



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1158 – Robotic image-guided stereotactic precise beam radiosurgery and radiotherapy for lung cancer and prostate cancer

Applicant: Accuray Incorporated

Date of MSAC consideration: 29-30 November 2012

1. Purpose of application

In June 2012, applications were received from Accuray Incorporated, requesting Medicare Benefits Schedule (MBS) listing of robotic image-guided stereotactic precise beam radiosurgery and radiotherapy via the CyberKnife[®] system for patients with primary non-small cell lung cancer (NSCLC) and lung metastasis from other controlled primary sites, and for patients with prostate cancer.

The applicant's claim was that the differentiating property of CyberKnife compared to other external beam radiotherapy (EBRT) systems is that it deploys a linear accelerator mounted on a robotic manipulator. The robotic manipulator allows for a greater range of treatment delivery angles and higher accuracy than conventional systems. The claimed accuracy of the CyberKnife system allows treatment to be hypo-fractionated, which means higher doses of radiation may be delivered per treatment thus reducing the total number of treatment sessions required.

Another feature is the delivery of radiation while employing continual image guidance. The continual image guidance allows intra-fraction motion tracking where every beam position can be automatically corrected and can compensate for any target motion without user intervention or treatment interruptions.

The combination of the motion tracking system with the robotic manipulator allows for the delivery of a large number of non-isocentric, non-coplanar beams without the need to reposition the patient for each beam. This enables CyberKnife to treat tumours from many angles throughout the body, with sub-millimetre accuracy and precision.

Radiotherapy delivered using the CyberKnife system is performed over three to five sessions for NSCLC and four or five sessions for prostate cancer with each treatment lasting typically 45-60 minutes.

CyberKnife delivers image-guided stereotactic radiosurgery and stereotactic radiotherapy which are

forms of conformal EBRT.

Conformal EBRT is currently reimbursed on the MBS under a number of items. The current items apply to either single- or dual-photon linear accelerators. CyberKnife is a single-photon linear accelerator. Image guidance is currently claimed under existing treatment verification items.

Stereotactic radiosurgery is currently reimbursed on the MBS under item number 15600. This is a general listing for stereotactic radiosurgery and does not specify the type of technology used. It was listed prior to the establishment of MSAC.

MSAC's Protocol Advisory Sub-Committee (PASC) noted that "the CyberKnife is sufficiently unique as to warrant an assessment as a stand-alone technology". MSAC's Evaluation Sub-Committee (ESC) agreed with the comment from PASC however noted that the submission did not provide the evidence to support this claim.

MSAC noted that image-guided radiotherapy (IGRT) and intensity-modulated radiotherapy (IMRT) are expected to be considered in the coming year and could incorporate further information about CyberKnife compared to other technologies.

The specific medical conditions addressed in the current applications are: inoperable early stage NSCLC; lung metastasis from other controlled primary sites; and prostate cancer of any risk category – low, intermediate or high.

2. Background

MSAC has previously appraised the use of conformal EBRT (MSAC 2001) for the treatment of cancer, including patients with lung and prostate cancer.

3. Prerequisites to implementation of any funding advice

The proposed MBS listing is consistent with the TGA approved indication. The intended purpose of the device is as listed in the Australian Register of Therapeutic Goods (ARTG): "A system intended to provide treatment planning, image-guided stereotactic radiosurgery for lesions, tumours and conditions anywhere in the body where radiation treatment is indicated". The TGA registration number is ARTG# 155887 with an ARTG start date of 10 October 2008.

Some training and accreditation would be required before using the CyberKnife system. Staffing requirements and quality assurance programs would be similar to facilities providing conventional EBRT.

4. Proposal for public funding

The following MBS item fees and descriptors were proposed by the applicant for radiation therapy using the CyberKnife system in lung cancer:

Category 3 – Therapeutic Procedures
MBS 152XX RADIATION ONCOLOGY TREATMENT, delivered by an image guided robotic stereotactic system – each attendance at which treatment is given – treatment delivered to primary site (lung). Fee: \$1,582
MBS 157XX RADIATION ONCOLOGY TREATMENT VERIFICATION - multiple projection acquisition when prescribed and reviewed by a radiation oncologist and not associated with item 15700 or 15705 or 15710 - each attendance (lung). Fee: \$596

The following MBS item fees and descriptors were proposed by the applicant for radiation therapy using the CyberKnife system in prostate cancer:

Category 3 – Therapeutic Procedures
MBS 152XX RADIATION ONCOLOGY TREATMENT, delivered by an image guided robotic stereotactic system – each attendance at which treatment is given – treatment delivered to primary site (prostate). Fee: \$1,582
MBS 157XX RADIATION ONCOLOGY TREATMENT VERIFICATION - multiple projection acquisition when prescribed and reviewed by a radiation oncologist and not associated with item 15700 or 15705 or 15710 - each attendance (prostate). Fee: \$596

The applicant’s submission did not comply with Departmental requirements for an input-based fee determination. The proposed fee structure for a course of treatment with CyberKnife was intended to be cost-neutral, compared with a course of treatment with EBRT. The rationale provided was that fewer treatments would be needed per course using CyberKnife rather than EBRT, so the individual item fee would be greater per fraction for a cost-neutral outcome. There was the potential for higher overall treatment costs should there be unrestricted funding regarding the number of treatment sessions that may be delivered using CyberKnife. The applicant was requested by PASC to explore a capped fee for an entire course of treatment, taking into account the expected patient throughput and referral patterns.

The administration of radiotherapy is carried out by a team including radiation oncologists, medical physicists, and radiation therapists. Depending on the site to be treated, additional expertise involved in the treatment planning and delivery may include a diagnostic radiologist, anaesthetist, dosimetrist or surgeon. The same patient referral procedure for conventional EBRT will apply to CyberKnife. There will be no changes to the treatment procedures or to the providers of those procedures.

5. Consumer Impact Statement

The applicant noted that patients living in remote areas would benefit from CyberKnife's listing on the MBS due to the reduction in the time taken to deliver a course of therapy from several weeks to one week. The submission assumed a minimum daily cost of accommodation, food and transport of \$150. On this basis the report claims the costs to the patient for treatment of lung cancer may be reduced from upwards of \$6,300 when radiation therapy is given over 30 sessions using 3-dimensional conformal radiotherapy (3DCRT) down to \$600 when treatment is given over four sessions with CyberKnife. For treatment of prostate cancer, the report claims the costs to the patient may be reduced from upwards of \$5,850 when radiation therapy is given over 39 sessions using 3DCRT down to \$750 when treatment is given over five sessions with CyberKnife.

ESC noted that these benefits would not be realised unless CyberKnife were to become commonly available within Australia and that information to support this assertion of benefit was not included in the economic evaluation provided by the applicant.

6. Proposed intervention's place in clinical management

NSCLC

The proposed intervention was presented as a direct replacement for conventional 3DCRT and IMRT where radiotherapy with curative intent is considered for patients with stage IA and IB NSCLC who are unsuitable for, or who refuse, surgery.

CyberKnife may be considered an alternative to surgery as the primary treatment for patients with early (stage I) NSCLC.

The treatment of pulmonary metastatic lesions is primarily by surgical resection. Similar to the treatment of stage I NSCLC, where a patient is not considered suitable for surgery, treatment of metastatic lung disease with radiotherapy was investigated.

After referring to the clinical practice guidelines published by the National Health and Medical Research Council (NHMRC), the CyberKnife Society and after consultation with clinical experts, it was determined that the use of the CyberKnife system to deliver radiotherapy is most applicable for the following patient groups:

Definitive treatment for non- metastatic (N0 and M0) NSCLC that is ≤ 5 cm in greatest diameter (T1 or T2a). This equates to stage IA and IB NSCLC patients under the TNM classification (published by the American Joint Committee on Cancer, 2010).

The applicant's submission stated that use of CyberKnife will be assessed in two separate contexts in this patient group:

1. As an alternative to surgery as the primary treatment for stage I NSCLC patients; and
2. As a replacement for EBRT as the secondary treatment option for stage I NSCLC patients who are unsuitable for, or who refuse, surgery.

Small cell lung cancer (SCLC) and other stages of NSCLC were not considered in this submission as CyberKnife is not explicitly recommended in these populations.

Clinical evidence provided by the applicant did not address the requirements of the agreed DAP. Many of the effectiveness outcomes included in the DAP were not considered. No justification was

given in the SBA report as to why this information was not included. Safety outcomes were not included in the report.

Prostate Cancer

For patients with low and intermediate risk prostate cancer undergoing radiotherapy as a primary treatment, CyberKnife was presented as an alternative intervention to the comparators, brachytherapy and EBRT. The applicant however did not provide comparative evidence between CyberKnife and brachytherapy on the basis that the latter is 'a minor comparator' as only a small proportion of patients with prostate cancer are treated with brachytherapy.

For patients with high risk prostate cancer receiving radiotherapy as an adjuvant to androgen deprivation therapy (ADT), CyberKnife was presented as the alternative to EBRT. PASC agreed that both enhanced systems of EBRT (3DCRT and IMRT) are appropriate comparators for CyberKnife. The applicant chose to position CyberKnife solely as an alternative to EBRT (3DCRT).

For patients with low and intermediate risk prostate cancer, CyberKnife would be a direct replacement for radiotherapy delivered by existing EBRT systems and an alternative to brachytherapy. The applicant claimed that CyberKnife is most suitable in the following settings:

- 1 Primary treatment for localised prostate cancer, 'low risk patient stratification': PSA <10ng/ml AND Gleason score \leq 6 AND T1-T2a.
- 2 Primary treatment for localised prostate cancer, 'intermediate risk patient stratification': PSA 10-20ng/ml OR Gleason score =7 OR T2b-c.

It was indicated that in the treatment of 'high risk' patients (defined as patients with PSA >20ng/ml OR Gleason score 8-10 OR T3/4) radiotherapy delivered using the CyberKnife system would be a replacement for other EBRT systems.

Clinical evidence provided by the applicant did not address the requirements of the agreed DAP. Many of the effectiveness outcomes requested by the DAP were not considered. No justification was given in the application as to why this information had not been included. Only late toxicity was included in the safety section.

7. Other options for MSAC consideration

If CyberKnife is listed on the MBS, consideration should be given to including the treatment and verification services into one single item, rather than separating them, given that the applicant has stated that verification is undertaken during each treatment. These two services are identified separately for other treatment types because the ratio of treatment to verification is not one to one. In this case the ratio is one to one.

To enable this, the item descriptor could include 'radiation oncology treatment and associated treatment verification - delivered by an image guided robotic stereotactic system - each attendance at which treatment is given'. The cost of the verification would be included in the fee.

8. Comparator to the proposed intervention

If CyberKnife is listed on the MBS, it is expected that conventional EBRT treatments and enhanced

treatments such as 3DCRT are the interventions most likely to be replaced for those patients treated with CyberKnife.

NSCLC

The applicant’s submission stated that CyberKnife may also be an alternative to surgery as the primary treatment for stage I NSCLC and pulmonary metastatic lesions. No evidence for this was provided.

The Final DAP identified both EBRT and surgery as comparators. In the submission only EBRT was included as a comparator on the basis that the comparator would be the intervention most likely to be used if the new treatment were not available.

ESC agreed that both EBRT and surgery are appropriate comparators.

MBS item numbers for the treatment of NSCLC cancer

Category 3 – Therapeutic Procedures
<p>MBS 15550</p> <p>SIMULATION FOR THREE DIMENSIONAL CONFORMAL RADIOTHERAPY without intravenous contrast medium, where: treatment set up and technique specifications are in preparations for three dimensional conformal radiotherapy dose planning; and patient set up and immobilisation techniques are suitable for reliable CT image volume data acquisition and three dimensional conformal radiotherapy treatment; and a high-quality CT-image volume dataset must be acquired for the relevant region of interest to be planned and treated; and the image set must be suitable for the generation of quality digitally reconstructed radiographic images. (Relevant explanatory notes – see T2.4)</p> <p>Fee: \$ 633.65 Benefit: 75% = \$475.25 85% = \$562.45</p> <p>Date listed: 1 November 2006</p>
<p>MBS 15562</p> <p>DOSIMETRY FOR THREE DIMENSIONAL CONFORMAL RADIOTHERAPY OF LEVEL 3 COMPLEXITY - where:</p> <p>(a) dosimetry for a three or more phase three dimensional conformal treatment plan using CT image volume dataset(s) with at least one gross tumour volume, three planning target volumes and one organ at risk defined in the prescription; or</p> <p>(b) dosimetry for a two phase three dimensional conformal treatment plan using CT image volume datasets with at least one gross tumour volume, and</p> <p>(i) two planning target volumes; or</p> <p>(ii) two organ at risk dose goals or constraints defined in the prescription.</p> <p>or</p> <p>(c) dosimetry for a one phase three dimensional conformal treatment plan using CT image volume datasets with at least one gross tumour volume, one planning target volume and three organ at risk dose goals or constraints defined in the prescription;</p> <p>or</p> <p>(d) image fusion with a secondary image (CT, MRI or PET) volume dataset used to define target and organ at risk volumes in conjunction with and as specified in dosimetry for three dimensional conformal radiotherapy of level 2 complexity. All gross tumour targets, clinical targets, planning targets and organs at risk as defined in the prescription must be rendered as volumes. The organ at risk must be nominated as planning dose goals or constraints and the prescription must specify the organs at risk as dose goals or constraints. Dose volume histograms must be generated, approved and recorded with the plan. A CT image volume dataset must be used for the relevant region to be planned and treated. The CT images must be suitable for the generation of quality digitally reconstructed radiographic images</p>

(See para T2.3 of explanatory notes to this Category)
Fee: \$1,078.30 Benefit: 75% = \$808.75 85% = \$1,007.10
Date listed: 1 November 2006
MBS 15705
RADIATION ONCOLOGY TREATMENT VERIFICATION - multiple projection acquisition when prescribed and reviewed by a radiation oncologist and not associated with item 15700 or 15710 - each attendance at which treatment involving three or more fields is verified (ie maximum one per attendance). (See para T2.4 of explanatory notes to this Category)
Fee: \$ 76.60 Benefit: 75% = \$57.45 85% = \$65.15
Date listed: 1 July 2008

Prostate Cancer

The applicant's submission stated that CyberKnife may also be an alternative to brachytherapy. Until late 2011, low-dose brachytherapy was listed on the MBS for use in patients with a gland volume of $\leq 40\text{cc}$ and who have a life expectancy of at least 10 years. There is now no reference to gland volume in the MBS listing, but it is recommended that low-dose brachytherapy may be performed in patients with a favourable anatomy allowing adequate access to the prostate without pubic arch interference. CyberKnife is being proposed to treat patients with a prostate gland volume of $\leq 140\text{cc}$.

The Final DAP identified both EBRT and brachytherapy as comparators. In the submission only EBRT was included as a comparator on the basis that the comparator would be the intervention most likely to be used if the new treatment were not available.

ESC agreed that both EBRT and brachytherapy are appropriate comparators.

Generic MBS item numbers for the treatment of prostate cancer with brachytherapy

MBS number	Procedure	Fee	Date listed
315550	simulation	\$646.30	1/11/2006
15562	dosimetry	\$1,099.85	1/11/2006
15705	verification	\$76.60	1/7/2008
15600	Stereotactic radiosurgery	\$1,670.55	1/11/1997

MBS item numbers for the treatment of prostate cancer with brachytherapy.

MBS number	Procedure	Fee	Date listed
15539	Brachytherapy planning	\$615.50	1/11/2001
15338	Radioactive seed implantation (radiation oncology component)	\$918.15	1/11/2001
37220	Radioactive seed implantation (urological component)	\$1,024.75	1/11/2001
Prosthesis list codes CL001, CI002, MB001, ON001, ON005	Brachytherapy seeds	\$6,500	Circa late 2001/2002

9. Comparative safety

NSCLC

The applicant's submission did not address comparative safety. Outcomes such as rates of acute and long term toxicity were requested in the Final DAP but were not included in the submission.

Prostate Cancer

The applicant's submission for comparative safety presented data on late toxicity following treatment with CyberKnife compared to 3DCRT therapy.

Evidence was sourced from three CyberKnife studies, two 3DCRT dose escalation studies and a previous MSAC Assessment on conformal Radiotherapy (Application 1038).

Comparative studies and associated reports

CyberKnife Studies

Freeman et al (2011), a study of 41 consecutive patients with clinically localised, low-risk prostate cancer, reported that no late grade 3 rectal toxicity occurred, and only one late grade 3 genitourinary toxicity occurred following repeated urologic instrumentation.

King et al (2012) also found that dysuria exacerbated by urologic instrumentation accounted for both patients with grade 3 toxicity. Apart from this, there were no grade 3 or 4 rectal or bladder toxicities (graded on the RTOG scale) in their 67 patient study.

McBride et al (2011) reported one episode of late grade 3 urinary obstruction and two episodes of late grade 3 proctitis in their study of 45 patients.

Table B5 summarises the late toxicity rates as reported in the above studies and other studies not provided in the applicant's submission.

Table B5 CyberKnife late Toxicity

<u>Study</u>	<u>≥ Late Grade 3</u>	<u>Study size</u>
King 2012	1 Grade 3 bladder	67
McBride 2011	1 Grade 3 urinary 2 Grade 3 proctitis	45
Townsend 2011	0	50
Freeman 2011	1 Grade 3 genitourinary	41
Kang 2011	0	83
Bolzicco 2010	1 Grade 3 rectal	45
Katz AJ 2010	0	304
Friedland 2009	1 Grade 3 rectal	112
King 2009	2 Grade 3 urinary	41

3DCRT

Dolezel et al (2010) compared 94 patients treated with 3DCRT 74 Gy with 138 patients treated with IMRT 78 Gy. At 3 years, the estimated cumulative incidence of grade 3 late gastrointestinal toxicity was 14% for 3D-CRT and 5% for IMRT. The estimated cumulative incidence of grade 3 late genitourinary toxicity was 9% for 3DCRT and 7% for IMRT.

Pollack et al (2002), a randomised radiotherapy dose escalation trial of 301 Stage T1-T3 patients with a median follow-up of 60 months, compared 70 Gy (150 patients) with 78 Gy (151 patients). The trial reported that rectal side effects were significantly greater in the 78 Gy group. Grade 2 or higher toxicity rates at 6 years were 12% and 26% for the 70 Gy and 78 Gy arms, respectively (p=0.001). Grade 2 or higher bladder complications were similar at 10%. In the 78 Gy arm, the late grade 3 rectal toxicity rate was 7% (10 patients) and late grade 3 bladder toxicity 3% (4 patients).

The results in the paper by Pollack et al are based on the M. D. Anderson Cancer Center (MDACC) randomised dose escalation trial initiated in 1993. This study was also cited in the 2001 Report on MSAC Application 1038 covering Conformal Radiotherapy.

The applicant's submission stated that based on the evidence available, CyberKnife has minimal late grade 3 or worse toxicities compared to the incidence of late grade 3 or worse toxicities associated with 3DCRT, especially when the 3DCRT dose is escalated to exceed 70 Gy.

10. Comparative effectiveness

NSCLC

The applicant's approach to comparative effectiveness was to present local control and overall survival results as reported in CyberKnife case series of patients with NSCLC deemed unsuitable for surgery alongside local control and overall survival results from 3DCRT studies in similar populations.

Comparative studies and associated reports

CyberKnife

15 papers were considered by the applicant as 'relevant' studies. Their relevance was determined by the type of study, size of patient populations and the treatment indication.

Table B2: Summation of results of Main Clinical Papers for CyberKnife

Paper	Dose	Patients	Follow-up - median	Kaplan-Meier	Local control	Overall survival
Chen VJ 2012 *	Median 48 Gy / 7 days	40 Stage I	44 months (12-72)	3 year	91%	75%
Lanni TB 2011 **	3D-CRT 70 Gy CK 48Gy in 4/5 f	86 Stage I (T1-2 NO)		36 months	3D-CRT 66% CT 88%	3D-CRT 42% CT 71%
Brown WT 2011	67 to 75 Gy in 5 f	20 peripheral Stage I to V	23 months (4 to 58)		Local control was achieved in all treated tumours.	
Van der		39 Stage 1	17 months	1 year		75%

Voort van Zyp NC 2010				2 years	97%	62%
Vahdat S 2010	42 – 60 Gy in 3 f	20 Stage IA	43 months	2 year	95%	90%
Brown WT 2009	60-67.5 Gy in 3-5 f	31 peripheral Stage I	27.5 (24-53)	4.5 years	85.5%	83.5%
Van der Voort van Zyp NC 2009	60 Gy in 3 f	70 peripheral early stage T1 & T2	15 months	1 & 2 years	96%	
Ahn SH 2009	36-54 Gy in 3 f	8 Stage I		2 years	87.5%	
Collins BT 2009	42-60 in 3 f	20 Peripheral Stage I	25 months	2 years	100%	87%
Coon D 2008	60 Gy in 3 f	26 stage I	12 months	1 year	85%	81%
Collins BT 2007	45-60 Gy in 3	24 Stage 1	12 months	1 year	100%	87%
Brown WT 2007	15 to 67.5 Gy in 1-5 f	59	1 to 33 months			85%
Brown WT 2007	15 to 67.5 Gy in 1-5 f	95	1 to 36 months			82%
Brown WT 2007	24 to 60 Gy in 3 f	19 Stage 1A	1-25 months		86%	
Nuyttens JJ 2006	30 to 60 Gy in 3 f	20	4 months		100%	

* Comparison with wedge resection

** Comparison with 3D-CRT

3DCRT

14 papers were considered by the applicant as ‘usable’. This usability was determined by the reporting of outcomes, especially overall survival, making it possible to compare the outcomes in these papers with those in the papers reporting on CyberKnife.

Table B3: Conformal Radiotherapy Relevant Papers

<u>Paper</u>	<u>Dose</u>	<u>Patients</u>	<u>Follow-up - median</u>	<u>Kaplan-Meier</u>	<u>Local control</u>	<u>Overall survival</u>
Price A 2012	55 Gy in 20 f	105 Stage T1-2 A w/o chemo B w chemo		2 years 5 years		A 56% B 52% A 20% B 33%
Bradley JD 2010	74 Gy	53 Stage I-III	19.3 months (13.1-57.9-72)	1 year		75.5%
Wurstbauer K 2010	88.2 GY 69.3 Gy 56.7 Gy	30 Stage I 8 Stage II 39 Stage IIIA 47 Stage IIIB	19 months	2 years 5 years		Stage I 57% 20% Stage II 75% 13%
Sandhu AP	66 GY with	102 Stage TI/TII	20.9 (4.0-			

2009	2.5 Gy per f		138.9)			
Belliere A 2009	74 Gy	50 Stage IIIA/B				
Campeau MP 2009	60 Gy in 30 f w chemo 60 Gy in 30 f w/o chemo 50-55 Gy in 20 f	73 Stage I	18 months (1-81)	2 year		57% w chemo 33% w/o chemo
Sura S 2008	IMRT	55 Stage I-IIIB	26 months	2 year	Stage I/II 50% Stage III 58%	Stage I/II 55% Stage III 58%
Low JSh 2007	55 Gy	23 Stage I	18.9 months (6.2- 117.4)	2 year 3 year		54.7% 24.3%
Sura S 2007	≥ 80 Gy	55 Stage I/II 27 Stage IIIA/B		5 year	Stage I/II 67% Stage IIIA/B 39%	Stage I/II 36% Stage IIIA/B 31%
Faria SL 2006	52.5 Gy in 15 f hyper	32 Stage T1-2		2 year		56%
Fang LC 2006	66 GY	85 Stage I	19 Months (3-77)	2 year 5 year	77% 70%	68% 36%
Chen M 2006	63 to 102.9 Gy in 2.1 Gy f	106 Stage I-III recurrent	104 months	1 year 2 years 3 years 4 years		86% 61% 43% 21%
Kong FM 2005	63 to 103 Gy in 2.1 Gy f	106 Stage I-III recurrent		5 year		63-69 Gy 4% 74-84 Gy 22% 92-103 Gy 28%
Rosenzweig KE 2001	70.2 Gy	32 early stage		2 year 5 year		54% 33%

Systematic Reviews of CyberKnife

None provided.

Reported two year local control ranged from 87.5% (n=8) to 100% (n=20) in the CyberKnife studies compared to 67% (n=55) to 77% (n=85) in the studies on 3DCRT. Two year survival ranged from 62% (n=39) to 90% (n=20) in the CyberKnife studies compared to 54.7% (n=23) to 61% (n=106) in the studies reporting on 3DCRT. Longer term data were available for patients in the 3DCRT studies (5 years) with one CyberKnife study reporting overall survival at 4.5 years.

Prostate Cancer

The applicant's submission on comparative effectiveness was to present biochemical progression free survival as reported in CyberKnife case series of patients with prostate cancer alongside biochemical progression-free survival results from 3DCRT studies in 'similar' populations. The submission focused on four studies: one CyberKnife study and three 3DCRT studies.

Comparative studies and associated reports

CyberKnife Studies

Freeman et al (2011), a study of 41 consecutive patients with clinically localised, low-risk prostate cancer, reported on outcomes with a median follow-up of five years; no patient received hormone therapy.

King et al (2012), a study with 67 low risk patients, reported a 94% four year Kaplan-Meier PSA relapse-free survival (95% confidence interval, 85%-102%).

McBride et al (2011), a study of 45 low risk patients, reported a 97.7% progression free survival rate at three years.

3DCRT Studies

Goldner et al (2012) reported, based on a retrospective analysis of 252 low-risk patients, on the five year actuarial bNED rates (Phoenix definition) of patients receiving EBRT of 70 Gy and 74 Gy. An earlier study by Goldner et al (2009) showed a slightly lower rate of 81% at five years for a mixed low and intermediate risk patient population.

The table below (Table B4) compares the progression free survival rate in Freeman et al (2011) to 'similar' studies using 3DCRT in a range of doses.

Systematic Reviews of CyberKnife

None provided.

Table B4: Papers used for Comparison - % Free from Biochemical Failure

Technology	Study	Dose	Pat No & risk classification		% free of Biochemical Failure	Median Follow-up and Range
CyberKnife	Freeman 2011	35-36.25 Gy in five fractions	41 low risk	5 year	92.7% (95% CI = 84.7% to 100%)	Median 60 months 4.2-6.2 years
3D-CRT	Goldner 2012	70 Gy 74 Gy	82 low 170 low	5 year	84.7% 91%	Median 46 months 1-148 months
3D-CRT	Martin 2009	79.8 Gy 87% 3D Conformal	59 low 163 intermediate 37 high	5 year	Low – 88.4% Intermediate = 76.5% High – 77.9%	Median 67.8 months 24.4-84.7 months
3D-CRT	Goldner	70 Gy for low	399	5 year	Low - 81%	Median 65

	2009	and intermediate 74 Gy for high	Low 29%, Intermediate 50%, High 21%		Intermediate - 80% High - 60%	months
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In a pooled cohort of 41 low-risk prostate cancer patients who had received EBRT with CyberKnife (35-36.25 Gy in five fractions) biochemical progression-free survival was 93% (95% CI: 84.7% to 100%). In comparison, biochemical progression free survival is presented from a retrospective analysis of 252 low-risk patients who received EBRT of 70 Gy and 74 Gy. Five year rates are reported as 84% and 91%, respectively.

The applicant’s submission stated that based on this limited comparison of the best available evidence, CyberKnife is at least as effective as 3DCRT when measured by freedom from biochemical failure five years after therapy.

The above results for NSCLC and prostate cancer should be interpreted with caution given:

- There were no studies that reported the relative effectiveness of CyberKnife in comparison to external beam radiotherapy.
- Conclusions about effectiveness of CyberKnife are based on small case series.
- Biochemical failure has been used as a surrogate marker in assessing effectiveness data in clinical studies. However, no evidence was presented that links biochemical response to overall survival or progression free survival. Many of the studies included in the applicant’s submission, for both CyberKnife and 3DCRT, include patients from the same series; consequently the results presented overestimate the body of evidence of effectiveness (duplication bias). This is particularly the case for studies assessing CyberKnife.
- The results in the report have also been presented and compared without consideration of the quality or characteristics of the individual studies. These issues are important in assessing internal and external validity and potential impact on the reported results.
- The comparative body of evidence for external beam radiotherapy is primarily based on studies of 3DCRT. Studies reporting on IMRT were not included

The overall clinical claim for CyberKnife was that the “external beam robotic-image guided radiosurgery delivered by CyberKnife is at least as effective, safe and cost-effective as the currently MBS funded 3D EBRT by a conventional linear accelerator”.

Surgery as comparator

Compared to surgery with curative intent, CyberKnife has the following potential benefits for treating primary lung cancer or pulmonary metastases:

- 1 Non-inferior rates of primary lung tumour control;
- 2 Non-inferior rates of pulmonary metastatic lesion control;
- 3 Ability to make treatment more acceptable to patients through being a non-invasive procedure; and
- 4 Elimination of surgical morbidity and improved quality of life.

Compared to surgery, CyberKnife has the following potential harms:

- 1 Possible reduced rates of primary lung tumour control;
- 2 Possible reduced rates of pulmonary metastatic lesion control; and
- 3 Toxicities associated with radiotherapy.

External Beam Radiotherapy as comparator

Compared to conventional EBRT, radiotherapy delivered by CyberKnife has the following potential benefits for treating primary lung cancer or pulmonary metastases and prostate cancer:

- 1 Ability to deliver radiotherapy more accurately which may lead to reduced toxicity and improved primary tumour control.
- 2 The potential to make treatment more acceptable to patients through its ability to hypofractionate and the reduced number of treatment sessions.

Compared to EBRT CyberKnife has the following potential harms:

- Possible reduced rates of tumour control.

11. Economic evaluation

The economic evaluation consisted of a costing analysis that compared the treatment costs of a course of radiotherapy treatment using the CyberKnife system with a course of treatment delivered using 3DCRT. This is based on the assumption that “due to the unique properties of CyberKnife and its equivalent or better clinical effectiveness compared to 3DCRT, delivering a course of treatment of CyberKnife at the current price of a course of 3DCRT, means that CyberKnife is at least as cost-effective as 3DCRT”.

No consideration of health outcomes was given in the economic evaluation. The presentation of a costing analysis is not consistent with the DAP which specified that a cost-effectiveness analysis be conducted.

The applicant’s submission states that this method was used as there are no head-to-head clinical trials comparing 3DCRT with CyberKnife available. The clinical studies on CyberKnife are all single arm.

The economic evaluation was structured as follows:

Current funding for a standard course of 3DCRT for NSCLC

The course of treatment cost using 3DCRT was calculated using current MBS item numbers and the Radiation Oncology Health Program Grant (ROHPG) payments.

Table C2: Cost of current Course of Treatment using Dual Photon 3DCRT

	<u>Description</u>	<u>MBS fee per attendance*</u>	<u>ROHPG payment per attendance</u>	<u>Number of attendances</u>	<u>Total</u>
15550	Simulation	\$646.30	\$101.94	1	\$748.24
15562	Dosimetry	\$1,099.85	\$107.44	1	\$1,207.29
15245	Treatment	\$58.55	\$55.97	30	\$3,435.60
15260	Treatment	\$170.30		30	\$5,109.00
15705	Verification	\$76.60		9	\$689.40
<u>Total</u>					\$11,190

* As at May 2012

The total cost (average) of a course of therapy of 70 Gy in 30 fractions using dual-photon and 5 fields is \$11,190.

Current funding for a standard course of 3DCRT for prostate cancer

The course of treatment cost using 3DCRT was calculated using current MBS item numbers and the Radiation Oncology Health Program Grant (ROHPG) payments.

Table C3a: Cost of current Course of Treatment using Dual Photon 3D-CRT

<u>MBS Item number</u>	<u>Description</u>	<u>MBS fee attendance*</u>	<u>ROHPG payment per attendance</u>	<u>Number of attendances</u>	<u>Total</u>
15550	Simulation	\$646.30	\$101.94	1	\$748.24
15562	Dosimetry	\$1,099.85	\$107.44	1	\$1,207.29
15248	Treatment	\$58.55	\$55.97	35	\$4,008.20
15263	Treatment	\$170.30		35	\$5,960.50
15705	Verification	\$76.60		11	\$842.60
Total					\$12,767

* As at May 2012

Proposed funding of a course of CyberKnife

The costs are based on running a CyberKnife facility that has the capacity to build up to a throughput of 250 patients per year. Two different throughput scenarios were then modelled assuming a ten year life for the capital equipment (CyberKnife).

It is important to note that it has been assumed that the predominant cancer treated with CyberKnife (assuming funding) will be prostate cancer. The following economic model determines the cost per fraction using CyberKnife based on this assumption.

Table C6: Proposed fees for a standard course of treatment for prostate cancer with CyberKnife

<u>MBS Item number</u>	<u>Description</u>	<u>Claims per patient</u>	<u>MBS fee attendance</u>	<u>ROHPG per attendance</u>	<u>Total cost per patient</u>
15550	Simulation	1	\$646.30	\$101.94	\$748.24
15562	Dosimetry	1	\$1,099.85	\$107.44	\$1,207.29
15xxx	Treatment	5	\$472.05	\$407.82	\$4,399.34
15xxx	Treatment	5	\$1,200.68	n/a	\$6,003.41
15705	Verification	5	\$76.60	n/a	\$383.00
Total					\$12,741

The cost per fraction in a course of therapy using CyberKnife for patients with early stage NSCLC unsuited for surgery appears to have been modelled as has been set out in the concurrent submission for prostate cancer.

Table C3: Proposed fees for an average course of treatment for NSCLC with CyberKnife

<u>MBS Item number</u>	<u>Description</u>	<u>Claims per patient</u>	<u>MBS Fee attendance</u>	<u>ROHPG per attendance</u>	<u>Total cost per patient</u>
15550	Simulation	1	\$646.30	\$101.94	\$748.24
15562	Dosimetry	1	\$1,099.85	\$107.44	\$1,207.29
15xxx	Treatment	4	\$472.05	\$407.82	\$3,519.47
15xxx	Treatment	4	\$1,200.68	n/a	\$4,802.73
15705	Verification	4	\$76.60	n/a	\$306.40
Total					\$10,584

The tables above, provided by the applicant, are suggestions of how CyberKnife treatment would achieve cost neutrality.

Patient Throughput

The applicant noted that most new medical technologies are slow to be adopted, therefore two different scenarios for the annual throughput of patients over a ten year life of CyberKnife (Scenarios A and B in Table C4) were used.

Table C4: Patient Throughput Scenario A & B – 10 year capital life

	A	B
Year	Patients	Patients
1	25	50
2	50	100
3	100	170
4	150	200
5	200	200
6	225	225
7	250	250
8	250	250
9	250	250
10	250	250

Based on the patient throughputs in Scenarios A and B, a capital life of ten years and a discount rate of 3.5%, the cost per course of treatment for Scenario A is \$13,504 and for Scenario B is \$11,975. It is not clear why a discount rate of 3.5% is assumed.

No consideration was given to health outcomes or modelling for resources in the economic evaluation as per Table 13 of the Final DAP.

The net present value (NPV) of a CyberKnife system with a ten year life plus associated staff and running costs and a patient throughput that built to a maximum of 250 in seven years was determined to be between \$18 and \$19 million dollars. The cost per course of therapy ranged between \$11,975 and \$13,165 which depended on different patient throughputs.

The applicant's submission states that as CyberKnife will be used as a replacement for the currently funded 3DCRT: for every new patient who requires a course of CyberKnife therapy, there will be one less patient who requires a course of 3DCRT.

NSCLC

The estimated cost of a course of treatment using CyberKnife (including simulation, dosimetry, treatment and verification) is \$10,584. Currently, the MBS and ROHPG funding of a course of 3DCRT (including simulation, dosimetry, treatment and verification) is \$11,190.

Prostate cancer

The estimated cost of a course of treatment using CyberKnife (including simulation, dosimetry, treatment and verification) ranges from \$11,975 to \$13,165 (based on a discount rate of 3.5%). Currently, the MBS and ROHPG funding of a course of treatment using 3DCRT (including simulation, dosimetry, treatment and verification) ranges from \$12,767 to \$15,435.

The applicant's submission stated that the financial implications for the MBS should be cost-neutral providing that:

1. The funding for a course of CyberKnife is the same as that for a course of 3DCRT; and
2. The patient throughput and growth of patient throughput for any given facility operating CyberKnife is sufficient to cover the cost of supplying the CyberKnife therapy.

The majority of EBRT is provided as an out-patient service. This means that the MBS reimbursement is 85% of the Schedule fee. However, the patient co-payments for out-patient services are covered by the Medicare Safety Net. Due to the severity of NSCLC and prostate cancer, it is likely that most patients would fall into the 80% coverage of the co-payments.

In summary, the applicant's submission stated that the financial implications to the MBS (including the cost associated with the Medicare Safety Net) approaches the full cost of a course of therapy using CyberKnife. However, if the MBS fees for a course of therapy using CyberKnife are approximately the same as the current MBS fees for a course of therapy using 3DCRT, the incremental cost impact should approach zero.

No consideration of health outcomes was given in the economic evaluation nor was any consideration given to modelling for resources used as per Table 12 of the Final DAP.

12. Financial/budgetary impacts

NSCLC

There were 9,703 new cases of lung cancer diagnosed in 2007 in Australia (AIHW & Cancer Australia 2011). Most sources estimated that approximately 85% of all lung cancer diagnosed was NSCLC. Furthermore, it was estimated that only between 25 – 35% of the NSCLC cases diagnosed were early stage. This provided an approximate incidence of 2,474 cases of early-stage NSCLC diagnosed in Australia per year. The number of patients expected to be considered for radiotherapy is 825 patients per year.

The applicant's submission provided another estimate of 1,349 as the potential patient population. This was based on the number of MBS claims made for treatment of lung cancer using 3DCRT in the 2009-10 financial year. The MBS item numbers associated with treatment were not detailed.

Prostate cancer

More than 19,400 cases of prostate cancer (more than 30% of male cancers) are diagnosed each year in Australia (Cancer Council of Australia).

Alternative MBS funded therapies for prostate cancer include:

- Brachytherapy (MBS 37220) with 689 claims in 2010-11;
- Radical prostatectomy (MBS 37210 & 37211) with 6,066 claims in 2010-11; and
- Prostatectomy endoscopic, using diathermy or cold punch (MBS 37203 & 37206) with 12,698 claims in 2010-11.

The optimal radiotherapy utilisation rate is estimated to be 60% of all prostate cancer patients, (Delaney, Geoffrey. "Radiotherapy in cancer care: estimating the optimal utilization from a review of evidence-based clinical guidelines." (2007)) which gives a total of 11,640 per year.

An estimate of the potential patient population, based on the number of patients receiving MBS funding for 3DCRT (the current alternative to CyberKnife) in the 2009-2010 financial year, was 5,910 patients.

It is important to note that the CyberKnife patient population will be restricted by the potentially limited number of CyberKnife units in Australia (currently zero). It also needs to be taken into account that the capacity of each unit may cover clinical indications other than lung and prostate cancer.

13. Key issues for MSAC from ESC

1 Main issues around the proposed eligible population for public funding and/or the proposed main comparator?

While CyberKnife has been considered separately in this application, there are other applications in progress that are considering IGRT and IMRT more broadly. These applications will undergo a departmental contracted assessment, which will look at all technologies and techniques (including CyberKnife) that deliver IGRT and IMRT, not limited to prostate and lung indications.

ESC agreed that the fee proposed by the applicant did not comply with requirements for input-based fee determination, but was derived from the episodic cost of a course of radiotherapy using existing techniques based on the current MBS funding for a standard course of 3DCRT using the highest reimbursement bracket. The applicant has indicated that CyberKnife would be cost-neutral compared to existing treatment, but has not provided information to support this assumption.

ESC noted that the capped fee of \$10,584 was based on the standard course of therapy of an average of four fractions. In comparison, the cost provided for 3DCRT was \$11,190 which was based on a course of treatment being delivered over 30 fractions with five fields delivered per treatment session.

ESC noted that the application based its fee model on the assumption that a course of treatment with CyberKnife is at least as safe and effective as 3DCRT.

ESC noted the claim of cost neutrality (in comparison with treatment delivered by 3DCRT) made in the report is likely to be highly uncertain. For prostate cancer, 35 treatment services (including

dosimetry, verification and ROHGP payment) costs around \$12,700. The applicant has identified that the same services can be provided by CyberKnife in 4.5 treatments, but the cost still adds up to \$12,700 (cost-neutral). This fee does not show the costs associated with the treatment.

ESC agreed that the main comparator for CyberKnife is EBRT, however was concerned that only studies examining 3DCRT were included in the presentation of evidence and that studies reporting on IMRT were not included. ESC noted that no comparative evidence between CyberKnife and surgery for NSCLC was provided and that this was a deviation from the DAP. For prostate cancer, ESC noted that brachytherapy was identified in the application as an additional comparator for CyberKnife. However, no evidence was considered for this comparison. Therefore ESC did not accept CyberKnife as an alternative to surgery for Stage I NSCLC or to brachytherapy for prostate cancer.

ESC recommended that the proposed MBS descriptor should include patients with both resectable and inoperable Stage IA or IB primary non-small cell lung cancer.

ESC also noted that the two CyberKnife vs 3DCRT case series comparison tables were difficult to analyse and that conclusions could not easily be made from the tables. ESC advised that the most effective way to assess the effectiveness of CyberKnife is with a randomised controlled trial which ESC considered was an appropriate and viable method for evaluating this technology.

ESC concluded that the applicant failed to present evidence of CyberKnife's claim of superiority, or of equivalent safety or effectiveness against other alternative treatments.

ESC agreed that CyberKnife was another example of image-guided radiotherapy (IGRT), not a new stand-alone technology as noted by PASC or claimed by the applicant, and concluded that CyberKnife belonged to the same class as other image-guided radiotherapy technologies.

ESC agreed that CyberKnife appeared to be another step on the path to more targeted radiotherapy and could be claimed under a current MBS item if it were available in Australia.

ESC noted the description of the disease as stated in the application: stage IA or IB non small-cell lung Cancer (NSCLC) and lung metastasis from other controlled primary sites. ESC commented that the application could have highlighted the advantage of targeting the lesions at sites that require precision to help strengthen their clinical algorithm. In addition, ESC recommended that the description of the type of tumour and the targeted population group needs to be appropriately defined as the current application did not describe this in detail. ESC commented that the application did not address patients with pulmonary metastases of extrapulmonary primary tumours. They also advised that confirmation as to which tumours CyberKnife is suitable for should be included in the application.

The applicant did not provide sufficient information to support the proposed MBS fee. Prior to consideration of the application by MSAC, the Department will conduct an assessment on the proposed MBS fees by comparing them with the existing fees for all stereotactic radiosurgery techniques. It is anticipated that the Department will be in a position to either provide support or an alternative MBS fee structure at that meeting.

2 Main issues around the evidence and conclusions for safety?

NSCLC

ESC confirmed that no safety data were provided for NSCLC and commented that the safety data provided for the CyberKnife prostate cancer application cannot be extrapolated to this indication.

Prostate cancer

ESC discussed the evidence put forward for clinical safety in the treatment of prostate cancer and concluded that the applicant's claims of clinical safety were not supported by evidence.

ESC highlighted that the results reported were selective and not representative of the overall body of evidence regarding the safety of radiation therapy. Furthermore only data on late toxicity following treatment of CyberKnife was presented and the results were biased with significant data missing, particularly in the CyberKnife studies. It was also inconsistent in its measurement criteria. No data on acute toxicity was provided and no direct comparative studies were also provided. There was limited analysis or interpretation of the comparison of results between the two interventions, with no explanation as to why the two dose escalation studies and the MSAC report were included in the safety section.

ESC agreed that the comparison table of toxicity could have been presented graphically and questioned whether these were the only studies available with toxicity data.

ESC noted that the selection criteria for the three safety studies were unclear and agreed that the details of trial eligibility need to be published. No consideration of the quality or characteristics of the individual studies was provided and no information on population characteristics. ESC highlighted that this information is important in assessing internal and external validity and the potential impact on the reported results. The omission of this information compromised the claimed safety of the proposed intervention. ESC was concerned that no information was provided in the submission to describe the utilisation of interventions associated with the management (nature, cost, frequency) of toxicity events. ESC also raised the issue that no evidence was provided to support the claim that there will be no adverse financial implication due to the treatment of toxicities resulting from CyberKnife treatment over 3DCRT.

ESC was concerned with the low methodological quality of the evidence and agreed that the methods employed to identify the included studies were unsatisfactory. This related to the search strategy, the inclusions and exclusion criteria and the application of these criteria. The critique outlined a number of studies that could have been included had a different methodology been employed. This may have impacted on the overall conclusions of the report. In addition, ESC agreed that due to the studies having similar populations, the results presented duplication bias (King 2011; Freeman 2011; Friedland 2009) and overestimated the effectiveness for each intervention, especially for the studies accessing CyberKnife.

On reviewing the safety data, ESC concluded that the results drawn from the comparative studies were not supported by evidence. Table B5 states that there was one grade 3 in the study of King 2012, however from the abstract of the published paper it is written "Grade 3, 2 and 1 bladder toxicities were seen in 3% (2 patients), 5 % (3 patients) and 23% (13 patients)" p.877. Rectal toxicities were also reported in the paper by King but were not included in the submission and no reason was given. The study by Katz (2010) reported one late grade 3 urinary toxicity which was

not represented in the submission's table. Toxicity was also measured using different criteria across the studies, which poses uncertainty on their generalisability.

In conclusion, ESC did not accept the claims of equivalent or superior clinical safety and advised that the applicant should provide stronger comparative evidence of CyberKnife against the comparator to strengthen their claim in the future.

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

ESC discussed the clinical effectiveness and concluded that the applicant's claims of clinical effectiveness were not supported by evidence.

NSCLC

ESC questioned the validity of the results for NSCLC as the 15 studies provided as 'relevant' evidence were from five centres and concluded that this should be reduced to nine studies.

MSAC outlined the primary sources of evidence that were provided in the applications and noted their concerns as follows:

1. these were limited and unsystematic literature reviews with no assessment of study quality;
2. no randomised or comparative trials of CyberKnife vs EBRT were provided;
3. there was considerable duplication bias due to the overlap of study series and considerable variability in treatment delivery;
4. the comparative studies of EBRT were limited to 3DCRT (IMRT was not included);
5. four studies had mixed populations (not limited to Stage I NSCLC);
6. surgery was not considered as an alternative; and
7. pulmonary metastases were not considered.

ESC was concerned with the low methodological quality of the evidence and agreed that the methods employed to identify the included studies were unsatisfactory. This related to the search strategy and the inclusions and exclusion criteria not being adequately defined. A search of PubMed by ESC identified the same studies and some additional studies, including a series of 100 patients, which were not mentioned in the application. Mixed populations were also included (primary advanced disease and metastatic disease). There was considerable variability among the CyberKnife studies which meant it was difficult to interpret effectiveness and safety objectively. Furthermore, little detail was described for the delivery of 3DCRT. ESC was concerned that the review group was unable to replicate the results from the applicant's submission. MSAC also identified that studies reporting on stereotactic radiotherapy in patients with lung cancer (by any system) were excluded despite the potential for results from these studies to be generalised to CyberKnife. ESC noted that while there was a reasonable number of series provided they all had small population sizes, which was likely to have biased the results.

In addition, no consideration of the quality or characteristics of the individual studies was provided. Characteristics such as age, stage, type of NSCLC and existing co-morbidities were not described. In addition, the DAP outlined several effectiveness outcomes; lesion response, local control, progression free survival rates, overall survival rates and quality of life, however only biochemical progression-free survival and local control was measured, despite many of the studies including the outcomes reported in the DAP. ESC also noted that no quality of life (QoL) data were provided. MSAC highlights that this information is important in assessing internal and external validity and the potential impact on the reported results. The omission of this information compromised the

claimed effectiveness of the proposed intervention.

As no direct comparative studies between CyberKnife and 3DCRT are available, clinical effectiveness was based on observational findings from small CyberKnife case series with data from 3DCRT studies in respect to local control and survival. ESC noted that the comparison of observational data from 3DCRT case series was inappropriate.

ESC agreed that the reported effectiveness should be interpreted with some caution, given that the evidence is limited and the quality of the methodology was poor.

Prostate cancer

ESC outlined the primary sources of evidence that was provided in the application and noted their concerns as follows:

1. these were limited and unsystematic literature reviews with no assessment of study quality;
2. no randomised or comparative trials of CyberKnife vs EBRT were provided and there was considerable variability in treatment delivery;
3. the comparative studies of EBRT were limited to 3DCRT (IMRT was not included); and
4. brachytherapy was not considered.

ESC advised that the most effective way to assess the effectiveness of CyberKnife is with a randomised controlled trial which MSAC concluded is an appropriate and viable method for evaluating this technology.

ESC agreed that the effectiveness evidence was poor and outlined a number of issues they had with the results. ESC identified that there were no direct studies that reported on the relative effectiveness of CyberKnife in comparison to EBRT. Studies reporting on stereotactic radiotherapy in patients with prostate cancer (by any system) were excluded despite the potential for results from these studies to be applied to a comparison with CyberKnife. Conclusions about the effectiveness of CyberKnife were based on small case series and biochemical failure was used as a surrogate marker in assessing effectiveness; however, no evidence was presented that links biochemical failure to overall or progression-free survival. ESC also noted that in parallel with the safety data, many of the studies included in the submission for both CyberKnife and 3DCRT included patients from the same series. This presented duplication bias and thus overestimated the body of evidence of effectiveness. No consideration regarding the quality or characteristics of the individual studies was provided. Characteristics such as age, previous or current treatments were not described. ESC felt this information was important in assessing internal and external validity and the potential impact on the reported results. ESC also agreed that the exclusion of this information did not allow evaluation of the generalisability of the results and compromised the claimed effectiveness of the proposed intervention.

There was considerable variability among the CyberKnife studies which meant it was difficult to interpret effectiveness and safety objectively. Furthermore, little detail was provided regarding the delivery of 3DCRT. ESC was also concerned that the review group was unable to replicate the results from the applicant's submission. In reference to the proposed eligible population, ESC highlighted inconsistencies between the applicant's submission and the data provided. An examination of the MBS usage statistics for MBS item number 15248 for the 2009-10 financial years could not be replicated by the review group. Their conclusion was that there is uncertainty in the estimation of the potential number of prostate cancer patients eligible to receive treatment with

CyberKnife. Based on the evidence provided, ESC did not accept the claims of equivalent or superior clinical effectiveness.

Many of the safety and effectiveness outcomes included in the DAP were not addressed by the applicant. Some studies included QoL outcomes but these were not included in the submission. ESC highlighted that this was a major disadvantage.

Based on the evidence provided, MSAC did not accept the claims of clinical effectiveness and advised that the applicant provide comparative evidence of CyberKnife against other stereotactic radiotherapy to strengthen their claim in the future.

4 Other important clinical issues and areas of clinical uncertainty?

ESC noted the applicant's claim that CyberKnife was superior as it needed fewer treatment sessions to other conventional radiotherapy treatments. ESC noted that each CyberKnife treatment is typically of 45-60 minutes' duration while other radiotherapy treatments usually take 15-20 minutes. ESC highlighted that fewer sessions does not necessarily equate to superiority.

Furthermore, ESC found that the applicant's claims of reduced toxicity, improved tumour control and improved health outcomes were not supported by evidence. ESC recommended that further evidence for downstream costs and evidence to support claims of cost neutrality should be provided in the future.

ESC considered the possibility that the weakness in the evidence stemmed from the applicant's using CyberKnife (the brand) as the platform for the intervention instead of stereotactic radiotherapy more generally. They were interested to view more evidence about stereotactic radiotherapy and if this made a stronger case for CyberKnife. ESC advised that the applicant take this into consideration and supplement sufficient evidence to support CyberKnife's claims of superiority.

5 Main economic issues and areas of uncertainty?

ESC was concerned that a standard economic evaluation, i.e. cost effectiveness analysis, was not conducted. Instead, a costing analysis was presented. ESC agreed that a costing analysis is not in line with the requirement of a cost effectiveness analysis specified in the DAP, and no reason was given for deviating from the approach agreed to by PASC.

It was brought to ESC's attention that in the original application, the applicant indicated that they would present a cost minimisation analysis, due to the fact that the proposed system was at least as safe, as effective (non-inferior) and thus as cost-effective as the comparator. The review group determined that the evaluation presented was not a cost-minimisation analysis and that the evidence presented did not establish equivalence.

The review group found that no consideration of health outcomes was given in the economic evaluation. ESC noted that the economic analysis was confined to likely costs associated with use of CyberKnife and that the time horizon was restricted to delivery of treatment only and did not provide evidence of long term equivalent efficacy. No sensitivity analyses or cost offsets were provided and the claimed benefit to patients from remote areas was not included in the economic evaluation. MSAC noted that this benefit was also unlikely be realised unless CyberKnife use were to become more common.

NSCLC

Due to the lack of information around the characteristics of the studies for NSCLC, ESC was unsure if the participants in the trials were comparable to the intended population for use in Australia. ESC identified this as a high uncertainty given the rates of lung cancer in Australia. In addition, the figures represented an overestimation of costs for the comparator and did not reflect current Australian practice.

ESC wanted justification regarding data extrapolation and an appropriate time horizon. They also wanted justification of whether the outcomes reported could be transformed into relevant clinical outcomes.

ESC acknowledged the Lanni, 2011 report as provided in the applicant's response to the ESC report. ESC agreed that this report was the closest piece of evidence to a randomised controlled study. ESC also agreed that a Kaplan-Meier curve in real time would be preferable as the one in the report was completed in sample time. In addition, ESC noted that the report was not well presented. They also highlighted that the costs and risks of inserting fiducial markers need to be incorporated into the costs and risks in future models.

Prostate cancer

The main concerns ESC had in regards to the economic evaluation regarding CyberKnife treatment for prostate cancer was that the DAP provided a list of resources to be considered, however many were not included, e.g., costs associated with treating recurrent disease and toxicities. There were incomplete estimations of total treatment costs for both interventions. The economic evaluation literature review was not described and the population was poorly defined. The average cost associated with delivering a course of radiation therapy was measured using a dual photon linear accelerator and not EBRT. The costing did not take into account that CyberKnife could be used across multiple indications (including lung cancer) if the service were to be approved. There was no evaluation of difference in costs due to the different treatment delivery regimens (3DCRT vs CyberKnife). The difference in the costs per patient (of delivering a course of CyberKnife) stems from differences in the projected number of patients (1,750 and 1,945 respectively) that receive treatment over a ten year timeframe.

ESC agreed that the lack of detailed information regarding calculations made it impossible to test the accuracy of the results. Furthermore, the fact that the results were unable to be replicated is a major flaw for the application. ESC advised that the applicant should provide more evidence to support the toxicity and effectiveness claims to ensure that a clear judgement of CyberKnife's superiority can be made.

ESC agreed that the claims of cost neutrality in the applicant's submission were unjustified based on the evidence presented. No analysis was undertaken to explore the uncertainty surrounding the assumptions made about overall cost-neutrality, out of pocket expenses or benefits for remote patients. ESC did not accept the applicant's cost-neutral claim.

6 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?)

NSCLC

A major concern for ESC was that no sensitivity analysis testing impact of changes in parameters was undertaken. What was of most concern to ESC was that the economic evaluation for NSCLC relied on calculations undertaken as part of the prostate cancer submission (fee structures and patient throughput).

Prostate cancer

ESC agreed that the conduct of a cost-effectiveness analysis would have facilitated the incorporation of a range of safety and effectiveness outcomes described in the DAP in the economic evaluation. Exclusion of these parameters from the economic evaluation stems from the applicant's claim of non-inferiority of CyberKnife in comparison to 3DCRT. In light of the issues relating to clinical uncertainty, ESC concluded that this claim was not supported by the evidence presented in the submission.

ESC also questioned the use of a 3.5% discount rate to estimate costs associated with treatment delivery using CyberKnife and recommended the applicant provide justification as to why this percentage was used.

ESC agreed that the comparator fees for EBRT were based on the highest level of complexity (highest cost MBS item) without evidence to support this. The applicant also used the highest reimbursement figures from ROHPG without any evidence to support their claim that CyberKnife should be approved for this reimbursement bracket.

ESC anticipated that, if CyberKnife were to be approved, there would be more than one CyberKnife unit available in Australia. Therefore, ESC highlighted that limiting the data to just one unit rather than the predicted number of units available added to uncertainty.

ESC noted that no estimation of the services likely to be provided was carried out. ESC also noted that the review group stated in their report that "the sponsor believes that an amount equivalent to the amount (\$11,190) of these current payments for a course of 3DCRT is financially feasible" and that therefore the financial implications for the MBS are cost neutral given that one service substitutes for the other.

ESC questioned the evidence provided and concluded that further analysis was needed for:

1. stratified graphical analysis of the case series comparisons;
2. data on adverse effects (complications of radiation); and
3. Australian data on number of sessions for EBRT, 3CDRT, IMRT and CyberKnife.

14. Other significant factors

MSAC highlighted that this application presents an emerging trend in clinical practice that as new technologies come onto the market, their descriptors need to be assessed as to whether they represent a new technology or an improvement on an existing technology. MSAC agreed that CyberKnife should be considered with other forms of IGRT which are currently under consideration but that further evidence must be submitted to MSAC for CyberKnife to be considered an

appropriate technology within this group. MSAC highlighted the need for existing technologies to be reviewed and identified in 'like' groups. Defined eligibility criteria will need to be established to assess whether a technology is deemed suitable for that group or not. MSAC agreed that applicants will be required to submit sufficient evidence specific to the eligibility criteria for a technology to be assessed in that group. Comparative evidence against other technologies within that group must also be presented to determine the ranking of the technologies in terms of safety, effectiveness and efficacy.

MSAC noted that should CyberKnife be approved for treatment for lung and prostate cancer, there would need to be specific advice as to whether the item descriptors were restricted to only these conditions, which would not allow treatment of other cancers (e.g. breast). ESC also noted that current MBS item descriptors are generic enough to allow these conditions to be claimed (as well as a ROHPG payment), and these item descriptors would need to be modified if this is not the intent. MSAC agreed that current 'generic' descriptors will not be amended to specifically exclude CyberKnife.

MSAC agreed that CyberKnife had the potential to be a superior technique of radiotherapy but deferred this conclusion until further sufficient evidence was provided to support this case. MSAC highlighted that they encourage the applicant to resubmit once substantial and strong evidence in favour of CyberKnife has been collected.

MSAC discussed the need of ROHPG funding, and that CyberKnife may be eligible for if approved or considered eligible under existing items.

15. Summary of consideration and rationale for MSAC's advice

MSAC noted robotic image-guided stereotactic precise beam radiosurgery and radiotherapy would be eligible for public funding through Medicare Benefits Schedule item 15600 if it were available in Australia. MBS item 15600 is a general stereotactic radiosurgery item that includes all radiation oncology consultations, planning, simulation, dosimetry and treatment, with an associated MBS schedule fee for service of \$1,670.55.

MSAC noted the applicant's claim that the technique was superior to conventional radiotherapy treatments, as it was delivered in fewer fractions; however no evidence of this superior clinical advantage was presented. MSAC also noted that each proposed treatment fraction typically takes three times longer than other therapies.

MSAC considered the applicant's proposed fee, which was calculated on the episodic cost of a course of radiotherapy using existing techniques, based on the current MBS funding for a standard course of three-dimensional conformal radiotherapy (3DCRT) using the highest reimbursement bracket. MSAC noted that the capped fee of \$10,584 for lung cancer treatment was based on standard proposed average course of therapy of four fractions. In comparison, the cost provided by the applicant for 3DCRT (including dosimetry, verification and ROHPG payment) was \$11,190 which was based on a course of treatment delivered over 30 fractions with five fields delivered per treatment session. Similar proposals were put forward for prostate cancer, using 35 3DCRT treatment fractions versus 3.5 fractions for robotically delivered procedures. MSAC agreed that the derivation of fees proposed by the applicant did not comply with requirements for input-based fee determination.

MSAC noted that the application based its economic justification on the assumption that a course of robotic image-guided stereotactic precise beam radiosurgery and radiotherapy is at least as safe and effective as 3DCRT and is cost-neutral. MSAC deliberated on the applicant's rationale of a cost-neutral approach considering fewer verification sessions and a shorter total duration of treatment (number of fractions x time per fraction) are required for the proposed procedure. MSAC identified that the verification procedure for both interventions is identical. On this basis, MSAC did not accept the claim of cost-neutrality, cost effectiveness or value for money for the patient to justify the higher fee difference based on the evidence presented.

MSAC noted that both brachytherapy and surgery were identified in the Decision Analytic Protocol (DAP) as additional comparators for robotic image-guided stereotactic precise beam radiosurgery and radiotherapy for prostate cancer.

MSAC highlighted that no comparison was made between brachytherapy and robotic image-guided stereotactic precise beam radiosurgery. Therefore MSAC did not accept the procedure as an alternative to brachytherapy. The DAP also identified surgery as a comparator to robotic image-guided stereotactic precise beam radiosurgery and radiotherapy for the primary treatment for stage I NSCLC and patients with pulmonary metastatic lesions. Again no such comparison was provided by the applicant.

MSAC considered that robotic image-guided stereotactic precise beam radiosurgery and radiotherapy was a variant of image-guided radiotherapy (IGRT) and not a new stand-alone technology. MSAC concluded that the procedure should be considered together with other image-guided radiotherapy technologies. MSAC noted that there are other MSAC applications in progress that are considering IGRT and intensity modulated radiotherapy (IMRT) more broadly. These applications will undergo a departmental contracted assessment, which will look at all IGRT and IMRT technologies and techniques for the treatment of cancer, not restricted to prostate and lung cancer. MSAC highlighted that this application exemplifies an emerging trend in clinical practice: as technologies become available, they need to be assessed to determine whether they represent a new technology or an advancement of an existing technology. If an advancement of an existing technology, the existing MBS descriptor may require modification.

MSAC agreed that the best way to assess the safety and effectiveness of hypofractionated radiotherapy (which is the technique proposed in the application) is with a randomised controlled trial, concluding that this is an appropriate and viable method.

MSAC resolved to refer to PASC the possibility of grouping like new and emerging techniques with a view to developing consolidated DAPs and submissions to MSAC. MSAC agreed that robotic image-guided stereotactic precise beam radiosurgery and radiotherapy had the potential to be a radiotherapy technique but felt that it should be considered with the other forms of IGRT which are currently under consideration in the MSAC assessment processes.

MSAC agreed that a consolidated IGRT submission would be useful, but if the applicant felt that robotic image-guided stereotactic precise beam radiosurgery and radiotherapy did not belong to this group, the applicant would need to make an alternative case which addressed the deficiencies identified in the current submission.

MSAC concluded that there was insufficient evidence to support public funding of the technique on

the following grounds:

- evaluation of evidence was inadequate;
- comparators and safety & effectiveness outcomes specified in the final DAP were not addressed;
- claims of superiority, reduced toxicity, improved tumour control and improved health outcomes were not supported by evidence;
- the economic evaluation was inadequate – a cost-benefit analysis was specified in the final DAP; and
- the proposed fee was not input-based and information to support cost-neutrality was not provided.

16. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, effectiveness and cost-effectiveness of robotic image-guided stereotactic precise beam radiosurgery and radiotherapy via the CyberKnife[®] system for patients with prostate cancer and patients with primary non-small cell lung cancer and lung metastasis from other controlled primary sites, MSAC does not support a new, higher MBS fee for the procedure.

17. Applicant's comments on MSAC's Public Summary Document

The sponsor, Accuray Incorporated, remains committed to the MSAC process and to those Australian patients we hope will benefit from accessible CyberKnife technology within the country. In line with this, the sponsor proposes to resubmit to provide greater clarity on the relevance of peer reviewed clinical publications, new and previously submitted, by showing their relevance with respect to today's research and draw closer conclusions to surgical and other radiation comparators. For information that is unavailable, the sponsor will provide satisfactory explanations as to why this is so. Additional safety processes and procedures will be expanded and further explained including a more comprehensive economic analysis for out-of-pocket expenses to the patient, the facilities investment and government health care reimbursements.

18. Context for decision

This advice was made in accordance with MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;

- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

19. Linkages to other documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.