diagnosis (AIHW & AACR 2012). It was also estimated to contribute to 15% of the cancer burden in 2012, the second leading cause of disease burden due to cancers, after lung cancer (19% of cancer burden) (AIHW & AACR 2012).

A.1.2 Treatment options

Prostate cancer may be localised (has not grown beyond the prostate), locally advanced (has spread outside the prostate but still remains in the prostate region), advanced (has invaded nearby organs) or metastatic (has spread to different parts of the body such as bones and lymph nodes). The condition is curable if the cancer remains confined to the prostate/prostate region (CCA 2010). Clinical management is therefore dependent on how far the cancer has spread (stage of disease) and how fast it is likely to grow (grade of tumour). Risk of recurrence, prostate-specific antigen (PSA) level, expected life expectancy and co-morbidities are also important considerations (CCA 2010).

Three factors have been shown to predict the risk of recurrence after diagnosis: the stage of disease (the T-stage), grading of tumour (the Gleason score) and the prostate-specific antigen (PSA) level. Staging of disease is based on the Tumour-Node-Metastasis (TNM) system, a detailed description of which is presented in Appendix B. Grading of tumour is according to the Gleason grading system. A Gleason score of 2-6 indicates a low risk as posed by the cancer while a Gleason score of 7 and 8-10 indicates a medium and high risk respectively (CCA 2010). PSA is a protein made by both normal and cancerous prostate cells so the higher the level, the greater the chance of presence of cancer cells at biopsy (CCA 2010). Patients are classified into low, intermediate and high risk groups based on these factors.

For patients with localised prostate cancer, treatment options include watchful waiting, active surveillance, surgery (radical prostatectomy) or radiotherapy (RT). For patients with locally advanced prostate cancer and receiving RT, long-term androgen deprivation therapy (ADT) is also recommended (CCA & ACN 2010). Chemotherapy may also be indicated in patients with metastatic disease. In patients who have had radical prostatectomy, it may also be used as adjuvant treatment in those with higher risk or can be used as salvage treatment following biochemical relapse (Appendix C).

A.1.3 External beam radiotherapy (EBRT)

For prostate cancer, there are two main types of RT: external beam radiotherapy (EBRT) with radiation source from outside the body or interstitial radiotherapy (or brachytherapy BT) with radiation source planted in the prostate (CCA 2010).

Many techniques to deliver EBRT are available. 3-dimensional conformal RT (3D-CRT) uses 3D planning systems to maximise dose to the prostate while sparing surrounding tissues, and is the current minimal standard in Australia. It is recommended for patients with locally advanced prostate cancer and receiving definitive EBRT for local control. Either dose-escalated 3D-CRT or reduced dose 3D-CRT in combination with high dose-rate BT (HDRBT) may be used (CCA & ACN 2010).

Intensity-modulated radiation therapy (IMRT) is a newer, more advanced technique and apart from using computer planning programs to map the tumour in 3D, radiation beams are delivered from several directions, with adjustable intensity (strength) of individual beams. This allows greater control over the conformity and heterogeneity of the dose planned and delivered. IMRT is preferred where organ-at-risk dose constraints are not achievable with 3D-CRT (Hayden 2010). Other newer emerging EBRT techniques include proton radiation therapy and stereotactic body radiation therapy. There are also newer dynamic or rotational IMRT techniques (eg helical tomography and volumetric-modulated arc therapy) versus standard static IMRT techniques. Only 3D-CRT or IMRT (static) are relevant to the current assessment report.

Australian guidelines recommend a minimum acceptable dose of 70 Grays (Gy) for low-risk patients and 74 Gy for intermediate and high-risk patients, and state that the benefit of dose-escalation (78-80 Gy) is seen across all risk groups; however, major clinical disagreement is noted for this recommendation (Hayden 2010).

A.1.4 Image guidance

Regardless of the type of EBRT delivered, image guidance using daily pre-treatment verification of prostate position is recommended in Australia when delivering definitive EBRT for prostate cancer (Hayden 2010). The aim of image guidance is to improve the accuracy of treatment delivery and minimise the risk of toxicity to surrounding organs. Images derived at the planning stages are used to determine the clinical target volumes (CTV). This in turn determines the planning target volumes (PTV), which are defined by specifying the margins that must be added around the CTV to compensate for the effects of the organ, tumour and patient movements, as well as inaccuracies in beam and patient set-up. These planning images are used as reference images for the subsequent images produced during the treatment stages. The use of imaging is particularly important in the delivery of radiotherapy for prostate cancer. This is because the prostate gland is mobile and is difficult to image using standard x-rays: its position in relation to external markers on the skin or to bony pelvic anatomy can vary from day to day and also during treatment (Greer 2008).

Traditionally external skin markers and bony landmarks are used as surrogates for prostate positioning. The disadvantage of this method is that these x-ray images do not confirm the position of soft tissues (CTV) within the bony confines of the area of interest. As such, RT fields are planned (PTV) to be larger than the soft tissue target to account for uncertainties in the position of the CTV. The consequences of this are that the surrounding volume of normal tissue is at risk of receiving radiation doses higher than desirable resulting in normal tissue toxicity and side effects and there is a limit to the overall radiation dose that can be delivered to the CTV (usually the cancerous growth), resulting in reduced tumour control probability (van Haaren 2009).

Pre-implanted radio-opaque fiducial markers (FM) facilitate image-guided radiotherapy (IGRT) by allowing the position of these markers to be checked during the delivery of RT against reference images derived at the treatment planning process. This, in turn, creates the possibility of improving the treatment by decreasing the PTV margin, the dose delivered to the adjacent critical structures (eg bladder and rectum) and thus may have the potential benefit of decreased RT-related toxicity. More accurate delivery of treatment may also allow escalated doses of RT to be delivered to the prostate.

The most commonly used IGRT technique in Australia is planar kilovoltage (kV) or megavoltage (MV) imaging of implanted FM (Hayden 2010). Alternative IGRT modalities include daily trans-abdominal prostate ultrasound and volumetric verification techniques (eg kV cone beam computerised tomography (CT), MV CT and CT on-rails) which allow visualisation of soft tissue structures are also increasingly used in clinical studies. Only FMs are relevant to the current assessment report.

A.1.5 Address all items in the Decision Analytic Protocol (DAP)

The Final Decision Analytic Protocol (DAP) for the current application, available on the MSAC website, outlines the questions that need to be answered in this assessment report. Table A.1

provides a summary of how this assessment report conforms to the Final DAP and any differences or changes that have occurred.

Table A.1 Checklist against the Final Decision Analytic Protocol (DAP) for Application 1147

Items in the PASC-approved DAP	Addressed in the Assessment Report	Reason/justification if not addressed
Details of the proposed intervention	Yes	N/A
Proposed MBS listing	Yes	N/A
Current clinical need and proposed clinical algorithm with the proposed listing	Yes	N/A
Comparator	Yes	N/A
Comparative clinical effectiveness	Yes	N/A
Comparative safety	Yes	N/A
Comparative cost-effectiveness	Yes	N/A

Abbreviations: DAP = Decision Analytic Protocol; N/A = not applicable; PASC = Protocol Advisory Sub-committee

This assessment report has fully addressed the questions defined in the DAP and no additional information has been provided in the assessment report compared to the approved DAP.

A.2 Proposed medical service

An application (referred to as 'the Application' hereafter) requesting the MBS listing of implantation of FMs into the prostate gland or prostatic surgical bed for radiotherapy was received from the Royal Australian and New Zealand College of Radiologists (RANZCR) and the Australian and New Zealand Association of Urological Surgeons (ANZAUS) by the Department of Health and Ageing (DoHA) in April 2010.

The proposed medical service involves the implantation of sterile, radio-opaque FMs (usually gold seeds ~5 mm long and ~1 mm in diameter) into the prostate to serve as fiducial reference points during RT in patients with prostate cancer.

Prior to RT treatment planning and delivery, FMs are implanted into the prostate using a trans-rectal or trans-perineal needle insertion approach under ultrasound guidance. The applicants have indicated that techniques of placement of FMs in conjunction with magnetic resonance imaging (MRI) and CT scan are also under development (Section 4.1, the Application). Some form of anaesthesia (local or general anaesthesia, or conscious sedation) may also be used during the procedure. A clinical expert (HESP member) has informed that the procedure is most commonly performed under local anaesthesia. During the delivery of RT, the position of the FMs is verified against reference images derived during the planning process, to ensure the accurate delivery of RT.

According to the Application, the proposed service may be provided in an ambulatory care setting or in a day surgery facility. In an ambulatory care setting, a radiologist skilled in trans-rectal ultrasound provides the service, with the assistance of a radiology nurse skilled in the management of minimally invasive procedures. In a day surgery facility, a urologist or radiation oncologist skilled in trans-rectal ultrasound provides the service, with the assistance of an anaesthetist and theatre staff.

The Application stated that the proposed service is not a therapeutic medical service on its own but rather is an integral part of the delivery of dose-escalated image-guided radiotherapy (IGRT).

The proposed indication in the Application is for:

> 'Prostate cancer patients who propose to undertake a course of radiotherapy that may consist of external beam radiotherapy alone or in combination with high dose rate brachytherapy as a boost.'

The Final DAP specifies that there are two target patient populations for the proposed service:

- primary population − patients with prostate cancer who are eligible for a course of radical EBRT as definitive treatment; and
- secondary population – patients with prostate cancer who had a radical prostatectomy as primary treatment and who are undergoing adjuvant or salvage EBRT.

A.2.1 Fiducial markers (FM) and current regulatory status

The proposed service involves the use of a medical device that is not exempt from the regulatory requirements of the *Therapeutic Goods Act 1989* (Section 2.5, the Application).

The medical device, 'Nucletron Pty Limited – Marker, lesion localization, implantable; Australian Register of Therapeutic Goods (ARTG) Entry 143069' mentioned in the Application (Section 2.5) can no longer be located at the time of this assessment and the reason is not clear.

A number of implantable medical devices under the same product name of 'marker, lesion localization, implantable' relevant to the current assessment are identified in the ARTG (Appendix D). The list may not be exhaustive.

The Application also stated that while commercial packs of sterilised pre-loaded needles are available, many public hospitals with a radiation oncology department produce their own material (Section 6.3, the Application).

A.3 Proposed MBS listing or other public funding sought

A.3.1 Proposed MBS listing

Table A.2 presents the proposed MBS item description for the proposed medical service.

Table A.2 Proposed MBS item descriptor

Category 3 – THERAPEUTIC PROCEDURES
MBS [item number XXXXX] Prostate, implantation of radio-opaque fiducial markers into the prostate gland or prostate surgical bed to assist in the delivery of external-beam radiotherapy. The procedure must be performed by a urologist or a radiation oncologist at an approved site, and be associated with a service to which item 55603 applies. Multiple Services Rule (Anaes.) **Fee**: $138.30 **Benefit**: 75% = $103.75 85% = $117.60

Abbreviations: MBS = Medicare Benefits Schedule

For MBS notes on Multiple Services Rule, see Appendix E.

Proposed fee is based on the current schedule fee for MBS item 37217, as on 1 May 2013.

Source: Proposed item descriptor in Table 4, p. 11 in the Final DAP; MBS Online [accessed 1 May 2013]

The proposed item descriptor is essentially the same as that approved by the PASC in the Final DAP (Table 4, p.11, Final DAP), except the proposed addition of the following qualifying statement:

> "The procedure must be performed by a urologist or a radiation oncologist at an approved site, and be associated with a service to which item 55603 applies."

The reasoning for the proposed addition is that the proposed procedure will be performed by a urologist or a radiation oncologist skilled in the use of trans-rectal ultrasound (as stated in p.14 of the Application), and that other similar implantation procedures also have similar item description (eg implantation of radioactive seeds for brachytherapy for MBS item 37220). **The MSAC may wish to consider whether the proposed inclusion is appropriate.**

The proposed schedule fee is the current schedule fee for the interim MBS item 37217, introduced on 1 July 2011 to cover the proposed medical service pending outcome of the current assessment (see Section A.3.2 below). Current MBS explanatory notes on multiple services rule are presented in Appendix E.

Table A.3 presents a brief summary of the development of the proposed item descriptor from the Application (April 2010), to the interim item 37217 (from 1 July 2011) and to the Final DAP.

Table A.3 Proposed item descriptors in the Application, interim-funded MBS item 37217 and the Final DAP

Source	Proposed item descriptor
The Application	'Prostate: Implantation of markers into prostate gland or prostate surgical bed (associated anaesthesia)' (Section 2.2, page 3 in the Application)
Interim MBS item 37217	'Prostate, implantation of gold fiducial markers into the prostate gland or prostate surgical bed' Multiple Services Rule (Anaes.)
Final DAP	'Prostate, implantation of radio-opaque fiducial markers into the prostate gland or prostate surgical bed to assist in the delivery of external-beam radiotherapy' Multiple Services Rule (Anaes.)
Current assessment report	Essentially the same as in the Final DAP, except the proposed inclusion of the statement: "The procedure must be performed by a urologist or a radiation oncologist at an approved site, and be associated with a service to which item 55603 applies."

Abbreviations: DAP = Decision Analytic Protocol; MBS = Medicare Benefits Schedule

Source: Table 4, p. 11 in the Final DAP; MBS Online [accessed 1 May 2013]

A key difference of the proposed item descriptor in the Final DAP from the descriptor in the interim-funded MBS item 37217 or that proposed in the Application is that EBRT is specified as the RT indicated rather than RT in general. In addition, the limitation of FMs to being gold markers was removed from the proposed item descriptor in the Final DAP as the PASC considered that other sterile, radio-opaque materials may also be suitable in the future. The PASC also did not consider it necessary to specify the maximum number of FMs implanted as the proposed item descriptor is for the implantation procedure rather than for each FM implanted.

Note that the interim MBS item covers the cost of the procedure only. The cost of the FMs is to be borne either by the patient (private patients) or by the hospital (public patients). According to the Final DAP (p. 10), fiducial seeds are not eligible for listing on the prosthesis list and were declined for listing as recently as February 2010. The reasons for ineligibility were not reported.

A.3.2 Current interim funding of the proposed medical service

The proposed medical service is currently covered under interim-funded MBS item 37217 (Table A.4) which was introduced on 1 July 2011 to enable collection of data on usage to inform the current assessment. Prior to that, the service was claimed under another MBS item (37218) which referred to 'PROSTATE, needle biopsy of, or injection into (Anaes.)' without specifying what was injected or for what purpose. This claiming practice was prohibited by the DoHA from 1 January 2010. With the introduction of the interim item, MBS item 37218 has now been amended to specifically exclude the implantation of radio-opaque markers (Table A.5).

Table A.4 Current interim MBS item 37217 (from 1 July 2011)

Category 3 – THERAPEUTIC PROCEDURES
MBS 37217*   Prostate, implantation of gold fiducial markers into the prostate gland or prostate surgical bed   Multiple Services Rule   **Fee**: $138.30 **Benefit**: 75% = $103.75 85% = $117.60   (See para T8.54 of explanatory notes to this Category)
T8.54 Gold Fiducial Markers into the Prostate - (item 37217)   Item 37217 is for the insertion of gold fiducial markers into the prostate or prostate surgical bed as markers for radiotherapy. The service cannot be claimed under item 37218 or any other surgical item.   This item is introduced into the Schedule on an interim basis pending the outcome of an evaluation being undertaken by the Medical Services Advisory Committee (MSAC).   Further information on the review of this service is available from the MSAC Secretariat.

* Item Start Date: 1 July 2011; Description Start Date: 1 July 2011; Schedule Fee Start Date: 1 November 2012

For MBS notes on Multiple Services Rule, see Appendix E.

Source: MBS Online [accessed 1 May 2013]

Table A.5 Current item descriptor for MBS item 37218

Category 3 – THERAPEUTIC PROCEDURES
MBS 37218*
PROSTATE, needle biopsy of, or injection into, excluding for insertion of radiopaque markers
Multiple Services Rule
(Anaes.)
Fee: $138.30 **Benefit**: 75% = $103.75 85% = $117.60

* Item Start Date: 1 December 1991; Description Start Date: 1 July 2011; Schedule Fee Start Date: 1 November 2012

For MBS notes on Multiple Services Rule, see Appendix E.

Source: MBS Online [accessed 1 May 2013]

A.3.3 Medical services likely to be co-administered with the proposed procedure

Medical services likely to be co-administered with the proposed procedure are those directly associated with the implantation procedure itself:

- trans-rectal ultrasound guidance (MBS 55603) (Table A.6); and
- specialist attendance (MBS 104) (Table A.7).

For patients who undergo the procedure under general anaesthesia, there will be an additional cost for the service by an anaesthetist (MBS 21980) (Table A.8), although the procedure is most commonly performed under local anaesthesia.

Table A.6 MBS 55603

Category 5 - DIAGNOSTIC IMAGING SERVICES
MBS 55603
PROSTATE, bladder base and urethra, ultrasound scan of, where performed: a) personally by a medical practitioner who undertook the assessment referred to in (c) using a transducer probe or probes that: i. have a nominal frequency of 7 to 7.5 megahertz or a nominal frequency range which includes frequencies of 7 to 7.5 megahertz; and ii. can obtain both axial and sagittal scans in 2 planes at right angles; and b) following a digital rectal examination of the prostate by that medical practitioner; and c) on a patient who has been assessed by a specialist in urology, radiation oncology or medical oncology or a consultant physician in medical oncology who has: i. examined the patient in the 60 days prior to the scan; and ii. recommended the scan for the management of the patient's current prostatic disease (R) (K) Bulk bill incentive **Fee:** $109.10 **Benefit:** 75% = $81.85 85% = $92.75 (See para DIQ of explanatory notes to this Category)
DIQ Bulk Billing Incentive
To provide an incentive to bulk bill, for out of hospital services that are bulk billed the schedule fee is reduced by 5% and rebates paid at 100% of this revised fee (except for item 61369, and all items in Group I5 - Magnetic Resonance Imaging). For items in Group I5 - Magnetic Resonance Imaging, the bulk billing incentive for out of hospital services is 100% of the Schedule Fee listed in the table.

Abbreviations: MBS = Medicare Benefits Schedule

Source: MBS Online [accessed 1 May 2013]

Table A.7 MBS 104

Category 1 - PROFESSIONAL ATTENDANCES
MBS 104 **SPECIALIST, REFERRED CONSULTATION - SURGERY OR HOSPITAL** (Professional attendance at consulting rooms or hospital by a specialist in the practice of his or her specialty where the patient is referred to him or her) **- INITIAL** attendance in a single course of treatment, not being a service to which ophthalmology items 106, 109 or obstetric item 16401 apply. **Fee:** $85.55 **Benefit:** 75% = $64.20 85% = $72.75 Extended Medicare Safety Net Cap: $256.65

Abbreviations: FM = fiducial marker

Source: MBS Online [accessed 1 May 2013]

Table A.8 MBS 21980

Category 3 – THERAPEUTIC PROCEDURES
MBS 21980 INITIATION OF MANAGEMENT OF ANAESTHESIA for radiotherapy (5 basic units) **Fee**: $99.00 **Benefit**: 75% = $74.25 85% = $84.15

Abbreviations: MBS = Medicare Benefits Schedule

Source: MBS Online [accessed 1 May 2013]

Other additional medical services likely to be co-administered with the proposed procedure are those associated with the planning (simulation, dosimetry) and delivery (treatment verification, treatment) of EBRT (3D-CRT or IMRT) with or without HDRBT. In patients who are receiving adjuvant/salvage EBRT, medical services related to prostatectomy may also be administered (Table A.9).

Table A.9 Medical services likely to be associated with the planning and delivery of EBRT ± HDRBT

	Implantation procedure	Planning (simulation, dosimetry)	Treatment verification	Radiation oncology treatment	Surgery
EBRT	37217, 55603, 104	15550, 15553, 15556, 15559, 15562	15700, 15705, 15710	15218, 15233, 15248, 15263	–
HDRBT	37227, 15331 or 15332	15850	15800	–	–
RP	–	–	–	–	37210, 37211

Abbreviations: EBRT = external-beam radiotherapy; FM = fiducial marker; HDRBT = high-dose rate brachytherapy; RP = radical prostatectomy

Source: MBS Online [accessed 1 May 2013]

A.3.4 Other relevant applications/reviews

Other applications/reviews relevant to the current assessment are summarised in Table A.10 below.

Table A.10 Other applications/reviews relevant to the current assessment

No	Application title	Progress
1319	The use of Image Guided Radiation Therapy (IGRT) in the treatment of cancer	2nd PASC in December 2012, Final DAP released
1211	Volumetric Modulated Arc Therapy for Lung, Prostate, breast and other extra-cranial cancers such as spine, kidney, liver and pancreatic	2nd PASC in December 2012, Final DAP released
1182	The use of Intensity Modulated Radiation Therapy (IMRT)	2nd PASC in December 2012, Final DAP released
1158	Robotic image-guided stereotactic precise beam radiosurgery and radiotherapy for lung cancer and prostate cancer	Completed, MSAC appraisal in December 2012, MSAC minutes released
1089.1	Review of Interim Funded Service: Brachytherapy for the Treatment of Prostate Cancer	Completed, considered by the MSAC in December 2010, MBS item 15338 implemented

Abbreviations: BT= brachytherapy; MSAC = Medical Services Advisory Committee; PASC = Protocol Advisory Sub-committee

Source: MSAC website [accessed 1 May 2013]

Applications (1319, 1182 and 1211) most relevant to the current assessment are under consideration in the MSAC assessment process and were recently considered by the PASC in December 2012.

For Application 1158, the MSAC concluded that the evidence submitted did not support a new, higher MBS fee for image-guided stereotactic precise beam radiosurgery and radiotherapy and that the technology should be considered together with other image-guided RT technologies (Applications 1319, 1182).

For Application 1089.1, the following is the advice of the MSAC to the Minister:

- MSAC supports public funding for low dose-rate ^{125}I BT for localised prostate cancer (clinical stage T1 or T2) with a PSA level of ≤10 ng/mL and a Gleason score of ≤7.
- MSAC agreed that BT is appropriate as a first-line monotherapy where the Gleason score is < (3+4) = 7, and if used for Gleason (4+3) = 7, should be part of combined modality treatment. Such advice forms part of the MBS item 15338 Explanatory Notes.

In addition, the Trans-Tasman Radiation Oncology Group (TROG) was commissioned by the DoHA to develop and pilot an evaluation framework for the assessment of new radiation oncology technologies and treatments. The project, 'Assessment of New Radiation Oncology Treatments and Technologies (ANROTAT)' was undertaken as non-interventional prospective evaluation of clinical activity, defined as a clinical audit rather than a clinical trial to help inform decision-making around new radiation oncology treatments. The use of FMs was included in both questions looking at IGRT:

- What is the safety, clinical and cost-effectiveness of IGRT compared to non-IGRT in patients with intermediate risk prostate cancer?; and
- What is the safety, clinical and cost-effectiveness of IMRT compared to 3D-CRT in patients with prostate cancer (post-prostatectomy)?

No results are publicly available as yet.

A.4 Comparator details

The proposed medical service is intended to directly substitute the traditional use of bony landmark-based image guidance. As stated in the Final DAP (p. 17), the comparator is intermittent imaging of the prostate using bony landmarks.

RT for prostate cancer has always been undertaken with some form of image guidance. According to the Application, prior to around 2006, almost all Australian centres used 'port-films' (x-ray images taken with a linear accelerator with the patient lying in the treatment position) to verify that the field placements were accurate. The effectiveness of this method is dependent on the matching of bony landmarks in films taken at the time of treatment planning with a comparison of x-ray images taken during the planning stages of treatment.

A.5 Clinical management algorithm(s)

The Faculty of Radiation Oncology Genito-Urinary Group (FROGG), a special interest group of the RANZCR, recommends that:

- IGRT using daily online verification of prostate position or surrogate should be used for definitive EBRT for prostate cancer;
- where implanted FMs are used, a minimum of three markers should be implanted under ultrasound guidance in the ipsi-lateral apex, base and contra-lateral mid-gland; and
- there should be an interval of one week between implantation and simulation to minimise potential prostate oedema (Hayden 2010).

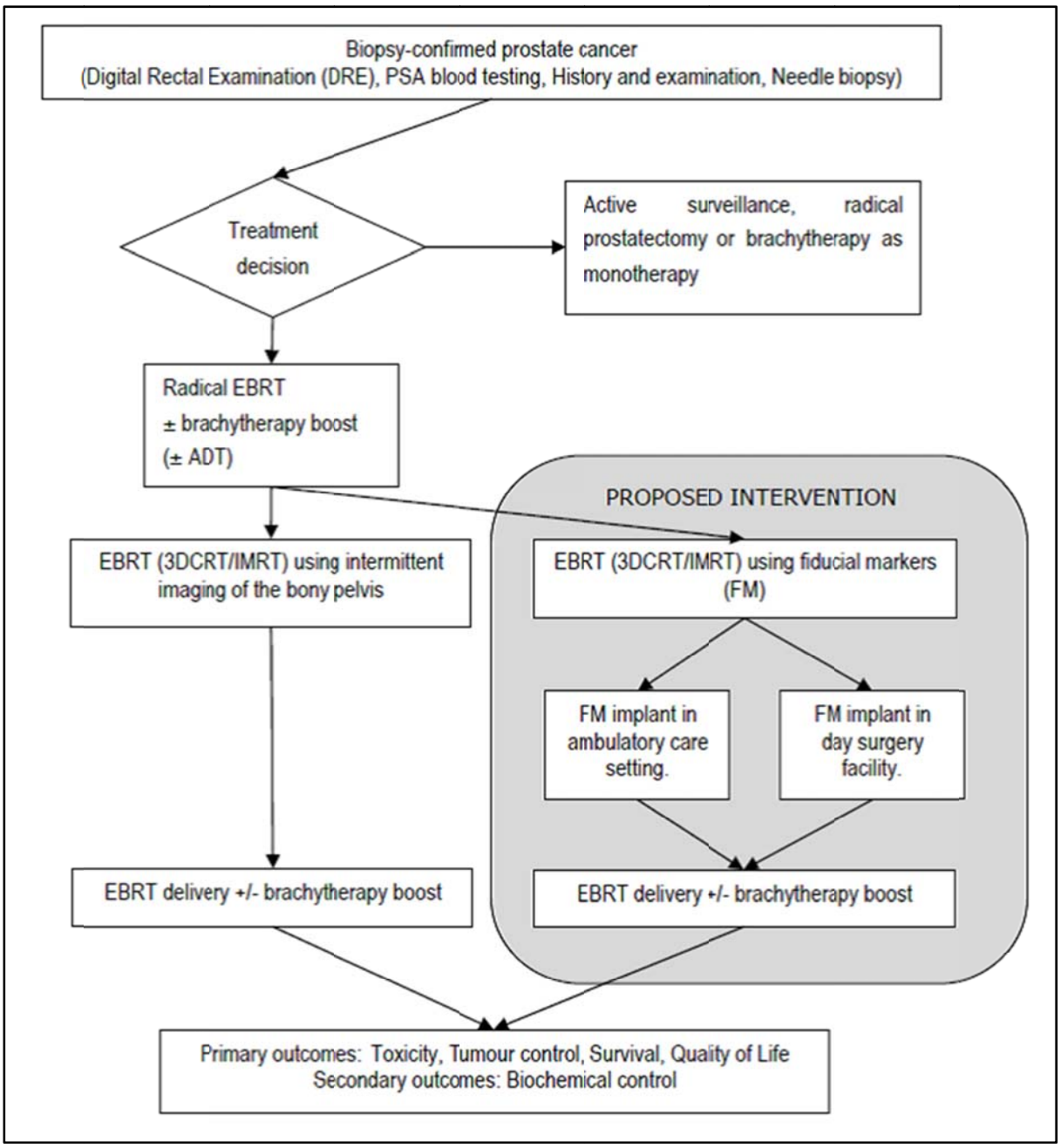
For target verification in definitive EBRT, the eviQ Cancer Treatment Online (Cancer Institute NSW) protocols recommend the following:

- acceptable = offline with port film or electronic portal image (EPI) daily first three fractions then weekly, matching to bony anatomy; and
- ideal = online daily imaging matching to FMs (on-board imaging or EPI, ultrasound, cone beam or CT).

For target verification in adjuvant or salvage EBRT post-prostatectomy, the recommendation for acceptable practice is the same as in definitive EBRT. However, online daily imaging (on-board imaging or EPI) matching to surgical clips or bony anatomy is considered ideal practice. A summary of the protocols are presented in Appendix C.

Figure A.1 presents the proposed use of FMs in prostate cancer patients who are indicated for definitive EBRT (±BT, ±ADT), and Figure A.2 presents the proposed use of FMs in patients indicated for adjuvant or salvage EBRT post-prostatectomy.

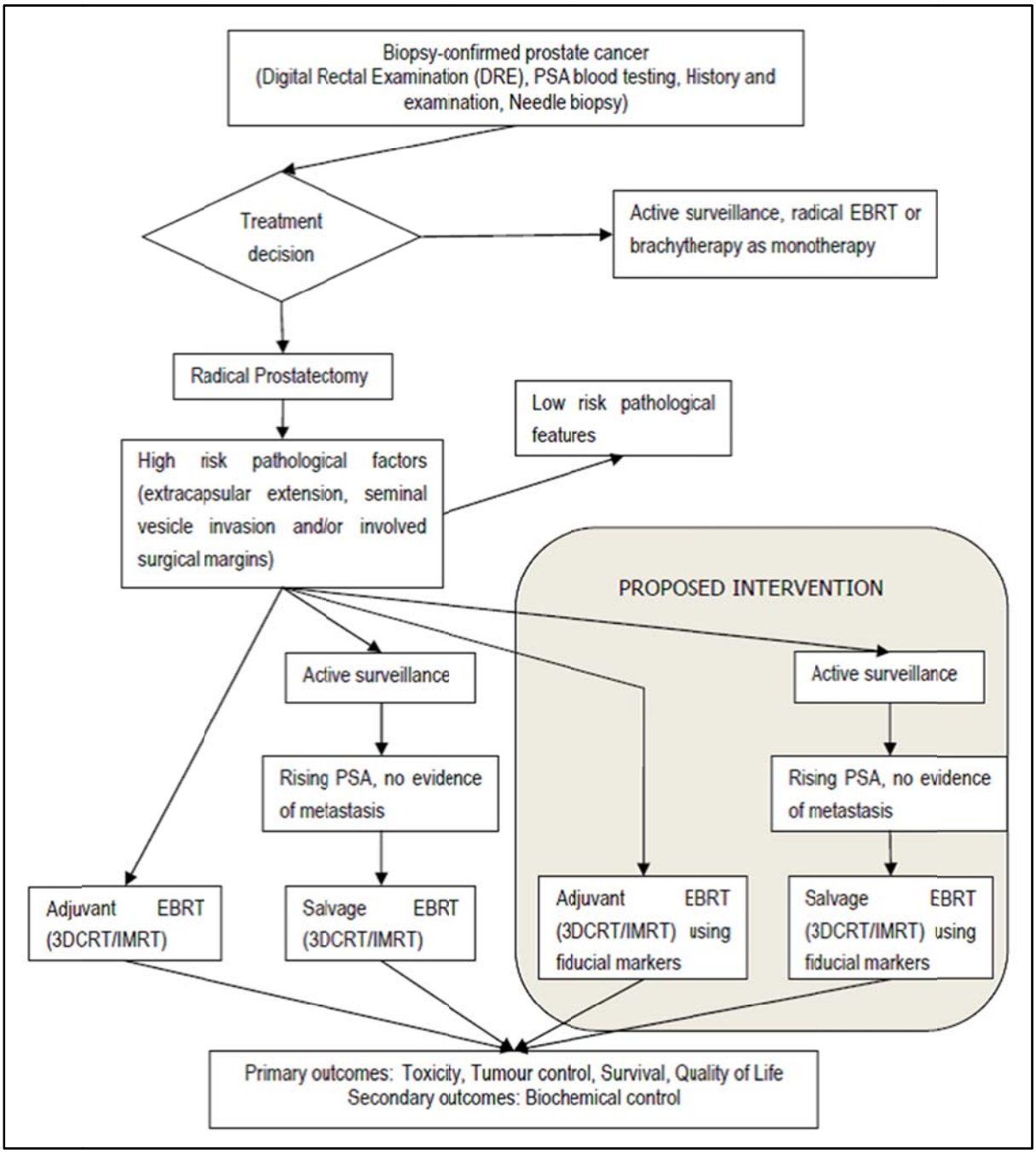
Figure A.1 Proposed clinical algorithm for FM-based radical EBRT



Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; FM = fiducial marker; IMRT = intensity-modulated radiotherapy

Source: Figure 2, p. 14 in the Final DAP for Application 1147

Figure A.2 Proposed clinical algorithm for FM-based adjuvant or salvage EBRT post-prostatectomy



Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; EBRT = external beam radiotherapy; FM = fiducial marker; IMRT = intensity-modulated radiotherapy; PSA = prostate-specific antigen

Source: Figure 3, p. 16 in the Final DAP for Application 1147

A.6 Differences between the proposed medical service and the main comparator

Table A.11 presents a summary of the key differences between FM-based EBRT and bony landmark-based EBRT.

Table A.11 Key differences between FM-based EBRT and bony landmark-based EBRT

	FM-based EBRT	Bony landmark-based EBRT
Prior to the course of RT	Requires an invasive procedure (implantation of the FM under local or general anaesthesia or conscious sedation) prior to planning	No invasive procedure
During the course of RT	Frequency of position verification/correction: daily, online	Frequency of position verification/correction: weekly, offline
Claimed advantages	• less inter-observer variation • increased accuracy with target position localisation • decreased random errors from inter-fractional prostate motion • allows decreased treatment margin, hence decreased radiation side effects with organs at risk • facilitates dose-escalation	–
Claimed disadvantages	• side effects/risks associated with the implantation procedure (eg bleeding, marker migration) • additional radiation doses due to more frequent imaging	–
Contra-indications	• bleeding disorders or on anticoagulant therapy which cannot be safety stopped for 7-10 days prior to implantation of FM • allergy to marker materials (eg gold) • abnormality of the anus or rectal canal that would prevent trans-rectal ultrasound • conditions in which trans-rectal needle placement is contraindicated or not desirable (eg malignancy in the anal-rectal area)	–

Abbreviations: EBRT = external beam radiotherapy; FM = fiducial marker; RT = radiation therapy

Source: Brown (2011); Shinohara (2008)

A.7 Clinical claim

The therapeutic claims made in the Application were:

- Implantation of 3-4 gold marker seeds into the prostate prior to RT planning allows a greater certainty of daily targeting positioning of the prostate to be achieved, a reduction in PTV margins and thereby unwanted radiation dose to adjacent normal critical structures (eg the rectum and bladder), and dose escalation in RT.
- The proposed procedure 'has a similar safety and side effect profile to ultrasound guided needle biopsies of the prostate performed for diagnostic purposes' (Attachment to Section 4.2, the Application).

Compared with bony landmark-based EBRT, FM-based EBRT may have the following:

- Potential benefits:
    - improved tumour control due to potentially more accurate treatment delivery and/or dose escalation;
    - improved health-related quality of life (HR-QoL); and
    - reduction in radiation-related toxicity (eg gastrointestinal/genitourinary toxicities) due to reduction in PTV margin and more accurate treatment delivery.
- Potential harms:
    - procedure-related adverse events (adverse events associated with the implantation of FM, eg infection, haematuria, haemotospermia, dysuria, rectal bleeding, pain, fever, and urinary incontinence)

A.8 Summarise the primary elements of the decision analysis (PICO)

Table A.12 presents a summary of the patient population, intervention, comparator and outcome (PICO) elements for this assessment report. It is a simplified version of the PICO criteria reported in Tables 9-10, pp 22-23 of the Final DAP.

Table A.12 Summary of the patient population, intervention, comparator and outcome (PICO) elements

Population of interest:	Patients with prostate cancer, scheduled for EBRT (radical/post-prostatectomy; 3D-CRT/IMRT) ± HDRBT boost ± ADT
Intervention of interest:	EBRT using FM-based target position verification/correction FMs refer to standard FMs (eg gold). The following are excluded: • FMs not registered with the TGA at the time of the writing of this report; and • studies that evaluated FM with use of non-MBS subsidised technologies (eg Stereotactic Body Radiotherapy)
Comparator:	EBRT using bony landmark-based target position verification/correction Excluded: • position verification/correction using any other method
Outcomes of interest:	Report on at least one of the following: • patient-relevant clinical outcomes (survival, clinical recurrence or relapse, acute/late rectal/urinary toxicities, quality of life); and • safety/complications related to the implantation procedure of FM

Abbreviations: 3D-CRT = 3-D conformal radiotherapy; ADT = androgen deprivation therapy; EBRT = external-beam radiotherapy; FM = fiducial marker (implanted via ultrasound); HDRBT = high-dose rate brachytherapy; IMRT = intensity-modulated radiotherapy; TGA = Therapeutic Goods Administration

The key research questions for this assessment report are:

- What is the comparative safety, clinical and cost-effectiveness of FM-based EBRT (3D-CRT or IMRT, with or without HDRBT, and/or ADT) versus bony landmark-based EBRT, in patients receiving (a) definitive EBRT or (b) adjuvant or salvage EBRT post-prostatectomy?
- What is the safety of the procedure of the implantation of FMs in the patient populations mentioned above?

B Clinical evaluation for the main indication

B.1 Search strategy and study selection

Literature searches were conducted to identify relevant published studies that evaluated the comparative effectiveness and safety of FM-based versus bony landmark-based verification in prostate cancer patients receiving EBRT.

To be eligible for inclusion in this review, clinical trials had to fulfil the following patient population, intervention, comparator and outcome (PICO) criteria as shown in Table A.12. Studies that recruited patients who received EBRT (3D-CRT or IMRT), as radical or as post-prostatectomy adjuvant/salvage RT, with or without dose-escalation and/or androgen deprivation therapy (ADT) are eligible for inclusion. Only studies that evaluated standard FMs (eg gold seeds) and patient-relevant clinical outcomes or safety are included.

The primary aim of the literature searches was to identify direct randomised comparative clinical trials. In the absence of direct head-to-head randomised trials, relevant non-randomised comparative studies that fulfilled the PICO inclusion criteria would be retrieved for further assessment. Comparative trials/studies with a sample size of <15 were excluded. The searches for published literature included the following:

- electronic databases (EMBASE, MEDLINE, the Cochrane Library);
- websites of international health technology assessment (HTA) agencies;
- International Clinical Trials Registry platform, eg the Australian and New Zealand Clinical Trials Registry (ANZCTR); and
- the reference lists of relevant articles identified (manual searches).

Table B.1 outlines details of the databases searched.

Table B.1 Electronic databases searched

Database searches	Date search	Date span of the search
MEDLINE	24-25 January 2013	Beginning of database-January 2013
EMBASE	31 January 2013	Beginning of database-January 2013
All EBM Reviews (includes: Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts and Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CCTR), NHS Economic Evaluation Database (CLEED), Health Technology Assessment (CLHTA), Cochrane Methodology Register (CLMCR)	21 February 2013	Beginning of database-January 2013

The search strategies were revised after pilot searches identified no relevant direct randomised comparative trials. Literature searches of the databases were broadened to include single-arm studies that evaluated FM-based EBRT. Studies with a sample size <50 were excluded. Searches were conducted in three stages, with each stage applying different search terms and/or filters. The first stage focused on the identification of randomised controlled trials. Terms associated with the patient (P), intervention (I) and comparator (C) components of the research question were used in the search strategies and a text word filter was applied to identify randomised

controlled trials. In the second stage the search was broadened, removing the text word filter, thereby allowing all non-randomised comparative studies to be identified. The last stage involved removing the search terms associated with the comparator. This last step was undertaken to aim to capture additional evidence that may help inform the clinical effectiveness and safety of FM-based EBRT in the longer term. Further details of the search terms and results are presented in Appendix F. Abstracts of the identified articles were screened by two independent reviewers and any differences in screening results were resolved by discussion. Full-text publications were retrieved for further assessment in the event of uncertainty.

B.2 Listing of relevant non-randomised comparative studies

B.2.1 Search results

Table B.2 presents a summary of the search results.

Table B.2 Summary of the search results

	MEDLINE	EMBASE	Other databases	Trial registries	Manual searches
Number of citations retrieved by search	140	401	7	6	–
Number of citations excluded after title/abstract review:	–	–	–	–	–
• characteristics of the recruited participants do not overlap with the main indication (EA1)	12	81	0	0	–
• not the right proposed service (includes use of non-reimbursed technologies) (EA2)	35	93	4	3	–
• not the right comparator (EA3)	5	4	0	0	–
• not patient-relevant or clinical outcomes (EA4)	56	135	1	0	–
TOTAL	108	313	5	3	–
Number of citations excluded after full text review:	–	–	–	–	–
• characteristics of the recruited participants do not overlap with the main indication (EF1)	0	0	0	0	–
• not the right proposed service (includes use of non-reimbursed technologies) (EF2)	3	2	0	0	–
• not the right comparator (EF3)	0	0	0	0	–
• not patient-relevant or clinical outcomes (EF4)	5	14	1	0	–
TOTAL	8	16	1	0	–
Number of citations of non-randomised studies that evaluated the use of FM-based verification/positioning with EBRT in patients with prostate cancer included from each database	24	72	1	3	6
Consolidated number of citations of relevant non-randomised studies (removing exact duplicates across different databases)	–	–	–	–	81
Consolidated number of citations of relevant non-randomised studies (removing conference abstracts)	–	–	–	–	42
Number of published non-randomised comparative studies included (removing non-comparative studies)	–	–	–	–	5

Systematic searches of electronic databases did not yield any direct randomised trials that compared the clinical effectiveness and safety of FM-based EBRT versus bony landmark-based EBRT in patients with prostate cancer.

A total of nine non-randomised comparative studies (FM-based EBRT versus bony landmark-based EBRT) were identified: five with full-text publication and four (Farrow 2009; Kok 2012; Pastor 2010; Sham 2011; Appendix F) were only available as conference abstracts.

Farrow (2009) did not report on any results and was therefore excluded from further assessment. Kok (2012) was a retrospective study which compared all patients who received 78 Gy IGRT with FM in 2008 (N=243) versus all patients who received 74 Gy without FM in 2006 (N=311) in a single centre in Australia. The records of all patients were reviewed at 27 months after the completion of radiotherapy (RT). Data audited were biochemical failure-free survival at two years and late severe gastrointestinal (GI) and genitourinary (GU) toxicities. Pastor (2010) was a Spanish study that evaluated the survival outcomes, acute and late toxicity of four groups of prostate cancer patients treated with high-dose RT: Group I 76 Gy IMRT (N=91); Group II 80 Gy IMRT (N=127); Group III 80 Gy IG-IMRT (N=49); and Group IV 70-72.5 Gy IG-IMRT (n=81). The follow-up period ranged from 12 to 99 months across the four groups. Sham (2011) was a small UK study which retrospectively compared the acute GI and GU toxicities in 15 patients who received FM-based IGRT versus 15 control patients. None of these 3 studies reported on comparability of patient characteristics (age, tumour stage, Gleason score, PSA level) or details of set-up positioning/correction used. Internal validity and applicability of results were highly uncertain and therefore these studies were not included in formal assessment in this report. Therefore, the five direct non-randomised comparative studies (available in full-text publication) form the key primary studies to inform on comparative effectiveness and safety in this report.

In addition, 37 single-arm studies that evaluated FM-based EBRT were identified as potentially relevant. Two were excluded because results were either not useable (n=1) or not available (n=1). Fifteen studies were further excluded because of sample size of <50. Therefore, 20 single arm studies are assessed further as potential studies for information on clinical effectiveness and safety of FM-based EBRT. Citation details of the 20 potential studies and the 17 excluded studies are presented in Appendix F.

B.2.2 Master list of relevant non-randomised comparative studies

Table B.3 presents the master list of the five key primary studies to inform on comparative effectiveness and safety.

Table B.3 Master list of the five non-randomised comparative studies (primary studies)

Study	Report(s) and citation
Gill (2011)	Gill, S., Thomas, J., Fox, C., et al. 2011. Acute toxicity in prostate cancer patients treated with and without image-guided radiotherapy, *Radiation Oncology*, 6, 145.
Lips (2007)	Lips, I., Dehnad, H., Kruger, A.B. et al. 2007. Health-related quality of life in patients with locally advanced prostate cancer after 76 Gy intensity-modulated radiotherapy vs. 70 Gy conformal radiotherapy in a prospective and longitudinal study, *International Journal of Radiation Oncology Biology Physics*, 69 (3), 656-661. Lips (2009) 3-year outcome study of the FM-based IMRT case series Lips, I.M., van Gils, C.H., van der Heide, U.A., Kruger, A.E., van Vulpen, M 2009. Health-related quality of life 3 years after high-dose intensity-modulated radiotherapy with gold fiducial marker-based position verification, *BJU International*, 103 (6), 762-767.
Singh (2013)	Singh, J., Greer, P.B., White, M.A. et al. 2013. Treatment-related morbidity in prostate cancer: A comparison of 3-dimensional conformal radiation therapy with and without image guidance using implanted fiducial markers, *International Journal of Radiation Oncology Biology Physics*, 85 (4), 1018-1023.
Zelefsky (2012)	Zelefsky, M.J., Kollmeier, M., Cox, B. et al. 2012. Improved clinical outcomes with high-dose image-guided radiotherapy compared with non-IGRT for the treatment of clinically localised prostate cancer, *International Journal of Radiation Oncology Biology Physics*, 84 (1), 125-129.
Chung (2009)	Chung, H.T., Xia, P., Chan, L.W. et al. 2009. Does image-guided radiotherapy improve toxicity profile in whole pelvic-treated high-risk prostate cancer? Comparison between IG-IMRT and IMRT, *International Journal of Radiation Oncology Biology Physics,* 73 (1), 53-60.

B.2.3 Relevant systematic review and meta-analyses identified

There were no systematic reviews that evaluated the implementation of FMs in the delivery of EBRT. Two systematic reviews (Viani 2009, Hummel 2010) that assessed EBRT with dose escalation versus EBRT without dose escalation were identified.

Viani (2009) was a meta-analysis of seven randomised controlled trials (RCTs) in men with localised prostate cancer. IMRT and IGRT were not used in any of the included trials. The aim of the analysis was to determine whether the outcomes in these men were better if they had been treated with high-dose RT versus conventional-dose RT. A literature search was undertaken in MEDLINE, CANCERLIT and the Cochrane Library for RCTs published up until December 2007. Treatment modality, treatment volume, set-up verification, risk-group definitions, biochemical failure definitions, and gastrointestinal (GI) and genitourinary (GU) toxicity were extracted for all seven trials. However, the total RT doses given to the intervention and comparator groups for each of the seven trials were not clear. There was only a summary statement that the total dose varied across the trials from 64 to 79.2 Gy. Meta-regression was undertaken in respect to RT dose to determine the impact of dose on the estimates of relative risk. The authors concluded that high-dose RT is superior to conventional-dose RT in preventing biochemical failure, although there was a corresponding increase in late grade >2 GI toxicity in men who underwent high-dose RT.

Hummel (2010) was a systematic review which assessed the clinical and cost-effectiveness of IMRT in prostate cancer. IMRT included systems using IGRT; however, this was not explicitly evaluated in the review. Comparators included 3D-CRT and radical prostatectomy. The literature was searched for RCTs published up until May 2009. No RCTs of IMRT versus 3D-CRT in

prostate cancer were identified, but 13 non-randomised studies comparing IMRT with 3D-CRT were found, of which five were available only as abstracts. Outcomes relating to survival were reported in one abstract. Biochemical relapse-free survival was reported in two full-text studies and one abstract. It was reported that biochemical relapse-free survival did not differ between the groups except where there was a dose difference, in which case, higher dose IMRT was favoured over lower dose 3D-CRT. IMRT also appeared to reduce GI toxicity in comparison to 3D-CRT, this being attributed to the increased conformality of IMRT in respect to the rectum. For GU toxicity, some studies reported an increase in late GU toxicity events in men treated with IMRT; however, most studies did not find a significant treatment effect. The authors also reported that health-related quality of life (HR-QoL) improved for both treatment groups following RT, with any group difference resolved by six months after treatment. The results however were based on non-comparative studies, and this was acknowledged as a limitation in regards to making a definitive conclusion.

As the use of FMs is often combined with newer approaches in IGRT and more advanced RT, it is difficult to assess the effect of FMs alone. This assessment report is not an evaluation of dose escalation or more advanced RT techniques. Such techniques, as outlined in Section A.3.4, are the subject of MSAC reviews in progress.

B.3 Assessment of the measures to minimise bias

B.3.1 Study design of the non-randomised comparative studies

Table B.4 presents a summary of the study design, classification of study type and the method of comparison used in the five non-randomised comparative studies identified. Four (Gill 2011; Lips 2007; Singh 2013; Zelefsky 2012) of the five studies were in essence case series with historical controls, comparing results of a single institution FM-based EBRT case series versus a historical bony landmark-based EBRT case series from the same institution. Two studies (Gill 2011; Zelefsky 2012) presented a 'before and after' comparison of the implementation of FM-based image guidance and one study (Singh 2013) presented a comparison of results during the transitional implementation phases. The fifth study (Chung 2009) was a small study which compared the results from two small case series from two centres in two countries (Singapore and United States). Owing to the lack of quality studies, Chung (2009) was included here for reference only.

Table B.4 Summary of study design of the five non-randomised comparative studies

Study	Study type	Study design and method of comparison
Gill (2011)	Case series with historical controls	Single centre, Australia: • IGRT case-series (3D-CRT with dose escalation, 78 Gy, FM-based IG, N=265) after implementation in 2007, versus • historical non-IGRT controls (3D CRT, 74 Gy, N=26) just prior to implementation Prospective data collection (toxicity, clinician-assessed) during RT via standard forms
Lips (2007)	Case series with historical controls	Single centre, the Netherlands: • IGRT case series (IMRT with dose escalation, 76 Gy, FM-based IG, N=116) treated in 2003-2004, versus • historical controls (3D-CRT, 70 Gy, N=99) treated in 1997-2001 Prospective, longitudinal data collection (HR-QoL, clinician-assessed) via questionnaires at 3 time points (baseline, 1 and 6 months after RT)
Singh (2013)	Case series with historical controls	Single centre, Australia: case series of 367 consecutive patients treated with RT during general implementation phase of FM-based IG in 2008-10. Comparison of outcomes in: • those selected for IGRT (3D-CRT with 'modest dose escalation', 70-76 Gy), versus • those selected for non-IGRT (3D-CRT 70-76 Gy) Retrospective data collection via postal questionnaire (treatment-related morbidities, patient-assessed) sent in November 2010 (8-26 months after RT)
Zelefsky (2012)	Case series with historical controls	Single centre, United States (FM-based IG implemented in 2007): • IGRT case-series (high-dose IMRT, FM-based IG, 86.4 Gy, N=186) treated in 2008-09, versus • historical non-IGRT case series (high-dose IMRT, no FM, 86.4 Gy, same margins, N=190) treated in 2006-08 Retrospective evaluation of clinical outcomes (toxicity, biochemical tumour control) at 3-6 months intervals (FU 2-4 years)
Chung (2009)	Comparison of the results of 2 or more single-arm studies	Comparison of 2 small case series from 2 centres in 2 countries: • a small IGRT case series treated by a single radiation oncologist in an US centre (IG-IMRT, 73.8 Gy, N=15), versus • a small non-IGRT case series treated by a single radiation oncologist in a Singaporean centre (IMRT 73.8 Gy, N=10) All patients received definitive IMRT (+ prophylactic nodal RT + prostate boost + ADT) for high-risk non-metastatic prostate cancer

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; ADT= androgen deprivation therapy; FU = follow-up; Gy = Gray; IG = image guidance; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; RT = radiotherapy
Source: Gill (2011); Lips (2007); Singh (2013); Zelefsky (2012); Chung (2009)

Gill (2011) compared the acute toxicity profile during RT of 265 patients who received IGRT (FM-based 3D-CRT or IMRT, 78 Gy) after its implementation in the centre in 2007 versus the acute toxicity profile of 26 patients who received 3D-CRT or IMRT (non-IGRT, 74 Gy) before implementation. All patients in both groups were treated according to the same protocols, target volume expansion margins and planning constraints. Patients not meeting rectal dose constraints were offered IMRT instead. Toxicity data for 10 symptoms were collected prospectively as part of quality assurance using standard assessment forms (electronic for the IGRT group and paper forms for the non-IGRT group) with details of toxicity grading. Patients were actively questioned about the 10 symptoms at each scheduled weekly review or at additional reviews by clinical staff (nursing, RT or medical staff). The authors argued that although the IGRT group received two more fractions (2 Gy/fraction) than the non-IGRT group, the majority of the toxicity assessments would not be affected as toxicity assessments were collected during RT rather afterwards. Patients with only one toxicity assessment (n=16 from IGRT group) or

toxicity assessments >grade 1 at baseline (n=15 from IGRT group; n=3 from non-IGRT group) were excluded from analyses. Overall, toxicity data from 249 patients (14,228 toxicity assessments) who received IGRT were compared with the toxicity data from 26 patients (1,893 toxicity assessments) who received non-IGRT.

Lips (2007) was a prospective longitudinal single centre study from the Netherlands. It compared the health-related quality of life (HR-QoL) of a series of patients (N=116) treated with dose escalated FM-based IMRT (76 Gy) for mostly locally advanced prostate cancer in the centre in 2003-04 versus the HR-QoL of another series of patients (N=99) treated with bony landmark-based conventional 3D-CRT (70 Gy) in 1997-2001. QoL data were collected via a generic health survey, cancer-specific and prostate tumour-specific questionnaires, at three measurement time-points (before treatment, at one and six months after completion of treatment). Only results for 79% of the eligible patients (N=92 for FM-based IMRT group; N=78 for conventional 3D-CRT group) were reported in Lips (2007). The reason(s) for exclusion was not reported, nor were the outcomes of the excluded patients.

Singh (2013) was a retrospective single institution (Australian) study. FM-based IGRT was implemented in the centre in 2008-10. The study compared the treatment-related morbidity results of patients selected to receive IGRT (FM-based 3D-CRT, 70-76 Gy) for localised prostate cancer versus the results of patients treated with non-IGRT (3D-CRT, 70-76 Gy) during the IGRT implementation stages. Morbidity data were self-assessed and were collected retrospectively through a postal questionnaire sent in November 2010, followed by a courtesy telephone reminder if completed questionnaires were not returned within three weeks. Eight-four per cent (n=154) of the patients treated with IGRT returned the questionnaires compared to only 70% (n=128) of the patients treated with non-IGRT. Six patients (4%) from the IGRT group and 10 patients (8%) from the non-IGRT group were excluded from analyses but reasons for exclusion were not reported. Patient-assessed morbidity data recalled by 148 patients treated with IGRT were compared with the data recalled by 118 patients treated with non-IGRT. The follow-up period ranged from 8 to 26 months after RT.

Zelefsky (2012) was another retrospective single institution (US) study. FM-based IGRT was initiated in 2007 in the centre. The study compared the clinical outcomes of a series of 186 patients treated with IGRT (high dose FM-based IMRT, 86.4 Gy) in 2008-09 versus an historical cohort of 190 patients treated with non-IGRT (IMRT without FM, 86.4 Gy) in 2006-07. The median follow-up time was 2.8 years (range 2-6 years).

Chung (2009) was a very small study which compared the toxicity profile of 15 consecutive patients treated with IG-IMRT (FM-based, 54 Gy) to the whole pelvic lymph nodes followed by a prostate boost (19.8 Gy) in a US centre in 2006 versus 10 consecutive patients treated to the same prescription dose with IMRT (non-FM-based) in a Singaporean centre.

B.3.2 Assessment of measures to minimise bias in the studies

Overall, all five studies had various limitations and weaknesses in study design and reporting of results. Table B.5 presents a summary of the assessment of the measures taken to minimise bias in the four case series with historical controls, and Table B.6 presents the assessment for Chung (2009).

Table B.5 Assessment of measures to minimise bias in the four case series with historical controls

Study	Selection of participants	Possibility of confounding	Adequacy of follow-up	Blinding of outcomes assessment
Gill (2011)	2	1	1	1
Lips (2007)	2	1	1	1
Singh (2013)	1	1	1	1
Zelefsky (2012)	1	1	1	1

Selection of participants:

1. The participants were selected retrospectively from case notes, and the investigators were probably aware of the responses to the old treatment at the time of selection.
2. The study was planned; prospective data collection was undertaken in both study periods, and selection of the participants was made without knowledge of the treatment responses.

Possibility of confounding

1. There were differences in factors between participants in the two study periods that were likely to influence the study outcome(s), and these were not adjusted for in the main analysis.
2. There were no differences in factors between participants in the two study periods that were likely to influence the study outcome(s), or any differences were adjusted for in the main analysis.

Adequacy of follow-up

1. Drop-out rates differed between the two study periods, with no assessment of study outcome(s) in the participants who dropped out.
2. There were no drop-outs in either study period, or study outcome(s) were assessed in all participants who began the treatment.

Blinding of outcomes assessment

1. The observer(s) responsible for outcome assessment were aware of which treatment the study participants had been receiving.
2. The observer(s) responsible for outcome assessment were kept fully blinded to the treatment being received by the study participants.

Source: Gill (2011); Lips (2007); Singh (2013); Zelefsky (2012)

Table B.6 Assessment of measures to minimise bias in Chung (2009)

Study	Selection of participants	Possibility of confounding	Adequacy of follow-up	Blinding of outcomes assessment
Chung (2009)	1	1	1	1

Selection of participants:

1. In the studies for either or both alternatives, the participants were selected retrospectively from case notes, and the investigators were probably aware of the responses to the old treatment at the time of selection.
2. The studies for both alternatives were planned, prospective data collection was undertaken for all consecutive patients in the study period, and selection of the participants was made without knowledge of the treatment responses.

Possibility of confounding

1. There were differences in factors between participants in the study populations for the two alternatives that were likely to influence the study outcome(s), and these were not adjusted for in the main analysis.
2. There were no differences in factors between participants in the study populations for the two alternatives that were likely to influence the study outcome(s), or any differences were adjusted for in the main analysis.

Adequacy of follow-up

1. Drop-out rates differed between the studies for the two alternatives, with no assessment of study outcome(s) in the participants who dropped out.
2. There were no drop-outs in the studies for either alternative, or study outcome(s) were assessed in all participants who were commenced on treatment.

Blinding of outcomes assessment

1. In the studies for one or both of the alternatives, the observer(s) responsible for outcome assessment were aware of which treatment the study participants had been receiving.
2. In the studies for both alternatives, the observer(s) responsible for outcome assessment were kept fully blinded to the treatment being received by the study participants.

Source: Chung (2009)

B.4 Characteristics of the included studies

Table B.7 presents a comparison of the study period, population, sample size, type and dose of radiotherapy and follow-up duration across the five studies.

Table B.7 Brief summary of the five non-randomised comparative studies

Study	Country	Study period	Study population	FM-based EBRT	Bony landmark-based EBRT	FU
Gill (2011)	AU, sc	2006-2009	All risks	3D-CRT 78 Gy (N=249)	3D-CRT 74 Gy (N=26)	During RT
Lips (2007)	Netherlands	2003/04 vs 1997/2001	Mostly locally advanced	IMRT 76 Gy (N=92)	3D-CRT 70 Gy (N=78)	6 months after RT
Singh (2013)	AU, sc	2008-2010	Locally advanced	3D-CRT 70-76 Gy (N=148)	3D-CRT 70-76 Gy (N=118)	8-26 months after RT
Zelefsky (2012)	US, sc	2006-2009	Clinically localised	IMRT 86.4 Gy (N=186)	IMRT 86.4 Gy (N=190)	2-4 years
Chung (2009)	Singapore, US	2006	High-risk, non-metastatic	IMRT 73.8 Gy (N=15)	IMRT 73.8 Gy (N=10)	NR

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; AU = Australia; EBRT= external beam radiotherapy; FM = fiducial marker; FU = follow-up; Gy = Gray; IMRT = intensity-modulated radiotherapy; n = number of participants analysed; RT = radiotherapy; sc = single centre; US = United States; vs = versus

Source: Gill (2011); Lips (2007); Singh (2013); Zelefsky (2012); Chung (2009)

Key inclusion and exclusion criteria and details of the positioning strategy and treatment delivery by comparison groups are presented in Appendix G.

Table B.8 presents the disease stage (tumour stage, Gleason score, pre-treatment PSA levels) of participants by comparison groups. Details of the RT and concomitant treatment received by comparison groups are presented in Table B.9.

Table B.8 Baseline characteristics – disease stage by comparison groups

Study	T1	T2	T3	T4	≤G6	G7	≥G8	PSA≤10	PSA10.1-20	PSA>20	ADH
Gill (2011)	–	–	–	–	–	–	–	–	–	–	–
IGRT (N=249)	29%	52%	17%	0%	23%	55%	13%	52%	32%	14%	49%
Non-IGRT (N=26)	35%	50%	12%	4%	35%	42%	23%	54%	31%	15%	42%
Lips (2007)	–	–	–	–	–	–	–	–	–	–	–
FM-IMRT (N=92)	13%	5%	82%	0%	NR	NR	NR	NR	71%*	29%	26%
3D-CRT (N=78)	5%	17%	77%	1%	NR	NR	NR	NR	64%*	36%	12%
Singh (2013)	–	–	–	–	–	–	–	–	–	–	–
IGRT (N=148)	41%	37%	22%	0%	10%	64%	26%	59%	24%	17%	NR
Non-IGRT (N=118)	50%	36%	14%	0%	18%	57%	24%	53%	29%	17%	NR
Zelefsky (2012)	–	–	–	–	–	–	–	–	–	–	–
IGRT (N=186)	80%^	20%#	NR	NR	30%	59%	11%	78%	15%	6%	42%
Non-IGRT (N=190)	75%^	24%#	NR	NR	27%	44%	28%	75%	16%	8%	53%
Chung (2009)	–	–	–	–	–	–	–	–	–	–	–
IG-IMRT (N=15)	13%	40%	47%	0%	7%	33%	60%	NR	NR	NR	NR
IMRT (N=10)	60%	10%	30%	0%	30%	40%	30%	NR	NR	NR	NR

Abbreviations: ADH = androgen deprivation therapy; G = Gleason score; NR = not reported; PSA = prostate-specific antigen (ng/mL); T = tumour stage

* PSA ≤20 ng/mL

^ T stage T1c-T2a

T stage ≥T2b

Note: Data presented in proportions except for mean PSA (ng/mL)

Source: Table 1 in Gill (2011); Table 1, p. 657 in Lips (2007); Table 1 in Singh (2013); Table 1, p. 126 in Zelefsky (2012); Table 1, p. 55 in Chung (2009)

Table B.9 Interventions received by comparison groups in the non-randomised comparative studies

Study/ comparison group	RT treatment: dose received	Concomitant treatment	Follow-up (FU)
Gill (2011)	–	–	–
IGRT 78 Gy (N=249)	3D-CRT: actual dose received NR (4% received IMRT)	Prior TURP 21% (n=56) Baseline ADT 50% (n=131)	During RT
Non-IGRT 74 Gy (N=26)	3D-CRT: actual dose received NR (12% received IMRT)	Prior TURP 23% (n=6) Baseline ADT 42% (n=11)	During RT
Lips (2007)	–	–	–
FM-IMRT 76 Gy (N=92)	76 Gy in 100% of the patients (n=92)	Adjuvant ADT in 26% (n=24)	One and 6 months after RT
3D-CRT 70 Gy (N=78)	70 Gy in 96% of the patients (n=75) ≤66 Gy in 4% (n=3)	Adjuvant ADT in 12% (n=9)	One and 6 months after RT
Singh (2013)	–	–	–
IGRT 70-76 Gy (N=148)	3D-CRT Dose received: • 70 Gy in 14% (n=21) • 74 Gy in 61% (n=90) • 76 Gy in 25% (n=37) Treatment extent: • prostate – 32% (n=47) • prostate and SV – 66% (n=98)	No ADT: 49% (n=73) 3-6 months ADT: 43% (n=64) >6 months ADT: 7% (n=11)	FU since completion of treatment: • 8-17.9 months in 62% • 18-26 months in 38%
Non-IGRT 70-76 Gy (N=118)	3D-CRT Dose received: • 70 Gy in 37% (n=44) • 74 Gy in 56% (n=66) • 76 Gy in 7% (n=8) Treatment extent: • prostate – 46% (n=54) • prostate and SV – 53% (n=63)	No ADT: 58% (n=69) 3-6 months ADT: 37% (n=44) >6 months ADT: 3% (n=4)	FU since completion of treatment: • 8-17.9 months in 36% • 18-26 months in 63%
Zelefsky (2012)	–	–	–
IGRT 86.4 Gy (N=186)	IMRT	Concomitant ADT*: 42% (n=78)	Median FU interval: 24 months
Non-IGRT 86.4 Gy (N=190)	IMRT	Concomitant ADT*: 53% (n=101)	Median FU interval: 49 months
Chung (2009)	–	–	–
IG-IMRT (US)	73.8 Gy (38 fractions)	NR	NR
IMRT (Singapore)	Same as IG-IMRT cohort	NR	NR

Abbreviations: 3D-CRt = 3-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; FM = fiducial marker; FU = follow-up; Gy = Gray; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; NR = not reported; RT = radiotherapy; SV = seminal vesicles; TURP = transurethral resection of the prostate

Source: Table 1, p. 657 in Lips (2007); Table 1 in Singh (2013); Table 1, p. 126 in Zelefsky (2012); Table 2, p. 55 in Chung (2009)

B.5 Outcome measures and analyses

Table B.10 presents a summary of the key outcomes presented in the non-randomised comparative studies relevant to this assessment report and their method of analyses.

Table B.10 Key relevant outcomes and statistical analyses in the non-randomised comparative studies

Study	Definition of outcomes	Method of statistical analysis
Gill (2011)	• 10 toxicity symptoms (urinary frequency, cystitis, bladder spasm, urinary incontinence, urinary retention, proctitis, skin discomfort, diarrhoea, haemorrhoid symptoms, fatigue) graded according to CTCAE criteria, version 3.0 • Overall maximum GU toxicity (urinary frequency, cystitis, bladder spasm, urinary incontinence, urinary retention) • Overall maximum GI toxicity (proctitis, diarrhoea) • Duration of toxicity (number of days experienced a ≥G2 or ≥G3 toxicity) – defined as the number of days from onset of a grade 2 or grade 3 toxicity until the grade of toxicity returned to <grade 2 or the end of treatment if it did not improve	• For each toxicity symptom: between-group frequencies of experiencing at least one ≥G2 or ≥G 3 toxicity event compared using Fisher's exact test • Between-group difference in median number of days tested by using Wilcoxon rank sum test
Lips (2007)	• General HR-QoL: RAND-36 generic health survey • Cancer-specific QoL: EORTC QLQ-C30(+3) • Prostate tumour-specific QoL: EORTC QLQ-PR25 • Toxicity based on the CTC version 2.0	Change in QoL (baseline vs 1 month, baseline vs 6 months) based on general linear model repeated-measures analyses; test results with a p value of <0.01 were considered statistically significant with Bonferroni correction
Singh (2013)	• Rectal symptoms (bowel frequency, diarrhoea, rectal pain, mucus discharge, urgency, rectal bleeding, change in bowel habits) • Urinary symptoms (frequency, nocturia, haematuria, weak flow, pain/dysuria, incontinence, dribbling) • Prevalence of rectal and urinary dysfunction symptoms (moderate to severe) (based on the scoring system from Litwin 1995)	Change in severity of dysfunctional symptoms, by shorter/longer FU
Zelefsky (2012)	• PSA relapse-free survival (PSA relapse defined according to the Phoenix definition: absolute nadir plus 2 ng/mL date at the call) • Acute and late toxicities classified and graded according to the CTCAE version 3.0	• Actuarial likelihood as determined by the Kaplan-Meier method • Cox regression analyses to identify predictors of outcomes
Chung (2009)	Acute rectal and bladder toxicities, graded by RTOG and CTCAE criteria, version 3.0 Exact definition of rectal or bladder toxicities not reported	Not reported

Abbreviations: CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30(+3) = European Organisation for Research and Treatment of Cancer core quality-of-life questionnaire; EORTC QLQ-PR25 = EORTC prostate cancer module; GI = gastrointestinal; GU = genitourinary; HR-QoL = health-related quality of life; RAND-36; PSA = prostate-specific antigen; RTOG = Radiation Therapy Oncology Group; vs = versus

Source: Gill (2011); Lips (2007); Singh (2013); Zelefsky (2012); Chung (2009)

Lips (2007) used three validated questionnaires to evaluate health-related quality of life (HR-QoL). General HR-QoL was measured by RAND-36, a generic health survey. Cancer-specific QoL was measured by the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30 (+3) version) which incorporates five functional scales, one global health/QoL scale, three symptom scales and six single items. Prostate tumour-specific QoL were measured by the EORTC prostate cancer module (QLQ-PR25). All scales and item

scores were rated/transformed into 0-100 scale. For RAND-36 and the EORTC functional scales, a high score value indicates better functioning and QoL. For the EORTC symptom scales a higher score indicates greater symptomatology and worse QoL. Any change in score of ≥10 points was considered clinically relevant. QoL data were collected at three time-points: baseline (before treatment), at one and six months after completion of treatment.

The National Cancer Institute (NCI) Common Toxicity Criteria (CTC) system (CTC v1.0) was first developed in 1983 for the grading of acute adverse effects of chemotherapy (18 criteria covering 13 organs). It was updated and expanded in 1998 (CTC v2.0) to include 260 criteria covering 22 organs, including the systematic inclusion of criteria for grading of the acute effects of radiotherapy. The Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) Late Morbidity System was created in 1984 and was appended to the CTC for late effects of treatment. However, there were known inconsistent concordance and correlations between the RTOG/EORTC and CTC systems highlighting the need for a common system as well as for comparing results from different studies. In 2003, CTC v2.0 underwent significant revision and was renamed the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) (370 criteria covering all organs, acute and late effects for all modalities). It became the first comprehensive, multimodality grading system to include both acute and late effects (Trotti 2003). Table B.11 presents a summary of the grading of severity of adverse events (AEs) in the CTCAE v3.0.

Table B.11 Grading of severity of adverse events (CTCAE v3.0)

Grading	Severity	Description
Grade 1	Mild AE	Usually asymptomatic, do not interfere with functional endpoints, interventions/medications generally not indicated
Grade 2	Moderate AE	Usually symptomatic, interventions such as local treatment or medications may be indicated, may or may not interfere with specific functions but not enough to impair activities of daily living
Grade 3	Severe AE	Very undesirable, usually multiple, disruptive symptoms, more serious interventions, including surgery or hospitalisation, may be indicated
Grade 4	Life-threatening or disabling AE	Potentially life-threatening, catastrophic, disabling, or result in loss of organ, organ function, or limb
Grade 5	Death related to AE	–

Abbreviations: AE = adverse event; CTCAE v3.0 = Common Terminology Criteria for Adverse Events version 3.0
Source: Trotti (2003)

Severity of rectal and urinary AE was graded using CTCAE v3.0 in general. One study (Lips 2007) used version 2 (Trotti 2002) while Singh (2013) used the scoring system by Litwin (1995).

B.6 Systematic overview of results

B.6.1 Survival outcomes

None of the non-randomised comparative studies reported on overall survival, cause-specific survival, or distant metastasis-free survival outcomes.

B.6.2 Local tumour control

Only one non-randomised comparative study (Zelefsky 2012) reported on prostate-specific antigen (PSA) relapse-free survival. Table B.12 presents the PSA relapse-free survival outcomes for the IGRT case series and the non-IGRT historical controls in high-risk patients in the study (risk classification was based on the National Comprehensive Cancer Network (NCCN)). The authors reported that there was significant improvement in biochemical control at three years for high-risk patients treated with IGRT versus patients treated with non-IGRT (PSA relapse-free survival: 97% versus77.7% at three years respectively (p=0.05). The survival outcomes for the low and intermediate risk patients were similar in both groups. In addition, regression analyses for the high-risk cohort also identified IGRT as being associated with significantly less PSA relapse. Note however that high-risk patients consisted of only 19% (N=35) of the IGRT cohort and 35% (N=89) of the historical non-IGRT cohort.

Table B.12 Local tumour control outcome in Zelefsky (2012)

Study/ Outcome	FM-based EBRT	Bony landmark-based EBRT	Difference
Zelefsky (2012)	**IG-IMRT 86.4 Gy (ADT 42%, median FU 24 months) (2008-09) (N=186)**	**IMRT 86.4 Gy (ADT 53%, median FU 49 months) (2006-08) (N=190)**	**–**
3-year PSA relapse-free survival	97% of 35 high-risk patients	77% of 67 high-risk patients	p=0.05

Abbreviations: ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; FM = fiducial marker; FU = follow-up; Gy = Gray; IG = image-guided; IMRT = intensity-modulated radiotherapy; n = number analysed; N/A = not applicable; PSA = prostate-specific antigen

Risk classification was based on the National Comprehensive Cancer Network (NCCN)

Source: Zelefsky (2012)7

B.6.3 Health-related quality of life (HR-QoL) outcomes

Only one non-randomised comparative study (Lips 2007) reported on comparative health-related quality of life (HR-QoL) in patients with locally advanced prostate cancer. The mean QoL scores at one and six months after completion of RT for patients treated with dose-escalated FM-based IMRT in 2003-04 or for patients treated with 3D-CRT (no FM) in 1997-2001 are presented in Appendix G. Lips (2007) reported that there was no statistically significant between-group difference in change in mean score from baseline to one or six months for the majority of the QoL items, including bowel symptoms/function and sexual functioning/activity as assessed by

the prostate tumour-specific instrument EORTC QLQ-PR25. Between-group difference in change in mean scores from baseline however, was statistically significant at one month for six QoL items (Table B.13), favouring FM-based dose-escalated IMRT except for one item – pain as measured by RAND-36. Mean reduction in pain score at one month for the 3D-CRT cohort was 10.3, considered as clinically relevant by the authors. Mean increase in urinary symptoms/problems (EORTC QLQ-PR25) from baseline was 16.4 for the 3D-CRT cohort, considered also as reaching clinical relevance (see Section B.6.5 below for further information on urinary adverse events).

Table B.13 Change in mean score from baseline to one month for selected six QoL items in Lips (2007)

	IMRT (76 Gy, FM, ADT 26%) (2003-04) (N=92)	3D-CRT (70 Gy, no FM, ADT 12%) (1997-2001) (N=78)	Difference (*p* value)
RAND-36	–	–	–
Social functioning	3.5	−7.4	0.006
Pain	−1.0	**−10.3 (<0.0001)**	0.01
Change in health	**9.9 (0.002)**	−8.7 (0.01)	<0.001
EORTC QLQ-C30(+3)	–	–	–
Physical functioning	−0.3	−5.7 (0.002)	0.006
Role functioning	−1.8	**−12.2 (<0.0001)**	0.006
EORTC QLQ-PR25	–	–	–
Urinary symptoms/problems	2.5	**16.4 (<0.0001)**	<0.0001

Abbreviations: 3D-CRT= 3-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; EORTC QLQ-C30(+3) = European Organisation for Research and Treatment of Cancer core quality-of-life questionnaire; EORTC QLQ-PR25 = EORTC prostate cancer module; FM = fiducial marker; Gy = Gray; IMRT = intensity-modulated radiotherapy; N, number analysed; QoL = quality of life

A change in score of ≥10 points is considered clinically relevant and significant

Change in QoL in **bold** indicates statistically significant change from baseline

Source: Table 3, p 659 in Lips (2007)

Table B.14 presents the change in mean scores for the six items from baseline to six months. There was no statistically significant between-group difference in change in mean score from baseline at six months. The authors concluded that despite the use of a higher dose (76 Gy) in the IMRT group, there was no significant deterioration in QoL compared with the 3D-CRT (70 Gy) group.

Table B.14 Change in mean score from baseline to six months for selected six QoL items in Lips (2007)

	IMRT (76 Gy, FM) (N=92)	3D-CRT (70 Gy, no FM) (N=78)	Difference (*p* value)
RAND-36	–	–	–
Social functioning	**7.6 (<0.0001)**	4.3	NS
Pain	3.5	−4.2	NS
Change in health	**18.7 (<0.0001)**	6.0	NS
EORTC QLQ-C30(+3)	–	–	–
Physical functioning	−0.7	−2.3	NS
Role functioning	1.5	−2.2	NS
EORTC QLQ-PR25	–	–	–
Urinary symptoms/function	−2.3	−4.0	NS

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; EORTC QLQ-C30(+3) = European Organisation for Research and Treatment of Cancer core quality-of-life questionnaire; EORTC QLQ-PR25 = EORTC prostate cancer module; FM = fiducial marker; Gy = Gray; IMRT = intensity-modulated radiotherapy; N = number analysed; NS = non-significant; QoL = quality of life

A change in score of ≥10 points is considered clinically relevant and significant

Change in QoL in **bold** indicates statistically significant change compared with baseline

Source: Table 3, p 659 in Lips (2007)

B.6.4 Treatment-related morbidity – gastrointestinal (GI) adverse events (AEs)

All five non-randomised comparative studies reported on gastrointestinal (GI) or rectal adverse events (AEs). Four studies (Gill 2011; Lips 2007; Zelefsky 2012; Chung 2009) reported on acute AEs during or at six months after completion of RT. Singh (2013) and Zelefsky (2012) reported on late AEs 8-26 months and 2-4 years after RT respectively.

Three studies (Gill 2011; Zelefsky 2012; Chung 2009) graded severity of AEs using the CTCAE v3.0. Lips (2007) used CTCAE v2.0 while Singh (2013) reported on moderate to severe AEs based on Litwin (1995). GI or rectal AEs in all of the studies were clinician-based evaluation except in Singh (2013) which used patient-assessed questionnaires.

Acute GI AEs

Table B.15 presents a summary of the occurrence of acute GI AEs by comparison groups and by severity in the four non-randomised comparative studies that used CTCAE.

Table B.15 Acute gastrointestinal (GI) AEs in the non-randomised comparison studies

	FM-based EBRT: n (%)	Bony landmark-based EBRT: n (%)
Gill (2011)*	**3D-CRT (78 Gy, FM, ADT 49%) (2007-09) (N=265)**	**3D-CRT (74 Gy, no FM, ADT 42%) (2006) (N=26)**
Grade 1	132 (49.8%)	9 (34.6%)
Grade 2	23 (8.7%)	5 (19.2%)
Grade 3	0 (0.0%)	0 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)
Lips (2007)	**IMRT (76 Gy, FM, ADT 26%) (2003-04) (N=92)**	**3D-CRT (70 Gy, no FM, ADT 12%) (1997-2001) (N=78)**
Grade 1	NR	NR
Grade 2	NR	NR
Grade 3	0.0%	0.0%
Grade 4	0.0%	0.0%
Zelefsky (2012)	**IMRT (86.4 Gy, FM, ADT 42%) (2008-09) (N=186)**	**IMRT (86.4 Gy, no FM, ADT 53%) (2006-08) (N=190)**
Grade 1	43 (23.1%)	32 (16.8%)
Grade 2	2 (1.1%)	2 (1.1%)
Grade 3	0 (0.0%)	1 (0.5%)
Grade 4	NR	NR
Chung (2009)	**IMRT (73.8 Gy, FM, ADT NR) (2006) (N=15)**	**IMRT (73.8 Gy, no FM, ADT NR) (2006) (N=10)**
Grade 1	8 (53.3%)	4 (40.0%)
Grade 2	1 (6.7%)	5 (50.0%)
Grade 3	0.0%	0.0%
Grade 4	0.0%	0.0%

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; CTCAE v3.0 = Common Terminology Criteria for Adverse Events version 3.0; EBRT = external beam radiotherapy; FM = fiducial marker; FU = follow-up; Gy = Gray; IMRT = intensity-modulated radiotherapy; N = number of patients; NR = not reported

Grading of severity was according to CTCAE v3.0 except for Lips (2007) which used CTCAE v2.0

Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: life-threatening or disabling

* Overall maximum toxicity: two (proctitis and diarrhoea) of the 10 symptoms evaluated were grouped together in Gill (2011)

Source: Table 3 in Gill (2011); p 658 in Lips (2007); Table 2, p 127 in Zelefsky (2012); Table 5, p 58 in Chung (2009)

Severe acute GI AEs were rare across all four studies. Only one patient treated with high-dose IMRT (without FM) in Zelefsky (2012) had acute grade 3 (severe) GI AE.

In Zelefsky (2012), when compared with the historical cohort of patients treated with high-dose IMRT (no FM), patients treated with the same dose of IMRT but with FM also experienced a greater risk of acute grade 1 GI AEs (23% versus 17%). The risk of acute grade 2 GI AEs was rare in the study (1% for both groups).

In Gill (2011), when compared with the small historical cohort of patients treated with 3D-CRT (no FM), patients treated with dose-escalated 3D-CRT (with FM) experienced a greater risk of acute grade 1 (mild) GI AEs (overall maximum toxicity) (49% versus 35%), but a lower risk of acute grade 2 (moderate) GI AEs (9% versus 19%). Risk of at least one ≥grade 2 acute diarrhoea

was significantly lower (3% versus 15%), but for longer (median 10.3 days versus 9.3 days) in the FM cohort than in the non-FM cohort (Table B.16).

Table B.16 Acute proctitis and diarrhoea in Gill (2011)

	3D-CRT (78 Gy, FM) (2007-09) (N=265)	3D-CRT (74 Gy, no FM) (2006) (N=26)	Difference *p*-value
At least one ≥grade 2 proctitis event	6%	15%	0.0862
At least one ≥grade 2 diarrhoea event	3%	15%	0.0174
Number of days with ≥grade 2 proctitis	10.5 (7.8-18)*	20.8 (11.5-28.4)*	0.0616
Number of days with ≥grade 2 diarrhoea	10.3 (4.8-10.6)*	9.3 (7-12.9)*	0.0033

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; FM = fiducial marker; Gy = Gray; N = number of patients
Grading of severity was according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.
Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: life-threatening or disabling
* Median (interquartile range)
Source: Tables 2 and 4 in Gill (2011)

Late GI AEs

Two non-randomised comparative studies reported on comparative late GI or rectal AEs.

Zelefsky (2012) reported that three-year actuarial likelihood of ≥grade 2 rectal AEs was similar and low for the FM and the non-FM cohorts: 1.0% and 1.6% respectively (p=0.81).

Singh (2013) only reported on moderate to severe rectal AEs. Table B.17 presents the seven late rectal AEs reported in the study by comparison groups. The authors reported that less patients in the FM group experienced moderate to severe rectal AEs than the non-FM group across all seven rectal AEs. The odds of experiencing diarrhoea, rectal pain, urgency and a change in bowel habit were significantly lower in the FM group than in the non-FM group.

Table B.17 Moderate to severe late rectal AE in Singh (2013)

	Univariable: n (%)	–	–	Multivariable analysis	–
Rectal AE	**3D-CRT (FM) (70-76 Gy, 76 Gy 25%) (STFU 62%, 2008-10) (N=148)**	**3D-CRT (no FM) (70-76 Gy, 76 Gy 7%) (STFU 36%, 2008-10) (N=118)**	*p*	**OR (95% CI)**	*p*
Bowel frequency	21 (14.2%)	19 (16.1%)	.617	0.74 (0.33, 1.64)	.46
Diarrhoea	4 (2.7%)	15 (12.7%)	.001	**0.09 (0.02, 0.35)**	.0001
Rectal pain	1 (0.7%)	6 (5.1%)	.011	**0.07 (0.009, 0.70)**	.02
Mucus discharge	3 (2.0%)	4 (3.4%)	.473	0.10 (0.009, 1.17)	.067
Urgency	10 (6.8%)	23 (19.5%)	.001	**0.27 (0.11, 0.63)**	.002
Rectal bleeding	4 (2.7%)	5 (4.2%)	.474	0.88 (0.11, 7.0)	.9
Change in bowel habits	6 (4.1%)	21 (17.8%)	.0001	**0.18 (0.06, 0.52)**	.002

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; AE = adverse event; CI = confidence interval; FM = fiducial marker; OR = odds ratio; STFU = short-term follow-up (8-17.9 months after completion of RT)
ORs in **bold** indicate reaching statistical significance
Source: Table 4 in Singh (2013), follow-up at 8-26 months after completion of radiotherapy

B.6.5 Treatment-related morbidity – genitourinary (GU) AEs

All five non-randomised comparative studies reported on genitourinary (GU) AEs. Four studies (Gill 2011; Lips 2007; Zelefsky 2012; Chung 2009) reported on acute AEs during or at six months after completion of RT. Singh (2013) and Zelefsky (2012) reported on late AEs 8-26 months and 2-4 years after RT respectively.

Acute GU AEs

Table B.18 presents a summary of the occurrence of acute GU AEs by comparison groups and by severity in the four non-randomised comparative studies that used CTCAE.

Table B.18 Acute genitourinary (GU) AEs in the non-randomised comparison studies

	FM-based EBRT: n (%)	Bony landmark-based EBRT: n (%)
Gill (2011)*	**3D-CRT (78 Gy, FM, ADT 49%) (2007-09) (N=265)**	**3D-CRT (74 Gy, no FM, ADT 42%) (2006) (N=26)**
Grade 1	80 (30%)	9 (35%)
Grade 2	145 (55%)	10 (38%)
Grade 3	23 (9%)	6 (23%)
Grade 4	0 (0%)	0 (0%)
Lips (2007)	**IMRT (76 Gy, FM, ADT 26%) (2003-04) (N=92)**	**3D-CRT (70 Gy, no FM, ADT 12%) (1997-2001) (N=78)**
Grade 1	NR	NR
Grade 2	NR	NR
Grade 3	1 (1%)	0 (0%)
Grade 4	0 (0%)	0 (0%)
Zelefsky (2012)	**IMRT (86.4 Gy, FM, ADT 42%) (2008-09) (N=186)**	**IMRT (86.4 Gy, no FM, ADT 53%) (2006-08) (N=190)**
Grade 1	115 (62%)	66 (35%)
Grade 2	34 (18%)	51 (27%)
Grade 3	0 (0%)	0 (0%)
Grade 4	NR	NR
Chung (2009)	**IMRT (73.8 Gy, FM, ADT NR) (2006) (N=15)**	**IMRT (73.8 Gy, no FM, ADT NR) (2006) (N=10)**
Grade 1	14 (93%)	4 (40%)
Grade 2	1 (7%)	4 (40%)
Grade 3	0.0%	0.0%
Grade 4	0.0%	0.0%

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; CTCAE v3.0 = Common Terminology Criteria for Adverse Events version 3.0; EBRT = external beam radiotherapy; FM = fiducial marker; FU = follow-up; Gy = Gray; IMRT = intensity-modulated radiotherapy; N= number of patients; NR = not reported

Grading of severity was according to CTCAE v3.0 except for Lips (2007) which used CTCAE v2.0

Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: life-threatening or disabling

* Overall maximum toxicity: five (urinary frequency, cystitis, bladder spasm, urinary incontinence, urinary retention) of the 10 symptoms evaluated were grouped together in Gill (2011)

Source: Table 3 in Gill (2011); p 658 in Lips (2007); Table 2, p 127 in Zelefsky (2012); Table 5, p 58 in Chung (2009)

There were no acute grade 4 (life-threatening or disabling) GU AEs across all four studies.

There were no acute grade 3 (severe) GU AEs in Zelefsky (2012) or Chung (2009). Only one patient (1%) in the FM group experienced acute grade 3 (severe) GU AE in Lips (2007). Nine per cent of the patients treated with dose-escalated 3D-CRT (FM) in Gill (2011) had acute grade 3 GU AEs compared to 23% in the much smaller historical cohort treated with 3D-CRT (no FM).

In Zelefsky (2012), 80% of the patients in the FM group had grade 1 (62%) or grade 2 (18%) acute GU AEs, compared with 62% of the patients in the non-FM group (35% grade 1; 27% grade 2). Chung (2009) reported similar results: 100% of the FM group (93% grade 1; 7% grade 2) compared with 80% of the non-FM group (40% grade 1; 40% grade 2) experienced acute GU AEs.

Gill (2011) reported somewhat different results: a greater risk of grade 2 GU AEs at six months after completion of RT in the FM group (55%) than in the non-FM group (38%), but a slightly lower risk of grade 1 GU AEs (30% versus 35%). Risk of at least one ≥grade 2 acute urinary frequency was numerically lower (35% versus 52%) and significantly shorter (median 14.5 days versus 28 days) in the FM cohort than in the non-FM cohort (Table B.19).

Table B.19 Acute genitourinary (GU) AEs in Gill (2011)

	3D-CRT (78 Gy, FM) (2007-09) (N=265)	3D-CRT (74 Gy, no FM) (2006) (N=26)	Difference *p*-value
At least one ≥grade 2 urinary frequency	35%	52%	0.1144
At least one ≥grade 2 cystitis	47%	42%	0.6857
At least one ≥grade 2 bladder spasm	1%	0%	1
At least one ≥grade 2 urinary incontinence	3%	0%	1
At least one ≥grade 2 urinary retention	7%	0%	0.3825
At least one ≥grade 3 urinary frequency	7%	23%	0.0188
At least one ≥grade 3 cystitis	1%	4%	0.3243
Number of days with ≥grade 2 urinary frequency	14.5 (10-26.5)*	28 (23.4-32.9)*	0.0179
Number of days with ≥grade 2 cystitis	15 (8.5-27)*	24.5 (19.3-31.3)*	0.7603
Number of days with ≥grade 2 bladder spasm	8.8 (8.1-9.4)*	No events	0.6566
Number of days with ≥grade 2 urinary incontinence	10.5 (7.8-15.3)*	No events	0.3919
Number of days with ≥grade 2 urinary retention	8.5 (6-15.5)*	No events	0.1746

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; AE = adverse event; FM = fiducial marker; Gy = Gray; N,= number of patients

Grading of severity was according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: life-threatening or disabling

* Median (interquartile range)

Source: Tables 2 and 4 in Gill (2011)

Late GU AEs

Two non-randomised comparative studies (Zelefsky 2012; Singh 2013) reported on comparative late GU AEs.

Zelefsky (2012) reported that three-year actuarial likelihood of ≥grade 2 GU AEs was significantly lower in patients treated with high-dose IMRT (with FM) than in patients treated the same but without FM: 10.4% versus 20.0% respectively (p=0.02) (Table B.20).

Table B.20 Actuarial likelihood of ≥grade 2 late GU AEs in Zelefsky (2012)

Study/ Outcome	FM-based EBRT	Bony landmark-based EBRT	Difference
Zelefsky (2012)	**IG-IMRT 86.4 Gy (ADT 42%, median FU 24 months) (2008-09) (N=186)**	**IMRT 86.4 Gy (ADT 53%, median FU 49 months) (2006-08) (N=190)**	**–**
3-year likelihood of grade 2 and higher urinary toxicity	10.4%	20.0%	*p*=0.02

Abbreviations: ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; FM = fiducial marker; FU = follow-up; GU = genitourinary; Gy = Gray; IG = image-guided; IMRT = intensity-modulated radiotherapy;
Source: Zelefsky (2012)7

Singh (2013) reported on a number of self-assessed late urinary dysfunctional symptoms. Table B.21 presents the dysfunctional symptoms by comparison group in the study. The authors reported that urinary dysfunction at 8-26 months after RT was similar in both treatment groups.

Table B.21 Comparison of late urinary symptoms between IGRT and non-IGRT groups in Singh (2013)

	3D-CRT (70-76 Gy, FM) (2008-10) (N=148)	3D-CRT (70-76 Gy, FM) (2008-10) (N=118)
Dribbling	3.5%	3.6%
Incontinence	16.9%	18.2%
Pain/dysuria	0.6%	0.8%
Weak flow	14.7%	17.0%
Haematuria	0.0%	0.0%
Nocturia	17.4%	17.7%
Frequency	31.6%	30.1%

Abbreviations: IGRT = image-guided radiotherapy; TROG = Trans-Tasman Radiation Oncology Group
The authors included data from 62 men who received 66 Gy to the prostate and seminal vesicles in 1996-2000 in TROG 96.01 trial to provide historical context
Source: Percentages were estimated from reading off Figure 2 in Singh (2013)

B.6.6 Evidence from the non-comparative case series

Of the 20 non-comparative case series that evaluated FM-based EBRT, only one recruited patients post-prostatectomy (Chua 2013). Apart from 3 studies which did not report on the method of implantation, all the other 17 studies implanted FMs under TRUS guidance. Three or four gold seeds were used as FMs in all 20 studies. Eight studies presented relevant information on the clinical effectiveness of FM-based EBRT. Table B.22 provides a brief summary of the characteristics of these studies and further details are presented in Appendix H. All eight studies were case series from single institutions and included men with localised prostate cancer. Only two of the studies were prospective, both being from Australia.

Table B.22 Summary of the characterises of the eight cohort/case-series studies

Study	Country Study period	Study design	N	Type of RT received	FU
Chua (2013)	Australia 2007-2010	Prospective case series	75	IG IMRT – nine-field, dose prescription to the PTV 64-66 Gy for adjuvant RT, 66 Gy for salvage RT IG – 3 gold seeds under TRUS guidance	Unclear
Eade (2011)	Australia 2007-2009	Prospective case series	101	IG IMRT– low dose 78-80Gy (56 Gy in 38 fractions) 82-84 Gy (60 Gy in 40 fractions) IG – 3 gold seeds under TRUS guidance	Median follow-up was 21 months (8-39 months)
Linden (2009)	United States 2003-2006	Retrospective case-series	98	IG IMRT – mean radiation 75.6 Gy (range 50-79.2) IG – 3 gold seeds under TRUS guidance	Unclear 70 patients had follow-up of 3 months
Lips (2008)	Netherlands 2001-2004	Retrospective case series	331	IG IMRT – mean dose of 76 Gy in 35 fractions IG – 3 gold seeds under TRUS guidance	Mean follow-up was 47 months (31-71 months)
Martin (2009)	Canada 2001-2003	Retrospective case series	259	IG EBRT – 3D-CRT or IMRT Mean dose of 79.87 Gy in 42 fractions IG – 3 gold seeds under TRUS guidance	Median follow-up was 67.8 months (24.4-84.7 months)
Nath (2011)	United States 2005-2008	Retrospective case series	100	IG-IMRT 74-78 Gy (median 76 Gy) IG – 3 gold seeds under TRUS guidance	Median follow-up was 22 months
Takeda (2012)	Japan 2003-2008	Retrospective case series	141	IG-IMRT: 76 (13pts) or 80 Gy (128pts) IG – 3 gold seeds	Median follow-up was 66 months (17-111 months)
Vesprini (2011)	Canada 1997-2003	Retrospective case series	362	IG-EBRT (IMRT/3DCRT): 75.6-79.8 Gy in 42 fractions IG – 3 gold seeds under TRUS guidance	Median follow-up was 58.3 months (8.5-124 months)

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; Gy = Gray; IG = image-guided; IMRT = intensity-modulated radiotherapy; N = number of study participants; PTV = planning target volume; RT = radiotherapy;
Source: Chua (2013); Eade (2011); Linden (2009); Lips (2008); Martin (2009); Nath (2011); Takeda (2012); Vesprini (2011)

Three studies reported on survival (Martin 2009; Nath 2011; Takeda 2012; Vesprini 2011); however, only one of these studies (Takeda 2012) provided sufficient detail to enable analysis (see Appendix H).

Three studies reported on biochemical control. Both Martin (2009) and Vesprini (2011) using the Phoenix definition with a five-year biochemical freedom from diseases of 79.4% (95% CI 74.1%, 84.6%) and 76% (95% CI 70%, 81%) respectively. Biochemical failure was also reported in the study by Takeda (2012) which noted that five-year actuarial PSA relapse-free survival outcomes for the intermediate and high risk groups were 100% and 82.2% respectively.

In terms of toxicity, acute GI rates reported in the case-series studies were largely consistent with the ranges reported in the FM arms of the non-randomised comparative studies, with the exception of the grade 2 rates reported by Lips (2008) and Chua (2013) (Appendix H).

Late GI toxicity was reported in four of the studies (Lips 2008; Martin 2009; Nath 2011; Takeda 2012) with one of these studies reporting instances of grade 3 or worse toxicities (Lips 2008).

Seven studies reported on GU toxicity. Rates varied across the studies; grade 3 toxicities following FM-based EBRT were reported in three studies. A grade 4 toxicity (incontinence) was also reported in Chua (2013); this condition however was pre-existing to RT.

Four of the studies reported on late GU toxicity, with grade 3 or worse GU toxicities reported in three studies.

Summary

Case-series studies are known to have a high degree of bias. Given the limited comparative evidence on the use of the FM in EBRT, the case-series evidence is presented here to assist with judgments around consistency of findings.

Little can be said regarding survival or local outcomes as comparative data is lacking; however, it would appear that rates of acute toxicities reported in the case-series studies are largely consistent with those reported in the historical case-controls studies.

B.6.7 Safety of the implantation of FMs (procedural complications)

Safety studies - study characteristics

Procedural complications were not evaluated or reported in any of the five non-randomised comparative studies. Four single arm studies (Escudero 2010; Gill 2012; İğdem 2009; Langenhuijsen 2007) specifically evaluated complications related to the implantation of FM rather than toxicity associated with EBRT. Table B.23 presents an overview of the main characteristics of the safety studies. Further details regarding the studies are presented in Appendix I.

All four studies were large case series and evaluated complications through the use of a questionnaire. Response rates ranged from 69% to 100%. The study by Gill (2012) had the lowest response rate, possibly because it required patients to post back the questionnaire, whereas in the studies by Langenhuijsen (2007), İğdem (2009) and Escudero (2010) the questionnaire was completed as part of the clinical follow-up. Gill (2012) however did provide the characteristics of the non-responders which showed that the two groups (responders and non-responders) were similar.

In Gill (2012), complications were assessed using the CTCAE, whereas in the remaining three studies an unspecified questionnaire was used to capture implant complications. Pain was also evaluated differently among the studies, with the publications by Gill (2012) and İğdem (2009) using the Wong Baker pain scale and Langenhuijsen (2007) using a visual analogue scale (VAS). Follow-up was similar among the three studies. In contrast, Escudero (2010) did not specifically evaluate pain and follow-up was not specifically recorded.

Table B.23 Overview of the main characteristics of the safety studies

Study, study population (N), study period	Study population	Study design	Methods of FM implantation	Follow-up	Outcomes
Escudero (2010) N=126 Netherlands 2001 – unclear	Men diagnosed with localised or locally advanced prostate cancer	Case-series (questionnaire)	Three (n=10) or four (n=116) FM were implanted under TRUS guidance. Prophylactic antibiotics taken if appropriate	Unclear	100% completion of questionnaire (assumption) Questionnaire designed for study to identify complications (type not specified)
Gill (2012) N=339 Australia 2006-2009	Men who underwent gold seed FM implantation during the study period	Case-series (questionnaire)	Local anaesthesia was used. Three FMs were implanted under TRUS guidance. Prophylactic antibiotics taken if appropriate	Median time from fiducial insertion to be being sent questionnaire was 21 months (range, 5-37 months)	234 (69%) returned the questionnaire Of all answers: - 7% answered don't remember - 76% answered no - 7% answered yes - 9% answered no more than usual CTCAE Wong Baker faces pain scale
İğdem (2009) N=177 Turkey 2005-2008	Men who underwent gold seed FM implantation as part of high-dose conformal/ IMRT during the study period	Case-series (questionnaire)	Three FM were implanted under TRUS guidance. Prophylactic antibiotics taken if appropriate	Median time from fiducial insertion to being sent questionnaire was 57 weeks (range, 1-146 weeks)	135 (76%) returned the questionnaire Questionnaire designed for study to identify complications (type not specified) Wong Baker faces pain scale
Langenhuijsen (2007) N=236 Netherlands 2001-2005	Men who underwent gold seed FM implantation during the study period	Case-series (questionnaire)	Three FM were implanted under TRUS guidance. Prophylactic antibiotics taken if appropriate	Questionnaire completed at a mean time of 90 weeks following FM implantation	209 (87%) returned the questionnaire Questionnaire designed for study to identify complications (type not specified) VAS 0-10 scale (0 no pain; 10 most pain)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; FM = fiducial marker; IMRT = intensity-modulated radiotherapy; N = number of study participants; TRUS = trans-rectal ultralsound; VAS = visual analogue scale
Source: Escudero (2010); Gill (2012); İğdem (2009); Langenhuijsen (2007)

Safety studies – complication rates

The complication rates across the four studies are reported below in Table B.24. In most cases complications were resolved within two weeks of implantation. Gill (2012) reported that 9% (n=21) of patients had symptoms that lasted for more than 14 days, which included frequency, dysuria, obstructive symptoms and rectal bleeding. In Langenhuijsen (2007), one patient reported

repeat blood loss for longer than two weeks; no other complications were described as lasting longer than seven days. In terms of moderation complications, antibiotics were given to patients with fever. Similarly in the study by İğdem (2009) antibiotics were given to three patients due to fever (infection) following FM implantation. No other medical intervention was reported. Escudero (2010) also noted that two patients out of 126 experienced infectious prostatitis and fever which required treatment with antibiotics. The most serious complication was reported in Gill (2012) which included a grade 4 infection resulting in septicaemia following insertion of FMs. Two other patients also experienced a grade 3 infection requiring admission to hospital.

Table B.24 Complication rates in the safety studies: n (%)

Complication/Adverse events	Langenhuijsen (2007) (N=209)	Gill (2012) (N=234)	İğdem (2009) (N=135)	Escudero (2010) (N=126)
Minor	–	–	–	–
Haematuria (length not specified)	–	–	20^ (14.8)	0 (0)
Haematuria ≤1 day	–	–	14 (10.4)	–
Haematuria >3 days	8 (3.8)	26 (12.5)	4 (3)	–
Haematospermia^	15 (18.5)	20 (9.6)	–	–
Rectal bleeding	19 (9.1)	26 (11.1)	5 (3.7)	8 (6.4)
Voiding complaints (dysuria, frequency)	4 (1.9)	43 (18.4)	–	–
Obstructive symptoms	–	9 (3.8)	–	4 (3.2)
Moderate	–	–	–	–
Pain requiring analgesics	6 (2.9)	1 (0.4)	–	–
Fever (symptomatic of infection)	4 (1.9)	7 (3)	3 (2.2)	2 (1.6)
Nausea/vomiting	2 (1.0)	–	–	–
Allergic reaction to antibiotic	1 (0.5)	–	–	–
Seed expulsion/marker migration	8 (3%)	3 (1.6)	–	9 (7.1)

^ It was assumed that 2 patients had haematuria for ≥1 but <3 days

In Gill (2012), percentages were based on the following denominators: pain (N=229 patients who completed pain score); seed expulsion (N=190 patients who answered); haematuria and haematospermia (N=208 patients who answered)

Source: Table 1, p. 40 in Escudero (2010); pp 1013-1014 in Gill (2012); p. 943 in İğdem (2009); Table 1, p. 673 in Langenhuijsen (2007)

Pain was assessed in three studies (Table B.25), with two studies (Gill 2011; Iğdem 2009) using the Wong Baker visual analogue scale (0-5 rating) and one study using a visual analogue scale of 0-10. In all three studies, the majority of patients reported no pain or very mild pain with a proportion experiencing moderate to severe pain. Six patients in the study by Langenhuijsen (2007) required analgesics for pain. It is worth noting that in the study by Gill (2012) local anaesthesia was administered to patients as part of the procedure. This was not the case in the other two studies and may explain the higher percentage of patients in the Gill study that experienced no pain or very mild pain. In Escudero (2010, six patients (4.8%) presented with pelvic prostate pain up to seven days following FM implantation; however, none of the patients required analgesics for the pain.

Table B.25 Reported pain in the safety studies

	No pain or very mild Wong Baker: 0-1 or VAS: 0-2	Mild to moderate pain Wong Baker: 2 or VAS: 3-5	Moderate to severe pain Wong Baker: 3-5 or VAS: 6-9
Gill (2011) (N=229)	73%	12%	15%
Langenhuijsen (2007) (N=209)	48%	37%	15%
İğdem (2009) (N=135)	45%	36%	19%

Abbreviations: VAS = visual analogue scale

Source: p 1013 in Gill (2012); p 943 in İğdem (2009); p 673 in Langenhuijsen (2007)

Other complications noted in the studies include marker migration. Escudero (2010) noted that in the first 10 patients, three markers were lost in two patients. A following seven patients experienced loss of markers; six patients losing single markers and one patient losing two. In two patients, the markers were located; one in the bladder and the other in the peritoneal cavity. The authors make the assumption that the remaining markers were expelled. Langenhuijsen (2007) also reported that during the procedure, marker misplacement outside the gland boundaries took place in 3% (n=8) of patients; occurring seven times into the bladder and once into the rectum.

An additional study was also identified (Shinohara 2008) that provided safety data in a large group of patients (n=705). Safety data however was not collected systematically; rather, patients were instructed to contact the clinic with unexpectedly severe or prolonged AEs. Out of 705 patients, one patient developed a urinary tract infection requiring additional antibiotic therapy. The authors reported that there were no instances of 'severe rectal bleeding or gross haematuria requiring further intervention'.

The non-comparative case series studies included in the clinical effectiveness section were also reviewed in terms of complications associated with FM implantation. Table B.26 lists the AEs in these studies.

Table B.26 Procedural complications in the non-comparative case series

Study	Adverse events – reported due to implantation of FM
Chua (2013)	NR
Eade (2011)	NR
Linden (2009)	FM placement proceeded without complications in all 98 patients. 'Through the IMRT course, no cases of haematuria, febrile illness, rectal bleeding, or migration were documented'
Lips (2008)	Three cases of acute grade 3 toxicity were reported after FM implantation (urinary tract infection, pneumonitis and a prostatitis)
Martin (2009)	NR
Nath (2011)	NR
Takeda (2012)	'No instances of fiducial migration during treatment' (p 3)
Vesprini (2011)	NR

Abbreviations: FM = fiducial marker; IMRT = intensity-modulated radiotherapy; NR = not reported

Source: Chua (2013); Eade (2011); Linden (2009); Lips (2008); Martin (2009); Nath (2011); Takeda (2012); Vesprini (2011)

Summary

The evidence for safety is primarily based on four large case-series studies. All four studies specifically assessed AEs/complications following implementation of FM for EBRT. Studies

included in the clinical effectiveness section were also reviewed in terms of AEs associated with FM implantation. Few however reported such information.

Most of the AEs were transitory in nature, with most resolving within two weeks of implantation. Minor AEs included haematuria lasting longer than three days, voiding complaints and obstructive symptoms. AEs reported across all four studies included rectal bleeding, pain and fever. For patients with pain, a proportion received analgesics; similarly, patients with fever were given antibiotics. In one study three patients required hospitalisation as a result of fever, with one of those patients developing septicaemia (grade 4 infection) following insertion of an FM.

Other AEs noted in the above studies included marker migration. This was reported in three studies but did not result in any clinical sequelae.

It would seem from the published literature that the majority of patients who undergo implantation of FM have no, or minor AEs. However, a small percentage of patients may experience moderate complications, potentially resulting in further medical intervention.

B.7 Interpretation and conclusion of the clinical evidence

Overall, the assessment of comparative clinical effectiveness of FM-based versus bony landmark-based EBRT was based on non-randomised comparative clinical studies: four single institution case series treated with FM-based EBRT compared with historical series treated with bony landmark-based EBRT (Gill 2011; Lips 2007; Singh 2013; Zelefsky 2012). A very small non-randomised comparative study (Chung 2009) was also included as reference only, owing to the lack of quality evidence. None of the non-randomised comparative studies included patients receiving adjuvant/salvage EBRT post-prostatectomy. Table B.27 presents a summary of the clinical evidence and results from the previous sections.

Table B.27 Summary of clinical evidence to inform comparative clinical effectiveness and safety

Clinical outcomes	Basis of evidence	Summary of evidence and interpretation
Survival	None	No comparative evidence identified
Local tumour control	One case series with historical controls (Zelefsky 2012)	• PSA relapse-free survival at 3 years was significantly better for high-risk patients in the high-dose IMRT (86.4 Gy) cohort with FM as image guidance (97%) versus the cohort without FM (77.7%) (Table B.12) Note however that only 35 high-risk patients contributed to the survival data in the FM group. In addition, it is not clear about the applicability of study results to clinical practice in Australia as the ultra-high dose of 86.4 Gy used in the study is rare in Australia (see eviQ clinical guidelines in Appendix C).
Health-related QoL	One case series with historical controls (Lips 2007)	• There was no significant difference in change in mean QoL scores between the FM group (IMRT) and non-FM group (3D-CRT) except for 6 QoL items at one month after completion of RT favouring FM for 5 of the 6 items (Table B.13) • Between-group difference was not statistically significant for any of the QoL items at 6 months after completion of RT Validity of results of between-group comparison is highly uncertain as the comparison groups differed in more than one aspect apart from the use of FMs in one group (eg dose-escalated IMRT was used in the FM group versus 3D-CRT without dose-escalation in the non-FM group; clinical practice may differ as there was a big gap in study period between the 2 groups-2003/04 versus 1997/2001)
Treatment-related morbidity – GI or rectal AEs	4 case series with historical controls	• Risk of acute grade 1 GI AEs appears to be greater with FM-based EBRT than with bony landmark-based EBRT, while risk of acute grade 2 GI AEs appears to be lower with FM-based EBRT (Table B.15) • Self-assessed moderate to severe rectal AEs (diarrhoea, rectal pain, urgency) were significantly lower in the FM group compared with the non-FM group at 8-26 months after 3D-CRT (Singh 2013; Table B.17) • 3-year ≥grade 2 rectal AEs was low and similar for both FM and non-FM groups, despite the use of ultra-high dose IMRT (86.4 Gy) (Zelefsky 2012)
Treatment-related morbidity – GU AEs	4 case series with historical controls	• Risk of acute grade 1 GU AEs was greater while grade 2 AEs was lower with the FM group than with the non-FM group in 2 studies (Zelefsky 2012; Chung 2009) (Table B.18) • Gill (2011) reported the reverse direction of results at 6 months after RT; in addition, risk of grade 3 GU AEs was lower with the FM group (Table B.18) • Self-assessed moderate to severe urinary AEs were similar in the FM and non-FM groups at 8-26 months after 3D-CRT (Singh 2013) • 3-year ≥grade 2 GU AEs were significantly lower in the FM group than in the non-FM group, despite the use of ultra-high dose IMRT (86.4 Gy) (Zelefsky 2012) (Table B.20)
Safety of the implantation of FMs	4 cohort studies/case series	It appears that the majority of patients who undergo implantation of FM have no, or minor AEs. However, a small percentage of patients may experience moderate complications, potentially resulting in further medical intervention.

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; AE = adverse event; EBRT = external beam radiotherapy; FM = fiducial marker; GI = gastrointestinal; GU = genitourinary; Gy = Gray; IMRT, intensity-modulated radiotherapy; PSA = prostate-specific antigen; QoL = quality of life; RT = radiotherapy

Overall, there is a lack of quality evidence to inform on the comparative clinical effectiveness of FM-based EBRT versus bony landmark-based EBRT in patients receiving definitive EBRT for prostate cancer. There is no evidence available to inform on comparative clinical effectiveness in patients receiving adjuvant/salvage EBRT post-prostatectomy.

The majority of patients who undergo implantation of FM have no, or minor AEs. However, a small percentage of patients may experience moderate complications, potentially resulting in

further medical intervention. None of the safety studies included patients receiving adjuvant/salvage post-prostatectomy.

C Translating the clinical evaluation to economic evaluation

There are no translation issues that need to be addressed with the current assessment.

D Economic evaluation for the main indication

As mentioned in Section A.2, the proposed medical service is not a therapeutic medical service on its own, but rather is intended to be used as part of the planning and delivery of EBRT. The clinical and cost-effectiveness of IGRT and IMRT are the subject of other concurrent MSAC assessments (Table A.10). The focus of this assessment report is therefore the procedure of implantation of FMs itself. In addition, there is a lack of quality evidence to draw conclusions on the impact of implantation of FMs on the comparative clinical effectiveness and safety of FM-based EBRT versus bony landmark-based EBRT (Section B.7). In the absence of this evidence, it is not possible to construct a full economic model of the cost-effectiveness of the implantation of FMs. Therefore, the economic evaluation for the current assessment report is a simple cost analysis of the proposed implantation procedure and other MBS items directly associated with the performance of the procedure.

D.1 Key assumptions and variables used

Table D.1 presents a summary of the key assumptions and cost components used in the simple cost comparison analysis of this report.

Table D.1 Key assumptions and cost components used in simple cost analysis

Cost component	Value/assumption (source)
Procedure	–
Implantation of FMs	$138.30 per implantation (proposed price, same as that of the interim funded MBS item 37217)
Trans-rectal US guidance	$109.10 per implantation (MBS 55603)
Specialist attendance	$85.55 per implantation (MBS 104)
Anaesthesia	$99.00 per implantation (MBS 21980) – applicable only when general anaesthesia is used with the implantation procedure Base case – assume 100% of the patients receive the implantation under local anaesthesia SA – assume general anaesthesia to be used in 20% of the patients
Peri-procedure	–
Prophylactic antibiotics	Base case: ciprofloxacin 500 mg tablet ×1 (HESP advice) SA: ciprofloxacin 250 mg tablet × 2; ciprofloxacin 250 mg tablet × 2/day × 7 days
Post-procedural plain antero-posterior and lateral pelvic radiograph	$60.90 per implantation (MBS 57715) (Thompson 2008) – assumed to be standard practice in the base case and excluded in SA
RT treatment	–
RT treatment verification for FM-based EBRT	Daily online treatment verification, once daily (source: eviQ), reviewed by a radiation oncologist (Bell 2010) - Assumed to be claimed under MBS 15705, pending outcome of another MSAC assessment 1319 (Table A.10)
RT treatment verification for bony landmark-based EBRT	Daily offline treatment verification first 3 fractions, then weekly (source: eviQ); performed by radiation therapist but reviewed by a radiation oncologist (Bell 2010)
A course of FM-based EBRT	Base case: 74 Gy, 37 fractions, 8 weeks; SA: 78 Gy, 39 fractions, 8 weeks (assume escalation of dose with FM)
A course of bony landmark-based EBRT	Base case: 74 Gy, 37 fractions, 8 weeks
RT treatment number of fields used	Base case: 5 fields (Gill 2011); SA: 6 fields (for IMRT, as advised by the HESP)

Abbreviations: EBRT= external beam radiotherapy; FM = fiducial marker; Gy = Gray; HESP = Health Expert Standing Panel; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Schedule; SA = sensitivity analysis; US = ultrasound

Source: MBS Online [accessed 8 April 2013]; Bell (2010); Thompson (2008)

The key assumptions used follow the Australian clinical practice (eg clinical guidelines, Australian studies from Section B) where possible. Unit costs used are from the current Medicare Benefits Schedule (May 2013) and the Pharmaceutical Benefits Scheme (PBS). The key assumptions are:

- Anaesthesia: it is assumed in the base case that local anaesthesia is used as it is most common in clinical practice in Australia. The impact of the assumption of 20% of patients requiring general anaesthesia is explored in sensitivity analysis (Table D.8).

- Prophylactic antibiotics: in the base case, it is assumed that a ciprofloxacin 500 mg tablet is prescribed as prophylactic antibiotics (based on advice from a HESP member). The impact of other dose strengths used (eg ciprofloxacin 250 mg, 2 tables or a full course according to the Product Information) is assessed in sensitivity analysis (Table D.8).

- Post-implantation pelvic x-ray: this is assumed not performed in the based case, based on advice from a HESP member. However, the MBS cost for a pelvic x-ray is included in sensitivity analysis (add reference) as this was reported in a published Australian implementation study (Thompson 2008).

- RT treatment verification: daily online pre-treatment verification for patients receiving FM-based EBRT; daily offline verification first three fractions in the first week then weekly afterwards for patients receiving bony landmark-based EBRT. This is based on recommendation in the eviQ clinical guidelines (Appendix C). It is assumed that a radiation oncologist reviews the treatment verification.

- RT treatment prescription dose: in the base case, the total prescription dose for a course of EBRT is assumed to be 74 Gy (37 fractions, 7-8 weeks) for patients receiving either FM-based or bony landmark-based EBRT. The impact of escalation of dose to 78 Gy for FM-based EBRT on costs is assessed in sensitivity analysis (Table D.8).

- RT treatment, number of fields: costing is based on the use of five fields in the base case (Gill 2011) and six fields in sensitivity analysis (for IMRT, as advised by the HESP).

- Treatment for procedural complications: none. It is assumed that there are no significant complications from the proposed procedure requiring interventions (eg pain, bleeding, seed migration, infection, sepsis, hospitalisations etc).

- Only the likely additional resource use directly relevant to the conduct of the proposed medical service are included.

D.2 Unit costs and estimation of cost components

D.2.1 Unit costs

Table D.2 presents the unit costs used in the cost analysis.

Table D.2 Unit costs used in cost analysis (base case and sensitivity analyses)

Item	Unit cost	Source
Implantation of FMs	$138.30	Proposed price, same as the interim funded MBS 37217
Trans-rectal US guidance	$109.10	MBS 55603
Specialist attendance	$85.55	MBS 104
Initiation of management of anaesthesia for radiotherapy (used in SA)	$99.00	MBS 21980
Diagnostic Imaging - Pelvic girdle (used in SA)	$60.90	MBS 57715
Radiation Oncology Treatment Verification (multiple projection)	$76.60	MBS 15705
Radiation Oncology Treatment (dual photon energy linac ≥10 MV photons, 1 field, each attendance, prostate)	$59.65	MBS 15248
Radiation Oncology Treatment (dual photon energy linac ≥10 MV photons, 2-5 additional fields (rotational therapy being 3 fields) - treatment delivered to primary site (prostate) The fee for item 15248 plus for each field in excess of 1, an amount of $37.95)	$37.95	MBS 15263
Ciprofloxacin 250 mg tablet (used in SA)	DPMQ $17.33	PBS 1208N
Ciprofloxacin 500 mg tablet	DPMQ $27.66	PBS 1209P

Abbreviations: DPMQ = Dispensed Price for Maximum Quantity; FM = fiducial marker; linac = linear accelerator; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Schedule; SA = sensitivity analysis; US = ultrasound

Source: MBS Online [accessed 1 May 2013]; PBS [accessed 1 May 2013]

D.2.2 Pre-RT treatment verification cost

Table D.3 presents the estimation of the likely treatment verification costs to the MBS. The treatment verification cost for FM-based EBRT is estimated to be greater than that for bony landmark-based EBRT, at an estimated incremental cost of $2,068.20 per course of RT.

Table D.3 Likely treatment verification costs to the MBS (base case)

	FM-based EBRT	Bony landmark-based EBRT	Increment
Course of RT	74 Gy, 37 fractions, 8 weeks	74 Gy, 37 fractions, 8 weeks	–
Number of pre-treatment verification claims	37	10 (=3+7)	27
Unit cost/pre-treatment verification claim (MBS 15705)	$76.60	$76.60	–
Cost of pre-treatment verification MBS claims	$2,834.20	$766.00	$2,068.20

Abbreviations: EBRT = external beam radiotherapy; FM = fiducial marker; Gy = Gray; MBS = Medicare Benefits Schedule; RT = radiotherapy

Source: MBS Online [accessed 1 May 2013]

If the prescription dose of FM-based EBRT is escalated to 78 Gy, then the incremental cost of treatment verification with FM-based EBRT will increase to $2,221.40 per course of RT. Table D.4 presents the details of the calculation. The impact of dose escalation on the total cost is assessed in sensitivity analysis (Table D.8).

Table D.4 Likely treatment verification costs to the MBS (sensitivity analysis – with dose escalation)

	FM-based EBRT	Bony landmark-based EBRT	Increment
Course of RT	78 Gy, 39 fractions, 8 weeks	74 Gy, 37 fractions, 8 weeks	–
Number of pre-treatment verification claims	39	10 (=3+7)	27
Unit cost/pre-treatment verification claim (MBS 15705)	$76.60	$76.60	–
Cost of pre-treatment verification MBS claims	$2,987.40	$766.00	$2,221.40

Abbreviations: EBRT = external beam radiotherapy; FM = fiducial marker; Gy = Gray; MBS = Medicare Benefits Schedule; RT = radiotherapy

Source: MBS Online [accessed 1 May 2013]

D.2.3 RT treatment cost

Apart from an increase in verification cost with dose escalation, there would also be an increase in treatment cost for the extra fractions. Table D.5 presents the details of the calculation. It is estimated that the incremental treatment cost of FM-EBRT dose escalated from 74 Gy to 78 Gy is $422.90 per course of RT. This is used in sensitivity analysis (Table D.8).

Table D.5 Treatment cost to the MBS (sensitivity analysis – with dose escalation)

	FM-based EBRT	Bony landmark-based EBRT	Increment
Course of RT	78 Gy, 39 fractions	74 Gy, 37 fractions	–
Cost/fraction (MBS 15248 x1 + MBS 15263 x 5)	$211.45	$211.45	–
Cost/course of RT	$8,246.55	$7,823.65	$422.90

Abbreviations: EBRT = external beam radiotherapy; FM = fiducial marker; Gy = Gray; MBS = Medicare Benefits Schedule; RT = radiotherapy

Source: MBS Online [accessed 1 May 2013]

D.2.4 Pharmaceutical costs

Prophylactic antibiotics (eg ciprofloxacin) are routinely prescribed prior to the FM implantation procedure, which will result in pharmaceutical costs to the Pharmaceutical Benefits Schedule (PBS). Depending on which pharmaceutical product and dosage or duration is prescribed, the cost to the PBS may differ. None of the five non-randomised comparative studies in Section B reported on which specific drug was used in the studies. Ciprofloxacin has been selected for the purpose of the current report as the medication was used in Thompson (2008), an Australian study reporting on the implementation of an implanted FM program as standard practice for radical dose prostate RT (74-78 Gy). The Product Information for ciprofloxacin recommends a dosage of 250-500 mg twice daily for 7-14 days in adults. A member of the HESP advised on the use of one ciprofloxacin 500 mg tablet in a local centre. This dose strength is therefore used in the base case. The use of two ciprofloxacin 250 mg tablets as well as a full course of antibiotics (ciprofloxacin 250 mg twice daily for seven days) is used in sensitivity analysis (Table D.8).

D.3 Results of the simple cost comparison analysis

The direct cost of the implantation of FMs to the MBS includes the implantation procedure (proposed medical service) carried out under trans-rectal ultrasound guidance (MBS 55603) by an urologist or radiation oncologist (MBS 104) under some form of anaesthesia (usually local anaesthesia). Table D.6 presents the results of the simple cost comparison analysis of FM-based EBRT versus bony landmark-based EBRT in the base case.

Table D.6 Results of simple cost comparison analysis (base case)

Cost components	Cost with FM-based EBRT	Cost with bony landmark-based EBRT	Incremental cost
MBS	–	–	–
Implantation of FMs (proposed medical service or interim MBS 37217)	$138.30	$0.00	$138.30
Trans-rectal US guidance (MBS 55603)	$109.10	$0.00	$109.10
Specialist attendance (MBS 104)	$85.55	$0.00	$85.55
Anaesthesia	$0.00	$0.00	$0.00
Post-procedural plain antero-posterior and lateral pelvic radiograph (MBS 57715)	$0.00	$0.00	$0.00
Pre-treatment verification (MBS 15705; Table D.3)	$2,834.20	$766.00	$2,068.20
RT treatment cost (MBS 15248, 15263)	$7,823.65	$7,823.65	$0.00
Total (MBS)	**$10,990.80**	**$8,589.65**	**$2,401.15**
PBS	–	–	–
Prophylactic antibiotics (PBS 1208N, ciprofloxacin 500 mg tablet ×1)	$1.98	$0.00	$1.98
Total (PBS)	**$1.98**	**$0.00**	**$1.98**
TOTAL (MBS + PBS)	–	–	–
Total cost	**$10,992.78**	**$8,589.65**	**$2,403.13**

Abbreviations: EBRT = external beam radiotherapy; FM = fiducial marker; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RT = radiotherapy; US = ultrasound

* Cost with FM-based EBRT minus cost with bony landmark-based EBRT

Source: MBS Online [accessed 1 May 2013]

The estimated total cost (MBS) of FM-based EBRT is $10,990.80 versus $8,589.65 for bony landmark-based EBRT. The incremental cost (MBS) with FM-based EBRT is therefore estimated to be $2,401.15 per course of RT.

The biggest contributor to the cost difference is the increase in frequency of pre-treatment verification with FM-based EBRT, which contributed to 86% of the incremental cost (MBS). The implantation procedure itself, together with the associated medical services, amounted to a cost of $332.95 per procedure (14% of the incremental cost to MBS).

When the cost to PBS is included, the total incremental cost (MBS and PBS) is estimated to be $2,403.13 per course of RT.

Note that the simple cost analysis excludes the cost of FMs which are borne by the patient or the hospital. Thompson (2008) reported that commercially available packs of sterile FMs and needles are available but are expensive and they are therefore generally manufactured in-house. The cost of unsterile materials of three needles, stylets and the gold seeds made in-house was reported to be less than $60 (Thompson 2008). Another published Australian study (Gill 2012) estimated

that the cost of the implantation of three gold seeds for IGRT was $130.70 per patient but details of the estimation were not reported. As IGRT typically involves newer equipment and technologies, it was estimated that the cost of IGRT with kilovoltage (kV) imaging or electronic portal imaging (EPI) ranged from $258.59 to $345.50 per fraction (2010 AUD estimates), including upfront capital, recurring costs, set-up time and treatment delivery time (Gill 2012) (Table D.7).

Table D.7 Additional resource use (hospital/other government) likely to be incurred but excluded from the analysis

Components	Estimated cost	Source of information
Implantation of 3 gold seeds for IGRT	$130.70/patient	Gill (2012): a new RT centre in Victoria
FM-IGRT with kV imaging and automated couch shifts	$258.79/fraction* (2010 AUD estimates)	Gill (2012): a new RT centre in Victoria (3D-CRT, 78 Gy, 2007-09, N=294) • Set-up time: mean 4.8 min (range 3.0-6.2 min) • Treatment delivery time: median 6.0 min (IQR 5.1-7.4 min) (median 5.1 min if no couch shift)
FM-IGRT with EPI with manual couch shifts	$345.50/fraction* (2010 AUD estimates)	Gill (2012): a new RT centre in Victoria (2007-09) • Set-up time: mean 4.8 min (range 3.0-6.2 min) • Treatment delivery time: median 10.0 min (IQR 8.3-11.8 min) (median 8.8 min if couch shift)

Abbreviations: EPI = electronic portal imaging; FM = fiducial marker; IGRT = image-guided radiotherapy; IQR = interquartile range; kV = kilovoltage; MBS = Medicare Benefits Schedule; MV = mega-voltage; OBI = on-board imaging; RT = radiotherapy

* Includes capital costs, recurring costs, set-up and treatment delivery costs

Source: Gill (2012)

D.4 Sensitivity analyses

Table D.8 presents the results of sensitivity analyses on the estimated total incremental cost to the MBS and PBS.

Table D.8 Estimated total incremental cost (MBS + PBS) – sensitivity analyses

	FM-based EBRT	Bony landmark-based EBRT	Increment
Total cost (MBS + PBS) (Base case)	**$10,992.78**	**$8,589.65**	**$2,403.13**
No change in frequency of treatment verification* [A]	$8,924.58	$8,589.65	$334.93
RT treatment, 6 fields (BC=5 fields) [B]	$12,396.93	$9,993.80	$2,403.13
Prophylactic antibiotics ciprofloxacin 250 mg, 2 tablets [C]	$10,993.28	$8,589.65	$2,403.63
Prophylactic antibiotics ciprofloxacin 250 mg tablets, twice daily, 7 days (BC: one ciprofloxacin 500mg tablet) [D]	$11,008.13	$8,589.65	$2,418.48
20% of patients requiring general anaesthesia (BC=0%) [E]	$11,012.58	$8,589.65	$2,422.93
Post-implantation pelvic x-ray included (BC: excluded) [F]	$11,053.68	$8,589.65	$2,464.03
Dose escalation to 78 Gy with FM-based EBRT [G]	$11,568.88	$8,589.65	$2,979.23
G and A	$9,347.48	$8,589.65	$757.83
G and E	$11,588.68	$8,589.65	$2,999.03
G and F	$11,629.78	$8,589.65	$3,040.13
G and B	$13,048.93	$9,993.80	$3,055.13

Abbreviations: BC = base case; EBRT = external beam radiotherapy; FM = fiducial marker; Gy = Gray

* No change in frequency of treatment verification refers to frequency of treatment verification with FM-based EBRT, same as the verification frequency with bony landmark-based EBRT (ie daily offline first three fractions in the first week of radiotherapy, then weekly afterwards)

The estimated total incremental cost (MBS + PBS) with FM-based EBRT is most sensitive to whether there is an increase in the frequency of treatment verification associated with FM-based EBRT.

If the frequency of treatment verification remains the same with FM-based EBRT, then the estimated total incremental cost (MBS + PBS) is decreased to $334.93 per course of RT, compared with $2,403.13 in the base case.

However, if daily online pre-treatment verification and dose escalation (to 78 Gy) is used with FM-based EBRT, then total incremental cost (MBS + PBS) with FM-based EBRT is estimated to increase to $2,979.23 per course of RT, with the increased cost with treatment verification contributing to 75% of the total incremental cost (MBS + PBS).

E Estimated extent of use and financial implications

The financial impact estimation of the proposed medical service is limited to the estimation of resource use directly associated with the conduct of the proposed service.

E.1 Key assumptions and variables used

The key assumption used in this section is that there are no changes in clinical practice in the first four years of listing, irrespective of the outcomes of relevant MSAC reviews currently under assessment (Table A.10). In other words, the current utilisation of the interim MBS item 37217 is a reasonable indicator of the utilisation of the proposed medical service in the first four years of listing.

E.2 Estimation of use and costs of the proposed medical service

E.2.1 Current utilisation of the interim funded MBS item 37217

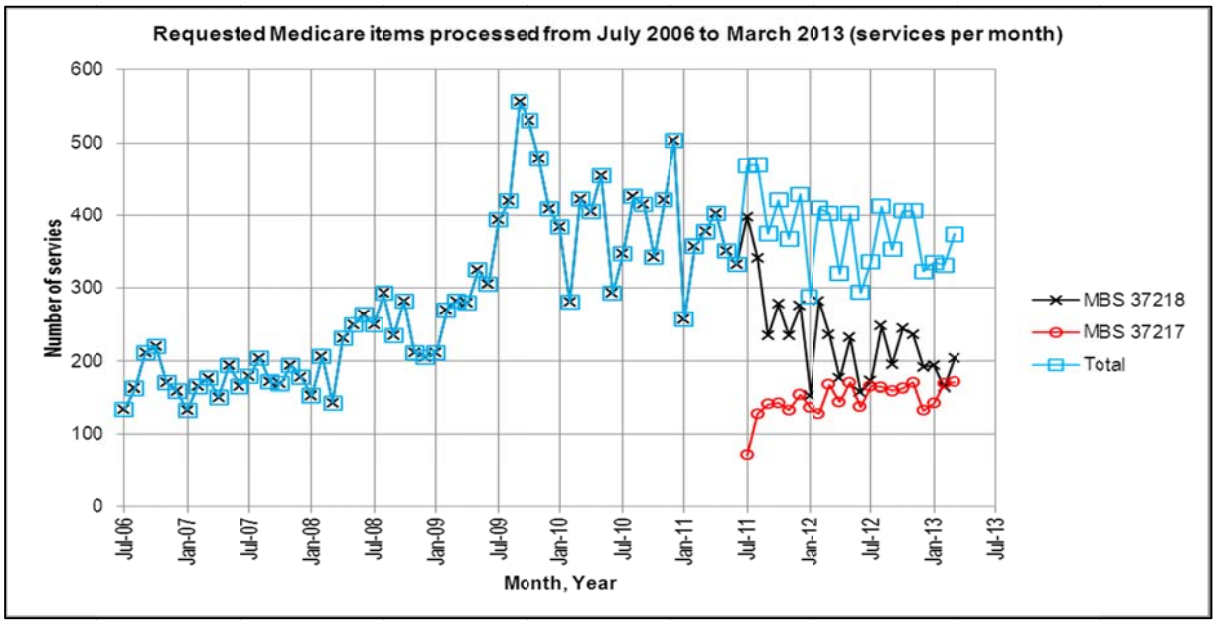
Table E.1 presents the actual yearly utilisation data of the interim MBS item 37217 since listing (July 2011 to March 2013 inclusive), and the change in utilisation of MBS item 37218 from July 2006. Figure E.1 presents the corresponding utilisation data for services by month and Figure E.2 presents the benefits by month.

Table E.1 Utilisation of MBS item 37218 and interim item 37217 (services and benefits by financial year)

	Services MBS 37218	Services MBS 37217	Services Total	Benefits MBS 37218	Benefits MBS 37217	Benefits Total	Average benefit/service MBS 37218	Average benefit/service MBS 37217
2006-07	2,037	N/A	2,037	$149,893	N/A	$149,893	$73.59	N/A
2007-08	2,337	N/A	2,337	$176,674	N/A	$176,674	$75.60	N/A
2008-09	3,147	N/A	3,147	$246,171	N/A	$246,171	$78.22	N/A
2009-10	5,030	N/A	5,030	$332,280	N/A	$332,280	$66.06	N/A
2010-11	4,537	N/A	4,537	$333,518	N/A	$333,518	$73.51	N/A
2011-12	2,997	1,652	4,649	$199,265	$170,355	$369,620	$66.49	$103.12
YTD 2012-13	1,846	1,434	3,280	$125,034	$152,536	$277,570	$67.73	$106.37

Abbreviations: MBS = Medicare Benefits Schedule; N/A = not applicable; YTD = year to date (up to March 2013)
Source: Medicare Item Reports, Medicare Australia [accessed 29 April 2013]

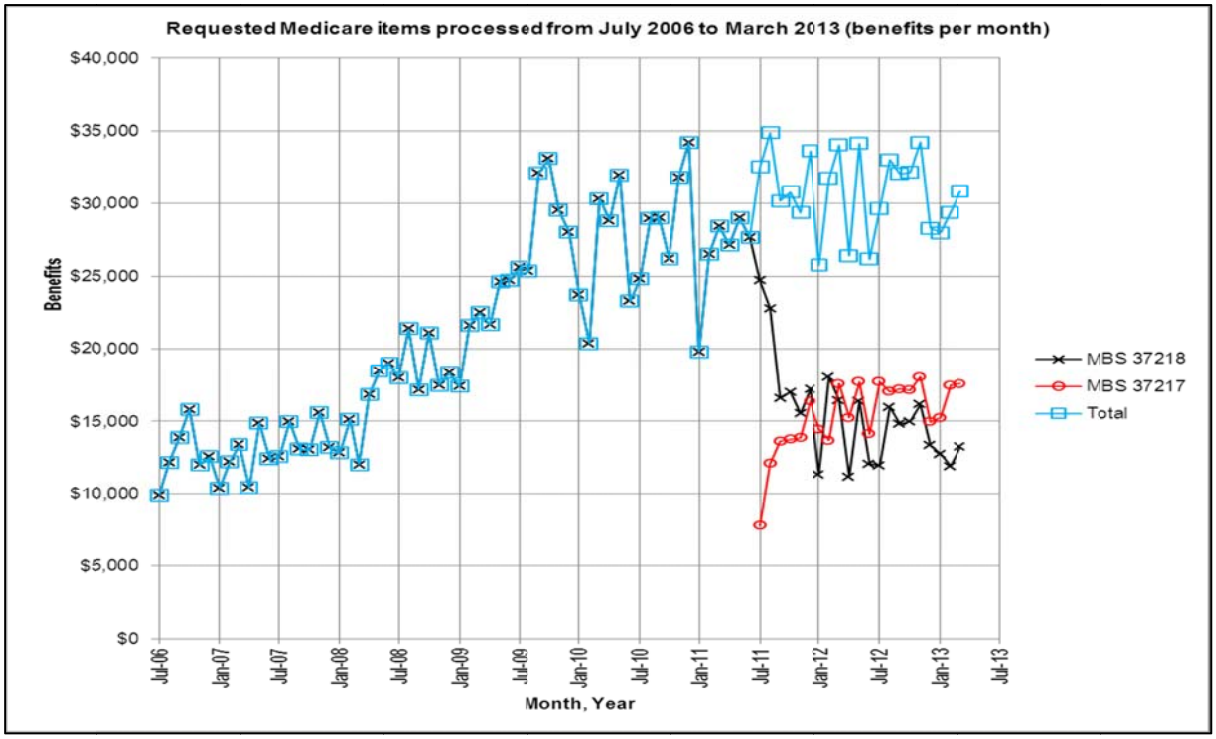
Figure E.1 Utilisation of MBS items 37217 and 37218 (services/month



Abbreviations: MBS = Medicare Benefits Schedule

Source: Medicare Item Reports, Medicare Australia [accessed 29 April 2013]

Figure E.2 Utilisation of MBS items 37217 and 37218 (benefits/month)



Abbreviations: MBS = Medicare Benefits Schedule

Source: Medicare Item Reports, Medicare Australia [accessed 29 April 2013]

There was a sharp decrease in the number of medical services claimed under MBS 37218 since July 2011, the month in which the interim item 37217 was first listed. The number of services claimed under MBS 37218 decreased from 4,537 services for 2010-11 to 2,997 for 2011-12. There were 1,652 services claimed under the interim item 37217 in the first year of listing. When

taken together, the total number of services claimed under MBS items 37217 and 37218 was 4,649 in 2011-12, not much different from the 4,537 services claimed under MBS 37218 in 2010-11.

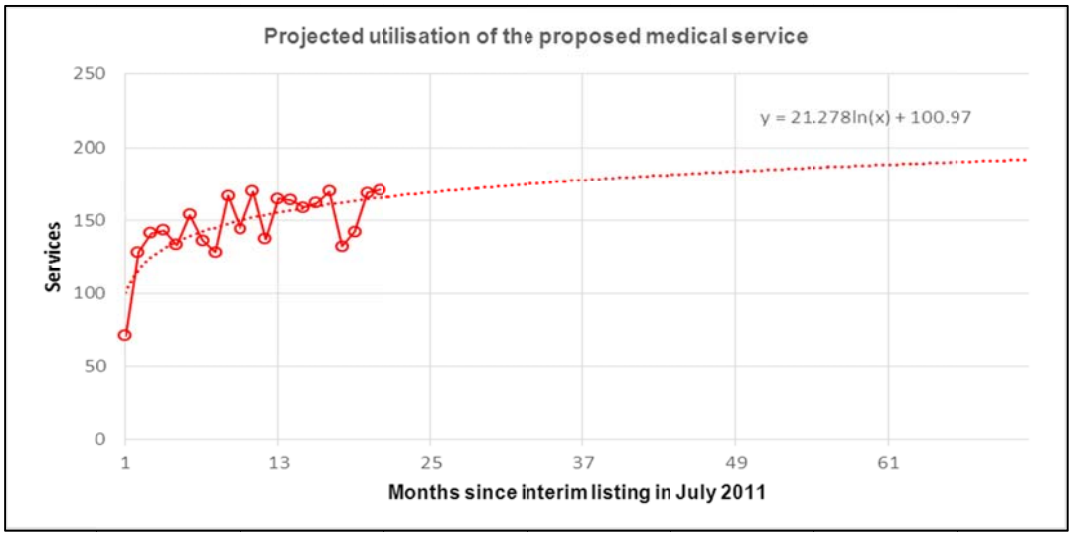
Note however that while the number of services claimed under MBS 37218 per month was greater than the number of services claimed under the interim item, the benefits claimed under the latter per month surpassed the former within the first six months of listing and have remained so since, despite the Medicare schedule fees being the same for both items. The average benefit per service count for the interim item 37217 has been around $100/service since listing, compared with the average benefit of $65-$80 claimed under MBS 37218 since 2006. It is not clear whether this can be partially explained by any difference in the relative proportions of claims under 100%, 85% and 75% MBS schedule fees for the two items.

Note also that the utilisation data based on MBS item reports presented above include only the services performed by a registered provider, for services that qualify for Medicare Benefit and for which a claim has been processed by Medicare Australia. Therefore, services provided by hospital doctors to public patients in public hospitals or services that qualify for a benefit under the Department of Veterans' Affairs National Treatment Account are not included (Medicare Australia).

E.2.2 Projected utilisation based on past/current utilisation

Figure E.3 presents the projected utilisation of the proposed medical service based on the utilisation of the interim funded MBS item 37217 since July 2011.

Figure E.3 Projected utilisation of the proposed medical service (services/month)



Source: Estimated utilisation of the proposed medical service in 2013-2017 (projected utilisation is based on actual utilisation of the interim-funded MBS item 37217 in the 21 months since listing)

Table E.2 presents the projected utilisation of the proposed medical service in the first four years of listing.

Table E.2 Projected utilisation of the proposed medical service (number of services)

	Current (2012-13)	Year 1 (2013-14)	Year 2 (2014-15)	Year 3 (2015-16)	Year 4 (2016-17)
Estimated utilisation: proposed medical service (number of services)	1,952	2,083	2,168	2,232	2,283

Source: Estimated utilisation of the proposed medical service in 2013-2017 (projected utilisation is based on actual utilisation of the interim-funded MBS item 37217 in the 21 months since listing)

The estimated number of services of the proposed medical service processed through Medicare Australia is: 2,083 in Year 1, rising to 2,283 in Year 4.

E.2.3 Estimated cost of the proposed medical procedure

Table E.3 presents the estimated cost (MBS) of the proposed medical service.

Table E.3 Estimated cost of the proposed medical service (MBS benefits)

	Current (2012-13)	Year 1 (2013-14)	Year 2 (2014-15)	Year 3 (2015-16)	Year 4 (2016-17)
Estimated cost: proposed medical service	$269,970	$288,031	$299,859	$308,687	$315,738

Abbreviations: MBS = Medicare Benefits Schedule

Source: Unit cost of the proposed medical service is based on the current cost of the interim-funded MBS item 37217 (MBS, May 2013, available from MBS Online, accessed 29 April 2013)

Based on the proposed fee of $138.30 for the proposed medical service, the estimated cost (MBS) of the proposed procedure is: $288,031 in Year 1, rising to $315,738 in Year 4.

E.3 Estimation of changes in use and cost of other medical services

As presented in Section D, each implantation procedure is associated with the use of other medical services. Table E.4 presents the estimation of the costs (MBS) of other medical services.

Table E.4 Estimated cost of other medical services (MBS benefits)

	Current (2012-13)	Year 1 (2013-14)	Year 2 (2014-15)	Year 3 (2015-16)	Year 4 (2016-17)
Trans-rectal US guidance (MBS 55603)	$212,970	$227,218	$236,548	$243,512	$249,074
Specialist attendance (MBS 104)	$166,999	$178,171	$185,487	$190,949	$195,310
Pre-treatment verification (MBS 15705)	$5,532,533	$5,902,659	$6,145,045	$6,325,964	$6,470,456
Treatment cost (MBS 15248, 15263)	$15,272,246	$16,293,957	$16,963,051	$17,462,469	$17,861,330
Estimated total cost (MBS) of other medical services	$21,184,748	$22,602,005	$23,530,131	$24,222,894	$24,776,170

Abbreviations: MBS = Medicare Benefits Schedule

Source: Unit costs are based on the MBS (May 2013), available from MBS Online [accessed 29 April 2013]

Estimated total cost (MBS) of the other medical services associated with the use of the proposed medical service amounts to $22,602,005 in Year 1, rising to $24,776,170 in Year 4.

E.4 Estimated financial implications for the MBS

Table E.5 presents the total estimated cost (MBS) with the proposed listing.

Table E.5 Estimated total cost (MBS) with the proposed listing

	Current (2012-13)	Year 1 (2013-14)	Year 2 (2014-15)	Year 3 (2015-16)	Year 4 (2016-17)
Proposed medical service	$269,970	$288,031	$299,859	$308,687	$315,738
Other medical services	$21,184,748	$22,602,005	$23,530,131	$24,222,894	$24,776,170
Total cost (MBS)	**$21,454,718**	**$22,890,036**	**$23,829,990**	**$24,531,581**	**$25,091,907**

Abbreviations: MBS = Medicare Benefits Schedule

The estimated total cost (MBS) of the proposed listing is $22,890,036 in Year 1, rising to $25,091,907 in Year 4.

E.5 Estimated financial implications for government health budgets

Table E.6 presents the estimated cost (PBS) with the proposed listing: $4,115 in Year 1, rising to $4,511 in Year 4.

Table E.6 Estimated total cost (PBS) with the proposed listing

	Current (2012-13)	Year 1 (2013-14)	Year 2 (2014-15)	Year 3 (2015-16)	Year 4 (2016-17)
Estimated cost of prophylactic antibiotics (PBS 1209P, ciprofloxacin 500 mg tablet ×1)	$3,857	$4,115	$4,284	$4,410	$4,511
Estimated total cost (PBS)	**$3,857**	**$4,115**	**$4,284**	**$4,410**	**$4,511**

Abbreviations: PBS = Pharmaceutical Benefits Scheme

Source: PBS Online [accessed on 29 April 2013]

Table E.7 presents the estimated cost (MBS + PBS) with the proposed listing: $22,894,150 in Year 1, rising to $25,096,418 in Year 4.

Table E.7 Estimated total cost (MBS + PBS) with the proposed listing

	Current (2012-13)	Year 1 (2013-14)	Year 2 (2014-15)	Year 3 (2015-16)	Year 4 (2016-17)
Estimated total cost (MBS)	$21,454,718	$22,890,036	$23,829,990	$24,531,581	$25,091,907
Estimated total cost (PBS)	$3,857	$4,115	$4,284	$4,410	$4,511
Estimated total cost (MBS + PBS)	**$21,458,574**	**$22,894,150**	**$23,834,273**	**$24,535,991**	**$25,096,418**

Abbreviations: MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme

Source: MBS Online [accessed 29 April 2013]; PBS Online [accessed on 29 April 2013]

E.6 Identification, estimation and reduction of uncertainty

Table E.8 presents the results of sensitivity analyses on the estimated total incremental cost to the MBS and PBS.

Table E.8 Estimated total cost (MBS + PBS) with FM-based EBRT (sensitivity analyses)

	Year 1 (2013-14)	Year 2 (2014-15)	Year 3 (2015-16)	Year 4 (2016-17)
Base case (BC)	**$22,894,150**	**$23,834,273**	**$24,535,991**	**$25,096,418**
No increase in frequency of treatment verification with FM-based EBRT*	$18,586,805	$19,350,052	$19,919,747	$20,374,734
Dose escalation to 78 Gy (BC=74 Gy)	$24,093,967	$25,083,360	$25,821,852	$26,411,650
RT treatment, 6 fields (BC=5 fields)	$25,818,509	$26,878,718	$27,670,069	$28,302,081
Projected estimates of utilisation under-estimated by 20%	$27,472,980	$28,601,128	$29,443,189	$30,115,701
Projected estimates of utilisation under-estimated by 40%	$32,051,811	$33,367,983	$34,350,388	$35,134,985
Dose escalation to 78 Gy (BC=74 Gy) and projected estimates of utilisation under-estimated by 20%	$28,912,761	$30,100,032	$30,986,223	$31,693,979
Dose escalation to 78 Gy, 6 fields and projected estimates of utilisation under-estimated by 20%	$32,611,680	$33,950,842	$34,950,407	$35,748,710
Dose escalation to 78 Gy, 6 fields and projected estimates of utilisation under-estimated by 40%	$38,046,960	$39,609,316	$40,775,475	$41,706,828

Abbreviations: BC = base case; EBRT = external beam radiotherapy; FM = fiducial marker; Gy = Gray; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme

* No change in frequency of treatment verification refers to frequency of treatment verification with FM-based EBRT same as the verification frequency with bony landmark-based EBRT (ie daily offline first 3 fractions in the first week of radiotherapy, then weekly afterwards)

The estimated total cost (MBS + PBS) with FM-based EBRT is most sensitive to the accuracy of the projected estimates of utilisation used and the change in frequency of treatment verification with FM-based EBRT versus bony landmark-based EBRT.

F Options to present additional relevant information

The Applicants have indicated that FMs are traditionally manufactured in-house in many hospitals. Should the MSAC recommend the proposed listing, the MSAC may wish to consider the issue of regulatory and quality assurance aspects associated with implementation.

Appendix A Health Expert Standing Panel and Assessment Group

Application 1147: Implantation of fiducial markers into the prostate gland or prostate surgical bed for radiotherapy

Health Expert Standing Panel (HESP)

Member	Expertise or Affiliation
Dr Thomas Eade	Radiation oncologist Senior Staff Specialist, Northern Sydney Cancer Centre Royal North Shore Hospital

Assessment Group

Name	Organisation
Elizabeth Seil	NHMRC Clinical Trials Centre, the University of Sydney
Sally Wortley	NHMRC Clinical Trials Centre, the University of Sydney
Briony Jack	NHMRC Clinical Trials Centre, the University of Sydney

Appendix B Tumour-Node-Metastasis (TNM clinical classification)

TNM clinical classification for histologically confirmed adenocarcinoma of the prostate

Classification	Description
T	**Primary tumour**
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging
T1a	Tumour incidental histological finding in ≤5% of tissue resected
T1b	Tumour incidental histological finding in >5% of tissue resected
T1c	Tumour identified by needle biopsy (eg because of elevated PSA)
T2	Tumour confined within prostate#
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule^
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall
N	**Regional lymph nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	**Distant metastasis**
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c

^ Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2

Source: Appendix 3, pp 129-130 in CCA & ACN (2010)

Appendix C Clinical practice guidelines

Clinical practice guidelines for definitive EBRT in prostate cancer patients at low, intermediate and high risk of recurrence in Australia (eviQ)

	Low risk	Intermediate risk	High risk
Patient population	• Prostate adenocarcinoma • T1a-T2a and Gleason score 2-6 and PSA <10 ng/mL • Expected life expectancy >10 years • ECOG 0-2	• Prostate adenocarcinoma • T2b-2c or Gleason score 7 or PSA 10-20 ng/LI • ECOG 0-2	• Prostate adenocarcinoma • T3 or T4 or Gleason score 8-10 or PSA >20 ng/ml • ECOG 0-2
Concurrent treatment	No	No	Yes, ADT
EBRT	Definitive EBRT: • 3D-CRT or IMRT techniques recommended • 73.8-81 Gy (1.8-2 Gy/fraction, 39-41 fractions)	Definitive EBRT: • 3D-CRT or IMRT techniques recommended • 73.8-81 Gy (1.8-2 Gy/fraction) • Doses of 78 Gy or slightly higher are favoured if can be delivered safely using IGRT and/or IMRT techniques and DVH constraints can be met • If delivering doses <73.8 Gy, use of neoadjuvant or adjuvant hormone therapy is recommended • Phase 1 (45-54 Gy) + 2 EBRT	• Same as for intermediate risk
Target verification	• Acceptable – offline with port film or EPI daily first 3 fractions then weekly, matching to bony anatomy • Ideal – online daily imaging matching to FMs (OBI or EPI, US, CB or CT)	Same as for low risk	Same as for low risk
CTV	Prostate only	• Phase 1: Prostate + proximal 10 mm of SV (base) • Phase 2*: Prostate only	• Phase 1: Prostate, extracapsular extension + SV • Phase 2*: Prostate, extracapsular extension + proximal 10 mm of SV (base) if uninvolved; include entire SV if involved
PTV (no daily localisation)	CTV + 5-10 mm uniform expansion except posteriorly where 5-10 mm is used	• Phase 1: CTV + 5-10 mm uniform expansion except posteriorly where 5-10 mm is used • Phase 2*: CTV +10 mm uniform expansion except posteriorly where 5 mm is used	• Phase 1: CTV + 10-15 mm uniform expansion except posteriorly where 5-10 mm is used • Phase 2*: CTV +10 mm uniform expansion except posteriorly where 5 mm is used
PTV (daily localisation)	CTV + 5-10 mm	• Phase 1: CTV + 5-10 mm uniform expansion except posteriorly where 5-7 mm is used • Phase 2*: CTV + 5-10 mm uniform expansion except posteriorly where 5 mm is	• Phase 1: CTV + 5-10 mm uniform expansion except posteriorly where 5-7 mm is used • Phase 2*: CTV + 5 mm uniform expansion

	Low risk	Intermediate risk	High risk
		used	

Abbreviations: ADT = androgen deprivation therapy; CB = cone beam; CT = computerised tomography; CTV = clinical target volume; DVH = dose volume histogram; ECOG = Eastern Cooperative Oncology Group; EBRT = external beam radiotherapy; EPI = electronic portal imaging; Gy = Gray; OBI = on-board imaging; PSA = prostate-specific antigen; PTV = planning target volume; SV = seminal vesicles; US = ultrasound

* If required

Note: The Eastern Cooperative Oncology Group (ECOG) was established in 1955 as one of the first cooperative groups launched to perform multi-centre cancer clinical trials. It is funded primarily by the National Cancer Institute (NCI) and has evolved from a five-member consortium of institutions on the east coast to one of the largest clinical cancer research organisations in the United States. Westmead Hospital, Sydney is one of the ECOG international member institutions. The ECOG Performance Status scale and criteria are used by doctors and researchers to assess disease progression and effect on daily living abilities of patients and are based on Oken (1982):

0 Fully active, able to carry on all pre-disease performance without restriction
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg light house work, office work
2 Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4 Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5 Dead

Source: *Protocol – Radiation oncology, prostate, low risk, EBRT, definitive* (last modified 21 March 2011), *Protocol – Radiation oncology, prostate, intermediate risk, EBRT, definitive* (last modified 21 March 2011), *Protocol - Radiation oncology, prostate, high risk, EBRT, definitive* (last modified 22 March 2013), eviQ Cancer Treatments Online, Cancer Institute NSW [accessed 25 March 2013]

Clinical practice guidelines for adjuvant/salvage EBRT in patients with prostate cancer post-radical prostatectomy (eviQ)

	Adjuvant EBRT, post-radical prostatectomy for prostate cancer	Salvage EBRT, previous radical prostatectomy for prostate cancer
Patient population	• Post-radical prostatectomy for adenocarcinoma prostate • One of the following: o extraprostatic extension (pT3a, pT4) o SV invasion (pT3b) o positive resection margins • No evidence of lymph node or distant metastases • Undetectable PSA • ECOG 0-2 • Ideally, within 4 months of radical prostatectomy	• Previous radical prostatectomy for adenocarcinoma prostate • A persistently elevated PSA >6 weeks post-radical prostatectomy, including elevations in the ultrasensitive range • A rising PSA from previously undetectable level • No evidence of distant metastases • ECOG 0-2
Concurrent treatment	• Role of adjuvant hormone therapy yet to be defined • ADT may be beneficial in men at high risk of local or distant failure with RT alone, such as high pre-salvage PSA (>1 ng/mL), high Gleason score (8-10) and macroscopic focal recurrence	• Same as for adjuvant EBRT
EBRT	Adjuvant EBRT: 60-64 Gy (1.8-2 Gy/fraction, 30-32 fractions)	Salvage EBRT: 60-66 Gy (1.8-2 Gy/fraction, 30-33 fractions)
Target verification	• Acceptable – offline with port film or EPI daily first 3 fractions then weekly, matching to bony anatomy • Ideal – online daily imaging (OBI or EPI) matching to surgical clips or bony anatomy	Same as for adjuvant EBRT

Abbreviations: ADT = androgen deprivation therapy; CTV = clinical target volume; EBRT = external beam radiotherapy; ECOG = Eastern Cooperative Oncology Group; EPI = electronic portal imaging; Gy = Gray; OBI = on-board imaging; PSA = prostate-specific antigen; PTV = planning target volume; SV = seminal vesicles

Source: *Protocol – Radiation oncology, prostate, post radical prostatectomy, adjuvant* (last modified 21 March 2011), *Protocol – Radiation oncology, prostate, post radical prostatectomy, salvage* (last modified 21 March 2011), eviQ Cancer Treatments Online, Cancer Institute NSW [accessed 25 March 2013]

Appendix D TGA-registered implantable medical devices

List of TGA-registered implantable medical devices relevant to the current assessment

ARTG entry, product name	Product category	Sponsor	Effective date	Intended purpose
108382 Marker, lesion localization, implantable	Medical Device Class IIb	CMS Alphatech Pty Ltd	9/09/2004	Implantable localisation markers for improved accuracy in the delivery of therapeutic radiation
159089 Marker, lesion localization, implantable	Medical Device Class IIb	Life Healthcare Pty Ltd	2/02/2009	Device intended use is as implantable gold seed markers for interstitial placement to serve as localisation devices for the purpose of radiation therapy
160221 Marker, lesion localization, implantable	Medical Device Class IIb	Hologic Australia Pty Ltd	18/03/2009	Intended to be implanted to mark tumour/lesions to allow accurate localisation for therapy
178718 AnchorMarker - Marker, lesion localization, implantable	Medical Device Class III	MD Solutions Australasia Pty Ltd	24/12/2010	AnchorMarker is intended for placement in soft tissue before initiating a therapeutic procedure, providing for clearer identification of anatomic regions by providing reference positions around a proposed treatment site and as a result permits better dosimetric coverage of the targeted site
194396 Marker, lesion localization, implantable	Medical Device Class IIb	Aurora BioScience Pty Ltd	7/02/2012	The SuperLock fiducial markers are gold seeds implanted in and/or around a soft tissue, to act as a radiologic landmark, to define the target position with high precision
200124 Marker, lesion localization, implantable	Medical Device Class IIb	Emergo Asia Pacific Pty Ltd T/a Emergo Australia	16/08/2012	Radiopaque strands and markers are used to mark soft tissue for future therapeutic procedures. It is indicated for use in soft tissues or organ tissue for use in radiation therapy procedures
206021 Marker, lesion localization, implantable	Medical Device Class IIb	Advantage Health Care Pty Limited	13/02/2013	Implantable tissue marker

Abbreviations: TGA = Therapeutic Goods Administration

Source: Australian Register of Therapeutic Goods (ARTG) [accessed 30 April 2013]

Appendix E MBS notes on multiple services rule

Medicare Benefits Schedule - Note T8.2

Multiple Services Rule (source: MBS online, accessed 30 April 2013)

The fees for two or more operations, listed in Group T8 (other than Subgroup 12 of that Group), performed on a patient on the one occasion (except as provided in paragraph T8.2.3) are calculated by the following rule:

- 100% for the item with the greatest Schedule fee
  plus 50% for the item with the next greatest Schedule fee
  plus 25% for each other item.

Note:

a) Fees so calculated which result in a sum which is not a multiple of 5 cents are to be taken to the next higher multiple of 5 cents.
b) Where two or more operations performed on the one occasion have Schedule fees which are equal, one of these amounts shall be treated as being greater than the other or others of those amounts.
c) The Schedule fee for benefits purposes is the aggregate of the fees calculated in accordance with the above formula.
d) For these purposes the term "operation" only refers to all items in Group T8 (other than Subgroup 12 of that Group).

This rule does not apply to an operation which is one of two or more operations performed under the one anaesthetic on the same patient if the medical practitioner who performed the operation did not also perform or assist at the other operation or any of the other operations, or administer the anaesthetic. In such cases the fees specified in the Schedule apply.

Where two medical practitioners operate independently and either performs more than one operation, the method of assessment outlined above would apply in respect of the services performed by each medical practitioner.

If the operation comprises a combination of procedures which are commonly performed together and for which a specific combined item is provided in the Schedule, it is regarded as the one item and service in applying the multiple operation rule.

There are a number of items in the Schedule where the description indicates that the item applies only when rendered in association with another procedure. The Schedule fees for such items have therefore been determined on the basis that they would always be subject to the "multiple operation rule".

Where the need arises for the patient to be returned to the operating theatre on the same day as the original procedure for further surgery due to post-operative complications, which would not be considered as normal aftercare - see paragraph T8.2, such procedures would generally not be subject to the "multiple operation rule". Accounts should be endorsed to the effect that they are separate procedures so that a separate benefit may be paid.

Extended Medicare Safety Net Cap

The Extended Medicare Safety Net (EMSN) benefit cap for items subject to the multiple operations rule, where all items in that claim are subject to a cap are calculated from the abated (reduced) schedule fee.

For example, if an item has a Schedule fee of $100 and an EMSN benefit cap equal to 80 per cent of the schedule fee, the calculated EMSN benefit cap would be $80. However, if the schedule fee for the item is reduced by 50 per cent in accordance with the multiple operations rule provisions, and all items in that claim carry a cap, the calculated EMSN benefit cap for the item is $40 (50% of $100*80%).

Appendix F Search results

Database: Ovid MEDLINE(R) 1946 to January Week 3 2013 searches results

#	Searches	Results
1	prostate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	111,823
2	(cancer or neoplasm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1,162,722
3	1 and 2	72,534
4	radiotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	161,679
5	radiation therapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	44,460
6	4 or 5	183,551
7	3 and 6	8,775
8	fiducial.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1,604
9	7 and 8	140
10	random*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	746,793
11	9 and 10	26
12	bony.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	27,103
13	landmark*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	15,166
14	12 or 13	41,390
15	9 and 14	19

Database: Embase Session Results

#	Query	Results
#11	#9 AND #10	12
#10	random*	902,172
#9	#7 AND #8	51
#8	bony OR landmark	43,779
#7	#5 AND #6	401
#6	fiducial	2,229
#5	#3 AND #4	31,215
#4	'radiotherapy'/exp OR radiotherapy OR 'radiation'/exp OR radiation AND ('therapy'/exp OR therapy)	643,354
#3	#1 AND #2	165,841
#2	'cancer'/exp OR cancer OR 'neoplasm'/exp OR neoplasm OR 'carcinoma'/exp OR carcinoma	3,740,151
#1	prostat*	221,740

List of excluded non-randomised comparative studies that evaluated FM-based versus bony landmark-based EBRT for prostate cancer (reason for exclusion: only available as abstracts, no full-text publication)

Study	Report(s) and citation
Farrow (2009)	Farrow, C., Frantzis. J., Sisson. T. et al. 2009. The effect of treatment technique on acute toxicity for prostate radiotherapy, *Journal of Medical Imaging and Radiation Oncology*, 53 (s1), A185.
Kok (2012)	Kok, D., Gill, S., Bressel, M. et al.2012. Late toxicity and biochemical failure in 554 prostate cancer patients treated with and without fiducial marker based image guided radiotherapy, *Journal of Medical Imaging and Radiation Oncology*, 56 (Suppl 1), 242.
Pastor (2010)	Pastor, J., Lopez Torrecilla, J., Aimendros, P. et al. 2010. High dose radiotherapy in prostate cancer. Comparation between IMRT vs IG-IMRT with two fractionations, *Radiotherapy and Oncology*, 96 (Suppl 1), S403.
Sham (2011)	Sham, J., Rosenfelder, N., Ashley, S. et al. 2011. Does marker-based prostate radiotherapy cause worse acute toxicity? *Radiotherapy and Oncology*, 99 (Suppl 1), S380.

List of 17 excluded single-arm studies that evaluated FM-based EBRT for prostate cancer

Study	Report(s) and citation	Reason for exclusion
Brown (2011)	Brown, S., Lehman, M., Ferrari-Anderson, J. et al. 2011. Assessment of prostatic fiducial marker introduction: patient morbidity, staff satisfaction and improved treatment field placement, *Journal of Medical Imaging and Radiation Oncology*, 55, 417–424.	Sample size <50
Cahlon (2008)	Cahlon, O., Zelefsky, M., Shippy, A. et al. 2008. Ultra-High Dose (86.4 Gy) IMRT for localized prostate cancer: toxicity and biochemical outcomes, *International Journal of Radiation Oncology Biology Physics,* 71 (2), 330-337.	Use of FM was implemented in routine IMRT only 'recently' and results are not segregated
Cheung (2005)	Cheung, P., Sixel, K., Morton, G. et al. 2005. Individualized planning target volumes for intrafraction motion during hypofractionated intensity-modulated radiotherapy boost for prostate cancer. *International Journal of Radiation Oncology Biology Physics*, 62 (2), 418–425.	Sample size <50
Dehnad (2003)	Dehnad, H., Nederveen, A.J., Van Der Heide, U.A. et al. 2003. Clinical feasibility study for the use of implanted gold seeds in the prostate as reliable positioning markers during megavoltage irradiation, *Radiotherapy and Oncology*, 67 (3), 295-302.	Sample size <50
Duffton (2012)	Duffton, A., McNee, S., Muirhead, R. et al. 2012. Clinical commissioning of online seed matching protocol for prostate radiotherapy, *British Journal of Radiology*, 85 (1020), e1273–e1281.	Sample size <50
Ghadjar (2008)	Ghadjar, P., Vock, J., Vetterli, D. et al. 2008. Acute and late toxicity in prostate cancer patients treated by dose escalated intensity modulated radiation therapy and organ tracking, *Radiation Oncology*, 3, 35.	Sample size < 50
Kudchadker (2009)	Kudchadker, R.J., Lee, A.K., Yu, Z.H. et al. 2009. Effectiveness of using fewer implanted fiducial markers for prostate target alignment, *International Journal of Radiation Oncology Biology* Physics, 74 (4), 1283-1289.	Sample size <50
Lips (2011)	Lips, I.M., van der Heide, U.A., Haustermans. K. et al. 2011. Single blind randomized phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial): study protocol for a randomized controlled trial, *Trials*, 12, 255.	Protocol only, no published results yet
Lips (2012)	Lips, I.M., van Gils, C.H., Kotte, A.N. et al. 2012. A double-blind placebo-controlled randomized clinical trial with magnesium oxide to reduce intrafraction prostate motion for prostate cancer radiotherapy, *International Journal of Radiation Oncology Biology Physics*, 83 (2), 653-660.	Sample size <50 each comparison arm
Moman (2010)	Moman, M.R., van der Heide, U.A., Kotte, A.N. et al. 2010. Long-term experience with transrectal and transperineal implantations of fiducial gold	Sample size <50

Study	Report(s) and citation	Reason for exclusion
	markers in the prostate for position verification in external beam radiotherapy; feasibility, toxicity and quality of life, *Radiotherapy & Oncology*, 96 (1), 38-42.	
Poggi (2003)	Poggi, M.M., Gant, D.A., Sewchand, W. et al.2003. Marker seed migration in prostate localization, *International Journal of Radiation Oncology Biology Physics*, 56 (5), 1248-1251.	Sample size <50
Schiffner (2007)	Schiffner, D.C., Gottschalk, A.R., Lometti, M. et al. 2007. Daily electronic portal imaging of implanted gold seed fiducials in patients undergoing radiotherapy after radical prostatectomy, *International Journal of Radiation Oncology Biology Physics*, 67 (2), 610-619.	Sample size <50
Singh (2007)	Singh, A.K., Guion, P., Sears-Crouse, N. et al. 2007. Simultaneous integrated boost of biopsy proven, MRI defined dominant intra-prostatic lesions to 95 Gray with IMRT: early results of a phase I NCI study, *Radiation Oncology*, 2, 36.	Sample size <50
Swamy (2009)	Swamy, K., Sathiya Narayanan, V.K., Basu, S. et al. 2009. Dose escalation in image-guided, intensity-modulated radiotherapy of carcinoma prostate: initial experience in India, *Journal of Cancer Research and Therapeutics*, 5 (4), 277-283.	Sample size <50
Tiberi (2012)	Tiberi, D.A., Carrier, J-F., Beauchemin, M-C. et al.2012. Impact of concurrent androgen deprivation on fiducial marker migration in external-beam radiation therapy for prostate cancer, *International Journal of Radiation Oncology Biology Physics*, 84 (1), e7-e12.	Sample size <50
Yang (2009)	Yang, J., Abdel-Wahab, M. and Ribeiro, A. 2009. EUS-guided fiducial placement before targeted radiation therapy for prostate cancer, *Gastrointestinal Endoscopy*, 70 (3), 579-583.	Sample size <50
Yang (2011)	Yang, J., Abdel-Wahab, M. & Ribeiro, A. 2011. EUS-guided fiducial placement after radical prostatectomy before targeted radiation therapy for prostate cancer recurrence, *Gastrointestinal Endoscopy*, 73 (6), 1302-1305.	Sample size <50

Master list of 20 single arm studies that evaluated FM-based EBRT for prostate cancer (secondary studies)

Study	Report(s) and citation
Chua (2013)	Chua, B., Min, M., Wood, M. et al. 2013. Implementation of an image guided intensity-modulated protocol for post-prostatectomy radiotherapy: planning data and acute toxicity outcomes, *Journal of Medical Imaging and Radiation Oncology*. doi: 10.1111/1754-9485.12043 [first published online 27 February 2013].
Eade (2011)	Eade, T.N., Guo, L., Forde, E. et al. 2011. Image-guided dose-escalated intensity-modulated radiation therapy for prostate cancer: treating to doses beyond 78 Gy, *BJU International*, 109, 1655-1660.
Escudero (2010)	Escudero, J.U.J, Peidro, J.P., de Campos, M.R. et al. 2010. Insertion of intraprostate gold fiducial markers in prostate cancer treatment, *International Journal of Nephrology and Urology*, 2 (1), 265-272.
Gill (2012)	Gill, S., Li J., Thomas, J. et al. 2012. Patient-reported complications from fiducial marker implantation for prostate image-guided radiotherapy, *British Journal of Radiology*, 85 (1015), 1011-1017.
İğdem (2009)	İğdem, Ş., Akpinar, H., Alço, G. et al. 2009. Implantation of fiducial markers for image guidance in prostate radiotherapy: patient-reported toxicity, *The British Journal of Radiology*, 82, 941-945.
Kaprealian (2012)	Kaprealian, T., Weinberg, V., Speight, J.L. et al. 2012. High-dose-rate brachytherapy boost for prostate cancer: comparison of two different fractionation schemes, *International Journal of Radiation Oncology Biology Physics*, 82 (1), 222-227.
Langenhuijsen (2007)	Langenhuijsen, J.F., van Lin, E. N., Kiemeney, L. A. et al. 2007. Ultrasound-guided transrectal implantation of gold markers for prostate localization during external beam radiotherapy: complication rate and risk factors, *International Journal of Radiation Oncology Biology Physics*, 69 (3), 671-376.
Langenhuijsen (2011)	Langenhuijsen, J.F., Smeenk, R.J., Louwe, R.J.W. et al. 2011. Reduction of treatment volume and radiation doses to surrounding tissues with intraprostatic gold markers in prostate cancer radiotherapy, *Clinical Genitourinary Cancer*, 9 (2), 109-114.

Study	Report(s) and citation
Linden (2009)	Linden, R.A., Weiner, P.R., Gomella, L.G. et al. 2009. Technique of outpatient placement of intraprostatic fiducial markers before external beam radiotherapy, *Urology*, 73 (4), 881-886.
Lips (2008)	Lips, I.M., Dehnad, H., van Gils, C.H., et al. 2008. High-dose intensity-modulated radiotherapy for prostate cancer using daily fiducial marker-based position verification: acute and late toxicity in 331 patients. *Radiation Oncology,* 3, 15.
Lips (2009)	Lips, I.M., van Gils, C.H., van der Heide, U.A., Kruger, A.E., van Vulpen, M. 2009. Health-related quality of life 3 years after high-dose intensity-modulated radiotherapy with gold fiducial marker-based position verification. *BJU International*, 103 (6), 762-767.
Martin (2007)	Martin, J.M., Rosewall, T., Bayley, A. et al. 2007. Phase II Trial of hypofractionated image-guided intensity-modulated radiotherapy for localized prostate adenocarcinoma, *International Journal of Radiation Oncology Biology Physics*, 69 (4), 1084–1089.
Martin (2009)	Martin, J.M., Bayley, A., Bristow, R. et al. 2009. Image guided dose escalated prostate radiotherapy: Still room to improve. *Radiation Oncology*, 4, 50 (correction in 4, 65).
Nath (2011)	Nath, S.K., Sandhu, A.P., Sethi, R.A. et al. 2011. Target localization and toxicity in dose-escalated prostate radiotherapy with image-guided approach using daily planar kilovoltage imaging, *Technology in Cancer Research and Treatment*, 10 (1), 31-37.
Quon (2012)	Quon, H., Cheung, P.C., Loblaw, D.A. et al. 2012. Hypofractionated concomitant intensity-modulated radiotherapy boost for high-risk prostate cancer: late toxicity, *International Journal of Radiation Oncology Biology Physics*, 82 (2), 898-905.
Shinohara (2008)	Shinohara, K. & Roach, M.2008. Technique for implantation of fiducial markers in the prostate, *Urology,* 71, 196-200.
Skala (2007)	Skala, M., Rosewall, T., Dawson, L. et al. 2007. Patient-assessed late toxicity rates and principal component analysis after image-guided radiation therapy for prostate cancer, *International Journal of Radiation Oncology Biology Physics*, 68 (3), 690-698.
Takeda (2012)	Takeda, K., Takai, Y., Narazaki, K. et al. 2012. Treatment outcome of high-dose image-guided intensity-modulated radiotherapy using intra-prostate fiducial markers for localized prostate cancer at a single institute in Japan, *Radiation Oncology,* 71 Article Number 105.
Vesprini (2011)	Vesprini, D., Catton, C., Jacks, L. et al. 2011. Inverse relationship between biochemical outcome and acute toxicity after image-guided radiotherapy for prostate cancer, *International Journal of Radiation Oncology Biology Physics,* 83 (2), 608-616.
Wu (2012)	Wu, J.S.Y., Brasher, P.M.A., El-Gayed, A. et al. 2012. Phase II study of hypofractionated image-guided radiotherapy for localised prostate cancer: outcomes of 55 Gy in 16 fractions at 3.4 Gy per fraction, *Radiotherapy and Oncology*, 103, 210-216.

Appendix G Non-randomised comparative studies

Inclusion and exclusion criteria of the non-randomised comparative studies

Study	Inclusion criteria	Exclusion criteria
Gill (2011)	• All prostate cancer patients who received RT between 22 June 2006 and 24 June 2009 in the centre	• Patients with only one day of toxicity information • Patients with >grade 1 toxicity at baseline
Lips (2007)	• IMRT cohort: patients with locally advanced prostate cancer who received IMRT between October 2003 and November 2004 • 3D-CRT cohort: patients with locally advanced prostate cancer who received conformal RT between December 1997 and October 2001	• Patients who completed all 3 questionnaires at all 3 measurement points
Singh (2013)	• T1-T3N0M0 prostate adenocarcinoma • A pre-treatment serum PSA • No previous history of pelvic irradiation • Returned completed questionnaire with attached consent	• Underwent prostatectomy • Received chemotherapy • Failed to complete full course of RT
Zelefsky (2012)	• Prostate cancer patients (biopsy-proven adenocarcinoma, Stages T1-T3*) treated with monotherapy EBRT at the centre	• Not reported
Chung (2009)	• High-risk non-metastatic prostate cancer • Underwent definitive IMRT to the whole pelvic lymph nodes followed by a prostate boost, with neoadjuvant and concurrent androgen suppression therapy	• Not reported

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; EBRT = external beam radiotherapy; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; PSA = prostate-specific antigen; RT = radiotherapy

* Staging classification according to the 2005 American Joint Committee on Cancer staging classification system

Source: Gill (2011); Lips (2007); Singh (2013); Zelefsky (2012); Chung (2009)

Treatment planning and delivery by comparison groups in the non-randomised comparative studies

Study/ comparison groups	Treatment planning (positioning strategy: target identification, verification, correction)	Treatment delivery (prescription dose, delivery)
Gill (2011)	–	–
IGRT	• 1 week before CT scan: 3 FM (gold seeds) implanted • Margins for CTV to PTV expansion: 10 mm cranio-caudal, laterally and anterior; 7 mm posteriorly • Daily pre-treatment orthogonal verification imaging	Conformal RT (5 or 7 fields) Prescription dose: 78 Gy (39 fractions: 2 Gy/fraction, 5 fractions/week)
Non-IGRT	• Daily pre-treatment orthogonal verification imaging in 1st week of RT, matched to bony anatomy on DDRs from planning CT scan • Margins for CTV to PTV expansion: 10 mm cranio-caudal, laterally and anterior; 7 mm posteriorly • Correction threshold: average bony anatomy displacement >5 mm in first week • Weekly pre-treatment orthogonal imaging after the first week	Conformal RT (5 or 7 fields) Prescription dose: 74 Gy (37 fractions: in 2 Gy/fraction, 5 fractions/week)
Lips (2007)	–	–
IMRT	• Position verification: daily, using gold FM implanted transrectally	• IMRT with a multileaf collimator and 10-MV photons • Dose escalation: prescription dose 76 Gy (2.17 Gy/fraction, 35 fractions)
3D-CRT t	• Position verification: by visualising bony anatomy using ePI	• 3D-CRT (3-field, using 6- and 18-MV photons, and a multileaf collimator) • Prescription dose: 70 Gy (2 Gy/fraction, 5 fractions/week)
Singh (2013)	–	–
IGRT	• CT simulation in supine (standard bladder and bowel preparation protocol) • US-guided insertion of 3 FM (gold seeds) by a urologist with antibiotic cover • MR scanning in treatment position	• 3D-CRT (6- and 18-MV photons): • PTV receiving 70-76 Gy in 2.0 Gy fractions
Non-IGRT	• CT simulation in supine (standard bladder and bowel preparation protocol)	Same as the IGRT cohort
Zelefsky (2012)		
IGRT	• One week before simulation and treatment planning: 3 gold FM implanted transrectally into the prostate via US guidance under LA, antibiotic coverage for all patients • At treatment planning: FM were identified on CT images and projected onto DDRs which were then used as reference images at time of treatment • PTV included prostate and entire SV with a 10 mm margin except at prostate-rectal interface (6 mm) • Before treatment: daily orthogonal kV radiographs were obtained and registered to the reference DRRs, patient position corrected if discrepancy was ≥2 mm in any direction, a second verification set of kV radiographs was then obtained to ensure proper position before treatment • During treatment: daily 2-D kV imaging	• HD-IMRT: prescription dose 86.4 Gy

Study/ comparison groups	Treatment planning (positioning strategy: target identification, verification, correction)	Treatment delivery (prescription dose, delivery)
Non-IGRT	• Weekly ePI used to corroborate set-up (daily imaging not used) • PTV included prostate and entire SV with a 10-mm margin except at prostate-rectal interface (6 mm)	Same as the IGRT cohort
Chung (2009)	–	–
IG-IMRT	• 1-2 weeks before start of treatment: CT image acquisition (3-mm slice thickness, scanning with knee sponges and foot straps), 3 intra-prostatic FMs implanted ≥1 week before CT simulation • PTV prostate/SV margins: 2-3 mm circumferentially • Set-up verification: orthogonal images taken before each fraction, online corrections according to location of FMS before treatment, >2-mm displacement in any of the 3 axes as threshold for realignment according to local protocol	All patients underwent definitive IMRT to the whole pelvic lymph nodes followed by a prostate boost, with neo-adjuvant and concurrent androgen suppression therapy. IMRT was given in 2 phases: PTV: Phase 1: prostate/SV 54 Gy (27 fractions), pelvic nodes 48.6 Gy (27 fractions) Phase 2: prostate/SV 19.8 Gy (11 fractions) Total: 73.8 Gy (38 fractions)
IMRT	• 1-2 weeks before start of treatment: CT image acquisition (3 mm slice thickness, scanning with an alpha cradle), no FMs • PTV prostate/SV margins: 10 mm circumferentially, except for 5 mm posteriorly • Set-up verification/correction: daily orthogonal portal images for first 3 fractions, then once weekly thereafter; alignment determined by skin surface markers and bony anatomy; 3 mm displacement in any of the 3 axes as threshold for realignment in general	Same as for the IG-IMRT cohort

Abbreviations: 3D-CRT= 3-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; CT = computed tomography; DRR = digitally reconstructed radiographs; ePI = electronic portal imaging; FM = fiducial marker; HD = high-dose; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; kV = kilovoltage; LA = local anaesthesia; PTV = planning target volume; RT = radiotherapy; SV = seminal vesicles; US = ultrasound

Source: Gill (2011); Lips (2007); Table 1 in Singh (2013); Zelefsky (2012); Table 2, p 55 in Chung (2009)

Mean scores of quality of life (QoL) at baseline, one and six months after completion of radiotherapy in Lips (2007)

	IMRT	–	–	3D-CRT	–	–
RAND-36	**Baseline**	**1 m**	**6 m**	**Baseline**	**1 m**	**6 m**
Physical functioning	85	81	84	86	84	85
Social functioning	80	73	84	82	86	90
Physical role restriction	78	55	76	78	72	82
Emotional role restriction	77	75	86	78	85	91
Mental health	75	77	79	76	78	80
Vitality	70	64	70	69	68	69
Pain	90	79	86	88	87	91
General health	68	67	70	66	66	68
Change in health	50	42	56	44	54	63
EORTC QLQ-C30(+3)	**Baseline**	**1 m**	**6 m**	**Baseline**	**1 m**	**6 m**
Physical functioning	91	85	89	89	88	88
Role functioning	88	75	86	87	85	89
Emotional functioning	75	81	82	78	87	88
Cognitive functioning	86	85	84	89	86	86
Social functioning	90	84	90	90	92	94
Global health/QoL	79	75	79	78	78	81
Fatigue	21	30	21	20	24	20
Nausea and vomiting	1	3	3	2	2	2
Pain	11	16	14	12	13	9
Dyspnoea	12	12	11	9	12	15
Insomnia	24	30	19	23	26	16
Appetite loss	2	4	3	6	2	3
Constipation	2	8	4	3	6	7
Diarrhoea	6	12	8	6	13	13
Financial difficulties	1	4	4	3	3	2
EORTC QLQ-PR25	**Baseline**	**1 m**	**6 m**	**Baseline**	**1 m**	**6 m**
Urinary symptoms/problems	18	34	14	19	22	17
Bowels symptoms/function	5	11	7	5	9	8
Treatment-related symptoms	6	9	10	9	13	12
Sexual functioning	26	25	28	23	24	26
Sexual activity	69	56	57	66	60	51

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; EORTC QLQ-C30(+3) = European Organisation for Research and Treatment of Cancer core quality-of-life questionnaire; EORTC QLQ-PR25 = EORTC prostate cancer module; FM = fiducial marker; IMRT = intensity-modulated radiotherapy; QoL = quality of life

Source: Table 2, p 658 in Lips (2007)

Appendix H FM-based EBRT cohort studies/case series

Inclusion and exclusion criteria in the FM-based EBRT cohort studies/case series

Study	Inclusion criteria	Exclusion criteria
Chua (2013)	Patients were eligible if they received post-prostatectomy radiotherapy within study period; included 20 receiving radiotherapy for adjuvant indications and 55 receiving for salvage indications	Not reported Nine patients were excluded because radiotherapy plans were unavailable
Eade (2011)	Patients with localised disease who were entered on the database between April 2007 and August 2009, treated with IG-IMRT with a minimum dose of 78 Gy and who had toxicity assessed during treatment and at first follow-up	Not specifically reported: It is stated that 11 patients excluded due to lack of baseline information (n=1), lack of toxicity recorded during treatment (n=2) and lack of follow-up in the first 3 months (n=8)
Linden (2009)	Unclear	Unclear
Lips (2008)	Prostate cancer patients that were treated with IMRT with a minimum follow-up of 31 months	Not reported
Martin (2009)	Eligible patients had biopsy confirmed adenocarcinoma of the prostate with clinical stage T1-3N0 M0	• Patients enrolled on a concurrent randomized trial receiving 5 months of bicalutamide in the experimental arm • Patients with <2 years of follow-up data available (to reduce bias in under-reporting of toxicity due to an insufficient period of observation)
Nath (2011)	Prostate cancer patients that were consecutively treated with definitive external beam IG-IMRT	Not stated
Takeda (2012)	Patients had to have a biopsy-confirmed adenocarcinoma of the prostate with the clinical stage T1-3N0M0 and were classified in the National Comprehensive Cancer Network (NCCN)-defined (www.nccn.com) intermediate or high-risk groups	NCCN-defined low-risk patients with a T1-2a clinical stage tumour, a Gleason score <7, a pre-treatment PSA level <10 ng/ mL, and N1 disease. Patients with a T4 clinical stage tumour, the presence of metastasis, other concurrent invasive cancers, or active collagen disease were also not included. Additionally, patients with salvage intent were not enrolled, including patients with a biochemical relapse following a prior prostatectomy, prior pelvic radiotherapy and hormonal therapy. Patients with a follow-up period within 1 year were also not registered in this analysis
Vesprini (2011)	Patients had to have T1-T3, NX, M0 adenocarcinoma of the prostate, presenting PSA <20 ng/mL and undergone 75.6-79.8 Gy using EBRT or IMRT	Patients receiving adjuvant androgen therapy (ADT)

Abbreviations: ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; Gy = Gray; IG-IMRT = image-guided intensity-modulated radiotherapy; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen

Source: Chua (2013); Eade (2011); Linden (2009); Lips (2008); Martin (2009); Nath (2011); Takeda (2012); Vesprini (2011)

Treatment planning and delivery in the FM-based EBRT cohort studies/case series

Study	Treatment planning	FM implantation	RT treatment (dose received)	Concomitant therapy
Chua (2013)	CTV definition: not specified. Margins for CTV to PTV expansion: 8 mm except posteriorly where 7 mm used	3 gold FM marks in the prostate gland. Repositioning with on-board imager during treatment	IG-IMRT 64-66 Gy in 2 fractions given to 20 patients 66 Gy in 55 patients (salvage) Rectal dose: 65 Gy and 40 Gy to less than 17% 35% respectively Bladder dose: 65 Gy to less than 25% and 40 Gy to less than 50%	ADT was given to a proportion of patients (not stated)
Eade (2011)	CTV definition: prostate and 9mm of the seminal vesicles. Margins for CTV to PTV expansion: 7-8 mm except posteriorly where 5-6 mm used	3 gold FM marks in the prostate gland. Repositioning with on-board imager during treatment	IG-IMRT 78-81 Gy given to 86 patients 82-84 Gy in 15 patients	ADT was given to 20 patients
Linden (2009)	No details provided	3 gold markers in the prostate gland using TRUS. Patients were given local anaesthesia.	IMRT Median radiation dose administered was 75.6 Gy (range 50-79.2 Gy) No further details supplied	No details provided
Lips (2008)	CTV definition: prostate and seminal vesicles. Margins for CTV to PTV expansion: 8 mm	FMs were implanted transrectally with antibiotic prophylaxis. Daily portal images of the FM were taken to determine the position variations during treatment	IMRT – five beam A mean dose of 76 Gy in 35 fractions was prescribed to the PTV and 95% of the prescription dose (72 Gy) was prescribed to 99% of the PTV. No elective pelvic node irradiation was performed	ADT in 95 patients
Martin (2009)	CTV definition: prostate and in some men seminal vesicles. Margins for CTV to PTV expansion: 10mm circumferentially except posteriorly where 7 mm margin used	3 gold markers in the prostate gland using TRUS. Daily portal images of the FM were taken to determine the position variations during treatment	3D-CRT and IMRT 79.8 Gy in 42 fractions given in 5 fractions per week If dose constraints exceeded, an IMRT inverse plan used No elective pelvic node irradiation was performed	ADT patients were excluded
Nath (2011)	CTV definition: prostate and seminal vesicles. Margins for CTV to PTV expansion: 8-10mm margin except posteriorly where 5mm margin used	3 gold markers in the prostate gland using TRUS. Repositioning with on-board imager during treatment	IMRT- 7 field technique Prescribed doses ranged between 74-78 Gy (median 76 Gy) in 2 Gy fractions 56-60 Gy was delivered to the initial PTV, which include the prostate and the first third of the seminal vesicles, and the remaining dose to the prostate 22 high-risk patients received pelvic nodal IMRT to doses of 46-50 Gy, followed by a boost to bring the prostate and seminal vesicles to full dose	ADT was given to a proportion of patients (not stated)
Takeda	CTV definition: prostate	3 gold markers in the	IMRT 5-8 coplanar beams	ADT in 124

Study	Treatment planning	FM implantation	RT treatment (dose received)	Concomitant therapy
(2012)	and seminal vesicles. Margins for CTV to PTV expansion: 5mm circumferentially	prostate gland. Repositioning with on-board imager during treatment	Prescribed dose 76 Gy (2 Gy fractions) in 13 patients (9%) and 80 Gy in 128 patients (91%)	patients
Vesprini (2011)	CTV definition: prostate. Margins for CTV to PTV expansion: 10mm circumferentially, except posteriorly where 7mm margin used	3 gold markers in the prostate gland using TRUS	Patients were planned using a six-field coplanar 3D-CRT or a five field sliding window IMRT Patients prescribed 75.6 Gy or 79.8 Gy	ADT patients were excluded

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; CTV = clinical target volume; FM = fiducial marker; Gy = Gray; IG-IMRT = image-guided intensity-modulated radiotherapy; IMRT = intensity-modulated radiotherapy; PTV = planning target volume

Source: Chua (2013); Eade (2011); Linden (2009); Lips (2008); Martin (2009); Nath (2011); Takeda (2012); Vesprini (2011)

Characteristics of study participants in the FM-based EBRT case series

Study	FM-based EBRT
Chua (2013)	**N=75**
Age median	67 years
No other details supplied	-
Eade (2011)	**(N=101)**
Age (years): median (range)	71 (46-83)
Tumour stage: no (%)	
T1c	29
T2	49
T3	22
Gleason score: no (%)	
≤ 6	16
7	49
≥8	35
Presenting PSA level (ng/mL): mean (median)	13.1 (1.0-160.0)
Baseline AUA-IPSS: median (range)	7 (0-35)
Lips (2008)	**(N=331)**
Age (years): mean (range)	-
Tumour stage: no (%)	
T1	37 (11)
T2	31 (9)
T3	262 (79)
T4	1 (1)
Gleason score: no (%)	
≤4	39 (12)
5-7	228 (69)
≥ 8	64 (19)
PSA (ng/mL): mean (range)	20 (0.5-175)
Hormonal treatment	

Study	FM-based EBRT
None	236 (71)
Short term	70 (21)
Long term	40 (12)
Linden (2009)	**-**
Age (years): median (range)	NR
Tumour stage: no (%)	NR
Gleason score: no (%)	NR
Presenting PSA level (ng/mL): mean (median)	0.6-320 ng/dL (mean 12.9)
Martin (2009)	**(N=259)**
Age (years): mean (range)	71 (45-84)
Tumour stage: no (%)	
T1b	1
T1c	83
T2a	125
T2b	15
T2c	28
T3a	2
T3b	2
TX	3
Gleason score: no (%)	
5-6	96 (37)
7	141 (55)
8-10	21 (8)
Presenting PSA level (ng/mL): mean (median)	7.6 (0.26-51.4)
Risk stratification	
Low	59 (22)
Intermediate	163 (63)
High	37 (14)
Nath (2011)	**IMRT (N=100)**
Age (years): median (range)	69 (46, 85)
Tumour stage: no (%)	
T1a	1 (1)
T1b	0(0)
T1c	56 (56)
T2a	22 (22)
T2b	8 (8)
T2c	7 (7)
T3	5 (5)
T4	1 (1)
Gleason score: no (%)	
≤6	33 (33)
7	38 (38)
8-10	29 (29)

Study	FM-based EBRT
PSA (ng/mL): no (%)	
0-10	71 (71)
10-20	23 (23)
>21	5 (5)
Androgen deprivation: no (%)	
None	53 (53)
6 months or less	23 (23)
>6 months	24 (24)
Pelvic node treatment	
Yes	22 (22)
No	78 (78)
Takeda (2012)	**IMRT (N=141)**
Age median (range years)	71 (50-83)
Tumour stage: no (%)	–
T1	34 (24%)
T2b	40 (28%)
T3	67 (48%)
Gleason score: no (%)	–
<8	73 (52)
8-10	68 (48)
PSA (ng/mL): no (%)	–
≤ 20	93 (66)
>20	48 (34)
NCCN risk group	–
Intermediate	36 (26)
High	105 (74)
ADT	–
Yes	124 (88)
No	17 (12)
Comorbidities	–
Diabetes	23 (16)
Hypertension	50 (35)
Haemorrhoid	37 (26)
Vesprini (2011)	**N=362**
Age (years): median (range)	70.5 (65,73)
Tumour stage: no (%)	–
T1	164 (45%)
T2	197 (54%)
T3	1 (0.3%)
Gleason score: no (%)	–
5-6	136 (38%)
7	210 (58%)
8-9	16 (4%)

Study	FM-based EBRT
PSA (ng/mL): median	7.87 ml
Risk stratification	–
Low	87 (24%)
Intermediate	251 (69%)
High	24 (7%)

Source: Chua (2013); Eade (2011); Linden (2009); Lips (2008); Martin (2009); Nath (2011); Takeda (2012); Vesprini (2011)

Key relevant outcomes and statistical analyses reported in the FM-based EBRT cohort studies/case series

Study	Definition of outcomes	Method of statistical analysis
Chua (2013)	Acute GI and GU toxicities, recorded using CTCAE criteria, version 3.0	• Frequency of experiencing at least one toxicity event
Eade (2012)	GI and GU toxicities, recorded using CTCAE criteria, version 3.0 (unclear if just refers to acute toxicities) Toxicity measured 'at treatment' and at 3 months Urinary symptoms: IPSS Exact definition of rectal or bladder toxicities not reported	• Comparisons between groups (low and high dose) were made using the Mann-Whitney U-test • Time to grade 2 late toxicity was estimated using Kaplan-Meier survival analysis
Linden (2009)	• Acute toxicity was scored using the Common Toxicity Criteria (version 3.0) • Urinary symptoms: IPSS No further details provided	• No analysis undertaken
Lips (2008)	Acute toxicity was scored using the Common Toxicity Criteria. Acute toxicity was present when one of the symptoms occurred within 90 days after the start of treatment. Late toxicity was scored according to the RTOG/EORTC morbidity version scale version 9	• Frequency of experiencing at least one toxicity event • Calculation of relative risks was provided looking comparisons with those with acute and late toxicity
Martin (2009)	• 5-year bNED was assessed according to the nadir + 2 definition. The bNED using the previous ASTRO definition is also reported • Instigation of salvage therapies and evidence of clinical disease progression prior to a PSA rise were also counted as a failure. For the ASTRO definition, hormone use lead to patients being excluded from bNED analysis • Peak physician assessed acute and late toxicity was graded according to the RTOG criteria for actuarial reporting	• Patients were censored at the time of event or last review • Kaplan Meier curves were generated using the two failure definitions • Univariate analyses for potential prognostic factors were performed • Multivariate analyses were performed using a Cox-Regression model
Nath (2011)	• Acute toxicity included side effects occurring during the course of radiotherapy and up to three months following the completion of treatment • Late toxicity included any symptoms occurring more than three months after the completion of treatment. Symptoms present before radiotherapy were not included in this data unless those symptoms became more severe • Symptom severity was graded on a scale of 1-5 according to the CTCAE criteria • Biochemical response rates were according to the Phoenix definition of PSA evaluation of 2ng/mL above the nadir	• Frequency of experiencing at least one toxicity event • No additional analysis undertaken
Takeda	• Acute and late GI GU toxicity recorded using CTCAE	• 5-year PSA relapse-free survival calculated

Study	Definition of outcomes	Method of statistical analysis
(2012)	criteria, version 3.0 (unclear if just refers to acute toxicities) • Patients with documentation of biochemical or metastatic relapse disease who subsequently died were scored as deaths (cause-specific survival) • Biochemical response rates were according to the Phoenix definition of PSA evaluation of 2ng/mL above the nadir	using Kaplan–Meier curves for biochemical control using the one failure definition • 5-year actuarial distant metastasis-free survival, cancer-specific survival and overall survival rates were also evaluated by Kaplan–Meier curves • Univariate analyses and multivariate analyses were performed to determine the related PSA relapse-free survival predictors • Multivariate analyses were performed using a Cox regression model
Vesprini (2011)	• Biochemical failure according to the nadir + 2 and the ASTRO definition • Instigation of salvage therapies and evidence of clinical disease progression prior to a PSA rise were also defined as a failure • Peak physician-assessed acute and late toxicity graded according to the RTOG criteria for actuarial reporting	• Fisher's exact test or the Cochran-Armitage trend test was used for variables with a natural ordering • Kaplan Meier curves were generated using the two failure definitions • Univariate analyses for potential prognostic factors were performed • Multivariate analyses were performed using a Cox-Regression model

Abbreviations: ASTRO = American Society for Therapeutic Radiology and Oncology; bNED = biochemical no evidence of disease; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; GI = gastrointestinal; GU = genitourinary; IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen; RTOG = Radiation Therapy Oncology Group

Source: Chua (2013); Eade (2011); Linden (2009); Lips (2008); Martin (2009); Nath (2011); Takeda (2012); Vesprini (2011)

Overall survival, local control outcomes reported in the FM-based EBRT cohort studies/case series

Study Outcome measure	Result
Martin (2009)	–
5 year biochemical response	Overall (79.4% CI 74.1-84.6) 78.2%, low 65.2% immediate and 62.7% high- risk patients
Local control and salvage	Unclear
Distant disease and survival	Unclear
Nath (2012)	–
Biochemical response, local failure and survival	'By last follow-up, only one patient experience biochemical failure according to the Phoenix definition'
Takeda (2012)	–
5-year actuarial PSA relapse-free survival	100% for intermediate and 82.2% for high-risk groups
5-year actuarial distant metastasis-free survival	100% for intermediate and 95% for high -risk groups
5-year cause-specific survival	100% for intermediate and 91.7% for high-risk groups
Vesprini (2011)	–
5-year biochemical failure-free rate (ASTRO)	(76% CI 70-81)
5-year biochemical failure-free rate (Phoenix)	(67% CI 62-72)

Source: Martin (2009); Nath (2011); Takeda (2012); Vesprini (2011)

Acute and late gastrointestinal (GI) toxicity in the FM-based EBRT cohort studies/case series

Study Outcome measure	Baseline	Acute	Late
Chua (2013)	**N=101**	**IG-IMRT (N=101)**	**–**
CTCAE (v3.0) grade 0	57 (76)	26 (35)	–
CTCAE (v3.0) grade 1	18 (24)	32 (43)	–
CTCAE (v3.0) grade 2	0 (0)	16 (21)	–
CTCAE (v3.0) grade 3	0 (0)	1 (1)	–
CTCAE (v3.0) grade 4	0 (0)	0 (0)	–
Eade (2011)	**N=75**	**N=75**	**–**
CTCAE (v3.0) grade 0	45 (45)	91 (90)	–
CTCAE (v3.0) grade 1	49 (49)	8 (8)	–
CTCAE (v3.0) grade 2	6 (6)	1 (1)	–
CTCAE (v3.0) grade 3	0 (0)	0 (0)	–
CTCAE (v3.0) grade 4	0 (0)	0 (0)	–
Lips*	**N=331**	**N=331**	**N=320**
CTCAE (v2.0) grade 0	305 (92)	63 (19)	–
CTCAE (v2.0) grade 1	20 (6)	169 (51)	–
CTCAE (v2.0) grade 2	6 (2)	99 (30)	–
CTCAE (v2.0) grade 3	0 (0)	0 (0)	–
CTCAE (v2.0) grade 4	0 (0)	0 (0)	–
RTOG grade 0	–	–	193 (60)
RTOG grade 1	–	–	94 (29)
RTOG grade 2	–	–	30 (9)
RTOG grade 3	–	–	2 (1)
RTOG grade 4	–	–	1 (0.3)
Martin (2009)	**–**	**N=257**	**N=256**
RTOG grade 0	–	(39)	(91.8)
RTOG (v2.0) grade 1	–	(50.9)	(3.9)
RTOG (v2.0) grade 2	–	(10.1)	(3.1)
RTOG (v2.0) grade 3	–	(0)	(1.2)
Nath (2012)	**–**	**N=100**	**N=100**
CTCAE (v3.0) grade 0	–	–	–
CTCAE (v3.0) grade 1	–	42 (42)	7 (7)
CTCAE (v3.0) grade 2	–	11 (11)	2 (2)
CTCAE (v3.0) grade 3	–	0 (0)	0(0)
Takedea	**–**	**N=141**	**N=141**
CTCAE (v4.0) grade 0	–	–	–
CTCAE (v4.0) grade 1	–	29 (20)	–
CTCAE (v4.0) grade 2	–	2 (1.4)	8 (5.7)*
CTCAE (v4.0) grade 3	–	0 (0)	–
CTCAE (v4.0) grade 4	–	0 (0)	0(0)

* Takeda (2012) combined grade 2 and grade 3 toxicities. Linden (2009) did not provide enough information to be tabulated and Vesprini (2011) combined results which did not allow for tabulation.

Source: Chua (2013); Eade (2011); Linden (2009); Lips (2008); Martin (2009); Nath (2011); Takeda (2012); Vesprini (2011)

Acute and late genitourinary (GU) toxicity in the FM-based EBRT cohort studies/case series

	Baseline	Acute	Late
Chua (2013)	**N=75**	**N=75**	**–**
CTCAE grade 0	57 (76)	17 (23)	–
CTCAE grade 1	18 (24)	35 (47)	–
CTCAE grade 2	0 (0)	20 (27)	–
CTCAE grade 3	0 (0)	2 (3)	–
CTCAE grade 4	57 (76)	1 (1)	–
Eade (2011)	**N=101***	**N=101**	**–**
CTCAE (v3.0) grade 0	11	65	–
CTCAE (v3.0) grade 1	50	28	–
CTCAE (v3.0) grade 2	35	6	–
CTCAE (v3.0) grade 3	4	1	–
Lips (2008)	**N=331**	**N=331**	**N=320**
CTCAE (v2.0) grade 0	150 (45)	19 (6)	–
CTCAE (v2.0) grade 1	108 (33)	147 (44)	–
CTCAE (v2.0) grade 2	71 (22)	155 (47)	–
CTCAE (v2.0) grade 3	2 (1)	10 (3)	–
CTCAE (v2.0) grade 4	0 (0)	0 (0)	–
RTOG grade 0	–	–	152 (48)
RTOG grade 1	–	–	86 (27)
RTOG grade 2	–	–	68 (21)
RTOG grade 3	–	–	13 (4)
RTOG grade 4	–	–	1 (0.3)
Martin (2009)	**–**	**N=256**	**257**
RTOG grade 0	–	(16.3)	(83.3)
RTOG (v2.0) grade 1	–	(50.4)	(8.2)
RTOG (v2.0) grade 2	–	(33.3)	(7.4)
RTOG (v2.0) grade 3	–	(0)	(1.2)
RTOG (v2.0) grade 4	–	(0)	(0)
Nath (2011)	**–**	**100**	**N=100^**
CTCAE (v3.0) grade 0	–	NR	–
CTCAE (v3.0) grade 1	–	40 (40)	17 (18)
CTCAE (v3.0) grade 2	–	39 (39)	15 (16)
CTCAE (v3.0) grade 3	–	0 (0)	0(0)
Takeda (2012)	**–**	**N=141**	**N=141**
CTCAE (v4.0) grade 0	–	–	–
CTCAE (v4.0) grade 1	–	84 (60)	NR
CTCAE (v4.0) grade 2	–	12 (8.5)	9 (6.4)**
CTCAE (v4.0) grade 3	–	0 (0)	–
CTCAE (v4.0) grade 4	–	0 (0)	0 (0)

* Eade (2011) reported at treatment rather than at baseline.

^ assumed, as not specified.

**Takeda (2012) combined grade 2 and grade 3 toxicities.. Linden (2009) did not provide enough information to be tabulated and Vesprini (2011) combined results which did not allow for tabulation.

Source: Chua (2013); Eade (2011); Linden (2009); Lips (2008); Martin (2009); Nath (2011); Takeda (2012); Vesprini (2011)

Appendix I FM-based EBRT safety studies

Characteristics of study participants in the safety studies

Study	T1	T2	T3	T4	≤G6	G7	≥G8	ADH
Escudero (2010) N=126	NR	NR	NR	NR	NR	NR	NR	NR
Gill (2012) N=234	25%	54%	21%	0.4%	25%	54%	21%	NR
İğdem (2009) N=135	–	72%*	27%	NR	NR	NR	NR	69%
Langenhuijsen (2007) N=209	9%	31%	61%	NR	NR	NR	NR	NR

Abbreviations: ADH = androgen deprivation therapy; G = Gleason score; NR = not reported; T = tumour stage

* T1, T2

Source: Escudero (2010); Table 1 in Gill (2012); Table 1, p. 657 in Lips (2007); Table 2 in İğdem (2009); Table 2 in Langenhuijsen (2007)

Key relevant outcomes and statistical analyses reported in the safety studies

Study	Definition of outcomes	Method of statistical analysis
Escudero (2010)	Not specifically reported. Patients were reported to attend emergency services in the event of complications and complications were recorded as part of radiotherapeutic oncology visits Migration was assessed using the ExacTrac system	Not specifically reported. Incidence and frequency reported
Gill (2012)	Pain was assessed using the Wong-Baker faces pain scale (ranging from smiling to crying where 0 implied no pain and 5 was severe pain) The questions about symptoms enquired about pain in the week after the procedure, fever or shivers, dysuria, frequency of urination more than usual, rectal bleeding, haematuria, haematospermia and obstructive symptoms. Patients had to respond, 'yes', 'no', 'no more than usual' or 'don't remember' For yes severity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0	The grade of symptoms was reported as a percentage of all patients
İğdem (2009)	Pain was assessed using the Wong-Baker faces pain scale (ranging from smiling to crying where 0 implied no pain and 5 was severe pain). Patients were asked to compare pain of FM implantation with diagnostic biopsy Tolerance and quality of life were assessed via a questionnaire asked about complications, duration of symptoms and medication (no further details provided)	Fisher's exact test was used
Langenhuijsen (2007)	Questionnaire completed in the patient's home as part of follow-up. Questionnaire asked for the presence or absence of haematuria, haematospermia, rectal bleeding, fever and pain Minor complications were defined as side effects with transient minimal discomfort and required no additional medical intervention Moderate complications were those that required additional treatment Pain was scored on a 0-10 scale (0 no pain; 10 the worst pain imaginable) Patients were asked to compare pain of FM implantation with diagnostic biopsy	Statistical analysis was performed using t tests to compare continuous variables and Fisher's exact test to compare categorical variables

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