MRI-US fusion targeted biopsy

for diagnosis of prostate cancer

Technology Guidance from the MOH Medical Technology Advisory Committee

Guidance Recommendations

The Ministry of Health's Medical Technology Advisory Committee has recommended:

- ✓ Magnetic resonance imaging-ultrasound (MRI-US) fusion targeted biopsy alone or combined with non-targeted biopsy may be considered for the initial diagnosis of prostate cancer in men aged 18 years or older
  - who are suspected of having prostate cancer due to persistently elevated prostate-specific antigen (PSA) levels of 4ng/ml or more, abnormal digital rectal examination (DRE), or if clinical suspicion of prostate cancer persists; and
  - who have had a positive pre-biopsy multi-parametric magnetic resonance imaging (mpMRI) with Prostate Imaging – Reporting and Data System (PIRADS) 3 to 5 lesions;

- ✓ mpMRI should be performed and assessed using PIRADS scores consistent with the prevailing version of standards; and

- ✓ MRI-US fusion targeted biopsy should not be used in patients with contraindications to mpMRI or have known metastatic prostate cancer.

Subsidy status

Subsidies should apply to MRI-US fusion targeted biopsy in the initial and repeat biopsy settings, in line with stated recommendations.

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Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1 The MOH Medical Technology Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation on MRI-US fusion targeted biopsy for diagnosis of prostate cancer. The Agency for Care Effectiveness conducted the evaluation in consultation with senior clinicians in urology, diagnostic radiology or imaging, and oncology.

1.2 The evidence was used to inform the Committee's deliberations around five core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Overall benefit of the technology to the patient and/or the system;
- Cost-effectiveness (value for money), which covers the incremental benefit and cost of the technology compared with existing alternatives;
- Estimated annual technology cost and the number of patients likely to benefit from the technology; and
- Organisational feasibility, which covers the potential impact of adopting the technology, especially barriers for diffusion.

1.3 Considerations such as ethical or social issues related to adoption of the technology may also inform the Committee's deliberations.

Clinical need

2.1 The Committee noted that, in men who are suspected of having prostate cancer, prostate biopsy is the gold standard for diagnosis. Conventionally, prostate biopsy is commonly performed using non-targeted systematic or saturation transrectal or transperineal ultrasound (US)-guided biopsies. Systematic biopsies involve the extraction of core tissue from pre-defined biopsy schemes to arbitrarily demarcate core extraction locations and may involve a template to enable reproducible sampling. Saturation biopsy is a form of systematic biopsy that involves extensive sampling, typically 20 or more cores.

2.2 Non-targeted US-guided prostate biopsies cannot distinguish malignant from benign lesions during the biopsy process. Although US provides excellent images of the boundaries of the prostate gland and structures of

adjacent organs, US alone is insufficient to target specific lesions as a significant proportion of these lesions cannot be distinguished on US. This limitation can result in over-sampling (i.e. over-representation of low-grade tumour) or under-sampling (i.e. under-representation of high-grade tumour), and sub-optimal detection of clinically significant disease.

Overall benefit of technology

3.1 The Committee noted that MRI-US fusion targeted biopsy is a type of targeted biopsy technique that uses software to integrate data from pre-biopsy mpMRI with real-time US imaging data to allow real-time movements of the US probe and biopsy needles to be visualised with MRI guidance during prostate biopsy. MRI-US fusion targeted biopsy can be combined with systematic or saturation biopsy in initial and repeat biopsy settings or used alone in repeat biopsy setting.

3.2 The Committee noted that the main comparator is systematic biopsy alone without pre-biopsy mpMRI. Other comparators include systematic biopsy with pre-biopsy mpMRI, and saturation biopsy alone without pre-biopsy mpMRI. The evidence base included published health technology assessment reports, primary studies and systematic reviews including a 2019 Cochrane review by Drost et al which provided up-to-date meta-analyses on MRI targeted biopsy for detecting prostate cancer.

3.3 The Committee agreed that MRI-US fusion targeted biopsy is likely to have good safety profile, especially if transperineal access is used. It has been shown to have similar or lower post-procedural bleeding rates, and lower pain intensity and pain duration than systematic transrectal US-guided biopsy. Major complications that are potentially life-threatening such as sepsis are rare.

3.4 The Committee agreed that based on low to moderate quality evidence in the initial biopsy setting where patients were biopsy-naïve, compared to the main comparator, MRI-US fusion targeted biopsy combined with systematic biopsy gave higher overall or clinically significant prostate cancer detection rates, and proportion of cores with cancer particularly in larger prostates where sampling error may be more common. It can potentially upgrade the cancer risk category of the biopsy. However, it did not appear to reduce detection of clinically insignificant prostate cancer or

differ in concordance of biopsy pathology with radical prostatectomy surgical pathology.

3.5 The Committee noted that in the repeat biopsy setting where patients had one or more prior negative biopsies, the quality of evidence ranged widely from very low to high. Compared to the main comparator, MRI-US fusion targeted biopsy combined with systematic biopsy gave higher overall prostate cancer detection and clinically significant prostate cancer detection rates, with added advantage in sub-groups with more prior negative biopsies. It gave lower or similar detection of clinically insignificant prostate cancer but can potentially upgrade the cancer risk category of the biopsy. It also showed better diagnostic accuracy with significantly higher sensitivity but similar specificity. There was no difference in health-related quality of life at 24 hours and 30 days post-biopsy. Compared to saturation biopsy alone, moderate quality evidence showed that MRI-US fusion targeted biopsy combined with saturation biopsy did not differ in the detection of clinically significant prostate cancer in the repeat biopsy setting.

3.6 The Committee noted that most guidelines did not state the strength of recommendations, with the exception of the European Association of Urology (EAU) guidelines which gave a strong recommendation for using MRI targeted biopsy combined with systematic biopsy in the initial biopsy setting, and a weak recommendation for MRI targeted biopsy alone in the repeat biopsy setting. The Committee pointed out that the need for clinical evidence on longer-term patient health outcomes of MRI-US fusion targeted biopsy combined with non-targeted biopsy could be more pertinent in the repeat biopsy setting, given the propensity for many biopsies to be performed in this setting for a largely slow-growing cancer.

3.7 The Committee agreed that key limitations of the clinical evidence include: scarce direct comparative evidence for safety, diagnostic test accuracy outcomes and longer-term patient health outcomes; influence of patient-related factors (e.g. prostate size) and procedure-related factors (e.g. number of biopsy cores extracted) on safety and effectiveness; poor adverse events reporting; lack of use of valid independent reference standard tests; and variations in definitions on clinical significance and insignificance used in studies.

Cost effectiveness

4.1 The local de novo cost-effectiveness model compared various diagnostic strategies in the diagnosis of prostate cancer. The diagnostic strategies involved MRI-US fusion targeted biopsy, systematic biopsy, and saturation biopsy, arranged in different testing combinations and sequences. The Committee noted that base case incremental cost-effectiveness ratios (ICERs) ranged from $15,000 to <$45,000 per quality-adjusted life year (QALY) gained for strategies in the initial biopsy setting. Strategies that used MRI-US fusion targeted biopsy combined with systematic biopsy in the initial biopsy setting consistently yielded the most QALYs per dollar spent.

4.2 The Committee noted that probabilistic sensitivity analyses showed that diagnostic strategies involving MRI-US fusion targeted biopsy combined with systematic biopsy in the repeat biopsy setting yielded a higher ICER or were dominated (i.e. more costly, less effective). Strategies involving the use of saturation biopsy too early in the diagnostic strategy were also dominated.

4.3 The Committee further noted that the ICERs were most sensitive to annual discounting rate, prevalence of prostate cancer, and detection rate of systematic biopsy as a first biopsy for patients with low-risk prostate cancer.

Estimated annual technology cost

5.1 The Committee noted that the estimated annual cost to the Government for subsidising MRI-US fusion targeted biopsy was <$1 million in both initial and repeat biopsy settings.

Organisational feasibility

6.1 Although a positive subsidy recommendation for MRI-US fusion targeted biopsy could have downstream implications on service capacity of pre-biopsy mpMRI, the Committee noted that mpMRI of the prostate was unlikely to substantially impact national MRI capacity as it constituted only a small proportion of the total MRI load.

6.2 To maximise the benefits of MRI-US fusion targeted biopsy, the Committee agreed on the need to continually ensure quality interpretation of pre-biopsy mpMRI.

6.3 The Committee further noted that key operational challenges in public healthcare institutions were the inability to optimally track patient movements and existing billing systems to differentiate between the initial and repeat biopsy settings.

Additional considerations

7.1 Besides strength of recommendation, the Committee noted that clinical guidelines recommendations on use of MRI-US fusion targeted biopsy could also vary by initial or repeat biopsy setting and whether MRI targeted biopsy was used alone or in combination with non-targeted biopsy. The Committee acknowledged that guidelines are evolving rapidly, and subsequent updating of PIRADS version may potentially improve results of MRI-US fusion targeted biopsy.

7.2 The Committee also noted that overseas countries, namely Australia and the United Kingdom, did not distinguish between settings for the reimbursement of MRI targeted biopsy in the diagnosis of prostate cancer.

Recommendation

8.1 Based on the evidence presented, the Committee recommended subsidy for MRI-US fusion targeted biopsy alone or combined with non-targeted biopsy in the initial and repeat biopsy settings based on the following criteria:

- MRI-US fusion targeted biopsy alone or combined with non-targeted biopsy may be considered for the initial diagnosis of prostate cancer in men aged 18 years or more
  - who are suspected of having prostate cancer due to persistently elevated PSA levels 4ng/ml or more, abnormal DRE, or if clinical suspicion of prostate cancer persists; and
  - who have had a positive pre-biopsy mpMRI with PIRADS 3 to 5 lesions;
- mpMRI should be performed and assessed using the PIRADS scores, in a manner consistent with the prevailing version of standards; and

- MRI-US fusion targeted biopsy should not be used in patients with contraindications to mpMRI or have known metastatic prostate cancer.

8.2 The Committee advised that saturation biopsy should not be used prematurely in the diagnostic strategy subject to clinician discretion, as strategies that used saturation biopsy early in the pathway were dominated. For example, diagnostic strategies such as MRI-US fusion targeted biopsy + systematic biopsy → systematic biopsy → saturation biopsy gained more QALY than when saturation biopsy was used earlier in strategies such as MRI-US fusion targeted biopsy + systematic biopsy → saturation biopsy → systematic biopsy.